Motor evoked potentials
in predicting motor and functional outcome
after stroke

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Motor evoked potentials in predicting motor and functional outcome after stroke

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

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To Carla, Filip and Gilles

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Contents

CHAPTER 1

GENERAL INTRODUCTION

Strokes are a common cause of death in the western world and it may lead to severe disabilities in the survivors. The incidence in the Netherlands is approximately 28,000 cases per year, including 4,000 patients with recurrent stroke[1]. The stroke syndrome is clinically defined as a rapid development of focal neurological deficits of vascular origin. In pathophysiological terms we can distinguish infarction from hemorrhage. Infarction is most common, about 80% of all stroke patients suffer from an infarction, whereas 20% of all stroke patients are struck by an hemorrhage. The clinical presentation varies from minor neurological symptoms to severe deficits, depending on the location and the size of the brain lesion. Hemiparesis, one of the most striking features in the acute phase, occurs in 80-90% of all stroke patients[2] and may be accompanied by hemihypesthesia. Other striking features are represented by cognitive deficits such as aphasia, apraxia, and hemineglect[3]. Many other deficits may be present at onset, including loss of consciousness, dysfunction of the cranial nerves, postural imbalance, coordination disorders, and loss of sphincter control. Complications secondary to the initial neurological deficits may develop in the subacute and chronic phase. These include, shoulder-hand syndrome as a result of multiple traumatizations in patients with paralysis of the upper extremity and hemineglect[4], or contractures caused by severe spasticity. Within this context, also the learned non-use syndrome as a result of a psychological avoidance reaction to an impaired hand function should be mentioned[5].

All persistent neurological deficits, in combination with the secondary medical and psychological complications, may cause more or less severe activity limitations in several domains of human functioning. For example, the inability to perform basic activities of daily live, the inability to stand up and walk, the inability to divide attention to various issues, and the inability to communicate. These activity limitations may even lead to restricted participation of the patient within a social, cultural and vocational context.

Apart from the level of impairments, personal and psychosocial factors have been proposed as determinants for the perceived activity limitations and restricted participation[6].

Recovery

The term recovery may refer to various pathophysiological and clinical processes that occur in stroke patients. According to the International Classification of Human Functioning of the World Health Organization[6], we generally discriminate between the recovery of the primary neurological deficits (restoration of body functions) and functional recovery (improved performance of activities). Apparently, the restoration of neurological deficits will result in functional recovery. However, functional recovery may also occur in patients who do experience no or only partial neurological recovery. In these cases, functional recovery is the result of the development of novel adaptive strategies following therapy and learning[7].

Several mechanisms have been suggested that may account for recovery after stroke. The reversal of diaschisis[8,9], the resolution of edema, blood and toxic metabolic products, and the survival of ischemic penumbra[10,11] have been described in the early phases post-stroke. In the subacute and chronic phases, functional reorganization processes are supposed to contribute to recovery. Motor evoked potentials (MEPs), positron emission tomography and more recently functional magnetic resonance imaging studies have shown increased activation of the unaffected motor cortex[12] and rearrangement of brain motor cortical output of the affected hemisphere[13-17]. For recent reviews, see Nudo et al.[18] and Rossini and Pauri[19].

Prediction of outcome

Early prediction of functional outcome remains an important topic in stroke management and related research. Functional recovery is affected by a variety of biological and environmental factors and recovery profiles are

characterized by a high interindividual variability. Nevertheless, a valid prognosis for the individual stroke patient is required as early as possible after stroke onset in order to inform the patient and his relatives adequately, to initiate optimal rehabilitation according to realistic therapy goals, and to facilitate discharge planning (including necessary home adjustments and support).

Extensive prognostic studies have been performed to address the prediction of stroke outcome. Many prediction models have been proposed, but their predictive validity appeared to be rather poor[20]. A critical review of the literature[21] on this matter indicated that several clinical and demographic variables might be valid predictors of general functional recovery, including neurological factors such as consciousness at onset, disorientation in time and place, sitting balance, and severity of motor deficits. The severity of initial motor deficits has been identified as an important predictor for functional outcome in many other studies[22-24]. Patients with initial paralysis have the worst prognosis for motor outcome[22], although some of these patients will show partial or even complete motor recovery. Clinical examination alone lacks the possibility to detect the potential for motor recovery in these cases. Moreover, particularly in noncooperative patients or severely cognitively impaired patients (i.c. global aphasia, attention deficits, apraxia and neglect), the clinical motor evaluation may be invalid in the early phase post stroke and thus inconclusive with respect to functional prognosis.

Transcranial magnetic stimulation

Merton and Morton[25] showed 30 years ago that it was possible to stimulate the motor areas of the human brain through the intact scalp by a brief high-voltage electric shock. This stimulation generated relatively synchronous muscle responses of the contralateral hemibody with latencies compatible with the activation of the fast corticospinal tracts. Electrical stimulation appeared to be painful and therefore it was less applicable in daily practice. Several years

later, Barker et al.[26,27] developed an alternative method of external brain stimulation, namely transcranial magnetic stimulation (TMS). The scientific principle on which magnetic stimulation is based was discovered by Michael Faraday in 1831. He described the phenomenon of mutual induction, whereby current flows in a secondary circuit when it is brought near a current-carrying primary circuit. In 1896, D'Arsonval reported that flickers of light were seen by volunteers when their heads were placed in a time-varying magnetic field. In 1965 Blickford and Freming demonstrated muscular contractions in animals and humans after magnetic stimulation. It was not until 1985 that Barker stimulated the human brain with a magnetic stimulator. In contrast with electrical stimulation, magnetic stimulation is a method of stimulating neuromuscular tissues that does not rely on the passage of electric current through electrodes and the skin. A pulse of magnetic field passes into the body and induces an electric field. The mechanism of stimulation at the cellular level is thus supposed to be the same for electric and magnetic stimulation, namely current passing across the membrane of neural tissue, resulting in activation of excitatory or inhibitory synaptic inputs of corticospinal neurons. Excitatory effects are reflected in the motor evoked potentials, the MEPs, whilst the inhibitory activation is represented by an interval of inability to contract the target muscle. The results of the stimulation are usually recorded with a conventional electromyograph, using surface electrodes fixed to the target muscle.

Several physical variables affect TMS, including the magnitude, the wave form, and the rise time of the magnetic field. Furthermore, the diameter, the thickness, and the insulation of the coil determine the stimulation parameters. As for the site of stimulation, precise placement of the magnetic coil on the scalp is not necessary, since the magnetic field is widely distributed. Excitation of the motor area of the arm is achieved most easily with the coil center in the region of the vertex. More anterior placement is usually performed for excitation of the motor areas of the leg. The corticospinal tract

may be stimulated directly or indirectly via cortico-cortical connections. It is hypothesized that magnetical stimulation with near treshold intensities acts preferentially indirectly.

Soon after the development of brain stimulation it became apparent that preexisting voluntary contraction decreases the stimulation threshold and increases the amplitude of the response. This potentiating effect is generally indicated as facilitation and may occur both after contralateral and ipsilateral contraction[28,29]. Both cortical and spinal mechanisms have been suggested as generators for this phenomena[28,29].

Several adjunctive parameters of TMS have been studied in healthy volunteers and in patients. They include the amplitude and latency of the motor responses, the excitability threshold of corticospinal tracts, the effects of facilitation on the excitability, the analysis of TMS-induced inhibitory phenomena, as well as the position and extension of the excitable area devoted to a muscle.

TMS is a relatively simple and well-tolerated procedure, that allows an objective and quantitative assessment of the integrity of the motor pathways[30,31]. Provided that certain elementary precautions are taken into account, magnetic stimulation of the brain appears to be a remarkable safe method. Epilepsy, previous neurosurgery, cardiac prosthetic valve and pacemaker implantation should be regarded as contraindications. Adverse effects have seldom been described[32-34]. Nowadays, TMS is commonly used in clinical practice and as a research tool.

Transcranial magnetic stimulation in stroke patients

The obtained data showed decreased excitability threshold, increased latency and decreased amplitude of the MEPs after stimulation of the affected

hemisphere (compared to the non-affected hemisphere)[35-37]. In the case of severe stroke, responses were even abolished.

The data from TMS studies in stroke patients have specifically been used (1) to assess the motor impairments , (2) to predict motor and functional recovery analogues to prognostic studies using somatosensory evoked potentials[38,39], (3) to study cortical reorganization processes as the neurophysiological representation of clinical recovery, and (4) to study inhibitory phenomena induced by the stimulation.

(1) Motor dysfunction after stroke may be caused by loss of cortical excitability and disruption of sensorimotor pathways. The integrity of the motor pathways can be assessed properly by MEPs. Studies of MEPs in stroke patients have shown evident correlations between the clinical motor scores and several MEP parameters[40,41].

(2) The degree of MEP abnormalities in the (sub)acute phase after the stroke appeared to be prognostic for subsequent motor and functional recovery[35-37]. However, the prognostic use of MEPs in stroke management is still equivocal and studies seem to be contradictionary[42,43]. For instance, Arac et al.[43] evaluated the role of MEPs in predicting motor recovery in a heterogeneous sample of 27 acute stroke patients. The authors found no difference in motor scores at follow-up between patients who had a present or absent response at the early MEP assessment.

(3) Concerning cortical reorganization processes, longitudinal studies in stroke patients showed the development of ipsilateral activation of the paralyzed muscles[12,44], increased activation of the supplementary and premotor areas of the affected hemisphere[13,14], posterior shift of activation in the primary sensorimotor cortex[16], and increased activity at the rim of the infarction[17].

(4) As for the TMS induced inhibitory phenomena, the results in stroke patients are not uniform. The silent period appeared to be significantly prolonged when recordings were obtained from the affected side[45,46]. Nonetheless, in other studies a decrease of the silent period was reported[47,48], or both patterns[49,50].

Scope of the thesis

Motor outcome appears to be an important parameter for functional outcome. In general, insight in spontaneous motor recovery in the (sub)acute and more chronic phases after stroke is still limited. The initial severity of motor deficits has been identified an important predictor for motor and functional outcome, however, clinical assessment of the initial motor deficits is often invalid and thus inconclusive with respect to motor outcome. Moreover, in the case of initial paralysis clinical examination alone lacks the possibility to detect the potential for motor recovery. The integrity of the motor pathways can be assessed objectively and quantitatively by MEPs. From this perspective in this thesis we investigated MEPs as a predictor for motor and functional outcome after stroke.

The thesis is divided into three parts. Part I contains two pilot studies concerning the predictive value of SEPs and MEPs with respect to motor recovery of the upper extremity in a case series *(Chapter 2)* and a historic cohort of stroke patients *(Chapter 3)*.

Part II consists of two systematic reviews. The first systematic review is described in *Chapter 4*. The purpose of this study was to collect and integrate existing data concerning the extent, time course and prognostic determinants of motor recovery after stroke using a systematic methodological approach. The second systematic review (*Chapter 5*) addresses specifically the use of MEPs in predicting motor and functional outcome after stroke.

Part III contains three cohort studies. In the first cohort study *(Chapter 6)*, the predictive value of upper extremity MEPs with respect to arm and hand motor recovery, and recovery of functional abilities were assessed in subacute stroke patients with initial paralysis of the upper extremity. In the second cohort study *(Chapter 7)*, we addressed the predictive value of lower extremity MEPs with respect to motor recovery of proximal and distal muscles of the lower extremity, and functional recovery. *Chapter 8* describes a repeated investigation of interhemispheric differences of the amplitude and the latency of MEPs of proximal and distal muscles of the upper and lower extremity, in a homogeneous sample of stroke patients with complete paralysis of the upper and or the lower extremity. The aim of this study was to assess the recovery of fast corticospinal functions in stroke patients, and to assess the relationship between MEPs and the subsequent clinical motor scores for proximal and distal muscles in the arm and the leg.

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CHAPTER 2

THE VALUE OF SOMATOSENSORY EVOKED POTENTIALS FOR THE PREDICTION OF MOTOR RECOVERY OF THE UPPER EXTREMITY AFTER CEREBRAL INFARCTION

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Abstract

Until now prediction of recovery in the acute phase of stroke is primarily based on subjective clinical examination. Generally, the severeness of the initial motor deficit is used as the most important predictor of motor recovery. However, the integrity of the somatosensory system forms another important predictor. It can be assessed objectively and quantitatively by means of Somatosensory Evoked Potentials (SEPs). In this study, motor recovery of the upper extremity is predicted by measuring SEPs in seven patients suffering from acute cerebral infarction with a paralyzed upper extremity and no recovery tendency during the first 10 days. A follow-up during nine months showed excellent motor recovery in one patient and moderate motor recovery in three patients. In three other patients no motor recovery occurred. The prediction based on the SEPs findings was correct in all cases except one. Further examination of this patient provided evidence for a demyelinating disease. The value of SEPs as a predictive tool in the early assessment of stroke patients is discussed.

Introduction

Recovery after stroke is influenced by a variety of biological and environmental factors[1]. Recovery profiles are characterized by a high interindividual variability. Until now, objective and above all reliable predictive instruments, which can be used in the acute phase of stroke, are lacking. With regard to functional restoration after brain damage a distinction is normally made between spontaneous recovery as a result of reorganizing capacity of the brain[1,2] and the development of novel adaptive control strategies as a result of therapy and learning[3,4]. Spontaneous recovery may result, particularly in the (sub)acute phase, in a substantial recovery of the hemiplegic side, whereas the acquisition of adaptive control strategies may contribute to functional improvement in the latter post-lesion periods. This paper is aimed at the natural course of spontaneous sensorimotor recovery of the upper extremity and its predictability in the acute phase. Although sensory impairment is

common after stroke (it occurs probably in at least half of all stroke patients), it has received little attention, which is even more true for the study of recovery from sensory loss. Most attention has been focused on the actual performance and training of motor functions. However, because the tactile kinesthetic sensory system forms a crucial interface between the body and its environment, it plays an important role in motor control and learning. It is well known that loss of sensation in patients with hemiplegia forms a severe hindrance in rehabilitation. It has also been argued that spasticity and mass movement synergies may be related to sensory dysfunction[5]. Many therapeutic approaches of hemiplegic patients are based on the assumption that skilled movement requires a refined sensory feedback system. Therefore, it is argued here that the objective assessment of the somatosensory system may be important in predicting motor recovery following stroke.

The integrity of the sensory pathways can be assessed accurately and objectively by means of Somatosensory Evoked Potentials (SEPs). Recently, SEPs have been applied in the study of the consequences of stroke[6-10]. After stimulating the affected side in stroke patients, SEP abnormalities occur mainly in the N20-P27 regions: increases of latencies and reductions of amplitudes of components involved[6-9]. The evoked potentials have to be compared with those of the contralateral side and with reference data[8]. There is some evidence for a relationship between specific SEP abnormalities and the type of sensory deficit[6,9-10]. With loss of propioception, changes can be observed in the N20-P28 region, whereas with loss of pain and temperature sense changes can be found in the late components.

In the last decades the possible value of SEPs in predicting recovery after stroke has been reported[11-19]. The degree of abnormality of the SEPs appear to correlate with the subsequent level of residual disability. However, in a recent study[18] an early Barthel score provided more favorable data in the prediction of functional recovery at the level of specific abilities, compared with SEPs

data. Other studies[12,14,16] recommend the use of SEPs in predicting the recovery of upper extremity function.

Against this background the potential value of SEPs for predicting recovery will be further explored in the present study. It is expected that unimpaired SEPs will correlate with recovery of motor functions of the upper extremity, whereas absence or severe amplitude decrease of the SEPs is as a negative predictor of recovery.

Methods

Patients

SEPs were obtained in seven patients (ranging in age from 33 to 69 years, three males, four females) suffering from acute cerebral ischemia with paralyzed upper extremity in the acute phase and no recovery tendency during the first 10 days. After admission to a neurological ward, the diagnosis was confirmed by means of computed tomography (CT). Patients were only included if there were no other cerebral lesions, no peripheral neuropathy, no concomitant disorders affecting the arm or hand functions, no other major disease, and no dependency in daily living prior to the infarction. Informed consent was obtained from all subjects.

Apparatus

The somatosensory evoked potentials were recorded with a Neuropack Four EP system in a well-lit room with the subjects in a decline position. Electrical stimuli were applied percutaneously through disc electrodes to the left and right median nerves at the wrists. The stimuli were 0.1 ms rectangular pulses, adjusted above the motor threshold of the median nerve. The stimulus rate was 0.3 Hz and the evoked potentials were calculated by averaging the recordings after 1000 stimuli. The filter bandpass of the amplifiers was 10-1000 Hz. Cutaneous disc electrodes were placed at Erb's point, vertebra C7, and cortical C'3 and C'4. These were located 2 cm posterior to the C'3 and C'4 positions of

the international l0-20 system. Reference electrodes were placed pre-auricular, and were used contralateral to the stimulated side. The ground elektrode was placed at Fz. Two averages were recorded under identical conditions to assess the reproducibility of the evoked response components. Latency and amplitude of components N9 (Erb's point), N13 (cervical spine), N18 (pons) and the cortical complex (N20-P27) were analyzed. The recordings were compared with the opposite side and with reference data.

Procedure

After registration of the SEPs, recovery of motor function of the upper extremity was predicted according to the following criteria: in the case of absence of the N20-P27 complex or a decrease in amplitude of more than 75% (following affected side stimulation) compared to the contralateral side, no motor recovery of the paralyzed upper extremity was expected. Recovery of motor function was expected in cases of more symmetric evoked potentials. Motor recovery was evaluated 3, 6 and 9 months post-stroke by means of the Fugl-Meyer Motor Assessment[20]. This cumulative numerical scoring system is based on the sequential recovery stages, which can be observed in hemiplegic patients[19-20].

In this study, the upper extremity part of the assessment was used with a maximum score of 66 points. In accordance with the original assessment, reflex activity, motor functions, coordination and speed were scored using standardized test conditions. The motor functions of the shoulder/elbow/forearm, the wrist and the hand were scored separately. For example, if there was no volitional movement in the upper extremity and no reflex activity, the score was 4/66. If there was volitional movement within the dynamic flexor and/or extensor synergies, without any movement in the wrist or hand, the score was 22/66. All patients followed a similar treatment regime. The therapists were not aware of the SEPs results.

Results

The patient characteristics and the clinical symptoms at the time of admission are shown in tables 1 and 2. SEPs were performed in these patients between 14-24 days post-stroke (average 19 days). Four patients (no 1, 3, 4, and 6) were transferred to a rehabilitation center 22-24 days after onset (average 23.5 days). Two patients (no 2 and 5) were directly discharged home respectively 34 and 24 days poststroke. They received further rehabilitation treatment as an outpatient. The history of patient 2 raised diagnostic doubts. CT-scan showed however a hypodense lesion in the right parietal region, suspect for infarction. Lumbar puncture yielded colorless CSF with normal protein level; oligoclonal gammaglobuline production was detected. T2-weighted MRI revealed right parietal, cortical and subcortical a circumscript signal increase. Furthermore several lesions were detected in the periventricular white matter. Patient 7 suffered from several pulmonary infarctions due to embolism during hospitalization. He exhibited poor recovery tendency and was transferred to a nursing home 52 days after onset.

Table 1. Patient characteristics

Patient Number	Gender	Age (yr)	Medical history
1	Male	69	Hypertension
2	Male	33	Haemolytic anemia, spleen extirpation
3	Female	35	No relevant facts
4	Female	53	Migraine
5	Female	37	Eosinophylic pneumonia
6	Female	37	Brain stem infarction, no residual impairments
7	Male	62	Myocard infarction, left bundle branch block, atrial fibrillation, gout

The results shown in table 3 indicate that in four cases (no 1, 2, 3, and 7) no cortical responses could be elicited after stimulation of the affected side (Figure 1). Three of these four patients (no 1, 3 and 7) showed no recovery of the upper extremity, as predicted. Patient 2, however, showed moderate motor recovery reflected by a 39/66 Fugl-Meyer score 3 months poststroke. In two

Table 2. Clinical symptoms at time of admission

Patient Number	Affected Side	Symptoms
1	Left	Hemianopia, hemiparalysis, mixed aphasia, incontinence
2	Right	Paralysis of the arm, paresis of the leg, hypesthesia of the upper extremity, dysarthria
3	Left	Somnolence, gaze palsy, hemianopia, paralysis of the arm, paresis of the leg, mixed aphasia
4	Right	Somnolence, gaze preference, hemineglect, paralysis of the arm, paresis of the leg, hemihypesthesia
5	Right	Hemineglect, hemiparalysis, hemihypesthesia
6	Left	Somnolence, gaze preference, hemineglect, hemiparalysis, mixed aphasia
7	Right	Hemianopia, paralysis of the arm, paresis of the leg, hemisomatoagnosia, dysarthria

cases (no 4 and 5) the N18-P27 complex was present, however with a marked amplitude decrease. Patient 4 had a 50% amplitude decrease and also exhibited a N20 latency shift of 3.6 ms (Figure 2). She showed moderate motor recovery of the upper extremity with a 28/66 Fugl-Meyer score 3 months after onset. Patient 5 had a 70% amplitude decrease. She withdrew from the study and, thus, exact clinical evaluation was not possible. Some motor recovery occurred however: it was reported by her therapist that mass movements could be performed within synergy patterns at 3 months after onset. In one case (no 6) almost normal SEPs were recorded after stimulation of the affected side (Figure 3). The patient showed excellent motor recovery of the upper extremity reflected by a 66/66 Fugl-Meyer score 3 months poststroke.

Discussion

Until now, assessment in the acute phase of stroke and prediction of outcome are primarily based on subjective clinical examination. Generally, the severeness of the initial motor deficit is used as the most important predictor of motor recovery[23-28]. In this study, it is argued that the integrity of the somatosensory system may be another important predictor. Van Buskirk and Webster have described the prognostic value of sensory impairment in the functional outcome of stroke already in 1955[29]. However, in the following decades sensory impairment has hardly been used as a prognostic indicator, probably due to its subjective and non-quantifiable character[30]. In the last

Table 3. SEPs findings in combination with Fugl-Meyer score

Patient number	Cortical responses N20-P27	Fugl-Meyer score 3	6	9
1	Absent	4/66	4/66	4/66
2	Absent	39/66	46/66	51/66
3	Absent	4/66	4/66	4/66
4	Decreased amplitude (50%), prolonged latency (22,4ms)	28/66	32/66	34/66
5	Decreased amplitude (30%)	-	-	-
6	Broadened complex, decreased amplitude (75%)	66/66	66/66	66/66
7	Absent	4/66	4/66	4/66

In the first column the SEPs findings are listed. A decrease of amplitude after affected side stimulation is expressed as percentage comparised to non-affected side stimulation. The Fugl-Meyer score respectively 3, 6 and 9 months after onset.

decades, evoked potentials have been used to assess the integrity of the sensory pathways. Its possible value in predicting recovery after stroke has been reported[11-19].

In the present study, SEPs are employed to predict the motor recovery in seven patients suffering from cerebral ischemia with a paralyzed upper extremity and no recovery tendency during the first 10 days. Based on clinical assessment[24-28], poor motor recovery of the upper extremity was expected in this selected patient sample. Follow-up showed, however, excellent motor recovery in one patient and moderate recovery in three other patients. Based on the SEPs results, our prediction was correct in three of these four 'recovered' patients. In one patient no motor recovery was expected according to the absent cortical evoked potentials. He showed however moderate motor recovery. Supplementary imaging and laboratory assessment provided evidence for a demyelinating disease in this patient, which may have influenced the SEPs findings. In three patients no improvement of motor function occurred, as predicted according to the SEPs findings. These preliminary results show that SEPs may be of value for predicting sensorimotor recovery following stroke. Most research in this area, however, has been directed at the prediction of functional recovery, at the level of specific abilities[11,13-16,18-19]. Because such recovery is

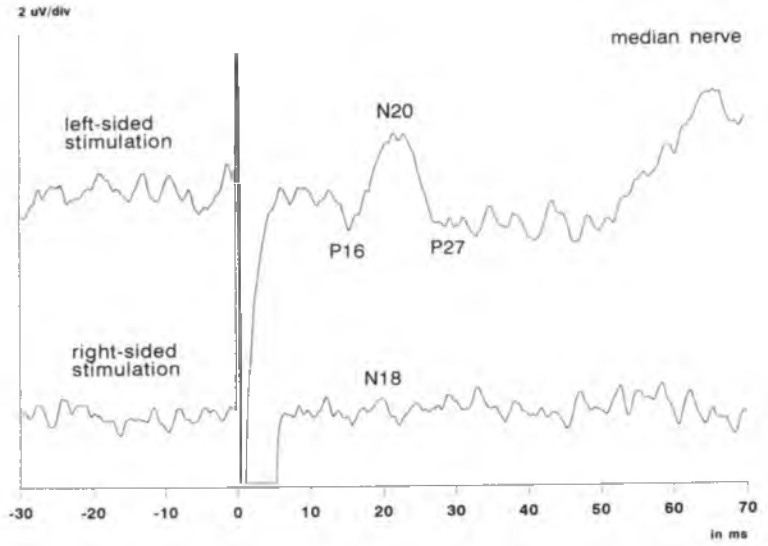

Figure 1. Normal short latency evoked potentials after left median nerve stimulation in patient 1. There are no cortical responses after right-sided stimulation.

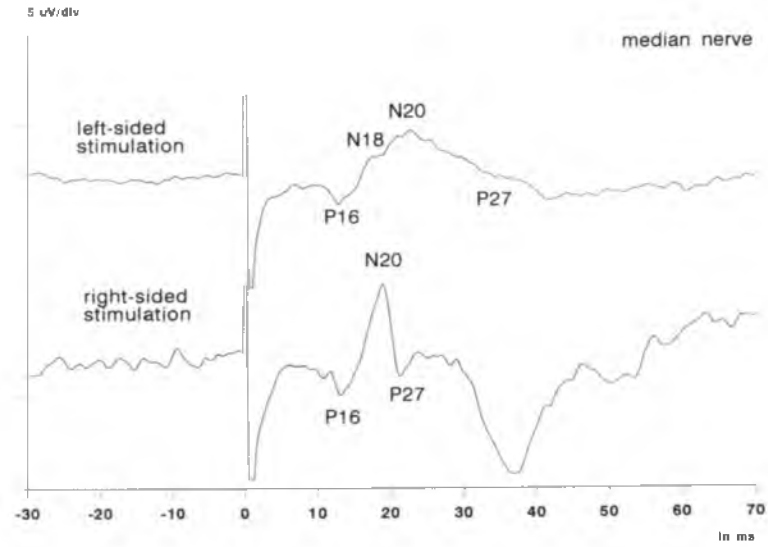

Figure 2. Normal short latency evoked potentials after right median nerve stimulation in patient 4. After left-sided stimulation a broadened N18-P27 complex was elicited with a decreased amplitude (50%) and a prolonged latency (22.4ms).

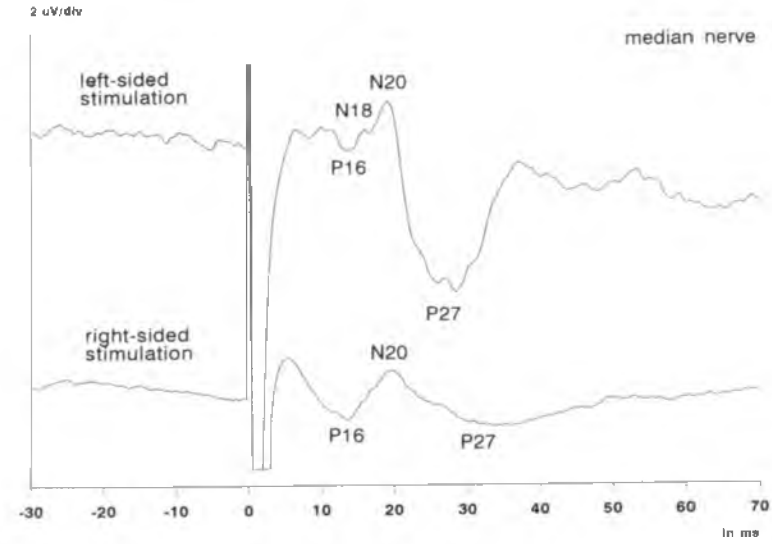

Figure 3. Normal evoked potentials after left median nerve stimulation 15 days poststroke in patient 6. After right-sided stimulation the N18-P27 complex was broadened and the peak-peak amplitude N20-P27 was decreased. The responses were not fully comparable because of a large stimulus artefact after right-sided stimulation.

highly dependent on cognitive and environmental factors, the prognostic value of evoked potentials should not be overestimated. On neurophysiologic and neuroanatomic grounds, it can be argued that the predictive value of SEPs is mainly limited to motor recovery of the upper extremity: after stimulation of the median nerve, evoked potentials can be recorded over the somatosensory cortex, the area where somatosensory input from the upper extremity converges. The persistence of this sensory input is essential for the survival of partially damaged neurons[31]. Residual somatosensory input to the cortex may be critically important for the reorganization of cortical maps during recovery of function following lesions, which only partially disrupt the integrity of such maps[32]. Because there exists a close anatomic relation between the somatosensory and the motor systems of the upper extremity, SEPs are in most cases a sensitive indicator for the integrity of both. In accordance with previous studies[12,14,16], our study shows that SEPs registration in patients suffering from cerebral infarction with a paralyzed upper extremity may play a useful role in prognostication, if other cerebral lesions have been excluded. The use of evoked potentials has clear advantages in the assessment of stroke. It is a noninvasive technique and the results are objective and quantitatively. SEPs can also be used in non co-operative patients, i.c. aphasia and impaired consciousness. SEPs can be obtained in an acute phase after stroke.

Because of its small sample size, this study cannot be conclusive. Further research is needed to provide statistical evidence for the value of physiologic impairment in predicting motor recovery of the upper extremity after cerebral infarction[33-34]. Repeated evaluation of physiologic impairment may also augment our knowledge of the neurophysiology of the processes associated with recovery following brain damage[33,35].

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CHAPTER 3

PREDICTION OF RECOVERY FROM UPPER EXTREMITY PARALYSIS AFTER STROKE BY MEASURING EVOKED POTENTIALS

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Abstract

Paralysis of the upper extremity is a severe motor impairment that can occur after stroke. Prediction of recovery from paralysis is difficult and is primarily based on subjective clinical evaluation. However, the integrity of the sensorimotor system can be assessed objectively and quantitatively by measuring evoked potentials. In this retrospective exploratory study, we evaluated the predictive value of motor and somatosensory evoked potentials for recovery from paralysis of the upper extremity. Motor and somatosensory evoked potentials were recorded in 29 patients who had had their first-ever infarction in the territory of the middle cerebral artery and who exhibited paralysis of the upper extremity. At follow-up, seven patients showed motor recovery. The evoked potential data were dichotomized into present or absent and related to the occurrence of motor recovery. Analysis revealed a significant association between the presence of evoked potentials early after stroke and the observed occurrence of motor recovery. These results suggest strongly that evoked potentials predict the occurrence of motor recovery of upper extremity paralysis in patients suffering from first-ever infarction in the territory of the middle cerebral artery.

Introduction

Recovery after stroke is influenced by a variety of biological and environmental factors[3], and recovery profiles show a high interindividual variability. To date, there have been no objective and reliable instruments available to predict recovery after stroke.

A distinction is usually made between spontaneous recovery, due to the self-organizing capacity of the brain, and the development of novel adaptive control strategies, as a result of therapy and learning. Spontaneous recovery results, particularly in the (sub)acute phase, in a substantial recovery from the sensorimotor impairments and cognitive disorders. Adaptive control strategies may play a role in the post-acute period[3]. Thus, the recovery of functional

skills may be attributable to both neurological recovery and behavioral compensation.

This study focuses on the spontaneous neurological recovery of patients with upper extremity paralysis after their first-ever stroke. Complete paralysis of the upper extremity is frequently seen after infarction in the territory of the middle cerebral artery, and is a severe condition, which may be complicated by subluxation, shoulder pain or even shoulder-hand syndrome. If no or poor motor recovery occurs, the patient has serious disabilities. However, even if motor recovery occurs, the patient must receive adequate training in order to optimize functional abilities. Inadequate training may lead to a learned disuse syndrome[31].

Early prediction of recovery from upper extremity paralysis after stroke remains a difficult issue. Until now, there were no clinical tests, which could accurately predict the rate of motor recovery. The severity of the initial motor deficit is usually used as the most important predictor[4,7,27,28,36]. Yet somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs), which provide information about the integrity of the somatosensory and the motor pathways, may provide more objective and reliable data in this context, when measured in the subacute phase after stroke. SEPs have been extensively studied in stroke patients[12,18,21,23,24,35], and more recently MEPs have also been studied in this population[1,2,5,6,8,11,13,15,19,20,22,25,32,33]. Earlier studies have indicated a powerful predictive value of SEPs[21,23] and MEPs[13,20,25] for motor recovery of the upper extremity. Hendricks et al.[21] used SEPs to predict the occurrence of motor recovery in 7 stroke patients, who exhibited upper extremity paralysis. The prediction based on the SEPs was correct in all cases but one. Further examination of this patient provided evidence for a demyelinating disease. Dominkus et al.[13] studied electrical motor evoked potentials in relation to motor recovery of the upper and lower extremity in 33 stroke patients. Eleven patients exhibited initial paralysis of the upper

extremity, of whom 6 patients had absent MEPs. No motor recovery occurred in 4 of them, 1 patient died and 1 patient showed minimal recovery. Of the 5 patients with present MEPs, 1 died and 4 experienced moderate to good recovery. Macdonell et al.[25] recorded SEPs and MEPs (electrical stimulation) in 19 stroke patients exhibiting different degrees of hemiparesis. Seven patients showed complete paralysis of the arm; both SEPs (N20) and MEPs were absent in these patients. None of them experienced any motor recovery. Arac et al.[2] evaluated the role of MEPs (abductor pollices brevis and tibialis anterior muscles) in predicting functional motor recovery (arm and leg) in 27 acute stroke patients. Six patients exhibited paralysis of the upper extremity and had absent evoked potentials (abductor pollices brevis muscles). Three of these 6 patients died, 3 showed considerable motor recovery. The authors concluded in contrast with other studies that MEPs had no value in predicting the outcome of hemiparesis or hemiplegia.

We assessed the predictive value of evoked potentials for recovery from paralysis of the upper extremity by reviewing data for motor and sensory evoked potentials in a historical cohort of stroke patients.

Methods

Subject selection

The historical cohort consisted of all patients admitted consecutively (Department of Neurology, Medical Spectrum Twente) over a 26-month period[32]. On admission, all patients underwent a standard clinical and neurological examination. Patients were included only if the current episode was the first-ever infarction in the territory of the middle cerebral artery, confirmed radiologically (CT-scan or NMR), and if they had been admitted within 24 hours of the onset of symptoms. Patients gave their informed consent before they were included in the study. They were excluded if they had a history of craniotomy, epilepsy, cardiac prosthetic valve or pacemaker implantation.

The initial motor scores for the upper extremity of these patients were reviewed. Motor impairments of the upper extremity were either classified as paralysis or paresis. Paralysis was defined as no voluntary motor action in the shoulder, arm and hand. Only those patients who exhibited paralysis at admission or who developed paralysis within the first three days after admission were examined at follow-up. Patients were excluded if they had died or had another stroke within 3 months.

In the period March 1992 to May 1994, 69 patients were initially included. However, 7 patients were excluded later because CT scans revealed a hemorrhage, more than one or no infarct (four patients), wrong location (two patients), and 15 patients had to be excluded for other reasons: 11 patients died within 3 months of the stroke, no follow-up data were available in 3 patients, 1 patient had another stroke within 3 months. Thus, 47 patients were eligible for this study, of whom 29 (15 females and 14 males, mean age 63.7 [range 22-85] years) exhibited paralysis of the upper extremity at admission or who developed paralysis within 3 days after admission. At follow-up, 1 to 4 years poststroke (mean 2.4 years), 20 patients with initial upper extremity paralysis were alive and available for clinical evaluation. The motor recovery of the patients who had died was assessed by reviewing the medical records.

Neurophysiological methods

Evoked potentials were recorded on day 3 or 4, 6 weeks and 3 months post-stroke. For cortical magnetic motor stimulation a Medicor Magstim 200 magnetic stimulator was used with a 70-mm coil, and for cervical stimulation a twin coil was used. Stimuli without facilitation were given with increasing intensity until a response of maximal amplitude was obtained. Muscle responses were recorded with surface electrodes taped over the abductor digiti quinti muscle, using an EMG Nicolet Viking EMG recording system. The computed central conduction time (CCT), i.e. the time difference between

cortical and cervical stimulation, was compared to normal values[14] and to values for the contralateral side. MEPs were scored as normal, delayed (difference of more than two standard deviations) or absent. Ipsilateral responses were registered when present.

SEPs were recorded after median nerve stimulation on both sides. We used a Nicolet Pathfinder system. Four averaging channels were used to record SEPs at the scalp (right C3-A2, left C4-A1), the neck (5th cervical spinal process), Erb's point and the elbow. The bandpass was 5-3000 Hz, 30-3000Hz, 100-3000 Hz and 100-3000 Hz, respectively. SEPs latency values were compared to those for the contralateral side and to normal data. SEPs were scored as normal, delayed (difference of more than 2 standard deviations) or absent.

Assessment

At follow-up, all patients with initial upper extremity paralysis were evaluated. Motor recovery was defined as any voluntary motor action in the affected shoulder, arm or hand. If motor recovery had occurred, the exact motor status was evaluated by means of the Fugl-Meyer Motor Assessment[17]. This cumulative numerical scoring system is based on the sequential stages of recovery observed in hemiplegic patients[10,34]. In this study, the upper extremity part of the assessment was used with a maximum of 66 points. In accordance with the original assessment, reflex activity, motor functions, coordination and speed were scored under standardized test conditions. If patients were not available for clinical examination, the medical records were reviewed.

Analysis

In the analysis both the MEPs and the SEPs were dichotomized into present (delayed or normal) or absent. This dichotomy forms the basis for outcome studies using evoked potentials[11,13,20,35]. The MEPs and SEPs data were related to evidence of motor recovery at follow-up. The relationships are illustrated by

'2x2' contingency tables according to Fletcher et al.[16]. The chi-square test was used to test the null hypothesis that evoked potentials, detected soon after stroke, are not related to the occurrence of motor recovery. Odds ratios were calculated to express the change in motor recovery when evoked potentials were detected.

Table 1. The motor scores of the upper extremity at follow-up, in relation to the evoked potentials

Patient number	Motor score (FMA)	MEPs	SEPs
3	-	Absent	Normal
17	-	Delayed	Absent
18	-	Normal	Normal
37	12	Absent	Absent
40	66	Normal	Normal
51	66	Normal	Normal
65	66	Delayed	Normal

Abbreviations: MEPs, motor evoked potentials; SEPs, somatosensory evoked potentials; FMA: Fugl-Meyer Motor Assessment[17].

Results

On clinical evaluation three patients showed excellent motor recovery and one patient showed minor improvement; three patients were not evaluated, because they had died, but their medical records indicated that they had shown motor recovery. The motor scores at follow-up in relation to evoked potentials are shown in Table 1. MEPs were present in five of the seven 'recovery' patients and in none of the 'no recovery' patients. SEPs were present in five of the seven 'recovery' patients and in six of the 'no recovery' patients.

The relationships between MEPs and SEPs and the occurrence of motor recovery are summarized in Tables 2 and 3. The chi-square values for MEPs and SEPs were 15.29; df=1; p=0.0001 and 4.39; df=1; p=0.0340, respectively. The null hypothesis could be rejected, as evoked potentials detected soon after stroke, were significantly associated with motor recovery. The Odds ratios for MEPs and SEPs were 46.00 (95% CI 6.75 –313.30) and 6.66 (95% CI 1.13-39.26), respectively. When calculating the odds ratio for MEPs, we added the value of 1 to each cell since one of the cells of the fourfold table was zero.

Table 2. The relationship between motor evoked potentials (MEPs) recorded in the subacute phase after stroke, and motor recovery of the upper extremity

	Motor recovery +	Motor recovery -	Total
MEPs +	5	0	5
MEPs -	2	22	24
Total	7	22	29

Table 3. The relationship between somatosensory evoked potentials (SEPs) recorded in the subacute phase after stroke, and motor recovery of the upper extremity

	Motor recovery +	Motor recovery -	Total
SEPs +	5	6	11
SEPs -	2	16	18
Total	7	22	29

Abbreviations: MEPs, motor evoked potentials; SEPs, somatosensory evoked potentials.

Twenty patients were re-assessed neurophysiologically at 6 weeks and 3 months. Nine patients refused to undergo the second and/or third assessment. MEPs improved over time in four 'recovery' patients, either from no response to delayed CCT or from delayed CCT to normal. None of the 'no recovery' patients showed any improvement of the MEPs. SEPs improved in seven patients, two of whom exhibited motor recovery.

Ipsilateral responses were initially present in six patients and were detected in three other patients at the second assessment. Only one 'recovery' patient showed ipsilateral responses.

Discussion

We reviewed the initial motor status of a defined cohort of patients, who had had their first-ever brain infarction in the territory of the middle cerebral artery, and in whom both somatosensory and motor evoked potentials were recorded in the subacute phase and at 6 weeks and 3 months after the stroke. Only those patients with initial paralysis of the upper extremity were clinically evaluated at follow-up. We found a close association between evoked potentials, recorded soon after the stroke, and the occurrence of motor recovery in patients who survived the first 3 months and who did not have another infarction.

The safety of magnetic stimulation has been assessed in several studies[9,30]. Transcranial magnetic stimulation appears to be a safe method. Side effects have been described especially in epileptic patients after rapid-rate transcranial magnetic stimulation[26]. However, in our study we only used single stimuli. Furthermore, we excluded those patients who had a history of epilepsy.

Despite the retrospective character of this study, the results strongly suggest that motor and somatosensory evoked potentials predict the occurrence of motor recovery from upper extremity paralysis. Earlier studies[13,20,21,23,25] indicated already such a relationship. However, in contrast with most other studies we focused on patients, who exhibited upper extremity paralysis. Only Arac et al.[2] reported other findings, probably because of the differences in patient selection and timing of neurophysiological assessment.

One can debate about the prognostic value of the somatosensory evoked potentials in this context. Hendricks et al.[21] addressed this point in an earlier paper. Since there is a close anatomic relation between the somatosensory and the motor systems of the upper extremity, SEPs may be a sensitive indicator for the integrity of both systems. However, the integrity of the motor systems can be assessed more directly by motor evoked potentials, which was confirmed in the present study.

Neurophysiological re-assessment 6 weeks and 3 months after the stroke showed changes in only nine patients. Improvement of the MEPs was found in four patients, and was accompanied by motor recovery. There was no clear relation between the presence or the occurrence of ipsilateral responses and motor recovery of the upper extremity in our study group. This is in accordance with an earlier study[29].

Several issues need to be investigated in a prospective study. The predictive value of MEPs in patients exhibiting different grades of paresis is not clear. Subgroups of patients should be identified, who would benefit most from an early prediction of motor recovery based on MEPs. Furthermore, repeated evaluation of neurophysiological impairments may increase our knowledge of the processes associated with recovery following brain damage.

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CHAPTER 4

MOTOR RECOVERY AFTER STROKE. A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

Objective: To collect and integrate existing data concerning the occurrence, extent, time course and prognostic determinants of motor recovery after stroke using a systematic methodological approach.

Data sources: A computer-aided search in bibliographic databases was done of longitudinal cohort studies, original prognostic studies and randomized controlled trials published in the period 1966 to November 2001, which was extended by references from retrieved articles and narrative reviews.

Study selection: After a preliminary screening, internal, external and statistical validity was assessed by a priori methodological criteria, with special emphasis on the internal validity.

Data extraction: The studies finally selected were discussed, based on quantitative analysis of the outcome measures and prognostic determinants. Meta-analysis was pursued, but was not possible due to substantial heterogeneity.

Data synthesis: The search resulted in 174 potentially relevant studies, of which 80 studies passed the preliminary screening and were subjected to further methodological assessment; 14 studies were finally selected. Approximately 65% of the hospitalized stroke survivors with initial motor deficits of the lower extremity show some degree of motor recovery. In the case of paralysis, complete motor recovery occurs in less than 15% of the patients, both for the upper and lower extremity. Hospitalyzed patients with small lacunar strokes show relatively good motor recovery. The recovery period in patients with severe stroke is twice as long as in patients with mild stroke. The initial grade of paresis is the most important predictor for motor recovery (odds ratios [ORs], >4). Objective analysis of the motor pathways by motor evoked potentials (MEPs) showed even much higher ORs (ORs, >20).

Conclusions: Our knowledge of motor recovery after stroke in more accurate, quantitative and qualitive terms is still limited. Nevertheless, our data synthesis and quantitative analysis comprises many data from methodologically robust studies, which may support the clinician in the

management of stroke patients. With respect to early prognosis of motor recovery, the present review confirms clinical experience that the initial grade of paresis (as measured on admission in the hospital) is the most important predictor, although the accuracy of prediction rapidly improves during the first few days after stroke. Initial paralysis implies the worst prognosis for subsequent motor recovery. Remarkably, the prognostic accuracy of MEPs appears much higher than that of clinical examination for different subgroups of patients.

Introduction

Early prediction of functional outcome remains an important topic in stroke management and related research. Functional recovery is influenced by a variety of biological and environmental factors[1] and recovery profiles are characterized by a high interindividual variability. A recent critical review[2] of the literature on this matter indicated that several clinical and demographic variables may be valid predictors of general functional recovery, including neurological factors such as consciousness at onset, disorientation in time and place, sitting balance, and severity of motor deficits. In other previously published reviews[3,4], severe hemiparesis has been identified as a negative predictor for functional outcome.

Our systematic review is specifically focused at the restoration of motor deficits following stroke. Motor recovery seems to occur predominantly in the first few months after stroke, although some patients may show considerable recovery in later phases. The initial grade of paresis is generally regarded as the most important predictor for motor recovery; however, it is not yet possible to accurately predict the occurrence and extent of motor recovery in individual patients during the (sub)acute phase of their stroke. Some patients may show complete recovery, whereas in others the degree of paresis may not change at all. It is also difficult to give a precise time window for motor recovery in individual patients. Despite the vast amount of literature on this

subject, so far no attempt has been made to summarize and integrate the findings of the most valid studies and provide a quantitative summary estimate of motor recovery after stroke.

Although fully dependent on the literature available in terms of methodological quality and accuracy of data presentation, we tried to answer the following a priori questions: (1) What proportion of the acute stroke patients exhibiting motor deficits on admission in the hospital shows motor recovery, and to what extent and over what time period poststroke? and (2) Which prognostic factors with respect to motor recovery can be identified and what is their strength in terms of recovery probability?

Methods

Data sources

Relevant studies were primarily identified by consulting the following bibliographic databases: MEDLINE (1966-November 2001); Psychlit (1967-November 2001); Current Contents (to December 2001); PubMed (to December 2001); EMBASE (to December 2001); and the Cochrane database for clinical trials (to December 2001). The keywords used were: stroke, cerebral hemorrhage, cerebral infarction, motor recovery, motor function, impairments, motor control, spontaneous recovery, and rehabilitation. The references used in the retrieved articles, as well as in narrative reviews, were also reviewed.

Study selection

Preliminary screening. A preliminary screening was conducted to select cohort studies in which at least some standardized assessment of motor deficits was used at stroke onset and at some point during follow-up. Assessment by global stroke scales that include evaluation of motor functions was accepted. Prognostic studies that evaluated specific diagnostic procedures (particularly evoked potentials) with respect to the prognosis of motor

recovery were also included. In addition, the control groups in randomized clinical trials (RCTs; receiving placebo treatment) were eligible. Only studies published in the English, French, German and Dutch languages were included. Case studies, letters, abstracts, comments and preliminary reports were excluded. Each study had to comprise more than 20 patients.

Assessment of methodological quality. All studies emerging from the preliminary screening were subjected to a systematic review using a checklist with a priori defined methodologic criteria. This checklist was constructed according to a system, originally developed for evaluating RCTs[5,6]. The character of our review, with its special emphasis on prognostic factors, demanded specific adaptations[7,8]. The constructed checklist (Table 1) assessed internal validity (11 items), external validity (3 items), and statistical validity (4 items). All items were scored yes/no, which resulted in a maximum sum score of 18 points. The selected studieswere independently analyzed by 2 authors (HTH and JvL). In case of disagreement, consensus was pursued in second instance.

Assessment of internal validity comprised the folowing items. The study population had to be homogeneous with respect to diagnosis and disease stage. Therefore, a confirmatory diagnosis by computed tomography (CT) or magnetic resonance imaging (MRI), was required in at least 90% of the cases, and patients had to be included in the study within 1 week after stroke onset. Both prognostic determinants and outcome measures had to have been assessed by using standardized tests. Outcome measurements had to be repeated after a period of at least 3 months. In the case of heterogeneity of initial motor impairments or other possible prognostic variables such as stroke type, first or recurrent stroke, subgroup analysis was required. The percentage of patients lost to follow-up was not to exceed 20%. The reasons for loss to follow up had to be given judge selective loss. Furthermore, these cases must

have been managed adequately in the analysis. Death or stroke recurrence during the study was regarded as loss to follow-up if these cases were not yet

Table 1. Methodological checklist

Internal validity.
1. Diagnosis confirmed by CT/MRI in at least 90% of the cases.
2. Study entry within 1 week post stroke onset.
3. Standardized assessment of possible prognostic determinants.
4. Standardized outcome measures.
5. Repeated measurements during the observation period.
6. Homogeneity of study sample or subgroups analysis done with respect to stroke type, subarachnoidal hemorrhage, recurrent stroke.
7. Homogeneity of study sample or subgroup analysis done with respect to initial impairments/ severity of stroke.
8. Minimal observation period of 3 months.
9. Loss to follow-up < 20%.
10. Description of relevant characteristics related to loss to follow-up.
11. Adequate management of loss to follow-up.
External validity
12. Hospital or community based.
13. Description of in- and exclusion criteria.
14. Demographic characteristics are given, including age, gender and comorbidity.
Statistical validity
15. Statistical analysis described.
16. Adequate sample size.
17. Statistical control for confounding, if applicable.
18. Appropiate statistical analysis done in relation to design used.

Abbreviations: CT, computed tomography, MRI, magnetic resonance imaging.

handled as such. External validity was assessed as follows. To prevent selection bias, the study population had to be extracted from a community base or a general hospital base. In- and exclusion criteria had to be described accurately and the relevant characteristics should have been given, including age, gender and comorbidity. Finally, statistical analysis was assessed. It was first determined whether the statistical analysis was described clearly. The requested sample size was calculated in relation to the statistical analysis performed. The ratio of the number of patients and the number of prognostic determinants had to equal or exceed 10. There had to be sufficient control for known confounders in the research design or in the analysis, if applicable. The statistical analysis also had to be appropriate for the design used and for the research objective.

The internal validity was judged as the most critical aspect of the selected studies, in particular the study entry (2) and the homogeneity (7) criteria (Table 1). To be included for quantitative analysis and final discussion, the study entry and homogeneity criteria had to be fulfilled, and the total minimal internal validity score had to be at least 9 (maximum 11). The statistical and external validity criteria were considered of secondary importance and their minimally required sum score had to be at least 5 (maximum 7). Studies fulfilling our inclusion criteria were used as primary evidence with respect to the research questions. Other studies that did not meet the criteria could have been used as secondary evidence.

Data extraction

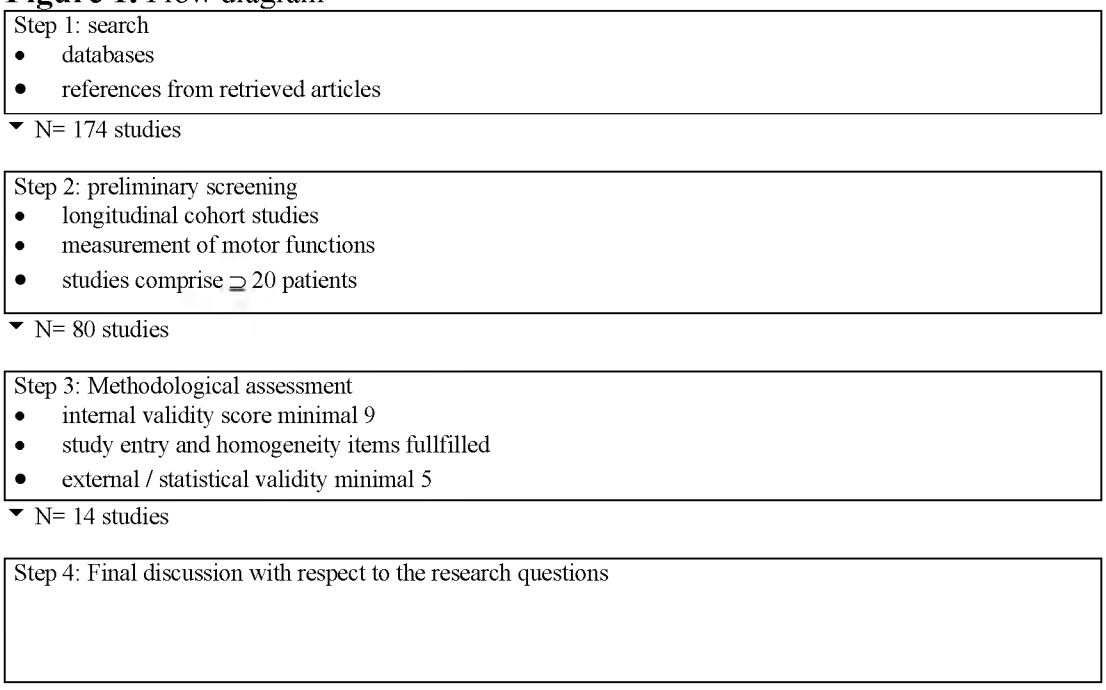
In studies in which the results could be expressed as proportions, odds ratios (ORs) for the occurrence of motor recovery and their confidence intervals (CIs) were calculated. In the case of continuous outcome variables, standardized effect sizes (z scores) were calculated in order to be able to compare (group) differences as a function of the pooled standard deviation: z score = $(x_a-x_b)/PSD$, where x_a and x_b are means of samples a and b, and PSD is the pooled standard deviation[9]. By convention, the cutoff criterion for considering a particular effect clinically relevant, a (group) difference of at least 1 standard score (z score $\geq$ 1.0) is chosen. Originally, a meta-analysis was pursued to generate summary estimates.

Data synthesis

The numbers of studies resulting from the primary search, the preliminary screening, and from the systematic methodological assessment for final selection and discussion are summarized in a flow diagram (Figure 1). The primary search resulted in 174 potentially relevant studies: 107 references from the databases, and 67 references from retrieved articles. Eighty studies[10-89] passed the preliminary screening and were subjected to a systematic methodological assessment. Several studies were identified, in which

previously published follow-up data were presented in an alternative way[26,60,63]. Such duplicative sources were excluded. Eight studies[12,36,38,44,46,50,73,87] had a minimal internal validity score of 9, but failed on the criteria 2 or 7 (Table 1). Another study[48] had a maximal internal validity score, but failed on the minimally requested statistical criteria. Ultimately, 14 studies[13,14,15,24,25,27,29,40,42, 43,57,61,70,72] met all a priori methodological criteria and were further reviewed. The results of the methodological assessments of these studies are listed in Table 2. Four community-based studies[15,42,43,57] were included, that comprise the vast majority of the patients. One RCT[29] was selected, from which the data of the control group were used. Five studies[24,27,40,61,70] were selected that assessed specifically the prognostic value of evoked potentials with respect to motor recovery.

Figure 1. Flow diagram



Many of the finally selected studies still had serious methodological limitations (Table 2). Several studies failed on the homogeneity criterion with respect to recurrent stroke[15,42,43,57] or stroke type[29]. Another frequent limitation concerned the minimally requested follow-up period of 3 months[13,24,70]. Biller et al.[13] studied the rate of neurological recovery only in the first hours after

stroke, and Rapisarda et al.[70] studied motor recovery following hand muscle paralysis only in the first 2 weeks after stroke onset. Conclusions on late motor recovery could not be drawn from these studies. Two studies[15,43] failed on the diagnosis criterion (confirmation by CT and MRI). Duncan et al.[25] did not cope adequately with patients lost to follow-up. Biller et al.[13] performed no formal control for confounding even though their patient sample was relatively small. Bonita and Beaglehole[15] inappropriately calculated ORs. Domincus et al.[24] failed to describe clear inclusion and exclusion criteria.

Table 2. Methodological assessment of selected studies

Study	Total score	Internal validity score (insufficient items)	External validity score (missing items)	Statistical validity score (missing items)
Biller[13]	15	10 (8)	3	2 (16, 17)
Bonita[15]	15	9 (1, 6)	3	3 (18)
Domincus[24]	16	10 (8)	2 (13)	4
Duncan[25]	16	9 (10, 11)	3	4
Escudero[27]	18	11	3	4
Feys[29]	17	10 (6)	3	4
Hendricks[40]	18	11	3	4
Jorgenson[42]	17	10 (6)	3	4
Jorgenson[43]	16	9 (1, 6)	3	4
Nakayama[57]	17	10 (6)	3	4
Samuelsson[72]	18	11	3	4
Rapisarda[70]	17	10 (8)	3	4
Palliyath[61]	18	11	3	4
Binkofski[14]	18	11	3	4

1= diagnosis confirmed; 6= homogeneity with respect to stroke type; 8= observation period; 10= description drop-out; 11= management drop-out; 13= in-/ excusion criteria; 16= sample size; 17= control for confounding ; 18= appropiate analysis. (for extended description of items, see text)

In Table 3, study design, base population, sample size, aim of the study, relevant data for the present review, type of assessment, follow-up period, sample homogeneity or stratification, and main outcome are given for the finally included studies. Calculated ORs for the proportions and z scores for the degree or time course of recovery are given in Table 4. Because of considerable methodological diversity, such as varying stratification procedures, motor assessment and follow-up periods, meta-analysis was not possible.

Synthesis of main outcomes

With respect to the research questions, a synthesis of the main outcomes of the finally included studies was as follows.

What proportion of acute stroke patients exhibiting motor deficits on admission in the hospital shows motor recovery, and if so, to what extent and in what time period? Bonita and Beaglehole[15] studied the natural history of hemiparesis after acute stroke. On admission, 89% of the patients had a hemiparesis. Proportions of survivors showing complete or partial motor recovery are given in Table 3. There was no differentiation between arm and leg recovery. More detailed data concerning motor recovery of the upper and lower extremity can be derived from other community-based studies[43,57] (Table 3). Jorgenson et al.[43] studied motor recovery of the lower extremity in acute stroke patients, stratified according to the severity of initial motor deficits, as measured on admission in the hospital. The subgroups were as follows: paralysis, severe paresis, moderate paresis, mild paresis, and no paresis. For example, motor recovery in patients with moderate leg paresis was as follows: complete motor recovery at the end of rehabilitation was seen in 44% of the patients, 29% showed partial recovery, whereas 20% experienced no changes and 7% deteriorated (Table 3). Approximately 65% of all survivors with motor deficits of the leg at admission showed motor recovery, as an estimate over all subgroups within this study. It was remarkable that a considerable number of the patients deteriorated, a fact on which the researchers did not comment. The deterioration might be explained by stroke recurrence, too early initial assessment in the case of progressive stroke, or initial motor assessment influenced by apraxia or neglect. For the upper extremity, Nakayama et al.[57] showed in a homogeneous patient sample with severe arm paresis (little or no active movement) on admission that 14% of the patients experienced complete motor recovery, and 30% partial recovery (Table 3).

As far as a comparison between community-based studies and smaller, more selected samples was possible, there seemed to exist no great differences with respect to proportions of patients who show motor recovery (Table 3, 4).

Table 3. Overview of the finally included studies with respect to aim, follow- up and main study outcome

Study	Study design	Sample size	Aim of the study	Subtracted data	Motor/ neurologic Assessm	Follow-up period	Sample homogeneity/ Stratification	Proportion of motor / neurological recovery, degree or time course of recovery
Biller[13]	Ps, Hb	29	Neurological recovery in the first hours	Neurological recovery in the first hours	NIH	6 hours after admission	Moderate to severe neurological deficit	52% recovery, 41% no change, 7% deterioration
Bonita[15]	Ps, Cb	680	Recovery from hemiparesis	Recovery from hemiparesis	SSS, motor part	6 months	Severe (33.8%)	7% complete, 31% partial
							Moderate (25.3%)	22% complete, 31% partial
							Mild (30%)	46% complete
Duncan[25]	Ps, Hb	146	Recovery from hemiparesis	Recovery from hemiparesis	FMA	6 months*	Severe motor deficit (31%), moderately-severe (12%), moderate (21%), mild (36%)	Most recovery in the first month, regardless initial severity, no significant recovery after 3 months
Jorgenson[42]	Ps, Cb	1197	Time course Neurological Recovery	Time course Neurological Recovery	SSS	Till death or end of rehabilitation*; 41 days (sd 46)	Very severe (9%)	13 (11.6-14.4) weeks†
							Severe (12%)	15 (13-17) weeks†
							Moderate (29%)	10.5 (9.5-11.5) weeks†
							Mild (50%)	6.5 (5.4-7.6) weeks†
Jorgenson[43]	Ps, Cb	804	Recovery of walking abilities	Recovery from leg paralysis/ paresis	SSS, motor part	Till death or end of rehabilitation*; 35 days (sd 41)	Paralysis (19%)	14% complete, 31% partial
							Severe paresis (10%)	34% complete, 41 % partial, 4 % no change, 21% deterioration
							Moderate paresis (11%)	44% complete, 29% partial, 20% no change, 7% deterioration
							Mild paresis (25%)	76% complete, 19% no change, 5% deterioration
							No paresis (35%)	24% deterioration
Nakayama[57]	Ps, Cb	214	Recovery of upper extremity function	Recovery from severe arm paresis	SSS, motor part	Till death or end of rehabilitation*; 71 days (sd 53)	Homogeneous, severe arm paresis (34%)	14% complete, 30 % partial
Samuelson[72]	Ps, Hb	81	Functional outcome in lacunar infarction	Motor recovery arm and leg	Own scale‡	36 months	Severe (17%)	At 6 months, 83 % of patients with initial severe deficits show some degree of motor recovery.
							Moderate (14%)	
							Mild (69%)	
Escudero[27]	Ps, Hb	54	Prognostic value of MEPs	Motor recovery hand muscle	MRC	6 months	MRC 0-1 (40%)	33% recovery ⊇ MRC 4
							MRC 2-3 (32%)	92% recovery ⊇ MRC 4
							MRC 4 (28%)	-
Feys[29]	Rct, Hb	108	Effect of additional sensorimotor treatment	Motor recovery arm	FMA	12 months	Moderate to severe paresis	FMA impovement 12.1 and 4.3 in first and second half-year, resp.
Hendricks[40]	Ps, Hb	29	Prognostic value of SEPs and MEPs	Motor recovery arm	FMA	1-4 years	Paralysis	10% complete, 13% partial
Dominkus[24]	Ps, Hb	33	Prognostic value of MEPs	Motor recovery arm	MI	2 months	Paralysis	36% partial recovery
							Paresis	50% partial recovery
Rapisarda[70]	Ps, Hb	26	Prognostic value of MEPs	Motor recovery hand	MRC, modified‖	2 weeks	Hand paralysis	27% partial, at 2 weeks poststroke
Palliyath[61]	Ps, Hb	38	Prognostic value of MEPs	Motor recovery arm	MRC	3 months	Paralysis (24%)	-
							Paresis(76%)	62% partial recovery
Binkofski, 2001[14]	Ps, Hb	52	Prognostic value of lesion size	Motor recovery arm	Own scale¶	6 months	Severe paresis (33%)	45% complete or partial recovery
							Moderate paresis (67%)	100% complete or partial recovery

Note, for the Scandinavian Neurological Stroke Scale[78], total score is 0-58; very severe is 0-14, severe is 15-29, moderate is 30-44, mild is 45-58. For the scale's motor part, severe equals little or no active movement, moderate equals movement against gravity or resistance, but limited in range of motion and not in an uncontrolled fashion, and mild equals functionally insignificant impairment of fine movements.

Abbreviations: Ps, Prognostic cohort study, Hb, Hospital-based, Cb, Community-based, RCT, Randomized controlled trial; NIH, National Institutes of Health Stroke Scale[76], modified (predominantly motor functions); FMA, Fugl-Meyer Motor Assessment[77]; MRC, Medical Research Council scale[79]; MI, Motricity Index; MEPs, motor evoked potentials.

*: Weekly assessment.

†: Best neurological recovery as measured in 95% of the patients, expressed as weeks post stroke (with confidence intervals).

‡: The authors used a motor scale which categorizes motor deficits as severe, moderate and mild. Severe is severe hemiparesis, cannot elevate the arm and leg against gravity, the hand cannot be used functionally, and walking with aid is not possible; moderate is moderate hemiparesis, can elevate the arm and leg against gravity and skilled movement of the hand and walking are clearly affected but the patient can walk with or without aid; mild is mild hemiparesis defined as motor function that permits a full range of movement but with reduced strength, and the patient is able to perform all ordinary motor activities without aid.

‖: Modified MRC range: 0, no movement; 1, movement, only if gravity is removed; 2, weakness against gravity; 3, weakness against slight resistance; 4, weakness against strong resistance; and 5, normal.

One remark about the generalizibility should be made. All selected studies concerned patients who were admitted to a hospital. However, in general, not all stroke patients will be admitted. For instance, patients with mild motor deficits an no self-care problems will often be treated as outpatients.

As to the extent of motor recovery, the data from the studies appear to be rather vague, particularly with respect to partial motor recovery. Only few (rather small) selected studies[13,24,40,70] supplied more detailed information on this issue, showing a broad range from little to nearly complete motor recovery.

One study was specifically aimed at the temporal aspects of recovery. Jorgenson et al.[42] studied time course of neurological recovery in acute stroke patients stratified according to initial stroke severity, as measured on admission in the hospital. There was a substantial difference in time course between the strata (Tables 3, 4) showing a recovery period approximately twice as long for patients with severe paresis (mean, 15 weeks) compared to those with only mild paresis (mean, 6.5 weeks), resulting in a z score of 12.18. This finding is consistent with the studies of Bonita and Beaglehole[15] and Duncan et al.[25], who both found that most of the overall improvement in motor functions occurred within the first month after stroke, although some degree of motor recovery continued in some patients for up to 6 months, especially in the initially severe subgroups.

Valid data concerning late motor recovery appear to be rather scarce in the present systematic review. In an RCT[29] concerning a therapeutic intervention for improving motor and functional recovery of the upper extremity, a mean change of the Fugl-Meyer Motor Assessment (FMA) of 12.1 points in the first half year and 4.3 points in the second half year poststroke was found in the control group (50 patients). Because of the limited data presented, z scores could not be calculated to quantify differences in the degree of recovery

during the first versus second half year poststroke. Yet substantial secondary evidence concerning late recovery is available[16,35,44,45,56,58,59,68,75,78]. These studies suggest that, in some patients, late motor recovery may occur even several months after stroke. Because most of these studies were conducted in rehabilitation centers, these observations were made in selected patient populations.

Two included studies[13,70] specifically addressed early recovery. Biller et al.[13] studied the degree of spontaneous neurological improvement (predominantly motor functions) during the first hours after admission (Table 3). A z score of .26 indicated no substantial neurologic recovery in the first hours after admission. Rapisarda et al.[70] studied motor recovery in 26 acute stroke patients with hand paralysis (table 3); 7 patients showed partial hand motor recovery at 2 weeks poststroke (Medical Research Council [MRC] Scale[93] range, 1-4).

Which prognostic factors with respect to motor recovery can be identified and what is their magnitude in terms of ORs? Based on the studies discussed previously, the initial grade of paresis appears the most important clinical predictor for motor recovery, as could be expressed by different ORs for different grades of initial motor deficits (Table 4). For example, Bonita and Beaglehole[15] found a significant association between motor recovery and initial grade of hemiparesis, as measured at admission. They calculated an OR of 10.8 for recovery after mild versus severe initial paresis, including non-survivors. Calculating motor recovery in survivors only, the OR was still 8.7 (CI 4.43-17.06). In the study of Jorgenson et al.[43], the calculated ORs indicated that a patient with initial mild leg paresis was 4 times as likely to show motor recovery as a patient with initial leg paralysis. Comparable ORs could be calculated for the upper extremity. Dominkus et al.[24] assessed motor recovery in the upper extremity (shoulder flexion, elbow flexion and handgrip) by means of the Motricity index[21]. A patient with initial paresis was 4.58 as likely to show motor recovery as a patient with initial paralysis. Quantitative

analysis of the data of Escudero et al.[27] resulted in a much higher OR of 24.00 (CI, 4.50-127.96) for motor recovery after initial moderate paresis (MRC score range, 2-3) versus severe paresis or paralysis (MRC score range, 0-1) (Table 4), indicating an extreme difference in recovery potential for the muscle group studied (abductor pollicis brevis). It should be argued here that valid assessment of motor recovery by the MRC is not possible in this small muscle group.

Table 4. Odds ratios and z scores for relevant outcome measures and predictive factors

Study	Outcome measures	Odds ratio (95% CI)	Z
Biller[13]	Early motor recovery: admission neurological scores vs. neurological scores at 6 hours	-	0.26
Bonita[14]	Complete motor recovery in initial mild vs. initial severe motor deficit	8.70 (4.43 -17.06)	-
Dominkus[21]	Any motor recovery in initial paresis vs. paralysis	4.58 (0.73 - 28.64)	-
	Any motor recovery in small (< 0.5 cm) vs. large infarction (>2.5 cm)	5.14 (0.47- 55.64)	-
	Any motor recovery in subcortical vs. cortical infarcton	2.22 (0.36- 13.53)	-
	Any motor recovery in present vs. absent MEP	28.00 (2.65 – 295.73)	-
Escudero[24]	Any motor recovery in moderate paresis (MRC 2-4) vs. severe paresis (MRC 0-1)	24.00 (4.50 – 127.96)	-
	Any motor recovery in the total group: present vs. absent MEP	56.00 (9.20- 340.52	-
Hendricks[36]	Any motor recovery of upper extremity paralysis in present vs. absent MEP	46.00 (6.75 –313.3)	-
	Any motor recovery of upper extremity paralysis in present vs. absent SEP	6.66 (1.1-39.2)	-
Jorgenson[38]	Time course of neurological recovery in initial very severe deficit vs. mild deficit	-	11.30
	Time course of neurological recovery in initial severe deficit vs. mild deficit	-	12.18
	Time course of neurological recovery in initial moderate vs. mild deficit	-	7.52
Jorgenson[39]	Any motor recovery lower extremity in initial mild paresis vs. initial paralysis	4.00 (2.21 - 7.26)	-
	Any motor recovery lower extremity in initial mild paresis vs. severe paresis	1.07 (0.53 - 2.15)	-
	Any motor recovery lower extremity in initial severe presis vs. initial paralysis	3.72 (1.71 - 8.10)	-
Nakayama[52]	Any motor recovery upper extremity in infarction vs. hemorrhage	1.28 (0.35 - 4.70)	-
Rapisarda[70]	Any recovery of hand muscle strength in present initial MEP vs.absent initial MEP	21.80 (2.54 -257.57)	-
Palliyath[61]	Any motor recovery of upper extremity in present vs. absent MEP	108.00 (8.78 -1327.83)	-
Binkofski, 2001[14]	Any motor recovery of upper extremity in severe vs. moderate paresis	21.17 (2.55 - 76.53)	-

Abbreviations: CI, confidence interval; MEP, motor evoked potentials; SEP, somatosensory evoked potentials.

Five studies[24,27,40,61,70] were specifically aimed at determining the predictive value of evoked potentials for motor recovery after stroke. Motor evoked potentials recorded in the early phase (first days) poststroke appeared highly predictive for the occurrence of motor recovery, as could be illustrated by very high ORs for present versus absent evoked potentials (Table 4). Despite the

differences in timing of the assessments (on day 1 clinical examination vs several days poststroke evoked potentials), evoked potentials seem to be considerably more predictive than clinical examination. MEPs assess objectively and quantitatively the integrity of the motor pathways and may generate valid prognostic information, since postlesional recovery appears strongly influenced by a critical residual spared function[14]. Especially in noncooperative or severely cognitively impaired patients (i.c. global aphasia, apraxia and neglect), the clinical evaluation is often questionable and thus inconclusive with respect to prognosis.

The timing of the prognostic assessment appears of great importance. Duncan et al.[25] prospectively measured the FMA[91] up to 6 months in a cohort of 104 acute hospitalyzed stroke patients, stratified according to the severity of initial motor deficits. Regression analysis revealed that on day 1, the initial FMA motor score accounted for only half of the variance in motor functions at 6 months, whereas the 5-day motor and sensory scores explained 74% of the variance and the 30-day motor score explained 86% of the variance. These results suggest that very early prediction of motor recovery based on clinical examination alone may be precarious and that the accuracy of prediction may rapidly increase within a few days after the stroke.

The selected studies were also assessed for other prognostic factors that might be associated with motor recovery. Bonita and Beaglehole[15] performed subgroup analysis for different age and gender; they reported no significant association between these patient characteristics and motor recovery. Domincus et al.[24] supplied sufficient data to perform subgroup analysis for different lesion size and site (table 4). Motor recovery seemed better for small than for large lesions (OR 5.14; CI, .47-55.64) and for subcortical compared with cortical lesion (OR2.22; CI, .36-13.53). Binkofski et al.[14], on the other hand, found no significant correlation between the initial lesion size (MRI, 1-3 days after stroke onset) and recovery of motor functions of the upper

extremity. There was also no correlation between the changes of the lesion size (as measured in proton density MRI) and motor deficits. Samuelsson et al. [72] studied motor recovery in a homogeneous sample of patients with lacunar stroke. Although the method of motor assessment was self-designed by the authors and rather global (table 3), some conclusions with respect to motor recovery can be drawn. Even in the subgroup of patients with severe motor deficits, some degree of motor recovery occurred in 84% of the patients (table 3). The supplied data were insufficient for further subgroup analysis. Nakayama et al.[57] found no significant differences between patients with and without motor recovery of the upper extremity for gender, age and stroke type (infarction or hemorrhage).

None of the selected studies discriminated hemispheric from brainstem stroke. Secondary evidence concerning the prognostic value of lesion site can be derived from the prognostic study of Turney et al.[82] (internal validity, 7; validity sum score, 14). This study was aimed at recovery profiles in first-ever hemispheric versus brainstem infarctions; 87% of the hospitalyzed patients with hemispheric infarctions (n= 505) showed motor deficits at onset versus 78% of the patients with brainstem infarctions (n= 188). At one year follow up, the proportions of patients with residual motor deficits had declined to 57% and 59%, respectively. An OR of .93 (CI, 0.62-1.37) indicated no significant difference between motor recovery in hemispheric and brainstem infarctions.

Several other studies provide secondary evidence concerning our second research question. Katrak et al.[44,45] studied early voluntary shoulder movements (shoulder shrug) as a prognostic indicator for recovery of hand paralysis in patients who were admitted to a rehabilitation center. Initial shoulder shrug in 71 patients (examined 11 d posstroke; range, 0- 23 d) predicted good hand movement and hand function[45]. Other clinical determinants, such as prolonged muscular flaccidity[31] and lack of early grip

strength[79], have also been suggested as negative predictors for motor recovery. However, there is insufficient evidence for the prognostic value of these more specific clinical signs.

Conclusions

This review attempted to establish quantitative estimates of different aspects of motor recovery after stroke, including prognostic factors, using only primary evidence from methodologically well-conducted studies. From a total amount of 174 studies, only 14 studies were included for further review and quantitative analysis. The main problem in the final analysis was the pluriformity in the applied assessment procedures for motor recovery, follow-up periods and stratification procedures, suggesting that meta-analysis was not possible. However, our data synthesis and quantitative analysis comprised data from many methodologically robust studies, that may support the clinician in the management of stroke patients. Some observations are as follows. Approximately 65% of the hospitalyzed stroke survivors with initial motor deficits of the lower extremity show some degree of motorrecovery. For the upper extremity, data were insufficient to give an overall estimate. In the case of initial paralysis, complete motor recovery occurs in less than 15% of the patients, both for the upper and lower extremities. Very little valid information is available about the extent of motor recovery. As for the time course of recovery, the recovery period in patients with severe stroke was twice as long as in patients with mild stroke. With respect to early prognosis of motor recovery, the present review confirms clinical experience that the initial grade of paresis is the most important predictor, although the accuracy of prediction rapidly improves during the first few days after stroke. Initial paralysis implies the worst prognosis for subsequent motor recovery. Remarkably, the prognostic accuracy of evoked potentials appears much higher than that of clinical examination for different subgroups of patients, although the ORs show wide confidence intervals, due to generally small sample sizes. Patients with small lacunar strokes seem to show relatively good recovery profiles

compared to larger hemispheric strokes. Perhaps somewhat counterintuitive for clinical reasoning, there is no epidemiological evidence of a systematic difference in recovery potential between hemorrhages and infarctions, or between brainstem and hemispheric infarctions.

In conclusion, this review shows that our knowledge of motor recovery after stroke in more accurate, quantitative and qualitive terms is still much more limited than it is perceived by many. The lack of precise and valid epidemiological data is in contrast with the general idea of global predictability of poststroke motor recovery based on the initial severity of motor deficits. The initial motor assessment may be invalid because of apraxia, neglect or aphasia. For clinical purposes and policy, a much more precise prognosis is required in individual patients. Hence, further research should be focused at a more precise prediction of the degree of motor recovery following stroke based on physical characteristics, type, size and site of the lesion. Special attention should be paid to the clinical prognostic value of motor evoked potentials.

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CHAPTER 5

SYSTEMATIC REVIEW FOR THE EARLY PREDICTION OF MOTOR AND FUNCTIONAL OUTCOME AFTER STROKE USING MOTOR EVOKED POTENTIALS

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Abstract

Objective: To clarify the prognostic use of motor evoked potentials (MEPs) in predicting motor and functional outcomes after acute stroke.

Data sources: A computer-aided search to identify original prognostic studies published from1988 to 2000; relevant references cited in the retrieved articles were also included.

Study selection: A preliminary screening selected studies in which transcranial magnetic stimulation was assessed as a prognostic determinant for outcome at the level of impairments (motor recovery) and disabilities (functional recovery). The studies were then subjected to a critical review according to a priori methodologic criteria.

Data extraction: Data from the studies were used to construct contingency tables with MEPs as prognostic determinant. The distribution of cells was statistically assessed with the Fisher exact test. The prognostic test properties were expressed as sensitivity and specificity. The clinical significance was determined by Odds ratios.

Data synthesis: Of 85 potentially relevant studies, 20 met the criteria for the preliminary screening; after the critical review 5 studies were included for analysis and discussion.

Conclusions: Analysis of the data from the included studies indicated obvious evidence for the prognostic value of MEPs, for both motor and functional recovery. The prognostic test properties for subgroups of patients could be established. In predicting motor recovery of the upper extremity, the specificity was consistently very high for subgroups of patients with paralysis or severe paresis; this test property might be used in clinical practice. We discuss the prognostic value of MEPs and offer suggestions for further research.

Introduction

Prediction of functional outcome after stroke remains an important topic in stroke management. A valid prognosis for each stroke patient is needed as

early as possible after stroke onset to initiate optimal rehabilitation according to realistic therapy goals. Several clinical and demographic variables have been identified as valid predictors for functional recovery[1], including age, sitting balance, severity of paresis, disability on admission, urinary incontinence, previous stroke, and the impact of social support. Motor evoked potentials (MEPs), obtained at various times after stroke, have also been studied as valid predictors. These motor potentials are evoked by means of noninvasive magnetical stimulation of the motor cortex, and they assess objectively and quantitatively the integrity of the motor pathways.

Particularly in noncooperative patients or severely cognitively impaired patients (i.e. global aphasia, attention deficits, apraxia and neglect), clinical evaluation may be invalid in the early poststroke phase and thus be inconclusive with respect to functional prognosis. However, the use of MEPs in stroke management is still equivocal and results of studies seem to be contradictory. To clarify these points, we performed a systematic review of the literatureto address the research question: What is the prognostic value of MEPs after acute stroke with respect to motor recovery and functional recovery?

Methods

Search

Relevant literature was identified primarily by assessing the following bibliographic databases: MEDLINE (1988-2000); PsychLit (1988-2000); Cochrane database for clinical trials (until 2001); PubMed (until 2001); EMBASE (until 2001); and Current Contents (until 2001). The following keywords were used: transcranial magnetic stimulation, TMS, evoked potentials, motor evoked potentials, MEP, MEPs, stroke, cerebral infarction, intracerebral hemorrhage, recovery, recovery processes, functional recovery, motor recovery, motor control, and prognosis. The references in the retrieved articles were also checked for inclusion.

Preliminary screening

Studies identified by the search were subjected to a preliminary screening to select cohort studies, in which MEPs were evaluated as prognostic indicator for outcome at the level of impairments and disabilities, or both. MEPs had to be elicited within 1 week after stroke onset. Only studies that used transcranial magnetic stimulation on at least 10 patients were included. Case series, case studies, letters, abstracts, comments, and published presentations were excluded. Studies had to have been published in the English, French, German or Dutch.

Assessment of methodological quality

All studies found in the preliminary screening were subjected to independent critical reviews (by HTH and MJZ) according to a methodologic checklist. In cases of disagreement, consensus was sought (JvL). The methodological checklist was constructed according to the prognostic character of the articles to be reviewed, with special emphasis on internal validity. In short, the following methodologic principals[2-4] needed to have been applied in the study design. The diagnosis had to be confirmed unambiguously, and all patients had to have been studied at the same stage of the disease (inception cohort). To prevent selection bias, the base population had to be described, including clear referral patterns and in- and exclusion criteria for study entry. The study population had to be homogeneous with respect to known prognostic variables as severity of initial impairments and disabilities. The study design or the statistical methods had to contain adjustments for (potential) confounding, if applicable. The method and assessment of TMS as the unique independent variable needed to be described sufficiently and unequivocally. Outcome measures had to be assessed objectively by standardized and validated tests during a sufficient follow-up period. The follow-up had to be as complete as possible. As for the statistical analysis, it had to be appropriate for the prognostic character of the studies. The sample size had to be adequate. All

these methodologic issues were operationalized in the following 4 internal validity (V1-V4) criteria and 7 data extraction (D1-D7) criteria. Each criterion was scored at 3 levels: positive (+), moderate (0) or insufficient (-).

INTERNAL VALIDITY CRITERIA (V1-V4)

V1: The diagnosis was confirmed by computed tomography or magnetic resonance imaging in all cases.

V2: The patients' follow-up started at admission.

V3: The study population was homogeneous with respect to known prognostic variables as severity of initial impairments and disabilities. In case of heterogeneity, relevant subgroup analysis had to have been performed. If no subgroup analysis was performed, the item score was insufficient. If there was sufficient information available for posthoc stratification and subsequent analysis, the item score was moderate.

V4: There was sufficient control for confounding in the research design (stratification and selection) and or in the statistical analysis. Stroke type, stroke localization, recurrent stroke and neurosurgical interventions in case of hemorrhages were regarded as potential confounders. If there were sufficient data available to control for confounding and for subsequent analysis, the item score is moderate.

DATA EXTRACTION CRITERIA (D1-D7)

D1: The base population was identified; in- and exclusion criteria are given; patients' characteristics were given. The score was sufficient if all these items were sufficiently described, the score was moderate if one item was not sufficiently expressed. Otherwise, the score was insufficient.

D2: Methods of TMS were sufficiently described in terms of stimulation level, with or without facilitation, and the absence or presence of responses was defined. The score was sufficient if all requested items were available; the score is moderate if 1 item was not sufficiently expressed; otherwise, the score

was insufficient. Reference to other studies was accepted, which implies assessment of the criterion in the original article.

D3: Outcome measurements were repeated during a relevant follow-up period. This period was set at a minimum of 3 months.

D4: Outcome measurement consisted of standardized and validated tests (impairments and/or disabilities).

D5: The prognostic relevance of MEPs was sufficiently expressed in terms of statistical and quantitative measures (eg Odds ratio [OR], sensitivity, specificity, likelihood ratio). If sufficient data were given for post hoc analysis, the score was moderate.

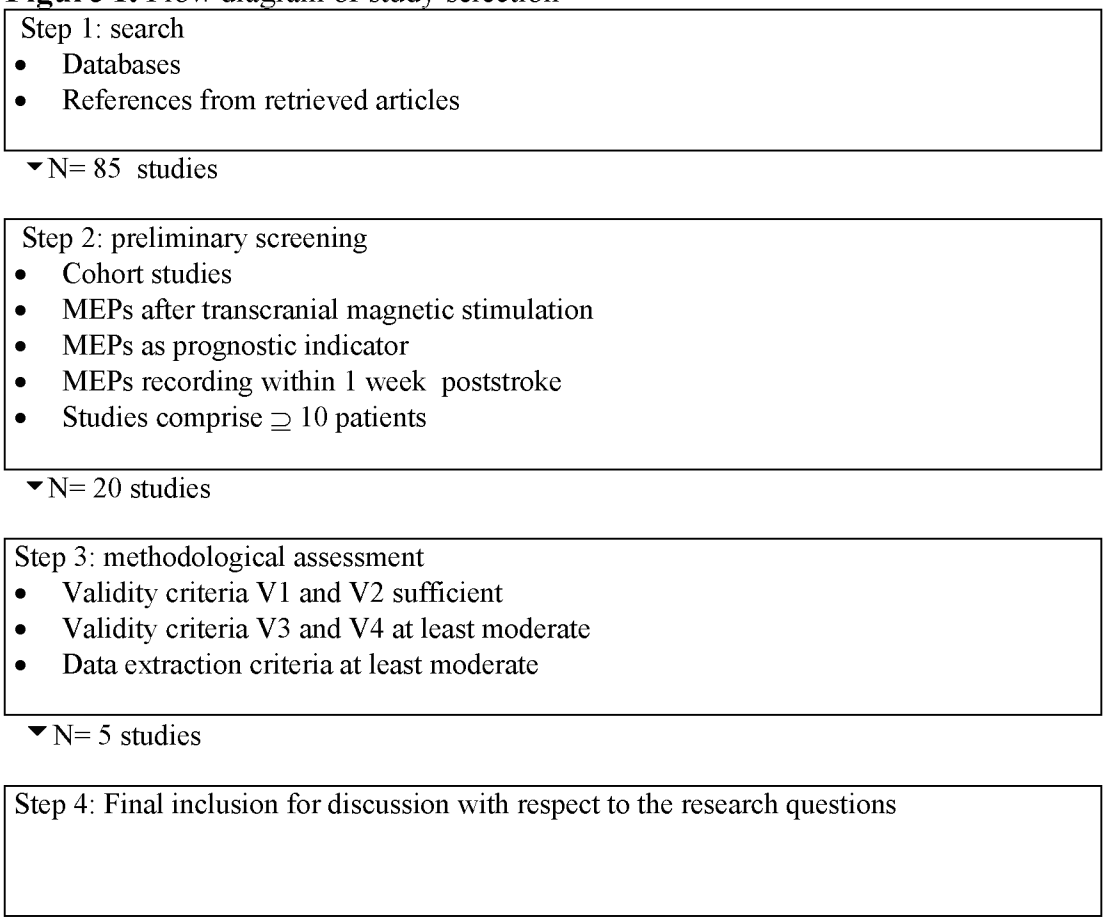
D6: Follow-up was nearly complete. The percentage of patients lost to follow up should not have exceeded 15%, according to convention. The reasons for lost to follow up were given and these cases were managed adequately in the analysis, which implies statistical analysis of the dropouts. Death and/or stroke recidivism was classified as a dropout if these cases were not handled adequately in the analysis.

D7: Sample size was adequate; the required sample size was estimated in relation to the statistical analysis performed, and the ratio of number of patients and number of determinants exceeded or equaled 10:1.

Best evidence synthesis

The following hierarchy concerning the internal validity and data extraction criteria was handled for selection of studies for final discussion. V1 and V2 were judged as crucial and their score had to be positive; any score less than positive was not accepted. V3 and V4, as well as the data extraction criteria, had to be scored at least moderate. Any insufficient scores meant automatic exclusion.

Figure 1. Flow diagram of study selection



Evaluation of prognostic and clinical significance

In the first instance, the data from the included studies concerning motor and functional recovery were used to construct contingency tables with MEPs as the prognostic determinant. The MEPs were dichotomized into present (normal response or delayed Central Motor Conduction Time [CMCT]) and absent. The outcome parameters were also dichotomized. Motor recovery was classified , if possible, as present (the occurrence of some degree of motor recovery) or absent (no motor recovery). The chance of motor recovery after stroke is highly dependent on the initial grade of motor deficits, with the worst prognosis for patients with initial paralysis[5]. Therefore, subgroup analysis was performed for subgroups with initial paralysis and initial paresis, respectively. Analogous to the dichotomization in two of the finally included studies, functional recovery was defined as present (Barthel Index $\supseteq$ 12) and absent (Barthel Index $\subset$ 12). The distribution of numbers of patients within the cells

of the contingency tables was statistically assessed by the Fisher exact test. The prognostic test properties were expressed as sensitivity and specificity. Sensitivity refers to the proportion of patients who do experience motor or functional recovery, and whose MEPs were present. Specificity refers to the proportion of patients who do not experience motor or functional recovery, and whose MEPs were absent. A sensitive prognostic test will rarely miss patients who will have motor or functional recovery. A specific test, however, will rarely misclassify patients, who will not have motor or functional recovery. ORs were calculated to express the clinical significance, if the contingency table contained no zero-cells. Quantitative analysis of the prognostic value of MEPs was only performed in studies in which relevant (sub)groups of patients were included. Given the rather small sample sizes in the available studies, the minimal sample size was arbitrarily set at 15 patients. Studies with lower numbers of patients were assessed as secondary evidence.

Table 1. The methodological assessment

First author, year of publication	V1	V2	V3	V4	D1	D2	D3	D4	D5	D6	D7
Arac, 1994	+	+	0	0	0	0	+	+	0	-	+
Bastings, 1997	+	+	+	+	0	+	-	+	0	-	+
Benetin, 1995	+	+	-	+	-	0	-	+	-	+	-
Binkofski, 1996	+	+	0	+	+	0	-	-	0	+	+
Catano, 1995	+	+	-	+	+	+	+	+	-	+	+
Chu, 1992	+	+	0	+	0	0	+	+	0	-	+
Cruz Martinez, 1999	+	+	*0*	+	*0*	*0*	+	+	*0*	+	+
D'Olhaberriague, 1997	+	+	-	+	0	0	+	+	-	+	+
Escuredo, 1998	+	+	+	+	+	*0*	+	+	+	+	+
Heald, 1993	+	+	*0*	*0*	+	*0*	+	+	+	+	+
Hendricks, 1997	+	+	+	+	+	*0*	+	+	+	+	+
Kandler, 1991	+	+	-	-	0	-	+	-	-	+	+
Nagao, 1992	+	+	0	0	0	-	+	0	0	+	-
Palliyath, 2000	+	+	0	+	0	0	+	+	0	+	+
Pennisi, 1999	+	+	+	+	0	0	+	+	-	+	+
Pereon, 1995	+	+	0	0	0	0	+	-	-	+	+
Rapisarda, 1996	+	+	+	+	0	0	-	+	0	+	+
Timmerhuis, 1996	+	+	-	+	+	+	+	+	-	-	+
Trompetto, 2000	+	+	0	0	0	+	+	+	0	-	+
Vang, 1999	+	+	-	+	0	0	-	+	-	+	+

Score +, positive; Score 0, moderate; Score -, insufficient.
The selected studies for final discussion are printed italic.
For extended explanation of the methodological criteria,see text (section data extraction).

Results

Figure 1 diagrams how the 5 studies included in this study were selected. The primary search resulted in 85 potentially relevant studies. Twenty studies[6-25] were selected by the preliminary screening for methodological assessment (Table 1). Five studies[12,14,15,16,19] met the validity and data extraction criteria and were selected for final discussion, although all 5 had several methodological limitations (Table 1). All relevant information concerning them is summarized in Table 2. Three studies[12,16,19] dealt with motor recovery only, whereas the other 2 studies[14,15] were aimed at both motor and functional recovery. Only 4 studies[14,15,16,19] contained sufficient numbers of patients for quantitative analysis of the prognostic value of MEPs. Table 3 provides contingency tables for motor and functional recovery for subgroups of patients with MEPs present and absent, the test properties of the MEPs, the results of the statistical assessment of the distribution of cells, and the ORs. The numbers of patients in the subgroups in 1 study[12] were too low for quantitative analysis.

Discussion

Quantitative analysis revealed large confidence intervals within the studies (Table 3), probably because of the small sample bases and nonhomogeneous patient samples. Furthermore, substantial interstudy variability was found. Clinical heterogeneity[31] may account in parts for this interstudy variability. Despite the preliminary selection procedure and the subsequent methodological assessment, several sources for clinical heterogeneity were still identified in this systematic review. These include the definition of amplitude presence, the exact time point of neurophysiologic assessment, whether MEP registration occurred with or without facilitation, the stimulus intensity, and the outcome parameters (Table 2). In the quantitative analysis, MEPs were dichotomized into present (delayed CMCT or normal) and absent response. Present versus absent response was not uniformly defined in the 5 studies. For example, Heald et al.[15] documented absent response if no response

was obtained after 10 stimuli at maximum output of the stimulator with facilitation by muscle contraction, Escudero et al.[14] defined absent MEPs when it failed to appear after 3 successive discharges with maximum output.

Table 2. Summary of the 5 included studies

Study	Sample size (n)	Stroke type	Outcome parameters	Assess-ment	MEPs registration				Follow-up	Subgroups (n)
					Time Point	Facil	Stim i	Muscles studied		
Cruz-Martinez[12]	20	ICVA	Motor recovery (hand)	CNS	Day 3-6	With and without	30% above treshold	*Thenar*	6 months	Paralysis (8) Severe Paresis (4) Mild (3) None (5)
Escudero[14]	50	ICVA	Motor recovery (APB); defined as MRC >4	MRC	Day 3-7	With	30% above treshold, max output	*APB* AH	6 months	MRC 0-1 (24) MRC2-4 (26)
			Functional recovery; defined as BI>12	BI						
Heald[15]	118	ICVA	Motor recovery arm, hand and leg	MI	Day 0-3	With	20% above treshold, max output	*Thenar* Biceps Triceps Pect maj	12 months	Paralysis/ very severe paresis (44) Paresis (74)
			Functional recovery; defined as BI>12	BI						
Hendricks[16]	29	ICVA	Motor recovery upper extremity	FMA	Day 3-4	Without	Incr int, stepwise	*ADQ*	12-48 months	Homogeneous, paralysis UE
Palliyath[19]	38	ICVA	Motor recovery upper extremity	MRC	Day 2-7	Without	90-100%	*ADM* TA	3 months	Paralysis (9) Paresis (29)

Note: For muscles studied: motor potentials have been recorded in some studies in several muscles of the upper and lower extremity. Muscle responses that were assessed for their prognostic value (motor recovery and or functional recovery) are printed italicized.
Abbreviations: Time point, time point of MEPs within the first week after stroke onset; Facil, facilitation; Stim i, stimulation intensity; ICVA , Ischemic Cerebrovascular Accident; CNS, Canadian Neurological Scale[26]; MRC, Medical Research Council[27]; BI , Barthel Index[28]; MI, Motricity Index[29]; FMA, Fugl-Meyer Motor Assessment[30];UE, upper extremity; APB, abductor pollices brevis muscle; AH, abductor hallucis muscle; ADQ, abductor digity quinty muscle; ADM = abductor digiti minimi muscle; Pect Maj, Pectoralis major muscle; TA, Tibialis anterior muscle.

Hendricks et al.[16] did not define absent response at all. None of the studies gave a precise definition for amplitude presence. Another important issue is the exact time point within the first week poststroke for the assessment by MEPs (Table 2). Heald et al.[15], for instance, performed MEPs within 12-72 hours after onset. Some of their patients deteriorated clinically and lost their initial responses. Escudero et al.[14], on the other hand, recorded the initial MEPs at day 3 through 7. Because brain tissue damage may increase in the

case of progressive stroke, but also spontaneous recovery may occur early after stroke onset[32], the prognostic properties of MEPs may improve gradually when they are recorded later in the first week after onset. Furthermore, facilitation as a technique to provoke in motor potentials should be explored. Facilitation in the 5 studies was defined as the voluntary contraction of the muscle studied prior to the electromagnetic assessment, and, in case of paralysis, contraction of the contralateral muscle. Facilitation decreases the stimulation treshold and the amplitude may increase or even appear in case of absent response[10,12]. With respect to prognosis, these effects imply that the sensitivity may increase. The differences in stimulation intensity (Table 2) may also account for the heterogeneity. As for the muscles studied, there was reasonable uniformity, according to Heald et al.[15], who demonstrated that thenar muscles had the highest correlations with clinical and functional measures.

With regard to the outcome parameters, we distinguished between motor and functional recovery. Motor recovery was evaluated by different measures in the studies (Table 2), and different aspects were assessed. In 3 studies[12,14,16], the extent of motor recovery was determined at follow-up and the occurrence, to some degree, of motor recovery could be deduced from the supplied data. Heald et al.[15], on the other hand, provided the these data for motor recovery only as test properties of MEPs for the occurrence of full recovery of pinch grip, arm strength, and leg strength.

The considerable clinical heterogeneity implies that meta-analysis was impossible. Nevertheless, some preliminary conclusions can be drawn from the compiled data (contingency tables) and the quantitative analysis. The distribution of numbers of patients within the cells of the contingency tables was highly significant for (sub)groups of patients, both for motor and functional recovery (Table 3), indicating robust prognostic relevance of MEPs. As for motor recovery, MEPs had a specificity of nearly 100% for the entire patient sample of Hendricks et al.[16] and the subgroup with a Medical Research

Research Council (MRC) Scale of 0 to 1 in the study of Escudero et al[14]. This indicates that little motor recovery can be expected in patients with initial paralysis or very severe paresis (MRC Scale score, 0-1) of the upper extremity if MEPs are absent in the first week poststroke. Because clinical examination

Table 3. The prognostic value and clinical significance of MEPs

Study	Outcome parameter (patient numbers)	Contingency tables			Test properties		Fisher exact Test	Odds ratio (CI)
					Sensitivity	Specifcity		
Hendricks[16]	Recovery from paralysis upper extremity (29)		MR+	MR-	71% (38-100)	99% (97-100)	0.0002	-
		MEPs +	5	0				
		MEPs -	2	22				
Escuredo[14]	Recovery from paresis upper extremity MRC 0-1 (24)				62% (28-95)	99% (97-100)	0.0013	-
		MEPs +	5	0				
		MEPs -	3	16				
	Recovery from paresis upper extremity MRC2-3 (19)				93% (82-100)	2% (0-22)	0.9231	-
		MEPs +	16	2				
		MEPs -	1	0				
Palliyath[19]	Recovery from paresis upper extremity MRC 1-4 (29)				94% (83-100)	99% (95-100)	0.0000	-
		MEPs +	17	0				
		MEPs -	1	11				
Heald[15]	Full recovery pinch grip (76)				92% (84-100)	48% (32-65)	0.0000	11.96 (3.10- 46.12)
		MEPs +	38	18				
		MEPs -	3	17				
	Full recovery arm paresis (76)				92% (83-100)	44% (28-60)	0.0002	9.44 (2.47- 36.11)
		MEPs +	35	21				
		MEPs -	3	17				
	Full recovery leg paresis (76)				89% (80-98)	50% (32-67)	0.0001	8.20 (2.53- 26.48)
		MEPs +	41	15				
		MEPs -	5	15				

Functional Recovery

Heald[15]	Barthel Index ≥ 12 (118)		FR +	FR -	79% (69-89)	58% (30-86)	0.0000	5.49 (1.49- 20.13)
		MEPs +	51	5				
		MEPs -	13	7				
Escuredo[14]	Barthel Index ≥ 12 (50)							
		MEPs +	27	3	77% (63-91)	80% (59-100)	0.0000	13.50 (3.03- 59.96)
		MEPs -	8	12				

Abbreviations: MR, motor recovery; FR, functional recovery; CI, confidence interval.

by itself lacks the capability to detect the potential for motor recovery in this subgroup, the added prognostic value of MEPs in this context seems established. The sensitivity was somewhat low and highly variable, indicating that not all patients who will show motor recovery can be identified by the presence of early MEPs. The data for the subgroups of patients with initial paresis were not uniform. Both the sensitivity and the specificity were high in the Palliyath study[19] (MEPs without facilitation), in contrast with the Escudero

study[14] (MEPs with facilitation). However, the dichotomization of the MEPs (in the present analysis) probably implies a substantial loss of important prognostic information with respect to motor recovery in these subgroups. A quantitative analysis of the CMCT and the amplitude may provide relevant prognostic information in these patients[14,15]. Also, the stimulation threshold[33] and ipsilateral abnormalities[34] have been suggested as prognostic factors in these cases. The data from Heald et al.[15] on motor recovery cannot be compared with the other studies because they only supplied data on complete motor recovery.

The assessment of functional recovery was much more uniform. Both Heald et al.[15] and Escudero et al.[14] used the Barthel Index[28] and even defined functional recovery similarly (a score $\geq$ 12). Quantitative analysis revealed consistent values for the sensitivity (table 3b), whereas the values for the specificity were rather inconsistent. The studies differed particularly with respect to the follow-up period (Table 2). The follow-up period in the Escudero[14] study of was 6 months compared to12 months in the Heald[15] study. This might explain the rather low specificity in the latter study. Nevertheless, the added prognostic value of MEPs compared to early clinical functional measures has not been established. The question arises as to whether the proper assessment instrument has been used for functional recovery. All studies assessed only upper-extremity MEPs in regard to functional prognosis, as measured by the Barthel Index, which is a general measure for disability that emphasizes mobility. It contains no specific scores for arm and hand abilities. Early lower- extremity MEPs would probably be more predictive in this context, but, to our knowledge, this relationship has not yet been assessed.

The calculated ORs in subgroups of patients provided substantial evidence about clinical significance both for motor and functional recovery.

Although the numbers of patients in several subgroups were too low for quantitative analysis, the results of these studies, summarized in contingency Table 4, are obviously consistent with the data that could be quantitatively explored.

Table 4. Contingency tables for (sub)groups of patients containing insufficient numbers of patients for quantitative analysis

Cruz Martinez[12]	Recovery from hand paralysis (8)		MR +	MR-
		MEPs +	2	0
		MEPs -	1	5
	Recovery from hand paresis (7)	MEPs +	5	0
		MEPs -	2	0
Palliyath[19]	Recovery from hemiparalysis (4)			
		MEPs +	0	0
		MEPs -	0	4

Abbreviations: MR, motor recovery.

Conclusions

The search, the selection procedure, and the methodologic assessment used in this review yielded 5 prognostic studies. In only 4 studies were the numbers of patients sufficient for quantitative analysis. Because of considerable clinical heterogeneity meta-analysis was not possible. Concerning the research question, evidence exists for the prognostic value of MEPs after acute stroke for both motor recovery and functional recovery. The data are most consistent for motor recovery in patients with initial paralysis or very severe paresis (MRC Scale score, 0-1) of the upper extremity; it seems justified to use MEPs prognostically in these patients in clinical practice. The prognostic value of MEPs with respect to motor recovery in patients with initial paresis needs to be further explored, as does its value in predicting functional recovery. A stratified analysis (according to initial disabilities) seems appropriate in this context. MEPs of the lower extremity may provide important prognostic information, both for motor and functional recovery and should be further examined.

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CHAPTER 6

MOTOR EVOKED POTENTIALS IN PREDICTING RECOVERY FROM UPPER EXTREMITY PARALYSIS AFTER ACUTE STROKE

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Abstract

Objective: The use of motor evoked potentials (MEPs) in predicting recovery after stroke still appears to be somehow equivocal. We assessed the prognostic value of MEPs with respect to arm and hand motor recovery in acute stroke patients.

Methods: A cohort study, including 43 consecutive acute stroke patients with complete paralysis of the upper extremity. MEPs of the abductor digiti minimi muscle (ADM) and the biceps brachii muscle (BB) were obtained within 10 days after stroke onset. The upper limb subset of the Fugl-Meyer Motor Assessment was used to evaluate the motor performance at regular intervals until 6 months poststroke.

Results: The follow-up was complete in 40 patients (2 patients died and 1 patient had a recurrent stroke); fourteen patients showed motor recovery of the arm and their mean 26-week arm motor score was 17.93 (range 3-30, standard deviation [SD] 11.68); hand motor recovery occurred in 11 patients and their mean 26-week hand motor score was 11.09 (range 4-14, SD 4.10). Stepwise logistic regression revealed prognostic models for both arm and hand motor recovery based on BB MEPs (Odds ratio [OR] 7.69, confidence interval [CI] 1.16-50.95) and ADM MEPs (OR 16.20, CI 2.51-104.40), respectively.

Conclusions: The predictive relevance of MEPs with respect to motor recovery of the upper extremity was obvious in our homogeneous sample of patients. This agrees with the paradigm that postinfarctional motor recovery is strongly dependent on a critical residual sparing of corticospinal function. In this context, the test properties of MEPs in predicting motor recovery are discussed. The added value of MEPs with respect to motor recovery of the upper extremity should be regarded as established for patients with initial paralysis, especially since clinical examination alone lacks the possibility to detect the potential for motor recovery in these cases.

Introduction

Functional abilities of the upper extremity are irrefutably inherited by the human race and they rely upon highly integrated sensorimotor and cognitive functions. From a functional-anatomical perspective, the proximal positioning and stabilization of the body, shoulder and arm can be distinguished from the distal fine hand and finger movements. In the case of complete paralysis, recovery of proximal and distal motor functions is a prerequisite to regain functional abilities. In fact, approximately 30% of all stroke patients exhibit very severe paresis or paralysis of the upper extremity at stroke onset, and they have a poor prognosis for subsequent motor recovery[1,2]. Nevertheless, some of these patients will experience partial or even complete motor recovery. Early identification of the potential for motor recovery in this subgroup is important in order to avoid 'learned disuse'[3] and to be able to initiate appropriate therapy with realistic goals. The occurrence of motor recovery is highly associated with the initial severity of the motor deficits[2], and clinical examination cannot detect the potential for motor recovery in patients with initial paralysis. Stroke localization and extend have been identified as prognostic indicators[4-6]. However, the present study focuses on motor evoked potentials (MEPs) to predict motor and functional recovery of the upper extremity in acute stroke patients. MEPs obtained from small hand muscles in an early phase after the stroke appeared to be predictive for hand motor recovery[7-10]. The prediction of proximal arm motor recovery based on MEPs has not been explored extensively[7] as yet. We performed a cohort study (1) to assess the occurrence and the degree of arm and hand motor recovery, and the recovery of functional abilities, and (2) to assess the prognostic value of MEPs with respect to arm and hand motor recovery in acute stroke patients with initial paralysis of the upper extremity.

Methods

Patients

Forty-three consecutive patients with acute ischemic stroke were recruited during a 1.5-year's period from the department of neurology of a university hospital. The study population comes from the region of Nijmegen, a middle-sized city in the eastern part of the Netherlands. The acute medical care for stroke patients is delivered by several hospitals, including our university hospital. Stroke patients are admitted to these hospitals in an unselected manner, therefore no referral bias is to be expected. Patients were included only if they exhibited paralysis of the upper extremity at admission or developed paralysis during the first days after admission. Paralysis was defined as no voluntary movement on request. Patients with poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity) and patients with pre-existent impairments or disabilities of the upper extremity were not included. Also, patients with a history of craniotomy, epilepsy, cardiac prosthetic valve, pacemaker implantation, or severe polyneuropathies were not included. Written informed consent was obtained from all patients before study entry. The local ethical committee approved the study protocol. All patients had neurological examination on admission, and stroke severity was classified according to the Scandinavian Stroke Scale[11]. The diagnosis was confirmed by CT in all patients. The stroke localization was categorized as cortical, subcortical, the basal ganglia or the brain stem. The lesion size was measured and classified as small (<2cm), moderate (2-5cm), extensive (5-10 cm), and very extensive (>10cm). All patients received standard medical treatment according to the guidelines of the Dutch Society of Neurology**,** including a multidisciplinary paramedical team approach. From day one all patients received physiotherapy to maintain optimal joint mobility and to regulate muscle tone of the upper extremity. No specific therapy was initiated to improve motor recovery. If immediate home discharge was not possible, further treatment was given in either a

rehabilitation center, a special therapy unit within a nursing home, or a standard nursing home.

Neurophysiological assessment

In all patients MEPs were performed between the third and tenth day (mean 6.8 days) after stroke onset by the same researcher (JP). Patients were positioned comfortably in a supine position. Two self-adhesive recording surface electrodes were placed 3 cm apart over the bellies of the abductor digiti minimi muscle (ADM) and biceps brachii muscle (BB). These muscles were regarded as representative of proximal and distal motor functions of the upper extremity. The MEPs were recorded using a Nicolet Viking or Oxford Synergy electromyograph. Band-pass filter 20 Hz and 3 kHz, amplifier range 100 mV and display sensitivity of 0.5 mV/division. The ADM and BB were studied separately for both the affected and unaffected side. Data from the unaffected side were compared to normative data and used as control. Transcranial magnetic stimulation (TMS) was performed using a Magstim 200 magnetic stimulator with a 9-cm mean diameter circular coil. For cortical stimulation the coil was placed in a tangential plane above the vertex. Stimulation intensity was set at 80% of maximum stimulator output. If no reproducible response was found, the stimulation intensity was increased to 100% (maximum output). The left hemisphere was stimulated by a counter-clockwise current; the right hemisphere was stimulated by a clockwise current. Cervical motor roots were stimulated by the same coil applied over the seventh cervical spinal level with a stimulation intensity of 80% or 100%. Additionally, the ulnar nerve was stimulated electrically (supramaximal) at the wrist in order to assess the maximal compound motor action potential (CMAP) of the ADM. The MEPs after cortical stimulation were recorded while the patient tried to perform a weak contraction of the contralateral muscle (i.e., the muscle under investigation). At least two responses were obtained to assess the reproducibility of the responses. The presence of a MEP was defined as a reproducible response with minimal peak-to-peak amplitude

of 200 μV. A 100-millisecond post-stimulus period was analyzed. Latencies were measured between the onset of the stimulus artifact and the onset of the first negative deflection from the baseline, excluding random EMG activity when the MEPs were recorded during voluntary contraction. The MEP latency after cervical stimulation was used as the measure for the peripheral conduction. Total motor conduction time (TMCT) was the shortest latency between cortical stimulation and muscle response. Central motor conduction time (CMCT) was calculated by subtracting the peripheral latency from TMCT. The ADM peak-peak amplitude after cortical stimulation was divided by the peak-peak-amplitude of the CMAP after electrical stimulation to calculate an amplitude ratio. The test sequence was from distal (electrical stimulation at the wrist) to proximal (cortical TMS).

Table 1. Characteristics of the patients, initial stroke severity, and CT findings

Gender (M/F)	21/22
Mean age in years (range)	66.93 (19-84)
Mean SSS score (range)	16.97 (2-32)
Infarct localization (n):	
Cortical	2
Subcortical	1
Cortical-subcortical	11
Basal ganglia	7
Subcortical-basal ganglia	5
Cortical-subcortical-basal ganglia	16
Brain stem	1
Infarct size (n):	
Small (<2cm)	2
Moderate (2-5cm)	17
Extensive (5-10cm)	20
Very Extensive (>10cm)	4

Abbreviations: M, male; F, female; SSS, Scandinavian Stroke Scale [11].

Outcome assessment

Motor assessment was performed at week 1, 2, 3, 6, 12 and 26 by the upper limb subset of the Fugl-Meyer Motor Assessment (FMA)[12]. This cumulative numerical scoring system is based on the sequential recovery stages that can be observed in hemiplegic patients. In accordance with the original assessment, the motor functions of the upper extremity were scored under standardized test conditions. The recovery pattern of the proximal and distal

motor functions appears to be different and therefore we defined a separate arm and hand motor score within the FMA. The arm score included motor functions of the shoulder, elbow and forearm, with a maximum score of 30 points, whereas the hand score concerned the 7 original hand items with a maximum of 14 points. According to the inclusion criteria, all patients had an entry arm and hand motor score of 0 points. Muscle tone at the elbow was measured by the modified Ashworth scale[13]. The Frenchay arm test[14] was used to assess the functional abilities of the upper extremity. Clinical follow-up was performed by one of the authors (HH) who was aware of neither the MEPs results nor the CT findings.

Analysis

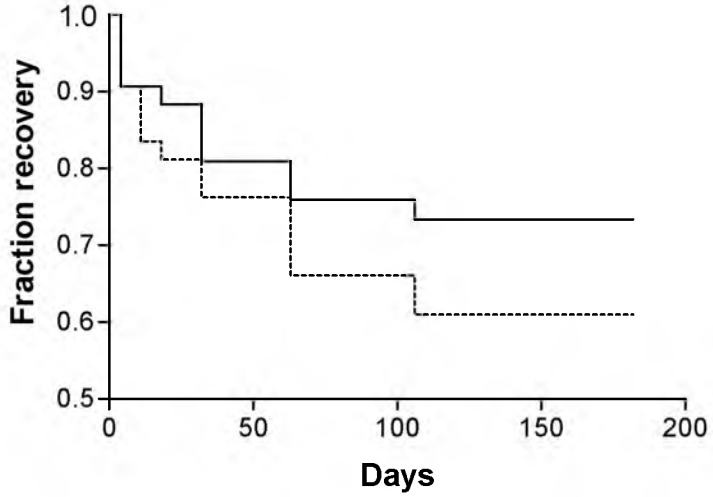
The occurrence of arm and hand motor recovery as the main outcome parameters was expressed in a Kaplan Meier curve. Stepwise logistic regression was performed in a stepwise forward selection manner to assess the prognostic significance of the MEPs and other prognostic variables. A p-value of 0.10 was used to select a factor into the model, and a p-value of 0.15 to remove a factor from the model. Dichotomization of the outcome and the MEPs parameters was performed as follows. The MEPs were judged as being present (normal response or delayed CMCT) or absent. The occurrence of motor recovery of the arm and hand was classified as present (the occurrence of some degree of motor recovery) or absent (no motor recovery).

The amplitude and the latency of present responses obtained from the affected side were compared with those obtained from the non-affected side and analyzed by the paired-samples t test. The relationship between the degree of motor recovery and the integrity of the MEPs was determined by the Pearson correlation coefficient.

The sensitivity and specificity of BB and ADM MEPs in predicting the occurrence of arm and hand motor recovery, including their 95% confidence

intervals (CIs), were calculated. Sensitivity is defined as the proportion of patients who show motor recovery and for whom MEPs were present. Specificity refers to the proportion of patients who exhibit no motor recovery and for whom MEPs were absent. Furthermore, we calculated the positive and negative predictive values.

Figure 1. Kaplan Meier curves for arm and hand motor recovery. Dotted line for arm motor recovery



Results

The characteristics of all included patients are shown in Table 1. Of the patients initially included, two patients died at day-5 and day-26, respectively, and one patient had a recurrent stroke at day-42 post stroke. Thus, 40 patients were eligible for the complete follow-up period. The occurrence of hand and arm motor recovery is shown in the Kaplan Meier curves (Figure 1). If patients experienced motor recovery, its onset was always 4 months post stroke, and in some cases motor recovery proceeded throughout the complete follow-up period. As shown in Table 2, 14 patients exhibited arm motor recovery and their mean 26-week arm motor score was 17.93 (range 3-30, standard deviation [SD] 11.68). Arm motor recovery was complete in five patients, whereas six patients only showed voluntary movements within synergies. In 26 patients, the arm remained paralytic. Hand motor recovery occurred in 11 patients and their mean 26-week hand motor score was 11.09

(range 4-14, SD 4.10). Six patients even exhibited complete hand motor recovery, whereas one patient only showed mass flexion of the fingers on request (Table 2). In 29 patients, the hand remained paralytic. In all cases, hand motor recovery was associated with arm motor recovery.

Table 2. The 26-week arm and hand motor scores and the amplitudes, the amplitude ratios and the CMCTs for all patients, in whom motor recovery of the arm and hand occurred, whether they had a MEP response (true positive with respect to motor recovery) or not (false negative), as well as all patients for whom MEPs could be elicited, without the occurrence of motor recovery (false positive). Patients with absent motor recovery and absent responses (true negative) are not included in the table

Patient Number	Week 26 arm motor score (0- 30)	Amplitude affected side	Amplitude non-affected side	CMCT affected side (msec)	CMCT non-affected side (msec)	
		BB	BB	BB	BB	
2	23	Absent	-	Absent	-	
5	7	Absent	-	Absent	-	
8	6	0.30	15.30	5.30	6.30	
10	30	Absent	-	Absent	-	
12	30	Absent	-	Absent	-	
15	30	2.50	1.50	8.20	7.00	
16	23	1.90	1.30	6.50	4.30	
17	30	3.50	12.90	5.30	4.60	
27	5	0.40	3.60	8.05	4.45	
29	27	Absent	-	Absent	-	
30	30	4.60	8.80	8.05	7.70	
34	0	0.30	3.20	51.45	6.25	
38	3	2.90	5.60	31.05	9.30	
39	26	Absent	-	Absent	-	
42	4	0.20	2.00	17.75	5.35	
43	0	1.20	5.50	20.45	5.10	
	Week 26 hand motor score (0- 14)	**Amplitude ratio affected side**	**Amplitude ratio non-affected side**	**CMCT affected side (msec)**	**CMCT non-affected side (msec)**	**Week-26 FAT score**
		ADM	ADM	ADM	ADM	
2	14	Absent	-	Absent	-	2
5	11	Absent	-	Absent	-	1
10	14	0.06	0.43	10.80	6.00	5
12	12	Absent	-	Absent	-	4
15	14	0.59	0.72	8.50	10.50	4
16	14	0.42	0.81	5.70	5.10	5
17	14	0.29	0.52	5.80	6.10	3
24	0	0.01	0.57	13.00	6.55	0
27	4	0.06	0.54	5.95	5.10	0
29	7	Absent	-	Absent	-	2
30	14	0.46	0.37	9.25	8.00	5
39	13	Absent	-	Absent		4

Abbreviations: CMCT, Central motor conduction time; FAT, Frenchay Arm Test [14]; BB, Biceps Brachii muscle; ADM, Abductor Digiti Minimi muscle.

The relationships between the occurrence of hand and arm motor recovery and MEPs as recorded over the ADM muscle and the BB muscle of the affected side, are shown in contingency tables (Table 3). Stepwise logistic regression revealed prognostic models for the occurrence of arm and hand motor

recovery, based on BB MEPs (Odds ratio [OR] 7.69, CI 1.16-50.94; p=0.0345) and ADM MEPs (OR 16.20, CI 2.51-104.40; p<0.0034) as parameters, respectively (Table 4). Other potential prognostic variables were added in the equations, including age, stroke localization, lesion size, arm and hand motor score at week 1, as well as ADM MEPs for arm motor recovery. None of the expanded models showed any improvement with respect to the prognosis of arm and hand motor recovery as compared to single parameter models. The product-term of BB and ADM MEPs for arm motor recovery also did not reach the significance level, indicating no interaction.

Table 3. Contingency tables for the occurrence of arm and hand motor recovery in relation with the MEP responses, and the test properties of the MEPs in predicting motor recovery of the arm and hand

	Arm motor recovery +	**Arm motor recovery -**
MEPs BB +	8	2
MEPs BB -	6	24

	Hand motor recovery +	**Hand motor recovery -**
MEPs ADM +	6	1
MEPs ADM -	5	28

	Sensitivity (CI)	**Specificity (CI)**	**Positive predictive value**	**Negative predictive value**
BB MEPs / arm motor recovery	57% (31-83)	92% (81-100)	80%	79%
ADM MEPs/ hand motor recovery	54% (25-84)	96% (91- 100)	86%	86%

Abbreviations: MEPs, Motor evoked potentials; BB, biceps brachii muscle; ADM, abductor digiti minimi muscle; CI, confidence interval.

BB and ADM MEPs could be obtained from the affected side in 10 and 7 patients, respectively (Table 2 and 3). The mean BB amplitude as obtained from the affected side was 1.78 mV (SD=1.55), compared to 5.97 mV (SD=4.88) for the nonaffected side (p= 0.010). The mean CMCT of the BB response for the affected and nonaffected side was 16.21 msec (SD 14.95) and

6.03 msec (SD 1.61), respectively, p=0.093. The mean ADM amplitude ratio of the affected side was 0.27 (SD=0.23), compared to 0.57 (SD=0.15) for the nonaffected side (p=0.006). The mean CMCT of the ADM response for the affected and nonaffected side was 8.43 msec (SD=2.81) and 6.76 msec (SD=1.91), respectively, p=0.093. The MEP data from the unaffected side felt within the range of normative data.

Table 4. Stepwise logistic regression model for the occurrence arm and hand motor recovery at week-26

Arm motor recovery	Coeff.	Std. Error	p-value	Odds ratio	95% CI upper	lower
% GM	-1.32	0.46	0.004	0.26	0.10	0.65
BB	2.03	0.96	0.034	7.68	1.16	50.94
ADM	2.06	1.23	0.094	7.88	0.69	89.05
Hand motor recovery						
% GM	-1.68	0.48	<0.001	0.18	0.07	0.48
ADM	2.78	0.95	<0.003	16.20	2.51	104.40

Abbreviations: BB, biceps brachii muscle; ADM, abductor digiti minimi muscle; GM, general mean; Coeff., coefficient; Std., Standard; CI, confidence interval.

The prognostic test properties of BB and ADM MEPs for arm and hand motor recovery are shown in Table 3. The specificity was 92% (CI 81-100) and 96% (CI 91-100) for arm and hand, respectively. The values for the sensitivity, conversely, were much lower, 57% (CI 31-83) and 54% (CI 25-84) for the arm and hand, respectively. The positive predictive values for BB and ADM MEPs were 80% and 86%, respectively. The negative predictive values were 79 and 86% for BB and ADM MEPs, respectively.

The degree of motor recovery in relation to the magnitude of the responses was as follows**.** For patients in whom BB and ADM MEPs were present, a strong association existed between the BB MEP amplitudes and the arm motor scores (Pearson correlation coefficient 0.780; p=0.004). Also a strong association was found between the ADM MEP amplitude ratios and the hand motor scores (Pearson correlation coefficient 0.690; p=0.041).

Apparently, functional recovery was closely related to motor recovery. FAT scores ranged from 0 to 5 (median score 3.5) for patients who exhibited arm and hand motor recovery (Table 2). Twenty-four (60%) patients showed increased muscle tone at follow up. The Ashworth scores ranged from 0 to 4, mean 1.40. For patients with arm hand motor recovery, muscle tone was higher, mean 1.58.

Discussion

Partial or even complete motor recovery of the upper extremity after initial paralysis represents an intriguing example of the recovery potential of the brain. Several mechanisms may account for motor recovery after stroke. In the early phase after the stroke, recovery from diaschisis, the resolution of edema, blood and toxic metabolic products, and the revascularization of penumbra have been suggested as the main factors. In the subacute and chronic phases, functional reorganization processes are supposed to contribute to motor recovery. MEPs, positron emission tomography, and more recently functional magnetic resonance imaging studies have shown increased activation of the unaffected motor cortex, increased activation of the supplementary and premotor areas of the affected hemisphere, and increased activity at the rim of the infarction (see for a recent review, Nudo et al., 2001[15]).

In the present cohort study, 14 patients (35%) showed motor recovery of the upper extremity, which is in accordance with previous studies[1,16]. As for the time window of motor recovery, the onset in all cases of motor recovery was within 4 months of the accident, and in some cases motor recovery proceeded throughout the complete follow-up period, confirming earlier studies concerning motor[16] and neurological recovery[17].

In the present study, the prognostic relevance of MEPs with respect to arm and hand motor recovery was obvious, which is in accordance with the paradigm that postinfarctional recovery is strongly dependent on a critical residual

sparing of corticospinal function. Apparently, this residual function can be detected in some cases during the subacute phase (present MEPs, subsequent motor recovery) by means of transcranial magnetical stimulation, and not by clinical evaluation. Moreover, there appeared to exist a strong association between the MEP amplitudes and the amplitude ratios and the week-26 arm and hand motor scores. In other cases, however, the sensitivity of the magnetical stimulation was insufficient to detect residual corticospinal function as the predictor for motor recovery. The lack of sensitivity in these cases may be the result of insufficient cortical stimulation in combination with the lack of facilitation by voluntary muscular contraction. On the other hand, recovery from diaschisis or functional cortical reorganization occurring after the first week poststroke may explain the low sensitivity of the early MEP registration.

The prognostic value of MEPs, and more specifically the sensitivity and specificity has been reported in other studies. In a recent systematic review, Hendricks et al.[18] analyzed the data from the methodologically most robust studies[7-9,19,20] and calculated the prognostic test properties of MEPs with respect to motor and functional recovery for different subgroups of patients (post hoc stratification according to initial deficits). For patients with paralysis or severe paresis (MRC 0-1) of the upper extremity at stroke onset, the specificity of MEPs for motor recovery appeared to be consistently very high across the studies (nearly 100%). The sensitivity, on the other hand, was relatively low. Our present study showed similar results. Since clinical examination on its own is unable to detect the potential for motor recovery, the added value of MEPs to predict motor recovery of the upper extremity has been established in these cases.

In contrast with earlier research, we have discriminated between arm and hand motor recovery. Within this context, most previous prognostic studies only assessed hand motor recovery from the relative narrow viewpoint that

functional abilities of the upper extremity rely completely upon hand motor functions, whereas many severely impaired patients use their paretic arm in a functional way as a support for the unaffected hand, without the highly selective fine motor functions of the affected hand. However, most functional gain will result from fine motor recovery of the hand in combination with gross motor recovery of the shoulder and arm.

In conclusion, the value of BB and ADM MEPs to predict arm and hand motor recovery and functional recovery in acute stroke patients with initial paralysis of the upper extremity, has been confirmed in this study. In particular, we could distinguish between arm and hand motor recovery. For patients with an initial upper extremity paralysis, the added value of MEPs to predict motor recovery of the upper extremity should be regarded as established. Further research should be undertaken to improve the test properties, in particular the sensitivity. Since patients with initial paralysis miss the possibility of facilitation by voluntary muscular contraction, paired-pulse stimulation might be used to generate sufficient facilitation to obtain a MEP response.

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CHAPTER 7

MOTOR EVOKED POTENTIALS OF THE LOWER EXTREMITY IN PREDICTING MOTOR RECOVERY AND AMBULATION AFTER STROKE: A COHORT STUDY

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Abstract

Objective: The prognostic value of motor evoked potentials (MEPs) of the lower extremity with respect to motor recovery and functional recovery in stroke patients.

Design: A cohort study.

Patients: 38 acute stroke patients with complete paralysis (paralysis subgroup) or severe paresis (paresis subgroup) of the lower extremity. MEPs of the vastus medialis muscle (VM) and the tibialis anterior muscle (TA) were performed between the 3rd and 10th day after stroke onset.

Outcome Measure: A separate proximal leg motor score (maximal 16 points) and crural motor score (maximal 2 points) was defined within the lower limb subset of the original Fugl-Meyer Motor Assessment to evaluate the motor performance at regular intervals until 6 months poststroke. The transfer item of the Barthel Index and the Functional Ambulation Categories were used to assess transfer and walking ability.

Results: For the paralysis subgroup (n=30), the follow-up was complete in 27 patients (two patients died and one patient underwent above knee amputation). At 26-week, 20 patients experienced proximal motor recovery (mean score was 11.70, standard deviation [SD] 4.48), and 12 of them also showed crural motor recovery (mean score 1.40, SD 0.51). Nine patients (33%) could perform an independent transfer safely and seven of this group (26%) learned to walk independently. Analysis revealed significant relationships for TA MEPs and motor recovery of crural leg muscles (Odds ratio [OR] 18.00, confidence interval [CI] 1.31-894.40), but not for VM MEPs and proximal motor recovery (OR 6.00, CI 0.53-303.00). No association between VM MEPs and recovery of ambulation was found. On the other hand, TA MEPs seem to provide a test with prognostic value with respect to the ability to perform independent transfers (OR 17.50, CI 1.36-267.00), but not for walking (OR 5.25, CI 0.40-77.57). Patients in the paresis subgroup experienced more favorable motor and functional recovery compared to the paralysis subgroup.

Conclusions: TA MEPs registered in subacute phase after stroke may contain important prognostic information, both for motor recovery of the crural muscles and for the ability to perform independent transfers in patients with initial complete paralysis of the lower extremity. VM MEPs were not predictive for motor and functional recovery.

Introduction

Standing and walking require highly integrated sensorimotor and perceptual functions of the central nervous system. Stroke may impair these functions, causing more or less severe postural imbalance and walking disability. The severity of lower extremity paresis represents an important determinant for the regaining of independent transfers and walking in severe stroke patients[1-3]. It has also been shown that the speed of hemiplegic gait is related to the muscle strength of the lower extremity[4,5]. Regarding the importance of early prediction for functional outcome, it is rather surprising that only few investigators have specifically assessed motor recovery of the lower extremity and its prognosis in an early phase after stroke onset[1,6]. The initial severity of motor deficits appears to be the most important predictor for motor recovery[1,7]. Even in the case of initial paralysis or severe paresis, some patients will show partial or complete motor recovery[1,6]. No clinical test exists that identifies the recovery potential in acute stroke patients with initial paralysis or severe paresis[7]. A reliable predictor for motor recovery of the upper extremity in an early phase after stroke onset is the presence of motor evoked potentials (MEPs) [8,9], see for a systematic literature review Hendricks et al.[10]. Only a few studies have assessed *lower* extremity MEPs in stroke patients[11,12,13], and to our knowledge, hardly any valid data concerning their predictive value with respect to motor and functional recovery in the early poststroke phase exist. Early insights in the potential for motor recovery in stroke patients with severe motor deficits of the lower extremity may be important for functional outcome, in particular for the regaining of independent ambulation[1,3], and these insights may support the clinician in

determining realistic therapy goals. Moreover, early valid prognostic information could be used to direct therapy in the subacute and the early chronic post stroke phase (e.g., prescription of orthotic devices and walking aids).

From this perspective, we conducted a cohort study (1) to assess the occurrence and the degree of motor recovery of proximal and crural muscles of the lower extremity in subacute stroke patients, with severe initial motor deficits of the lower extremity, and (2) to assess the predictive value of lower extremity MEPs with respect to motor recovery of proximal and distal muscles of the lower extremity, and functional recovery, in particular the ability to perform independent transfers and to walk.

Methods

Patients

Thirty-eight consecutive patients with acute ischemic stroke were recruited during a period of 1.5 years from the department of neurology at a university hospital. The study population comes from the region of Nijmegen, a middle-sized city in the eastern part of the Netherlands. The acute medical care for stroke patients is delivered by several hospitals, including the university hospital. Stroke patients are admitted in an unselected manner at these hospitals and therefore referral bias is not to be expected. Patients were included only if they exhibited severe motor deficits of the lower extremity at admission as measured by the lower limb subset of the Fugl-Meyer Motor Assessment (FMA)[14]. Severe motor deficits were defined as complete paralysis of the entire leg or paresis of the proximal leg muscles in combination with paralysis of the crural muscles. Paralysis was defined as no voluntary muscle contractions. Patients with poor prognosis for survival (loss of consciousness, severe CT disturbances, and severe co-morbidity) and patients with pre-existent impairments of the lower extremity were not included. Patients with a history of craniotomy, epilepsy, cardiac prosthetic

valve, pacemaker implantation, or severe polyneuropathies were also not included. Written informed consent was obtained from all patients (or their relatives) before study entry. The local ethical committee approved the study protocol. On admission, all patients underwent neurological examination and stroke severity was classified according to the Scandinavian Stroke Scale[15]. The diagnosis was confirmed by CT in all patients. The stroke localization was categorized as cortical, subcortical, the basal ganglia or the brain stem. The extend of the lesion was measured and classified as small (<2cm), moderate (2-5cm), extensive (5-10 cm), and very extensive (>10cm). The characteristics of the patients included (n=38) are shown in Table 1. All patients received standard medical treatment according to the guidelines of the Dutch Society of Neurology, including a multidisciplinary paramedical team approach. No specific therapy was initiated to improve motor recovery. If immediate home discharge was not possible, further treatment was given in either a rehabilitation center, a special therapy unit within a nursing home, or a standard nursing home.

Table 1. Characteristics of the patients, initial stroke severity, and CT findings

Gender (M/F)	21/17
Mean age (range)	65.57 (19-84)
Mean SSS score (range)	16.07 (2-37)
Infarct localization (n):	
Cortical	2
Subcortical	2
Cortical-subcortical	8
Basal ganglia	6
Subcortical-basal ganglia	4
Cortical-subcortical-basal ganglia	15
Brain stem	1
Infarct size (n):	
Small (<2cm)	4
Moderate (2-5cm)	13
Extensive (5-10cm)	16
Very Extensive (>10cm)	5

Abbreviations: M, male; F, female; SSS Scandinavian Stroke Scale[15].

Neurophysiological assessment

In all patients MEPs were performed between the 3rd and 10th day (mean and median 7.0 days) after stroke onset by the same researcher (JP). Patients were positioned comfortably in a supine position. Two self-adhesive recording

surface electrodes were placed 3 cm apart over the muscle bellies of the vastus medialis muscle (VM) and the tibialis anterior muscle (TA). These muscles were regarded as representants for proximal and distal motor functions of the leg. The MEPs were recorded using a Nicolet Viking or Oxford Synergy electromyograph. Bandpass filtering 20 Hz to 3 kHz, amplifier range 100mV and display sensitivity 0.5 mV/division. The VM and TA were studied both for the affected and unaffected side. Transcranial magnetic stimulation (TMS) was performed using a Magstim 200 magnetic stimulator with a 9 cm mean diameter circular coil. For cortical stimulation, the coil was placed in a tangential plane above the vertex. If no reproducible response was found at 80% of maximum stimulator output, the stimulation intensity was increased to 100% (maximum output). The left hemisphere was stimulated by a counter-clockwise current; the right hemisphere was stimulated by a clockwise current. The MEPs were recorded while the patient tried to perform a weak contraction of the muscle under investigation (contralateral to the side of cortical stimulation). Lumbar motor roots were stimulated by the same coil applied over the lumbar spine level with a stimulation intensity of 80% or 100%. Additionally, the peroneal nerve at the lateral popliteal fossa was electrically stimulated (supramaximal) in order to assess the maximal compound motor action potential (CMAP) of the TA. At least two responses were obtained in order to assess the reproducibility of the responses. The presence of a MEP was defined as a reproducible response with a minimal peak-to-peak amplitude of 200 μV. A 100-millisecond post-stimulus period was analyzed. Latencies were measured between the onset of the stimulus artifact and the onset of the first negative deflection from the baseline, excluding random EMG activity from voluntary contraction. The MEP latency after lumbar stimulation was taken as measure for the peripheral conduction. Total motor conduction time (TMCT) was the shortest latency between cortical stimulation and muscle response. Central motor conduction time (CMCT) was calculated by subtracting the peripheral latency from TMCT. The TA peak-peak amplitude of the response after cortical TMS was divided by the peak-peak-

amplitude of the CMAP after electrical stimulation to calculate an amplitude ratio. The test sequence was from distal (electrical stimulation of the peroneal nerve) to proximal (cortical stimulation).

Outcome assessment

Motor assessment was performed at week 1, 2, 3, 6, 12 and 26 by the lower limb subset of the FMA. This cumulative numerical scoring system is based on sequential recovery stages, that can be observed in hemiplegic patients. In accordance with the original assessment, the motor functions of the lower extremity were scored under standardized test conditions. Within the original assessment, we defined a proximal and a crural motor score, with maximal scores of 16 and 2 points, respectively (see addendum). Muscle tone at the knee was measured by the modified Ashworth scale[16]. Functional recovery was assessed at the level of mobility, in particular the ability to perform independent transfers and to walk. The transfer item of the Barthel Index (BI)[17] and the Functional Ambulation Categories (FAC)[18] were used to assess transfer and walking ability (see addendum). Clinical follow-up was performed by one of the authors (HH) who had no knowledge of either the MEPs results, nor the CT findings.

Analysis

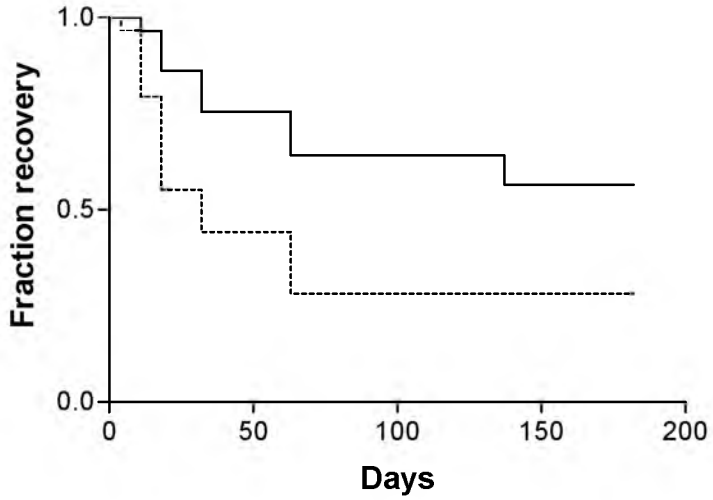
The occurrence of motor recovery of proximal and crural leg muscles as the main outcome parameters was expressed in a Kaplan Meier Curve. The MEP data were related to the occurrence of motor recovery and functional recovery in contingency tables. The distribution of numbers of patients within the cells was statistically assessed by the Fisher exact test. To quantify the prognostic significance, Odds ratios (ORs)and their 95% confidence intervals (CIs) were calculated.

Dichotomization of the outcome and the MEPs parameters was performed as follows. The MEP response was classified as being present (normal response

or delayed CMCT) or absent. The occurrence of motor recovery of the proximal and crural motor functions was classified as being present (motor scores of more than 0) or absent (motor score=0). The functional mobility items were dichotomized as follows. The ability to perform an independent bed to chair transfer (and back) was classified as being possible (BI transfer score=3) or not. The ability to walk independently on level ground was classified as being possible (FAC$\geq$4) or not.

The amplitude and the latency of present responses obtained from the affected side were compared with those obtained from the non-affected side and analyzed by the paired-samples t test. The relationship between the degree of motor recovery and the integrity of the MEPs was analyzed by the Pearson correlation coefficient.

Figure 1. Kaplan Meier Curves for motor recovery of the proximal and crural muscles of the lower extremity. Dotted line for motor recovery of the proximal muscles



Results

Of the included patients, 30 patients had complete leg paralysis at inclusion (paralysis subgroup), whereas eight patients exhibited a combination of paresis of proximal muscles with paralysis of the crural muscles (paresis subgroup). Two patients within the paralysis subgroup died within five and 20 days after stroke onset, respectively, and another patient underwent above knee

amputation (day-48) because of severe vasculopathy with ulceration at the heel. In the paresis subgroup one patient had a recurrent stroke (day-42). Twenty-seven patients of the paralysis subgroup and seven patients of the paresis subgroup completed the full follow-up period. The occurrence of motor recovery of proximal and crural leg muscles in the paralysis subgroup during the follow-up period is expressed in the Kaplan Meier Curves (Figure 1). Twenty patients showed motor recovery of proximal leg muscles and their mean 26-week proximal leg motor score was 11.70, range 2-16, standard deviation (SD) 4.48; 12 of these proximal recovery patients also exhibited crural motor recovery, and their mean score was 1.40 (range 1-2, SD 0.51). In all cases crural motor recovery was associated with proximal motor recovery. In 10 patients motor recovery occurred only in the proximal leg muscles and in seven patients the leg remained completely paralytic. For the patients who experienced motor recovery, it occurred within 6-weeks poststroke, except for three cases. In these three cases, the first signs of motor recovery were not seen until the 3-months assessment. Most recovery was seen within the first 3 months, although in some cases it proceeded throughout the complete follow-up period. At the MEP assessment only two patients showed proximal motor recovery, and none of the patients exhibited distal motor recovery at that moment.

Unfortunately, TA MEPs were not performed in four of the included patients. VM MEPs were performed in all cases. This implies that in 23 patients with complete 6-month follow-up, both TA and VM MEPs were performed. Table 2 shows the 26-week motor scores of the leg and the amplitudes and CMCTs for all patients in the paralysis subgroup, in whom motor recovery of the leg occurred, as well as all patients for whom leg MEPs could be elicited, without the occurrence of motor recovery. The relationships between the occurrence of motor recovery of the lower extremity and leg MEPs are shown in contingency tables (Table 3). In 10 from 11 patients for whom MEPs were present, subsequent motor recovery of proximal leg muscles occurred.

Table 2. The 26-week motor scores of the leg and the amplitudes and CMCTs for all patients in the paralysis subgroup, in whom motor recovery of the leg occurred, as well as all patients for whom leg MEPs could be elicited, without the occurrence of motor recovery

Patiënt number	Week-26 proximal leg motor score (0-16)	Amplitude (ratio) affected side	Amplitude (ratio) non-affected side	CMCT affected side (msec)	CMCT non-affected side (msec)
		VM amplitude	VM amplitude	VM	VM
1	12	Absent	-	-	-
2	16	Absent	-	-	-
4	14	1.00	2.00	13.40	13.60
5	15	Absent	-	-	-
6	12	Absent	-	-	-
8	14	0.30	7.80	20.20	12.90
9	4	0.30	2.30	21.10	17.10
11	4	0.30	5.20	17.50	17.60
13	13	0.20	3.90	20.75	16.50
14	12	Absent	-	-	-
15	16	0.60	3.10	17.30	13.55
16	11	0.20	3.00	24.45	15.95
17	4	Absent			
19	16	1.00	0.70	20.65	16.45
20	14	Absent	-	-	-
21	13	0.60	7.60	19.50	15.20
22	16	Absent	-	-	-
23	7	Absent	-	-	-
25	10	0.90	14.10	16.95	15.10
26	0	0.20	6.00	20.40	14.95
27	11	Absent	-	-	-
	Week-26 crural motor score (0-2)				
		TA amplitude ratio	TA amplitude Ratio	TA	TA
5	2	Absent	-	-	-
6	1	Absent	-	-	-
8	1	0.11	0.66	21.50	14.50
13	1	0.07	0.63	21.40	22.60
15	2	0.05	1.42	24.30	21.15
19	2	1.06	0.57	19.95	18.55
20	1	Absent	-	-	-
21	1	0.02	0.67	31.10	15.10
22	2	0.14	1.24	18.00	14.40
27	1	Absent	-	-	-
29	0	0.20	0.40	18.30	18.00

Abbreviations: VM, Vastus Medialis muscle; TA, Tibialis Anterior muscle; CMCT, Central Motor Conduction Time (see text for explanation); MEPs, Motor evoked potentials.

However, 10 of the 16 patients for whom MEP responses were absent also showed motor recovery. For the crural leg muscles, six of the seven patients for whom TA MEPs were present exhibited motor recovery, whereas only four of the 16 patients, for who TA MEPs were absent, showed motor recovery. Statistical analysis (Table 4) revealed significant relationships for TA MEPs and motor recovery of crural leg muscles (OR 18.00, CI 1.31-894.40*)*, but not for VM MEPs and proximal motor recovery (OR 6.00, CI 0.53-303.00).

Table 3. Contingency tables for MEPs and the occurrence of motor recovery of the proximal leg muscles and crural muscles at week 26, and functional recovery

	Motor recovery proximal leg muscles present	Motor recovery proximal leg muscles absent
VM MEPs present	10	1
VM MEPs absent	10	6

	Motor recovery crural muscles present	Motor recovery crural muscles absent
TA MEPs present	6	1
TA MEPs absent	4	12

	Independent transfers	No independent transfers
TA MEPs present	5	2
TA MEPs absent	2	14

	Independent walking	No independent walking
TA MEPs present	3	4
TA MEPs absent	2	14

Abbreviations: VM, Vastus Medialis muscle; TA, Tibialis Anterior muscle; MEPs, Motor evoked potentials.

The amplitudes and the CMCTs in patients, in whom responses could be elicited, were as follows. In 11 patients VM MEPs could be obtained from the affected side, and in seven of them, also TA MEPs (Table 2 and 3). The mean VM amplitude as obtained from the affected side was 0.54 mV (SD=0.33), compared to 5.18 mV (SD=3.95) for the non-affected side (p=0.005). The mean CMCT of the VM response for the affected and non-affected side was 19.15 msec (SD =2.99) and 15.22 msec (SD=1.59), respectively, p=0.002. The mean TA amplitude ratio of the affected side was 0.23 (SD=0.36), compared to 0.79 (SD=0.37) for the non-affected side (p=0.049). The mean CMCT of the TA response for the affected and non-affected side was 22.07 msec (SD=4.51) and 17.75 msec (SD=3.28), respectively, p=0.095.

The Pearson correlation coefficient between the amplitudes and amplitude ratios and the 26-week motor scores was calculated in patients in whom VM or TA MEPs could be elicited. A weak association was found between the VM MEP amplitudes and motor scores of the proximal leg (Pearson correlation coefficient 0.61; p=0.030). There was no association between the TA MEP

amplitudes and the crural motor scores (Pearson correlation coefficient 0.34; p=0.22).

Table 4. Relationships between lower extremity MEPs and the occurrence of motor recovery and functional recovery at 26-week

	p-value	Odds ratio	95% CI lower	upper
Motor recovery proximal leg muscles				
VM MEPs	0.091	6.00	0.53	303.00
Motor recovery crural leg muscles				
TA MEPs	0.009	18.00	1.31	894.40
Independent Transfers				
TA MEPs	0.005	17.50	1.36	267.00
Independent walking				
TA MEPs	0.071	5.25	0.40	77.57

Abbreviations: VM, Vastus Medialis muscle; TA, Tibialis Anterior muscle; MEPs, Motor Evoked Potentials; CI, confidence interval.

The results for recovery of ambulation in the paralysis subgroup were as follows. Nine patients (33%) could perform an independent transfer safely (transfer item BI score 3) at week 26; seven patients (26%) had also regained independent walking (FAC score 4 or 5). No association between VM MEPs and recovery of ambulation was found. On the other hand, TA MEPs seem to provide a test with prognostic value with respect to the ability to perform independent transfers (OR 17.50, CI 1.36-267.00), but not for walking (OR 5.25, CI 0.40-77.57), see Tables 3 and 4.

All patients within the paresis subgroup (seven patients with initial paresis of the proximal muscles and paralysis of the crural muscles) experienced crural motor recovery and their mean 26-week crural motor score was 1.57 (SD 0.20). Motor recovery of the proximal leg was nearly complete in all cases within this subgroup. The mean 26-week proximal leg score was 15.14 (SD 0.40). In four patients both VM and TA MEPs could be obtained. Within this subgroup, five patients regained independent transfers and walking abilities.

Increased muscle tone at follow up was seen in 12 patients (40%) within the paralysis subgroup and in three patients (43%) within the paresis subgroup.

Discussion

Motor functions of the lower extremity represent an important determinant for the ability to regain ambulation after stroke[1-3]. Based on this functional perspective we examined the potential for motor recovery in acute stroke patients with paralysis or severe paresis of the lower extremity at stroke completion. Compared to other studies, the recovery rate in our paralysis subgroup was rather high, 66% experienced recovery of proximal motor functions, and in 33% of the patients even crural motor recovery occurred (always in combination with proximal motor recovery). In a community-based study[1], motor recovery occurred in only 45% of the survivors who had had paralysis of the leg at admission in the hospital. The selection procedure and the longer follow-up period in our study may account for this difference. Most motor recovery was seen within the first 3 months, although it proceeded in some cases throughout the complete follow-up period, which confirms previous studies[1,6,7]. The prognosis concerning the recovery of ambulation appeared to be poor in the paralysis subgroup. Only 33% of the patients could perform an independent transfer at week 26 and 26% could walk independently on level ground. However, these percentages are comparable with earlier studies. A follow-up study[3] on the community-based study of Jorgenson et al.[1] showed that only 21% of the survivors, who had paralysis of the leg at admission in the hospital, achieved independent walking ability. Both motor and functional outcome was more favorable in the paresis subgroup, confirming previous research[1].

Most research concerning the prognostic value of MEPs after stroke has focused on motor recovery of the upper extremity[8-10,19,20,21]. Patients with initial paralysis or very severe paresis (MRC 0-1) of the upper extremity on admission, in whom motor responses of the hand muscles could be obtained

after cortical stimulation, were likely to experience motor recovery. Only few studies have addressed the prognostic value of upper extremity MEPs with respect to general functional recovery[8,9,22], and the results concerning the test specificity were inconsistent, probably in part due to different follow-up periods[10]. Timmerhuis et al.[22] compared the prognostic value of MEPs directly to an early functional score, and the authors found that functional outcome (as measured by the Barthel Index) was predicted best by the early functional score. In a recent study, Steube et al.[13] assessed the prognostic value of lower limb MEPs for impairment and disability in 100 stroke patients admitted in a rehabilitation center. MEPs were obtained from the anterior tibial muscle at four weeks or later after stroke onset. Patients with absent MEP response had lower motor scores at the beginning and the end of the rehabilitative treatment ($p<0.001$). However, no evidence for the predictive value of TA MEPs for functional recovery was found. In another prognostic study, D'Olhaberriague et al.[12] obtained MEPs from the hypothenar, biceps, brachialis, gastrocnemeus, and quadriceps muscles. The variables infarction size on second CT, age, and CMCT of the gastrocnemeus correctly classified 1-year outcome on discriminant analysis.

We assessed specifically the prognostic value of lower extremity MEPs with respect to motor recovery of the lower extremity and the ability of independent transfers and walking in an early phase after the stroke. A patient sample was selected with very severe motor deficits of the lower extremity, since clinical examination alone cannot detect the potential for motor recovery in this subgroup[7]. There appeared to exist no clear association between VM MEPs and the occurrence of motor recovery of proximal leg muscles, indicating that proximal leg motor recovery occurs relatively independent from residual corticospinal function. TA MEPs, on the other hand, were predictive for subsequent crural motor recovery and even functional recovery (the ability to perform independent transfers). However, both for motor and functional recovery the ORs showed wide confidence intervals, indicating that the

evidence should be regarded as preliminary. There appeared to exist only a weak correlation between the VM MEP amplitudes and motor scores of the proximal leg and no correlation between the TA MEP amplitudes and the crural motor scores, indicating that the degree of leg motor recovery cannot be predicted simply by the magnitude of the MEP amplitude (ratio) solely. The CMCT should probably also taken into account. However, the number of patients in whom a MEP response could be elicited were too small in our study to assess properly the relationship between amplitude ratio, CMCT and subsequent motor recovery.

The prognostic use of MEPs in acute stroke patients is still relatively uncommon on some comments on the risks should be made. The safety of TMS has been assessed[23,24] in several studies and it appeared to be a well-tolerated safe method. Epilepsy, previous neurosurgery, cardiac prosthetic valve and pacemaker implantation should be regarded as contraindications[25].

In conclusion, even in the case of severe initial motor deficits of the lower extremity, there seems to exist considerable potential for motor recovery, particularly for proximal leg muscles. TA MEPs registered during the first week after stroke onset may contain important prognostic information, both for motor recovery of crural muscles and for the ability to perform independent transfers. VM MEPs were not predictive for motor and functional recovery. The evidence concerning lower extremity MEPs in predicting motor and functional outcome after stroke is still limited and further research should be initiated to confirm our preliminary results.

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Addendum

Proximal leg motor score.

Flexor synergy

The patient in supine position is instructed to flex the hip-, knee-, and ankle joints maximally. Usually at the same time the hip will be abducted and outwardly rotated. During this motion, the distal tendons of the knee flexors are palpated to ascertain that active flexion of the knee occurs.

Score: 0: the specific detail cannot be performed; 1: the detail can be performed only partly; 2: the detail is performed throughout the total range of motion of each of the three joints.

Extensor synergy

At the end points of the flexor synergy, the patient should extend his hip-, knee-, and ankle joints, resistance being exerted in order to eliminate gravitational facilitation of the maneuver. Hip adduction against resistance is also performed. (The hip adduction may be evaluated in combination with hip extension.)

Score: 0: the specific detail cannot be performed; 1: some little strength; 2: normal or nearly normal strength (compared with the unaffected limp).

The patient in sitting position, knees free from the side of the bed or the chair is asked to flex his knee beyond 90°.

Score: 0: no active motion; 1: from a somewhat extended position, the knee can actively be flexed towards but not beyond 90° (simultaneously the tendons of the hamstrings are palpated; 2: the knee can be flexed beyond 90°.

Maximum proximal leg motor score: 16

Crural motor score.

From the same sitting position, the patient is asked to dorsiflex his ankle.

Scores: 0: cannot; 1: impaired active flexion; 2: normal dorsiflexion compared **with** the unaffected side.

Maximum crural motor score: 2

Transfer item of the Barthel Index

0: unable (no sitting balance)
1: major help (one strong skilled or two people, the patient can sit)
2: minor help (one person easily or supervision)
3: independent

Functional Ambulation Categories

3: Patient requires verbal supervision or stand-by help from one person without physical contact. (Category dependent- supervision)
4: Patient can walk independently on level ground, but requires help on stairs, slopes or uneven surfaces. (Category independent- on level ground)
5: Patient can walk independently anywhere. (Category independent)

CHAPTER 8

ANALYSIS OF RECOVERY PROCESSES AFTER STROKE BY MEANS OF TRANSCRANIAL MAGNETIC STIMULATION

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Submitted

Abstract

Objective: Motor evoked potentials (MEPs) to analyze the integrity of fast corticospinal functions as the neurophysiological basis for motor recovery in stroke patients.

Methods: A cohort study including 44 acute stroke patients with paralysis of the upper and or the lower extremity. MEPs of the abductor digiti minimi muscle (ADM), the biceps brachii muscle (BB), the vastus medialis muscle (VM) and the tibialis anterior muscle (TA) were performed within 10 days (mean 6.9, median 7) and 40 days (mean 27.8, median 25) after stroke onset. A separate score was defined for proximal and distal motor functions of the upper and lower extremity within the original Fugl-Meyer Motor Assessment. Motor performance was evaluated simultaneously with the MEP assessments and at 26-weeks poststroke.

Results: For all the muscles in which a response was present at the first investigation, obvious recovery of the fast corticospinal functions occurred. For the ADM amplitude ratio and the VM MEP amplitude the differences between the two investigations were statistically significant. A MEP response could be elicited in more cases on the second than on the first MEP assessment. A present MEP response at the first registration indicated nearly always subsequent motor recovery, both for proximal and distal motor functions of the upper and lower extremity. However, motor recovery was also observed in some patients for whom no MEP response could be elicited. Regression analysis showed significant relationships between the ADM and BB MEP amplitude parameters and the 26-week hand and arm motor scores. No relationship existed between the TA and VM MEP parameters and the leg motor scores.

Conclusions: Motor recovery manifests neurophysiologically often as the recovery of fast corticospinal functions. In many cases, assessment by MEPs is more sensitive than clinical examination to detect residual corticospinal functions, which forms the pathofysiological basis for the predictive value of MEPs for motor recovery after stroke.

Introduction

More than 80% of all acute stroke patients exhibit motor deficits with various degrees of severity[1]. Motor recovery occurs in most cases[1,2], and is more favorable in proximal than in distal muscles[3]. The occurrence of motor recovery illustrates the considerable recovery potential of the human brain, particularly in the case of complete paralysis of the affected extremity. In the early poststroke phase, the reversal of diaschisis, the resolution of edema, blood and toxic metabolic products, and the survival of ischemic penumbra have been suggested as the main pathofysiological processes responsible for short-term motor recovery. During the more chronic phases, functional reorganization processes are supposed to contribute to motor recovery; see for recent reviews Nudo et al., 2001[4] and Rossini and Pauri, 2000[5]. Despite the extensive research, the neurophysiological processes that account for motor recovery are not completely understood.

Transcranial magnetic stimulation (TMS) is a noninvasive neurophysiological technique, in which motor potentials are evoked by means of magnetical stimulation of the motor cortex. This procedure allows an objective and quantifiable assessment of the motor pathways within the central nervous system. It is assumed that TMS discharges the fast corticospinal connections involved in voluntary activation.

TMS has been used in the study of prognosis after stroke. Motor evoked potentials (MEPs) obtained from arm and hand muscles in an early phase after the stroke appeared to be predictive for arm and hand motor recovery[6-10]. Lower extremity MEPs have also been studied in the prognosis of motor and functional outcome[11,12]. However, the pathofysiological basis for the predictive value of MEPs has not been explored extensively.

The present study concerns a repeated investigation of the interhemispheric differences of MEP parameters for the proximal and distal muscles of the

upper and lower extremity, in a homogeneous sample of stroke patients with complete paralysis of the upper and or the lower extremity. The aim of the study was to assess the recovery of fast corticospinal functions as the neurophysiological manifestation of motor recovery in stroke patients. Furthermore we assessed the relationship between the MEP parameters and the clinical motor scores for proximal and distal motor functions of the upper and lower extremity.

Methods

Patients

Forty-four consecutive patients with acute ischemic stroke were recruited for 1.5 years from the department of neurology of a university hospital. Patients were included only if they had had a stroke with complete paralysis of the upper and or the lower extremity. Patients with poor prognosis for survival (loss of consciousness, or severe co-morbidity) and patients with pre-existent impairments or disabilities of the extremities were not included. Patients with a history of craniotomy, epilepsy, cardiac prosthetic valve, pacemaker implantation, or severe polyneuropathies were also not included. Written informed consent was obtained from all patients before study entry. The local ethical committee approved the study protocol. All patients had neurological examination on admission and stroke severity was classified according to the Scandinavian Stroke Scale[13]. Computed tomography (CT) was performed on admission and after one week. The stroke localization was categorized as cortical, subcortical, the basal ganglia, or the brain stem. The extend of the lesion was measured and classified as small (<2cm), moderate (2-5cm), extensive (5-10 cm), and very extensive (>10cm). The characteristics of all included patients are shown in Table 1. All patients received standard medical treatment according to the guidelines of the Dutch Society of Neurology, including a multidisciplinary paramedical team approach. If immediate home discharge was not possible, further treatment was given in either a

rehabilitation center, a special therapy unit within a nursing home or a standard nursing home.

Table 1. Characteristics of the patients, initial stroke severity, and CT findings

Gender (M/F)	21/22
Mean age in years (range)	66.93 (19-84)
Mean SSS score (range)	16.97 (2-32)
Infarct localization (n):	
Cortical	3
Subcortical	1
Cortical-subcortical	11
Basal ganglia	7
Subcortical-basal ganglia	5
Cortical-subcortical-basal ganglia	16
Brain stem	1
Infarct size (n):	
Small (<2cm)	2
Moderate (2-5cm)	18
Extensive (5-10cm)	20
Very Extensive (>10cm)	4

Abbreviations: M, male; F, female; SSS, Scandinavian Stroke Scale.

Neurophysiological assessment

Patients were assessed by TMS within 10 days (mean 6.9, median 7) (t1) and 42 days (mean 27.8, median 25) (t2) after stroke onset. The same researcher (JP) performed all the recordings. Patients were positioned comfortably in a supine position. Two self-adhesive recording surface electrodes were placed 3 cm apart over the muscle bellies of the abductor digiti minimi muscle (ADM), the biceps brachii muscle (BB), the vastus medialis muscle (VM), and the tibialis anterior muscle (TA). ADM and TA were regarded as representative of distal motor functions, and BB and VM of proximal motor functions. The MEPs were recorded using a Nicolet Viking or Oxford Synergy electromyograph. Band-pass filter 20 Hz- 3 kHz, amplifier range 100 mV and display sensitivity of 0.5 mV/division. The muscles were studied separately for both the affected and unaffected side. Data from the unaffected side were compared to normative data and used as control. The MEP data from the unaffected side felt within the range of normative data. Transcranial magnetic stimulation (TMS) was performed using a Magstim 200 magnetic stimulator with a 9-cm mean diameter circular coil. For cortical stimulation the coil was

placed in a tangential plane above the vertex. Stimulation intensity was set at 80% of maximum stimulator output. If no reproducible response was found, the stimulation intensity was increased to 100% (maximum output). The left hemisphere was stimulated by a counter-clockwise current; the right hemisphere was stimulated by a clockwise current. Cervical motor roots were stimulated by the same coil applied over the seventh cervical spinal level with a stimulation intensity of 80% or 100%. Additionally, the ulnar nerve and the peroneal nerve were stimulated electrically (supramaximal) at the wrist and at the lateral popliteal fossa, respectively, in order to assess the maximal compound motor action potential (CMAP). The MEPs after cortical stimulation were recorded while the patient tried to perform a weak contraction of the contralateral muscle (i.e., the muscle under investigation). At least 2 responses were obtained to assess the reproducibility of the responses. The presence of a MEP was defined as a reproducible response with minimal peak-to-peak amplitude of 200 μV. A 100-millisecond post-stimulus period was analyzed. Latencies were measured between the onset of the stimulus artifact and the onset of the first negative deflection from the baseline, excluding random EMG activity when the MEPs were recorded during voluntary contraction. The MEP latency after cervical stimulation was taken as measure for the peripheral conduction. Total motor conduction time (TMCT) was the shortest latency between cortical stimulation and muscle response. Central motor conduction time (CMCT) was calculated by subtracting the peripheral latency from TMCT. The ADM and the TA peak-peak amplitude after cortical stimulation were divided by the peak-peak-amplitude of the CMAP after electrical stimulation to calculate an amplitude ratio. The test sequence was from distal (electrical stimulation) to proximal (TMS).

Motor assessment

Motor assessment was performed at the first (t1) and the second (t2) MEP investigation, and regularly during follow-up until the 26-week (t3). We

defined a separate motor score for the proximal and distal motor functions within the upper and lower limb subset of the Fugl-Meyer Motor Assessment (FMA)[14]. This cumulative numerical scoring system is based on the sequential recovery stages that can be observed in hemiplegic patients. In accordance with the original assessment, the motor functions were scored under standardized test conditions. For the upper extremity, the proximal arm score included motor functions of the shoulder, elbow and forearm, with a maximum score of 30 points, whereas the hand score concerned the 7 original hand items of the FMA with a maximum of 14 points. For the lower extremity, the proximal leg motor score included motor functions of the hip and knee, with a maximum score of 16 points, whereas the crural score concerned dorsiflexion at the ankle (maximal score, 2 points). According to the inclusion criteria, all patients had an entry motor score for proximal and distal motor functions of the upper and lower extremity of 0 points. Clinical follow-up was performed by one of the authors (HH) who was not aware of the MEPs results, or the CT findings.

Analysis

The paired t test was used to compare the amplitudes, the amplitude ratios and the CMCTs of the affected with the non-affected side. The differences of the amplitudes and the amplitude ratios and the CMCTs between the first and second MEP investigation were also assessed by the paired t test. Regression analysis was performed to assess the relationship between MEP parameter and the 26-week motor scores, in patients in whom MEP responses were present at the first and or the second investigation.

Results

Of the initially included patients, 43 had complete paralysis of the upper extremity and 30 had complete paralysis of the lower extremity. Two patients died at day-5 and day-26, respectively. One patient had a recurrent stroke at day-42, and another patient underwent above knee amputation (day-48)

because of severe vasculopathy with ulceration at the heel. The follow-up was thus complete for 40 patients with initial paralysis of the upper extremity, and for 27 patients with paralysis of the lower extremity. Unfortunately, TA MEPs were not performed in four of the included patients. Four patients refused second MEP assessment.

Table 2. The amplitude ratios, the amplitudes, and the CMCTs for patients in whom responses were present at the first and or the second MEP assessment

		MEP Assessment	Affected		Non-affected		Significance
		1st /2nd	Mean	SD	Mean	SD	P
ADM	**Mean amplitude ratio**	**1st**	.27	.23	.57	.15	.006
		2nd	.29	.26	.63	.17	.002
	CMCT (msec)	**1st**	8.43	2.81	6.76	1.91	.093
		2nd	8.06	2.14	6.74	2.24	.106
BB	**Mean amplitude (mV)**	**1st**	1.78	1.55	5.97	4.88	.010
		2nd	1.68	1.71	6.24	3.21	.000
	CMCT (msec)	**1st**	16.21	14.95	6.03	1.61	.027
		2nd	16.50	15.03	6.08	1.83	.008
	Mean amplitude ratio	**1st**	.23	.36	.79	.37	.049
		2nd	.37	.34	.84	.45	.009
	CMCT (msec)	**1st**	22.07	4.51	17.76	3.28	.048
		2nd	22.00	3.83	16.92	2.97	.001
VM	**Mean amplitude (mV)**	**1st**	.54	.33	5.18	3.95	.001
		2nd	.84	1.00	4.03	2.27	.000
	CMCT (msec)	**1st**	19.15	2.85	15.22	1.59	.002
		2nd	18.73	5.92	13.88	2.78	.003

Abbreviations: ADM, Abductor digiti minimi muscle; BB, Biceps brachii muscle; TA, Tibialis anterior muscle; VM, vastus medialis muscle; MEP, Motor evoked potential; CMCT, Central motor conduction time; SD, Standard Deviation.

In many cases, no response could be elicited after maximal stimulation of the affected hemisphere. In patients for whom responses were present at the first and or the second MEP assessment, evident interhemispheric differences were measured for the amplitude ratios, the amplitudes, and the CMCTs (Table 2).

The relationships between the MEP assessments and the presence of motor recovery at t1 and t2 are expressed in contingency tables, as well as the relationships between MEPs and the presence of motor recovery at 26-week

Table 3. Contingency tables for the relationships between MEPs (first and second assessment) and the presence of motor recovery at t1 and t2, and the relationships between MEPs (first and second assessment) and the presence of motor recovery at 26-week follow-up (t3)

	1st MEP		2nd MEP	
	RECOVERY T1		RECOVERY T2	
ADM	YES	NO	YES	NO
YES	2	5	5	5
NO	1	32	0	26
BB				
YES	2	8	7	9
NO	2	28	1	19
TA				
YES	0	7	3	10
NO	0	16	0	7
VM				
YES	0	11	9	8
NO	2	14	3	4

	1st MEP		2nd MEP	
	RECOVERY T3		RECOVERY T3	
ADM	YES	NO	YES	NO
YES	6	1	8	2
NO	5	28	2	24
BB				
YES	8	2	10	6
NO	6	24	3	17
TA				
YES	6	1	9	4
NO	4	12	0	7
VM				
YES	10	1	14	3
NO	10	6	4	3

Abbreviations: ADM, Abductor digiti minimi muscle; BB, Biceps brachii muscle; TA, Tibialis anterior muscle; VM, vastus medialis muscle.

follow-up (Table 3). The results of the regression analysis are shown in table 4. Detailed results were as follows.

ADM MEPs

At the first and second MEP registration, 7 patients (18%) and 10 patients (28%) had a present ADM response, respectively. In the 7 patients with a present response at the first assessment, the amplitude ratio of the affected side increased from 0.27 (SD [Standard Deviation]=0.23) to 0.38 (SD=0.24) on the second assessment, p=0.028. The CMCT decreased from 8.43 msec (SD=2.81) to 8.17 msec (SD=2.43), p=0.314.

The relationships between ADM MEPs and the presence of hand motor recovery are shown in Table 3. Two of the 7 patients, in whom the ADM response was present at the initial assessment, showed hand motor recovery at

that moment and 4 patients still had complete hand paralysis. However, 6 of the 7 patients, for whom the ADM response was initial present, exhibited hand motor recovery at the 26-week motor assessment. At the second MEP assessment, 5 of the 10 patients in whom the response was present showed hand motor recovery, whereas ultimately 8 of these 10 patients exhibited hand motor recovery at 26-week motor assessment. Two patients exhibited hand motor recovery during follow-up, but had no ADM response at t1 or t2. Another patient exhibited already hand motor recovery at t1, but had no ADM response. Unfortunately she refused second MEP investigation. Her 26-week hand motor score was maximal.

Regression analysis (Table 4) showed that both the amplitude ratio at t1 and at t2 had a significant relationship with the 26-week hand motor score, however, the relationship at t2 was more evident. Figure 1 illustrates the relationship between the ADM amplitude ratios on the first and second investigation, and the chronologically (t1, t2, 26-week) measured motor scores.

BB MEPS

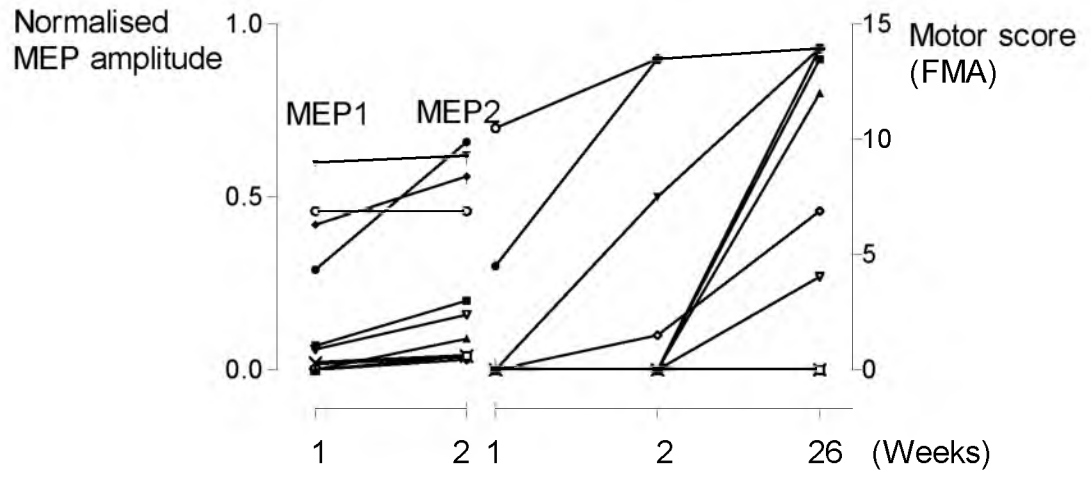
For BB, MEPs could be obtained in 10 (25%) and 16 patients (40%) from the affected side on the first and second investigation, respectively. In the 10 patients with a present response at the first assessment, the mean amplitude of the affected side increased from 1.78 mV (SD=1.55) to 2.17 mV (SD=1.97) on the second assessment, p= 0.210. The CMCT decreased from 16.21 msec (SD=14.95) to 9.47 msec (SD=2.74), p=0.140.

Table 3 shows the relationships between BB MEPs and the presence of arm motor recovery. Only 2 of the 10 patients, in whom a BB response could be elicited at the initial assessment, showed arm motor recovery at that moment, whereas 8 of these 10 patients exhibited arm motor recovery at the 26-week motor assessment. At the second MEP registration, 6 of the 16 patients with a present response showed arm motor recovery at that moment, and 10 patients

still had complete arm paralysis. Ultimately, 10 of the 16 patients with present BB response at the second investigation exhibited arm motor recovery at follow-up. Three patients exhibited motor recovery during follow-up, but had no responses at t1 or t2. Two patients exhibited already arm motor recovery at t1, but had no BB response. One of these had a MEP response at t2; the other patient refused second MEP investigation. Her 26-week arm motor score was maximal.

Regression analysis (Table 4) showed that both the BB amplitude at t1 and t2 had significant relationships with the 26-week arm motor score, p=0.000 and p= 0.012, respectively.

Figure 1. Relationships between MEPs and motor scores



Amplitude ratios of the abductor digiti minimi muscle after stimulation of the affected side at the first and second MEP investigation, in combination with the hand motor scores at the MEP investigations and at 26-week.

TA MEPs

At the first and second MEP registration a TA response could be obtained in 7 patients (30%) and 13 patients (65%), respectively. In the 7 patients with a present response at the first assessment, the amplitude ratio of the affected side increased from 0.24 (SD=0.37) to 0.45 (SD=0.17) on the second assessment,

p=0.150. The CMCT decreased from 22.07 msec (SD=4.51) to 20.20 msec (SD=1.77), p=0.200.

Table 4. Regression analysis

		Unstandardized Coefficients		Standardized Coefficients	t	Sign. level
		B	Std. Error	Beta		
Hand Model	(Constant)	5.996	2.021		2.966	.009
	ADM1	17.186	6.953	.658	2.472	.020
	Constant	4.425	2.080		2.128	0.009
	ADM 2	17.11	5.528	0.738	3.095	0.004
Arm Model	Constant	3.961	2.127	0.789	1.862	0.042
	BB1	3.820	0.796	4.802	0.000	0.000
	Constant	3.277	3.415		0.960	0.036
	BB2	3.701	1.445	0.565	2.561	*0.012*
Distal leg Model	Constant	0.773	0.216		3.571	0.002
	TA 1	1.187	0.713	0.449	1.665	0.062
	Constant	1.023	0.325		3.152	0.005
	TA 2	-0.268	0.643	-0.124	-0.416	0.343
Proximal leg Model	Constant	8.556	1.646		5.199	0.000
	VM 1	4.897	3.642	0.310	0.310	0.098
	Constant	9.942	1.384		7.185	0.000
	VM 2	9.743	0.006	0.004	0.017	0.493

Abbreviations: ADM, Abductor digiti minimi muscle at the first (1) and second (2) MEP registration; BB, Biceps brachii muscle; TA, Tibialis anterior muscle; VM, vastus medialis muscle; Std. Error, Standard error.

Table 3 shows the relationships between TA MEPs and the presence of crural motor recovery. None of the 7 patients, in whom a TA response could be elicited at the initial assessment, showed crural motor recovery at that moment, whereas 6 of these 7 patients exhibited crural motor recovery at the 26-week motor assessment. At the second assessment, 3 of the 13 patients with a present response showed crural motor recovery, and ultimately 9 of these 13 patients exhibited crural motor recovery at follow-up. One patient exhibited motor recovery during follow-up, but had no responses at t1 or t2.

No relationship was found between the TA MEP parameters and the 26-week crural motor scores (Table 4).

VM MEPs

At the first and second MEP registration 11 patients (41%) and 17 patients (71%) had a present VM response, respectively. In the 10 patients with a present response at the first assessment, the amplitude of the affected side increased from 0.54 mV (SD=0.33) to 1.20 (SD=1.24) on the second assessment, p=0.032. The CMCT decreased from 19.14 msec (SD=2.85) to 19.22 msec (SD=7.45), p=0.450.

Table 3 shows the relationships between VM MEPs and the presence of motor recovery. None of the 11 patients, in whom a VM response could be elicited at the initial assessment, showed proximal leg motor recovery at that moment, whereas 10 of these 11 patients exhibited proximal motor recovery of the leg at the 26-week motor assessment. Two patients with proximal motor recovery of the leg at t1 had no initial VM MEP. At the second assessment, 9 of the 17 patients with a present response exhibited proximal motor recovery of the leg at that moment, and ultimately 14 of these 17 patients exhibited proximal leg motor recovery. Three patients exhibited motor recovery during follow-up, but had no responses at t1 or t2.

No relationship was found between the VM MEP parameters and the 26-week proximal leg motor scores (Table 4).

Discussion

Partial or even complete motor recovery after initial paralysis represents an intriguing example of the recovery potential of the brain. The objectives of the present study were to assess neurophysiological recovery processes, and to explore the prognostic value of TMS with respect to recovery of proximal and distal motor functions of the upper and lower extremity.

The recovery of fast corticospinal functions was evident for the muscles studied. The amplitude ratios and the amplitudes improved substantially in

those patients in whom a MEP response could be elicited at the initial assessment. For the ADM amplitude ratio and the VM MEP amplitude the differences between the two investigations were statistically significant. Moreover, for all the muscles studied, a MEP response could be elicited in more cases on the second than on the first MEP assessment. These findings are in accordance with previous studies[6,15]. Heald et al.[6] studied the MEPs of the pectoralis major, biceps and triceps brachii, and thenar muscles sequentially in 118 first-ever stroke patients during a one-year follow-up. Decreased MEP amplitudes returned to normal, and on some occasions initially absent MEPs reappeared. The threshold to stimulation decreased at the follow-up investigations. Traversa et al.[15] used brain mapping by TMS to study functional reorganization of brain motor output longitudinally in 15 subacute stroke patients. The brain motor output area was significantly enlarged on the second versus the first assessment, as well as the MEP amplitudes. The CMCT improvements in our study were also comparable with previous research[6]. Compared to earlier studies we have assessed neurohysiological recovery in a homogeneous sample of stroke patients with complete paralysis of the affected extremity at onset, whose prognosis for subsequent motor recovery is generally poor[2,16]. We observed evident neurophysiological and motor recovery in several patients, both for proximal and distal muscles of the upper and lower extremity.

A recent systematic review for the early prediction of motor and functional outcome after stroke[17] showed obvious evidence for the prognostic value of MEPs. As for the prognostic test properties, the results of this review were as follows. The specificity for predicting motor recovery of the upper extremity was consistently very high for subgroups of patients with paralysis or severe paresis. The sensitivity, on the other hand, was rather low. The present study yielded some interesting findings within this context. A substantial proportion of the patients had a present response for some of the studied muscles at the first MEP investigation (t1), without the ability to contract those muscles

voluntary at that moment. Nevertheless, nearly all muscles that generated motor potentials after cortical stimulation at t1 showed ultimately motor recovery. This was observed both for proximal and distal muscles of the arm and leg. Apparently, the residual fast corticospinal functions as detected by MEPs were insufficient to exert any voluntary movements at t1. The fast corticospinal functions improved during follow-up, and at any moment voluntary movements became possible. The neurophysiological and the clinical data at t2 provide evidence for this course.

Several mechanisms may explain the dissociation between clinical and neurophysiological data at t1. First of all, the nonphysiological volley of electromagnetic transcranial stimulation might have evoked potentials in the muscles studied, whereas the physiological voluntary innervation was not possible at that moment. Furthermore, severe apraxia or motor neglect at t1 might have impeded voluntary movements. Although we performed no formal tests for cognitive functions, severe apraxia was observed in some of the patients who had present arm MEPs at t1, but were incapable to perform voluntary arm and hand movements.

On the other hand, in some patients no MEP response could be elicited for a given muscle at t1and t2, yet partial or even complete recovery of the related motor functions occurred. This phenomenon was most frequently observed for BB and VM MEPs and recovery of proximal motor functions. Several mechanisms might have accounted for this observation. First of all, long-term corticospinal recovery, occurring after t1 and t2, may explain the absence of early MEP responses in some cases. The recovery profiles of 2 patients in our study underline this explanation. In both patients arm and hand motor recovery occurred after t2. Furthermore, the observed motor recovery in some occasions could have been of non-corticospinal origin, which has particularly been described for the recovery of proximal motor functions[18]. Several alternative motor pathways have been described, including small, slowly conducting

corticospinal neurones[19] and indirect corticoreticulospinal pathways. The difference between proximal and distal motor functions within this context may also be explained by the fact that the fast corticospinal system exerts more influence on distal than on proximal muscles[20].

Regression analysis showed significant relationships between the ADM amplitude ratios and the 26-week hand motor score, and between the BB amplitudes and the 26-week arm motor scores. No relationship existed between the TA and VM MEP parameters and the crural and proximal leg motor scores. This finding confirms the paradigm that motor functions of the upper extremity are more dependent on the integrity of the fast corticospinal functions than the lower extremity.

In only few occasions present MEP at t1 was associated with absent motor recovery at follow-up. Absent response at t2, while the first investigation showed a present MEP was also seen. Nonsurvival of ischemic penumbra or subclinical recurrent stroke may have occurred in these cases. For all the muscles studied, a MEP response could be elicited in more cases on the second than on the first MEP assessment.

In conclusion, motor recovery manifests neurophysiologically often as the recovery of fast corticospinal functions. In many cases, neurophysiological assessment by MEPs is more sensitive than clinical examination to detect residual corticospinal functions, which forms the basis for the prognostic use of MEPs for motor recovery of the upper and lower extremity in stroke patients.

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CHAPTER 9

GENERAL DISCUSSION AND FINAL REMARKS

Strokes are one of the most frequently occurring disabling diseases in the western world. Early prediction of functional outcome represents an important topic in stroke management and related research. Several biological and non-biological variables may be predictors of general functional recovery, including neurological impairments[1-4]. For instance, the initial grade of paresis is an important predictor for motor recovery and subsequent functional recovery[2,3]. However, particularly in non-cooperative patients or severely cognitively impaired patients (i.e. global aphasia, attention deficits, apraxia and neglect), the clinical neurological examination may be invalid and thus inconclusive with respect to prognosis. Moreover, in case of initial paralysis, clinical examination alone lacks the possibility to detect the potential for motor recovery. From this perspective we have addressed the use of motor evoked potentials (MEPs) in predicting motor and functional outcome after strokes in this thesis, according to the paradigm that postinfarctional recovery is strongly dependent on a critical residual sparing of corticospinal functions, which can be detected most properly by MEPs. Motor potentials are evoked by means of noninvasive magnetical stimulation of the motor cortex and assess objectively and quantitatively the integrity of the motor pathways.

Both pilot studies in the first part of the thesis indicated the predictive value of somatosensory evoked potentials (SEPs) and MEPs for motor recovery of the upper extremity in subacute stroke patients with initial paralysis. Compared to SEPs, the predictive power of MEPs appeared to be more favorable.

The systematic methodological approach that we used in both studies of the second part of the thesis has been appreciated as a valuable research tool in the last years. However, some issues concerning our reviews should be addressed. First of all, the search. Our search was performed by using primarily electronic databases. It has been shown that by this strategy not all relevant studies might be retrieved (non-inclusion in the electronic databases) and it has been recommended to contact known experts[5]. We did not contact other authors to

find all relevant references. The language restriction should also be mentioned, although we presume that nearly all studies are published in English. A more serious problem concerns publication bias[6], the selective publication of studies based on the magnitude and the direction of their findings. For observational studies, if potential confounders yield negative results, they are usually not published. Furthermore, replication studies might not have been published in the international journals, as they do not add anything new to existing knowledge (claimed by editors). Publication bias may have favored the use of evoked potentials. The assessment of the methodological quality of the retrieved studies represents another important issue. There is no generally accepted checklist for critical appraisal of the validity of observational studies. We have constructed our checklist according to a system that was originally developed for evaluating randomized controlled trials, with some specific adaptations. This implies that our system lacks demonstrated validity. However, we have sought to control for known bias within control studies. Finally, the data-analysis should be discussed. Methodological reasoning revealed important sources for clinical heterogeneity and we have concluded that meta-analysis was not possible[7,8]. Summary estimates could thus not be calculated. We have used the data from the primary studies to construct 2x2 tables and to calculate the test properties and the Odds ratios (ORs) with their confidence intervals (CIs). This approach is insufficient to detect dose-response relations (MEP amplitudes and degree of motor recovery). Furthermore, the role of confounders cannot be detected properly.

However, our approach generated valuable information concerning the central issue of the thesis. First of all, the evidence concerning the predictive value of MEPs appeared to be still rather limited. Many studies retrieved by the search did not fulfill the basic methodological criteria for prognostic studies[9,10] and had to be disqualified for quantitative analysis. Nevertheless, analysis of the data from the finally selected studies showed evidence for the prognostic value of MEPs for both motor and functional recovery, although the confidence

intervals for the prognostic test properties and the ORs were rather wide. Compared to clinical examination the predictive power of MEPs with respect to motor recovery of the upper extremity is much higher. The prognostic test properties of MEPs could be established for different groups of patients. Most consistent were the findings for the predictive value of MEPs for motor outcome in patients with initial paralysis or severe paresis of the upper extremity: the specificity was consistently very high, the sensitivity, on the other hand, was rather low and highly variable in the selected studies. For patients with initial paresis, the data were not uniform. The dichotomization of the MEP data in our analysis might have caused an important loss of prognostic information. With respect to functional recovery, quantitative analysis revealed consistent values for the sensitivity, whereas the values for the specificity were rather inconsistent.

In the last part of the thesis we have further explored the central issue of the thesis by prospective cohort studies. The robust methodological approach of logistic regression was used to assess the predictive value of MEPs for motor recovery in a homogeneous cohort of patients with initial paralysis of the upper extremity. In contrast with most previous research, we have discriminated between arm and hand motor recovery. The prognostic and clinical relevance of MEPs with respect to arm and hand motor recovery was obvious, which is in accordance with the paradigm that postinfarctional recovery is strongly dependent on a critical residual sparing of corticospinal function. Compared to clinical evaluation this residual function can be detected most properly by MEPs. However, the CIs for the ORs were wide, probably because of low numbers of included patients. In accordance with the systematic review, the specificity was consistently very high, both for the prediction of proximal and distal motor recovery of the upper extremity. Again, the sensitivity of the MEPs was rather low. We have considered the cutoff point for the presence of a positive MEP response (200 μV). However, the variability of the MEP data appeared to be low in our patient sample. Only

one patient could be identified who exhibited an equivocal MEP response of 100 μV; she showed further motor recovery. According to our initial definition of a present MEP response, we regarded this patient as a false negative.

In the second prospective cohort study, we have addressed the predictive value of lower extremity MEPs with respect to motor recovery and functional recovery in a homogeneous cohort of patients with initial paralysis or severe paresis of the lower extremity. MEPs of the tibialis anterior muscle, registered in the subacute phase after stroke seem to contain important prognostic information, both for motor recovery of the crural muscles and for functional recovery. MEPs of the vastus medialis muscle were not predictive for motor and functional recovery in our patient sample.

In the last chapter of the third part we have focused on recovery issues. A repeated investigation of the amplitude and the latency of MEPs of proximal and distal muscles of the upper and lower extremity was performed in a homogeneous sample of acute stroke patients with complete paralysis of the upper and or the lower extremity. The MEPs parameters were related to the subsequent motor scores. For all the muscles studied, the recovery of fast corticospinal functions was obvious. A MEP response could be elicited in more cases on the second than on the first MEPs assessment. A present MEP response at the first registration nearly always indicated subsequent motor recovery, both for proximal and distal motor functions of the upper and lower extremity. However, motor recovery was also observed in some patients for whom no MEP response could be elicited. Regression analysis showed significant relationships between the MEP parameters of the upper extremity and the arm and hand motor scores, but not for MEP parameters of the lower extremity and the leg motor scores. We concluded that motor recovery manifests neurophysiologically often as the recovery of fast corticospinal functions. In many cases, assessment by MEPs is more sensitive than clinical

examination to detect residual corticospinal functions, which forms the pathofysiological basis for the predictive value of MEPs for motor recovery after stroke.

Implications for clinical practice

In the Netherlands, acute stroke patients are generally treated according to the guidelines of the Dutch Society of Neurology. Clinical, radiological, cardiovascular and laboratory examinations are performed to explore the cause of the stroke and to initiate appropriate secondary prevention. Some of these examinations may also generate important prognostic information[2,11]. Until now there has been no tradition (in the Netherlands) of performing neurophysiological examination with respect to the functional prognosis of an individual acute stroke patient. The present thesis offers sufficient evidence to consider the application of MEPs for outcome prediction.

Conclusion and future research

This thesis offers evidence concerning the use of MEPs in predicting motor and functional outcome after stroke. Particularly in patients with initial paralysis of the upper extremity, the added value of the predictive use of MEPs has been established. However, the prognostic test properties might be improved by the use of the more recently developed paired-pulse stimulation technique. The added prognostic value of MEPs in acute stroke patients with initial paresis has not yet been established and needs further scientific exploration. The main issue in these cases seems not to be whether they do experience motor recovery, but more to which degree they will recover. The evidence concerning the predictive value of lower extremity MEPs should be regarded as preliminary and further research is needed, particularly with respect to functional recovery. Spasticity, a frequent accompanying and complicating symptom of the motor syndrome in stroke patients, has also been associated with MEP parameters, in particular the silent period[12]. This

parameter might predict the development of (severe) spasticity in an early poststroke phase.

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SUMMARY

Strokes are a common cause of death in the western world and it may lead to severe activity limitations in the survivors. The stroke syndrome is characterized by a more or less acute onset of nonconvulsive focal neurological deficits. Functional recovery after stroke is influenced by many factors and recovery profiles are characterized by a high interindividual variability. Several clinical and demographic variables may be valid predictors of general functional recovery, including neurological factors such as consciousness at onset, orientation in time and place, sitting balance, and the severity of motor deficits. Until now, the use of motor evoked potentials (MEPs) in predicting motor and functional outcome is still equivocal and studies seem to be contradictory. This issue is outlined in *Chapter 1* and represents the central subject of the thesis. The thesis is divided into 3 parts. Two pilot studies (*Chapter 2 and 3*) are described in part I. Part II consists of 2 systematic reviews (*Chapter 4 and 5*), and the prospective cohort studies are described in part III (*Chapter 6, 7 and 8*).

The first pilot study is described in *Chapter 2*. In this study we used somatosensory Evoked Potentials (SEPs) to predict motor recovery in a case series of seven acute stroke patients with a paralyzed upper extremity and no recovery tendency during the first 10 days. A follow-up during nine months showed excellent motor recovery in one patient and moderate motor recovery in three patients. In three other patients no motor recovery occurred. The prediction based on the SEPs findings was correct in all cases except one. Further examination of this patient provided evidence for a demyelinating disease. We concluded that SEPs might be of value in predicting motor recovery following stroke.

Chapter 3 describes the second pilot study. In this exploratory study, we evaluated the predictive value of both MEPs and SEPs for motor recovery from paralysis of the upper extremity in a historic cohort of acute stroke patients. Evoked potentials were recorded in 29 patients who had had their

first-ever infarction in the territory of the middle cerebral artery and who exhibited paralysis of the upper extremity. At follow-up, seven patients showed motor recovery. The evoked potential data were dichotomized into present or absent and related to the occurrence of motor recovery. Analysis by the chi-square test revealed a significant association between the presence of evoked potentials early after stroke and the observed occurrence of motor recovery. The chi-square values for MEPs and SEPs were 15.29; df=1; p = 0.0001 and 4.39; df=1; p = 0.0340, respectively. The odds ratios (ORs) for MEPs and SEPs were 46.00 (95% confidence interval [CI] 6.75 – 313.30) and 6.66 (95% CI 1.13 - 39.26), respectively. These results suggest strongly that evoked potentials predict the occurrence of motor recovery of upper extremity paralysis in patients suffering from first-ever infarction in the territory of the middle cerebral artery. MEPs appeared to be more valid than SEPs in predicting motor recovery.

The first systematic review (*Chapter 4*) focuses at motor recovery after stroke. The purpose of the study was to collect and integrate existing data concerning the occurrence, extent, time course and prognostic determinants of motor recovery after stroke using a systematic methodological approach. A computer-aided search in bibliographic databases was performed to identify potentially relevant studies. Studies were selected by a preliminary screening and a critical review according to a priori methodological criteria, with special emphasis on the internal validity. The results were as follows. The search yielded 174 potentially relevant studies, of which 80 studies passed the preliminary screening and were subjected to further methodological assessment. Fourteen studies were finally selected and discussed, based on quantitative analysis of outcome measures and prognostic determinants. Meta-analysis was pursued, but was not possible due to substantial heterogeneity. Some observations were as follows. Approximately 65% of the hospitalized stroke survivors with initial motor deficits of the lower extremity show some degree of motor recovery. Data were insufficient to give an over all recovery

profile for the upper extremity. In the case of paralysis or severe paresis, only 45% of the patients show some degree of motor recovery, both for the upper and lower extremity. Hardly any valid information was available concerning the extent of motor recovery in a more detailed fashion. In the case of initial paralysis, complete motor recovery occurs in less than15% of the patients, both for the upper and lower extremity. Hospitalized patients with small lacunar strokes show relatively good motor recovery. The recovery period in patients with severe stroke is twice as long as in patients with mild stroke. The initial grade of paresis is the most important predictor for motor recovery (ORs, > 4). Objective analysis of the motor pathways by motor evoked potentials (MEPs) showed even much higher ORs (ORs, >20). We concluded that our knowledge of motor recovery after stroke in more accurate, quantitative and qualitative terms is still limited and a precise prediction of motor recovery in an individual acute stroke patient is not possible. MEPs seem to be promising within this context.

In the second systematic review (*Chapter 5)* we addressed specifically the use of MEPs in predicting motor and functional outcomes. A computer-aided search in bibliographic databases was performed to identify potentially relevant studies. Studies were selected by a preliminary screening and a critical review according to a priori methodological criteria. The data from the included studies were used to construct contingency tables with MEPs as prognostic determinant. The distribution of cells was statistically assessed by the Fisher exact test. The prognostic test properties were expressed as sensitivity and specificity. The clinical significance was determined by ORs. The results were as follows. Of 85 potentially relevant studies, 20 met the criteria for the preliminary screening; after the critical review 5 studies were included for analysis and discussion. The distribution of numbers of patients within the cells of the contingency tables was highly significant for subgroups of patients, both for motor and functional recovery, indicating the prognostic relevance of MEPs. As for the prediction of motor recovery of the upper

extremity, the specificity was consistently very high for subgroups of patients with paralysis or severe paresis. The data for the subgroups of patients with initial paresis were not uniform. The dichotomization of the MEPs (in the present analysis) might have caused a substantial loss of important data with respect to motor recovery in these subgroups. A quantitative analysis of the central motor conduction time (CMCT) and the amplitude may provide relevant prognostic information in these patients. With respect to functional recovery, quantitative analysis revealed consistent findings for the sensitivity, whereas the values for the specificity were rather inconsistent, probably due to clinical heterogeneity. We concluded that evidence exists for the prognostic value of MEPs with respect to motor and functional recovery. The specificity was consistently very high for subgroups of patients with paralysis or severe paresis, and this test property might be used in clinical practice.

The predictive value of MEPs with respect to arm and hand motor recovery, and functional recovery of the upper extremity, was further explored in *Chapter 6*. This cohort study included 43 consecutive acute stroke patients with complete paralysis of the upper extremity. MEPs of the abductor digiti minimi muscle (ADM) and the biceps brachii muscle (BB) were obtained within 10 days after stroke onset. The upper limb subset of the Fugl-Meyer Motor Assessment was used to evaluate the motor performance of the arm and hand at regular intervals until 6 months poststroke. The Frenchay arm test was used to assess functional abilities. The follow-up was complete in 40 patients (2 patients died and 1 patient had a recurrent stroke); 14 patients showed motor recovery of the arm and their mean 26-week arm motor score was 17.93 (standard deviation [SD], 11.68); hand motor recovery occurred in 11 patients and their mean 26-week hand motor score was 11.09 (SD, 4.10). Stepwise logistic regression revealed prognostic models for both arm and hand motor recovery based on BB MEPs (OR 7.69, CI 1.16-50.95) and ADM MEPs (OR 16.20, CI 2.51-104.40), respectively. The predictive relevance of MEPs with respect to motor recovery of the upper extremity was obvious in this

homogeneous sample of patients. This agrees with the paradigm that postinfarctional motor recovery is strongly dependent on a critical residual sparing of corticospinal function. In this context, the test properties of MEPs in predicting motor recovery are discussed. The added value of MEPs with respect to motor recovery of the upper extremity should be regarded as established for patients with initial paralysis, especially since clinical examination alone lacks the possibility to detect the potential for motor recovery in these cases.

Chapter 7 consists of a longitudinal study concerning the prognostic value of motor MEPs of the lower extremity with respect to motor recovery and functional recovery. The patient sample included 38 acute stroke patients with complete paralysis (paralysis subgroup) or severe paresis (paresis subgroup) of the lower extremity. MEPs of the vastus medialis muscle (VM) and the tibialis anterior muscle (TA) were performed between the third and tenth day after stroke onset. A separate proximal leg motor score (maximal 16 points) and crural motor score (maximal 2 points) was defined within the lower limb subset of the original Fugl-Meyer Motor Assessment to evaluate the motor performance at regular intervals until 6 months poststroke. The transfer item of the Barthel Index and the functional ambulation categories were used to assess transfer and walking ability. For the paralysis subgroup (n=30), the follow-up was complete in 27 patients (two patients died and one patient underwent above knee amputation). At 26-week, 20 patients experienced proximal motor recovery (mean score, 11.70, SD, 4.48), and 12 of them also showed crural motor recovery (mean score, 1.40, SD, 0.51). Seven patients (23%) could perform an independent transfer safely and five of this group (17%) learned to walk independently. The MEP data were related to the occurrence of motor recovery and functional recovery in contingency tables. The distribution of numbers of patients within the cells was statistically assessed by the Fisher exact test. To quantify the prognostic significance, ORs and their 95% CIs were calculated. Analysis revealed significant relationships

for TA MEPs and motor recovery of crural leg muscles (OR 18.00, CI 1.31-894.40), but not for VM MEPs and proximal motor recovery (OR 6.00, CI 0.53-303.00). Patients in the paresis subgroup experienced more favorable motor and functional recovery compared to the paralysis subgroup. It was concluded that TA MEPs registered in subacute phase after stroke may contain important prognostic information, both for motor recovery of the crural muscles and for functional recovery in patients with initial complete paralysis of the lower extremity.

Chapter 8 describes a study of repeated MEP assessment of proximal and distal muscles of the upper and lower extremity in a cohort of 44 acute stroke patients. The aim of the study was to assess the recovery of fast corticospinal influence as the electrophysiological manifestation of motor recovery in stroke patients. Furthermore we assessed the relationship between MEPs and the subsequent clinical motor scores for proximal and distal muscles in the arm and the leg. MEPs of the abductor digiti minimi muscle (ADM), the biceps brachii muscle (BB), the vastus medialis muscle (VM) and the tibialis anterior muscle (TA) were performed at 6.9 days (range 3-10) and 27.8 days (range 14-42) after stroke onset. A separate score was defined for proximal and distal motor functions of the upper and lower extremity within the original Fugl-Meyer Motor Assessment. Motor performance was evaluated simultaneously with the MEP assessments and at 6-months poststroke. The results were as follows. Obvious recovery of the fast corticospinal functions occurred. For the ADM amplitude ratio and the VM MEP amplitude the differences between the two investigations were even statistically significant. A MEP response could be elicited in more cases on the second than on the first MEPs assessment. A present MEP response at the first registration indicated nearly always subsequent motor recovery, both for proximal and distal motor functions of the upper and lower extremity. However, motor recovery was also observed in some patients for whom no MEP response could be elicited. Regression analysis showed significant relationships between the ADM amplitude ratios

and the 26-week hand motor score, and between the BB amplitudes and the 26-week arm motor scores. No relationship existed between the TA and VM MEP parameters and the crural and proximal leg motor scores. This finding confirms the paradigm that motor functions of the upper extremity are more dependent on the integrity of the fast corticospinal functions than the lower extremity. It was concluded that motor recovery manifests electrophysiologically often as the recovery of fast corticospinal influence in. The pathofysiological basis for the predictive value of MEPs for motor recovery of proximal and distal motor functions of the upper and lower extremity was discussed.

Chapter 9 summarizes and discusses the most important findings of our research. Implications for clinical practice and suggestions for further research were given.

SAMENVATTING

Het cerebrovasculair accident (CVA) is een belangrijke doodsoorzaak in de westerse wereld. De aandoening kan leiden tot ernstige beperkingen in het functioneren bij patiënten, die de initiële fase overleven. Het klinisch beeld van het CVA wordt gekenmerkt door het min of meer acuut optreden van focale neurologische uitvalsverschijnselen. Er bestaat een hoge mate van interindividuele variabiliteit met betrekking tot het optreden van functioneel herstel na CVA. Een aantal klinische en demografische variabelen worden beschouwd als valide predictoren voor functioneel herstel, waaronder neurologische factoren zoals bewustzijnstoestand bij opname, desoriëntatie in plaats en tijd, zitbalans, en de ernst van de motore uitvalsverschijnselen. De prognosebepaling op grond van klinische variabelen is evenwel verre van accuraat. Dit gegeven leidde tot verder onderzoek naar de elektrofysiologische mogelijkheden binnen dit kader. Het gebruik van motore opgewekte potentialen bij de prognostiek na CVA vormde aldus de centrale thematiek van dit proefschrift. De thesis bestaat uit 3 delen. Na het inleidende hoofdstuk *(Hoofdstuk 1)* worden twee pilot studies beschreven in deel I (*Hoofdstukken 2 en 3*). Deel II bestaat uit twee systematische literatuurstudies (*Hoofdstukken 4 en 5*) en drie prospectieve cohort studies zijn beschreven in deel III *(Hoofdstukken 6, 7 en 8).* Het proefschrift wordt afgesloten met een beschouwend hoofdstuk *(Hoofdstuk 9).*

De eerste pilot studie wordt beschreven in *hoofdstuk 2.* In dit onderzoek werden somatosensore opgewekte potentialen gebruikt om motorisch herstel te voorspellen bij zeven CVA-patiënten die een paralyse hadden van de bovenste extremiteit, en die geen motorisch herstel vertoonden gedurende de eerste 10 dagen na het CVA. De patiënten werden gedurende negen maanden vervolgd. Een patiënt vertoonde uiteindelijk volledig motorisch herstel en drie andere patiënten redelijk herstel. Bij de drie overigen trad er geen motorisch herstel op. De predictie op basis van de somatosensore opgewekte potentialen was correct in alle gevallen, behoudens een. Aanvullend onderzoek bij deze patiënt toonde aanwijzingen voor een demyeliniserende aandoening. We

concludeerden dat deze preliminaire resultaten indicatief zijn voor de predictieve waarde van somatosensore opgewekte potentialen ten aanzien van motorisch herstel van de bovenste extremiteit na CVA.

Hoofdstuk 3 geeft de tweede pilot studie weer. Deze studie betrof de predictieve waarde van motore en somatosensore opgewekte potentialen voor motorisch herstel van de bovenste extremiteit. Deze exploratieve studie werd uitgevoerd in een historisch cohort van 29 acute CVA-patiënten, die een herseninfarct doorgemaakt hadden in het stroomgebied van de arteria cerebri media. Alle patiënten hadden in de initiële fase na het CVA een paralyse van de bovenste extremiteit. De opgewekte potentialen waren gemeten binnen drie dagen na ontstaan van het herseninfarct. In de analyse werden de opgewekte potentialen als onafhankelijke variabelen gedichotomiseerd in aanwezig of afwezig en gerelateerd aan het optreden van motorische herstel. Gedurende het beloop trad motorisch herstel van de bovenste extremiteit op bij zeven patiënten. Statistische analyse middels de chi-kwadraat toets liet een significante associatie zien tussen het al dan niet aanwezig zijn van een respons bij de opgewekte potentialen en het optreden van motorisch herstel. De chi-kwadraat waarde voor motore opgewekte potentialen bedroeg 15.29; vrijheidsgraden 1; p=0.0001 en voor somatosensore opgewekte potentialen 4.39; vrijheidsgraden 1; p=0.034. De Odds ratio's waren respectievelijk 46.00 (95% betrouwbaarheidsinterval [BI] 6.75-313.30) en 6.66 (95% BI 1.13-39.26) voor motore en somatosensore opgewekte potentialen. Wij concludeerden dat opgewekte potentialen het optreden van motorisch herstel van de bovenste extremiteit paralyse na een eerste media-infarct kunnen voorspellen, waarbij de predictie op basis van de motore potentialen meer valide is dan die van somatosensore potentialen.

De eerste systematische literatuurstudie *(Hoofdstuk 4)* was gericht op motorisch herstel na CVA. Het doel van deze systematische methodologische benadering was om valide data te compileren en te analyseren betreffende het

optreden en de mate van motorisch herstel, het tijdsbestek waarin motorisch herstel plaatsvindt, en de prognostische determinanten voor motorisch herstel. Via elektronische databestanden werden potentieel relevante studies gezocht, die onderworpen werden aan een preliminaire screening. Vervolgens vond een methodologische beoordeling (interne, externe en statistische validiteit) plaats. De zoekstrategie leverde 174 relevante studies op en de preliminaire screening resulteerde in 80 studies. Uiteindelijk werden 14 studies via de methodologische beoordeling als voldoende valide beschouwd voor kwantitatieve analyse en discussie van de uitkomstmaten. De geplande meta-analyse bleek niet mogelijk vanwege aanzienlijke klinische heterogeniteit van de studies. Enkele bevindingen uit de geselecteerde studies waren als volgt. Ongeveer 65% van de gehospitaliseerde CVA-overlevenden met motorische uitval van de onderste extremiteit bij opname lieten motorisch herstel zien. Voor de bovenste extremiteit waren de gegevens onvoldoende om een algemene hersteltendens te geven. Indien er sprake was van paralyse of ernstige parese bij opname trad slechts herstel op bij 45% van de patiënten, zowel voor de bovenste als onderste extremiteit. Er was nauwelijks valide informatie aanwezig betreffende de exacte mate van motorisch herstel. Wel lieten studies zien, dat in geval van initiële paralyse van de bovenste of onderste extremiteit, compleet herstel optreedt bij minder dan 15% van de patiënten. Gehospitaliseerde patiënten met kleine lacunaire infarcten lieten relatief goed motorisch herstel zien. Het tijdsbestek waarin motorisch herstel plaatsvindt bleek voor patiënten met ernstige uitval twee maal zo lang te duren als voor patiënten met milde uitval. De initiële mate van parese was de belangrijkste predictor voor motorisch herstel (Odds ratio > 4). Objectieve analyse van de motore baansystemen via motore opgewekte potentialen liet evenwel aanmerkelijk hogere Odds ratio's zien (Odds ratio's > 20). We concludeerden dat onze kennis betreffende motorisch herstel na CVA in meer accurate, kwantitatieve en kwalitatieve zin nog steeds betrekkelijk gering is en dat een precieze predictie van het te verwachten motorische herstel bij een

individuele acute CVA-patiënt niet goed mogelijk is. Motore opgewekte potentialen lijken binnen dit kader veelbelovend.

De tweede systematische literatuurstudie *(Hoofdstuk 5)* was specifiek gericht op het gebruik van motore opgewekte potentialen bij de predictie van motorisch en functioneel herstel na CVA. In eerste instantie werd een systematische zoekactie uitgevoerd en de potentieel relevante studies werden onderworpen aan een preliminaire screening. Studies die voldeden aan deze screening werden vervolgens onderworpen aan een methodologische beoordeeld aan de hand van vooraf vastgestelde criteria. De data van de uiteindelijk geselecteerde studies werden gecompileerd in 2x2 tabellen. De verdeling van de patiëntenaantallen binnen de cellen werd statistisch getoetst met de Fisher exact test. De resultaten waren als volgt. Van de 85 potentieel relevante studies voldeden 20 studies aan de criteria voor de preliminaire screening en via de methodologische beoordeling werden uiteindelijk 5 studies geselecteerd voor verdere kwantitatieve analyse van de data en discussie. De verdeling van de aantallen binnen de cellen van de 2x2 tabellen was in hoge mate significant voor bepaalde subgroepen van CVA-patiënten, zowel voor motorisch als voor functioneel herstel. Ten aanzien van de prognostische testeigenschappen was de specificiteit consistent en erg hoog voor motorisch herstel bij patiënten met initiële paralyse of ernstige parese van de bovenste extremiteit. De data voor patiënten met initiële parese waren niet uniform. De dichotomisatie ten aanzien van de motore opgewekte potentialen (in de huidige analyse) heeft waarschijnlijk geleid tot een aanzienlijk verlies van informatie bij deze patiëntengroep. Kwantitatieve analyse van de centrale motore conductietijd (CMCT) en de amplitudo zouden wellicht relevante prognostische maten kunnen opleveren. Met betrekking tot functioneel herstel resulteerde de analyse in consistente bevindingen voor de sensitiviteit, terwijl de waardes voor de specificiteit nogal inconsistent waren, waarschijnlijk als gevolg van de klinische heterogeniteit. Vanwege de aanzienlijke klinische heterogeniteit was meta-analyse niet mogelijk. We concludeerden dat er

evidentie bestaat voor de prognostische waarde van motore opgewekte potentialen bij CVA-patiënten. Met name de consistente bevindingen voor motorisch herstel bij patiënten met initiële paralyse of ernstige parese zouden gebruikt kunnen worden in de klinische praktijk.

De predictieve waarde van motore opgewekte potentialen met betrekking tot motorisch en functioneel herstel van de arm en hand werd verder onderzocht in *Hoofdstuk 6*. In deze cohort studie werden 43 acute CVA-patiënten geincludeerd met complete paralyse van de bovenste extremiteit. Motore opgewekte potentialen van de musculus abductor digiti minimi (ADM) en de musculus biceps brachii (BB) werden gemeten binnen 10 dagen na ontstaan van het CVA. De Fugl-Meyer Motor Assessment werd gebruikt om motore functies te meten op reguliere tijdstippen, tot en met 6 maanden na ontstaan van het CVA. De Frenchay Arm test werd gebruikt om de functionele vaardigheden van de bovenste extremiteit vast te leggen. De vervolgdata waren compleet bij 40 patiënten (twee patiënten overleden en een patiënt ontwikkelde een recidief CVA); 14 patiënten lieten motorisch herstel van de arm zien en de gemiddelde motore score van de arm na 6 maanden bedroeg 17.93 (standaard deviatie [SD] 11.68); motorisch herstel van de hand trad op bij 11 patiënten en de gemiddelde motore score van de hand na 6 maanden bedroeg 11.09 (SD 4.10). Functioneel herstel was nauw gerelateerd aan motorisch herstel. In tegenstelling tot de eerdere literatuur werd in de onderhavige studie ten aanzien van de prognostiek onderscheid gemaakt tussen motore functies van de arm en de hand. Stapsgewijze logistische regressie liet voor zowel de arm als de hand prognostische modellen zien op basis van respectievelijk opgewekte potentialen van de BB en de ADM. De Odds ratio voor de BB ten aanzien van motorische herstel van de arm bedroeg 7.69 (BI 1.16-50.95) en voor de ADM ten aanzien van motorisch herstel van de hand 16.20 (BI 2.51-104.40). De predictieve waarde van de motore opgewekte potentialen was evident bij deze qua initiële motore uitval homogene populatie CVA-patiënten. Dit is in overeenstemming met het

paradigma dat motorisch herstel na CVA in hoge mate afhankelijk is van de residuele corticospinale connecties. Vanuit dit perspectief werden de prognostische testeigenschappen van de motore opgewekte potentialen bediscussieerd. De toegevoegde waarde van motore opgewekte potentialen met betrekking tot motorisch herstel van de bovenste extremiteit voor patiënten met een initiële paralyse is evident, zeker omdat het klinisch onderzoek in deze gevallen het optreden van motorisch herstel *niet* kan voorspellen.

Hoofdstuk 7 bestaat uit een cohort studie betreffende de prognostisch waarde van motore opgewekte potentialen van de onderste extremiteit voor motorisch en functioneel herstel. In de studie waren 38 acute CVA-patiënten geincludeerd met een complete paralyse (paralyse subgroep) of een ernstige parese (parese subgroep) van de onderste extremiteit. Motore opgewekte potentialen van de musculus vastus medialis (VM) en de musculus tibialis anterior (TA) werden geregistreerd tussen de derde en tiende dag na ontstaan van het CVA. Aan de hand van de originele Fugl-Meyer Motor Assessment (sectie onderste extremiteit) werd een separate motore score gedefinieerd voor proximale (maximale score 30) en distale (maximale score 2) motore functies. De motore scores werden op reguliere tijdstippen bepaald, tot en met 6 maanden na ontstaan van het CVA. Het transfer item binnen de Barthel Index werd gebruikt om het maken van zelfstandige transfers te beoordelen. Herstel van loopvaardigheid werd gemeten aan de hand van de Functional Ambulation Categories. De data werden gecompileerd in 2x2 tabellen en de verdeling binnen de cellen werd statistisch getoetst via de Fisher exact test. De resultaten waren als volgt. In de paralyse subgroep (n=30) waren er drie uitvallers (twee patiënten overleden en een patiënt onderging een bovenbeenamputatie). Na 6 maanden vertoonden 20 patiënten binnen deze subgroep motorisch herstel van de proximale beenfuncties (gemiddelde score 11.70, SD 4.48); 12 van deze patiënten vertoonden ook herstel van de crurale musculatuur (gemiddelde score 1.40, SD 0.51). Zeven patiënten (23%) konden

een zelfstandige transfer maken na 6 maanden, waarvan 5 patiënten (17%) uiteindelijk zelfstandig konden lopen. De verdeling binnen de cellen was statistisch significant voor motore opgewekte potentialen van de TA en motorisch herstel van de crurale motore functies (Odds ratio 18.00, BI 1.31-894.40), en voor het uitvoeren van zelfstandige transfers (Odds ratio 17.50, BI 1.36-267.00). De motore opgewekte potentialen van de VM waren niet duidelijk predictief voor motorisch en functioneel herstel. Patiënten in de paresegroep vertoonden aanzienlijk beter motorisch en functioneel herstel. We concludeerden dat motore opgewekte potentialen van de TA, geregistreerd in de subacute fase na het CVA, belangrijke prognostische informatie kunnen bevatten ten aanzien van motorisch herstel van de crurale motore functies en ten aanzien van herstel van zelfstandige transfers bij patiënten met initiële paralyse van de onderste extremiteit.

Hoofdstuk 8 beschrijft een studie waarbij herhaalde registratie plaatsvond van motore opgewekte potentialen van proximale en distale musculatuur van de bovenste en onderste extremiteit in een cohort van 44 acute CVA-patiënten. Het doel van de studie was om het herstel van snelle corticospinale functies te analyseren. Tevens werd de relatie onderzocht tussen motore opgewekte potentialen en de klinische motore scores. Motore opgewekte potentialen van de musculus abductor minimi (ADM), de musculus biceps brachii (BB), de musculus tibialis anterior (TA) en de musculus vastus medialis (VM) werden geregistreerd 6.9 dagen (3-10) en 27.8 dagen (14-42) na ontstaan van het CVA. Aan de hand van de originele Fugl-Meyer Motor Assessment werden separate motore scores gedefinieerd voor de proximale en distale motore functies van de bovenste en de onderste extremiteit. Motore functies werden gelijktijdig gemeten met de motore opgewekte potentialen en 6 maanden na het ontstaan van het CVA. De resultaten waren als volgt. De MEP parameters verbeterden in de loop van de tijd. Voor de ADM amplitudo ratio en de VM amplitudo van de motore opgewekte potentialen waren de verschillen tussen de 2 metingen statistisch significant. Bovendien werd er bij de tweede meting

in meer gevallen een aanwezige respons gevonden dan bij de eerste meting. Indien bij de eerste meting een respons aanwezig was, trad bijna altijd motorisch herstel op van de betreffende motore functies. Motorisch herstel trad echter ook op bij sommige patiënten, bij wie geen respons kon worden opgewekt. Regressieanalyse liet significante relaties zien tussen de amplitudo ratio van de ADM en de uiteindelijke motore score van de hand, en tussen de amplitudo van de BB en de motore score van de arm. Er bestond geen relatie tussen de motore opgewekte potentialen parameters en de motore functies van het been. Deze bevindingen bevestigen het paradigma dat motore functies van de bovenste extremiteit meer afhankelijk zijn van de integriteit van de snelle corticospinale functies dan die van de onderste extremiteit. We concludeerden dat motorisch herstel zich elektrofysiologisch vaak manifesteert als het herstel van snelle corticospinale functies, maar niet altijd. De pathofysiologische basis voor de prognostische waarde van motore opgewekte potentialen werd bediscussieerd.

In *Hoofdstuk 9* werden de belangrijkste bevindingen van de onderzoeken samengevat, kritisch beschouwd en bediscussieerd. Implicaties voor de klinische praktijk werden gegeven, evenals suggesties voor verder onderzoek.

NABESCHOUWING EN DANKBETUIGING

Wat betekent deze mijlpaal? Formeel gesproken wordt de proeve van bekwaamheid volbracht om zelfstandig wetenschappelijk onderzoek te kunnen verrichten. Een uitgesproken persoonlijke ambitie gaat hiermee in vervulling. Echter, ook de afsluiting van een periode waarin klinische werkzaamheden, taken als supervisor en opleider, wetenschappelijke activiteiten en het sociale leven zo efficiënt mogelijk gecombineerd dienden te worden. Wellicht is dit het moment voor enige reflectie en oriëntering op de toekomst.

Vanaf het prille begin van mijn artsenloopbaan heb ik veel uitdaging gevonden in het combineren van klinische werkzaamheden met het uitvoeren van toegepast wetenschappelijk onderzoek. Aldus vormden zich reeds snel preliminaire gedachten omtrent het schrijven van een proefschrift. Uiteindelijk heeft de voltooiing hiervan lang geduurd. Voor een deel is dit te wijten aan de aanvankelijk relatief gebrekkige onderzoekstraditie en mogelijkheden om wetenschappelijk onderzoek te verrichten binnen de revalidatiegeneeskunde. Gelukkig is er op dit vlak veel veranderd. De attitude van het management van revalidatieafdelingen in de ziekenhuizen en revalidatie-instellingen veranderde ten gunste van wetenschappelijk onderzoek, mede door stimulering vanuit Zon Mw en VRA-SGO. Inmiddels worden steeds meer jonge collega's opgeleid tot revalidatieartsonderzoeker binnen een AGIKO of fellowship constructie. Zelf heb ik in de laatste fase van mijn promotie kunnen profiteren van een persoonlijke stimuleringssubsidie (reg.nr. 014-32-022), verstrekt vanuit Zon MW. Ik ben de toewijzingscommissie zeer erkentelijk voor het in mij gestelde vertrouwen.

Mijn eerste ideeën omtrent het onderzoeksonderwerp dateren uit mijn AGNIO tijd neurologie in het De Wever ziekenhuis te Heerlen (inmiddels Atrium Medisch Centrum geheten), eind jaren tachtig. Vele CVA-patiënten werden opgenomen en ik vond het uitermate onbevredigend dat er ogenschijnlijk weinig inzicht bestond in het te verwachten beloop. Aanvullend onderzoek ten aanzien van dit aspect werd routinematig niet verricht, terwijl in hetzelfde

ziekenhuis dr. J.W. Vredeveld (klinisch neurofysioloog) gepromoveerd was op de prognostische waarde van somatosensore opgewekte potentialen bij acute CVA-patienten (Somatosensory evoked potentials in acute stroke; Lisse: Swets en Zeitlinger, 1985).

Mijn AGNIO contract liep ten einde en ik moest een opleidingsplek verwerven. De neurologie leek aantrekkelijk, de interne geneeskunde en de huisarts geneeskunde lonkten. Toch werd het de revalidatiegeneeskunde, het vakgebied van mijn eerste keuze. Nog steeds ben ik Dick Rijken dankbaar dat hij mij in 1990 aanbood bij de St. Maartenskliniek in opleiding te komen tot revalidatiearts. Weliswaar had hij weinig affiniteit met de neurorevalidatie, toch steunde hij mijn ideeën om het gebruik van opgewekte potentialen voor functionele prognostiek verder uit te werken als onderzoeksonderwerp voor mijn opleiding. Aldus werd de eerste bouwsteen gelegd voor het huidige proefschrift, waarbij ik begeleid werd door dr. Theo Mulder (inmiddels prof. dr. Th. Mulder, Rijksuniversiteit Groningen). Theo, ik dank jou voor de begeleiding in de initiële fase van mijn onderzoek.

Ik wilde niet blijven werken in het netwerk waar ik opgeleid was en ik aanvaardde een functie als revalidatiearts in het Roessingh te Enschede. Ondanks het verre reizen (dagelijks Arnhem-Enschede) beschikte ik relatief snel na mijn start over voldoende energie om het wetenschappelijk onderzoek te hervatten. De faciliteiten hiertoe werden mij in het Roessingh ruimschoots geboden.

De sfeer en de onderzoekscultuur (neurorevalidatie) die ik kende vanuit mijn opleidingstijd bleven echter door mijn hoofd spelen. Ik hoefde dan ook niet lang na te denken, toen ik in 1997 een baan aangeboden kreeg in de St. Maartenskliniek, met als specifieke taken detachering als revalidatiearts in het UMC St. Radboud en het Maasziekenhuis te Boxmeer. In de loop van 1999 kreeg het onderzoek geleidelijk een meer prominente plaats binnen mijn

takenpakket en met het instellen van de definitieve begeleidingsgroep werden de contouren van het huidige proefschrift steeds duidelijker.

Het schrijven van een dissertatie is uiteraard geen eenmansactie. Velen ben ik dank verschuldigd. In de allereerste plaats wil ik alle patiënten bedanken voor hun belangenloze deelname aan dit onderzoek. Vanwege methodologische redenen kon ik de uitslag van de motore opgewekte potentialen niet mededelen, toch gingen zij akkoord met de meting en de langdurige follow-up. Het onderzoek had niet plaats kunnen vinden zonder een goed geoutilleerde en georganiseerde afdeling klinische neurofysiologie (KNF). Ik heb me altijd welkom gevoeld op de KNF en alle medewerking ervaren van de administratie, de laboranten, het secretariaat en de neurofysiologen.

Promoveren als staflid betekent dat een aantal taken overgenomen moet worden door collegae. Ik wil in dit kader mijn directe collega revalidatieartsen in de St. Maartenskliniek (Margriet Poelma, Marion Verhulsdonck, Frits Lem, Sander Geurts, Dirk van Kuppevelt, Barbara Lo-A-Njoe, Nique Rijs, Albert de Fretes, Viola van den Donk) en het UMC St. Radboud (Peter Jongerius, Harmen van der Linde, Miriam de Haart, Annette van Kuijk) bedanken. Enkelen wil ik nader noemen. Sander Geurts wil ik danken voor zijn hulp bij het schrijven van de eerste systematische review. En Peter Jongerius, met wie ik sedert mijn doorstart in Nijmegen samenwerk binnen het UMC. Jij was langdurig de roerganger op de afdeling revalidatiegeneeskunde in het UMC. Jouw managerial kwaliteiten hebben aanzienlijk bijgedragen aan de huidige onwikkelingen op onze afdeling. Jouw aanmoedigingen heb ik altijd als zeer stimulerend ervaren. Met de komst van prof. dr. Fons Gabreels, hoofd ad interim van de afdeling revalidatiegeneeskunde in het UMC, zijn alle ontwikkelingen in een stroomversnelling geraakt. Een uitgebreide eigenstandige medische staf, integratie met de researchsectie (prof. dr. Jaak Duysens) en een goed uitgeruste afdeling (inclusief looplaboratorium en balansplatform) worden in de komende jaren gerealiseerd. Deze

ontwikkelingen moeten borg staan voor de academische taakstellingen: kwalitatief hoogwaardige patiëntenzorg, onderwijs binnen de faculteit voor medische wetenschappen, specialistenopleiding en wetenschappelijk onderzoek (klinisch toegepast en fundamenteel).

Bij het onderzoek werd ik uiteraard primair begeleid de promotor en de co-promotores. Als eerste wil ik dr. J.W. Pasman bedanken. Beste Jaco, jij hebt enorm veel werk voor mij verricht: alle neurofysiologische metingen werden door jou uitgevoerd en bij een viertal artikelen was je coauteur. Oneindig vaak hebben wij gediscussieerd over prognostisch onderzoek binnen de neurologie, over de pathofysiologische achtergronden voor de predictieve waarde van de motore opgewekte potentialen, maar ook veelvuldig over andere kwesties. Jij was mijn steun en toeverlaat in bange dagen. Ik ben blij dat je participeert in de begeleidingsgroep voor het vervolgonderzoek.

Speciale woorden wil ik richten tot dr. J. van Limbeek. Beste Jacques, jij hebt in belangrijke mate mede vorm gegeven aan de onderzoekscultuur die heerst binnen de revalidatie in Nijmegen. Jouw rol was ook uitermate belangrijk binnen mijn promotietraject, enerzijds in de randvoorwaardelijke sfeer, anderzijds als directe begeleider. Na mijn terugkeer in Nijmegen heb jij met mijn promotor de grote lijnen uitgezet voor het promotietraject. Het was jouw idee om belangrijke items binnen de onderzoeksmaterie te onderwerpen aan een kritische literatuuranalyse. Op een creatieve manier heb je mij als epidemioloog geholpen bij de analyse van alle data van de cohortstudies.

Tenslotte mijn promotor, prof. dr. M.J. Zwarts. Beste Machiel, veel dank ben ik jou verschuldigd. Al vrij snel na jouw start in Nijmegen benaderde ik je om onderzoek te verrichten. Er was binnen de afdelingen neurologie en klinische neurofysiologie in het UMC betrekkelijk weinig traditie betreffende prognostisch onderzoek bij CVA-patiënten. Jij toonde direct interesse en commitment. Dat heb je geweten. Ik overspoelde jou met protocollen,

manuscriptconcepten en voordrachten. Ik ontving ze binnen korte tijd retour met gedegen commentaar. Jij hebt de grote lijn bewaakt, zonder de details uit het oog te verliezen.

Op een gegeven moment waren de artikelen klaar, de manuscriptcommissie kon ingeschakeld worden en het boekje werd geprepareerd. Ik dank Karin van Rooyen voor de hulp in deze fase. Ook dank ik de paranimfen, Harmen van der Linde en Mia Hendricks-Leenen, voor de steun bij de verdediging.

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Hoe nu verder? Het wordt hoogste tijd om het blikveld weer te verruimen. De academische setting biedt talloze uitdagingen op het niveau van management, innovatieve patiëntenzorg, onderwijs en onderzoek. Samen met mijn collega's wil ik de revalidatiegeneeskunde binnen het UMC St. Radboud verder profileren. Ik ben erg verheugd dat het huidige prognostisch onderzoek gecontinueerd wordt binnen het UMC. Ook is de interesse gewekt bij onderzoekers van elders en aldus hoop ik dat replicaonderzoek plaats gaat vinden en implementatie.

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ABOUT THE AUTHOR

Henk Hendricks was born on August 3 1959 in Koningsbosch. After secondary school education he studied Medicine at the Catholic University of Nijmegen. During his study he became interested in Rehabilitation Medicine and he accomplished the scientific training at the dept. of Research and Development of the St. Maartenskliniek. In December 1987 he graduated. To gain further clinical experience he worked as resident Neurology at the Wever Hospital in Heerlen. In 1990 he started his post-graduate training at the dept. of Rehabilitation Medicine of the St. Maartenskliniek in Nijmegen. He was registered as a physiatrist in 1994. From 1994 to 1997 he worked in the Center for Rehabilitation Het Roessingh in Enschede. In August 1997 he returned to the St. Maartenskliniek and since then he is detached to the dept. of Rehabilitation Medicine of the University Hospital of Nijmegen. In March 2001 he was qualified as post-graduate trainer in Rehabilitation Medicine.