Prediction and monitoring upper-extremity motor recovery after severe stroke

Clinical and neurophysiological studies

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Chapter 1

General introduction

Introduction

Stroke is an important disease in the Western Society both in medical and socio-economic terms with an estimated incidence of 30.000 patients per year in the Netherlands [1]. One third of these stroke patients dies within the first year, while 41% experiences long-term disabilities [2]. In approximately 70 to 80% of the stroke survivors, upper-extremity motor function is impaired and in almost one third of these patients motor impairments are severe [2, 3]. Among those with severe impairments, two-thirds do not regain the functional use of the affected arm or hand [3-5], resulting in difficulty with arm or hand positioning in space, grasp, self-care, and other activities of daily living. Nevertheless, nearly 25% of these patients will regain partial motor recovery, and 5-20% even complete motor recovery of the upper limb [2, 4].

Although stroke is the leading cause of long-term disability in Western society, it is a condition for which there is no universally accepted, evidence based, rehabilitation approach. The general objective of rehabilitation is to enable individual patients to regain the highest possible degree of physical and psychological performance [6]. In this perspective, treatment goals should depend on the expected level of disability, as well as on the potential for motor recovery of stroke patients. In stroke patients with a potential for motor recovery it is important to focus on the restoration of motor function, preferably as early as possible [7, 8]. In these patients, repeated failures to use the paretic arm and hand in the acute and sub-acute phases after stroke can lead to negative reinforcement, the so-called ‘learned non-use’ [7], complicating the rehabilitation process later on. Moreover, in patients with the potential for motor recovery, there is evidence for the efficacy of specific targeted treatments, such as constrained induced movement therapy [9, 10]. On the other hand, focusing on the restoration of motor function in stroke patients without a potential for motor recovery will lead to frustration and disappointment among both patients and therapists. It also delays the shift of therapy focus towards learning compensation strategies. As a result, the functional outcome after rehabilitation may be suboptimal. To optimize stroke rehabilitation through appropriate goal setting and implementation of resources, clinicians are challenged at an early stage post-stroke to reliably and accurately predict the degree of disability the patient will ultimately experience [4, 11]. Such prediction requires fundamental knowledge of the essential determinants of functional recovery.

Several clinical and socio-demographic variables have been identified as determinants of functional recovery from stroke, including age, previous stroke, sitting balance, urinary incontinence, severity of paresis, initial disability, and the presence of social support [12]. Although functional recovery from stroke depends on behavioral modification as well,

allowing patients to accomplish the same objective by different strategies, motor function can be considered as a vital determinant of functional ability [13]. Accurate, early prediction of motor recovery seems particularly relevant in severe stroke patients, because the appropriate rehabilitation strategy depends on the probability of motor recovery and the chance of developing complications secondary to paralysis. For instance, patients with residual arm and hand function at the time of stroke onset are very likely to show some motor recovery, which warrants a treatment strategy promoting such recovery [10].

In patients with severe, middle cerebral artery strokes, the initial grade of paresis and the early patterns of motor recovery are the most important clinical determinants of functional recovery of the upper extremity [4, 14]. In patients with an initial flaccid hemiplegic arm who achieved at least 19 points on the upper-extremity subscore of the Fugl-Meyer motor assessment (FMA) at the end of the fourth week post onset, Kwakkel et al. [4] found a probability of 94% for regaining dexterity at 6 months after stroke. In the more acute phase, 1-week post onset, however, the predictive value of clinical assessment was substantially lower; a probability of only 74% for regaining dexterity at 6 months after stroke was found in those patients who reached some voluntary movement over the hip, knee, or foot (FMA lower-extremity subscore >10 points).

The rather low predictive value of clinical assessment in the acute phase might be due to the difficulty of clinical assessment of motor functions in the first weeks after stroke, particularly in patients suffering from concurrent cognitive deficits such as aphasia, apraxia, or sensorimotor neglect. These patients may lack the ability to move the arm and its segments selectively, whereas clinical scores such as the FMA rely on the patients' ability to voluntarily and selectively move their extremities. Therefore, early motor assessment may be biased by severe cognitive deficits. Particularly in these patients, neurophysiological assessment might be of additional value to clinical assessment.

Spasticity

Spasticity is a characteristic feature of the upper motor neuron syndrome in the post-acute and chronic phases of stroke. Spasticity develops in 20-40% of all stroke survivors, usually within 3 month after stroke [15-19]. It is defined as a velocity-dependent increase in muscle resistance against passive lengthening due to a supra-spinal disinhibition of both tonic and phasic stretch reflexes [20]. However, the spastic movement disorder is also characterised by efferent symptoms such as loss of selective muscle control and force, delayed and disrupted muscle synergies (e.g., co-contractions), or remote involuntary (associated) muscle activity during active movements, as well as massive flexion or extension reactions to touch, pain, and passive muscle stretch. In the upper extremity, spasticity may cause great difficulty

with arm positioning, grasping, self-care and other activities of daily living, in particular when spastic antagonists counteract selective voluntary muscle activity [19, 21-23]. In the long-term, untreated spasticity may lead to secondary complications such as changes in the visco-elastic properties of the musculo-tendinous apparatus, the development of contractures, and pain, which may further impede the functional use of the affected limb [16, 24].

Until now, anti-spastic treatments are usually instituted after spasticity has developed. Early and more pro-active treatment of spasticity with focal techniques (e.g., muscle injections with Botulinum toxin type A) applied in patients with a good potential for motor recovery, may result in a better functional outcome than currently achieved through the late application in unselected stroke survivors. The functional results of such treatments may inherently be improved by preventing secondary complications, learned disuse, and possibly adjusting reorganisation processes in the brain [9, 25]. However, not only stroke patients with a good potential for motor recovery may benefit from a pro-active treatment approach to prevent disabling spasticity. Even for patients with severe stroke it may be advantageous. In this subgroup, dexterity scores are anticipated to change only marginally and benefits can only be achieved with regard to “passive” skills in activities such as dressing, bathing and grooming, as well as with regard to limb positioning, cosmetics, and comfort [26-29].

This claim of possible therapeutic relevance requires further intervention studies. Furthermore, the clinical relevance of early identification of patients at risk of developing spasticity should be acknowledged considering the impact of spasticity on upper-extremity function and, subsequent also on quality of life after stroke [30]. Accurate, early prediction of spasticity is therefore considered relevant for developing a more proactive and efficient treatment approach than that is currently adopted in neurorehabilitation.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) of the human motor cortex is a non-invasive neurophysiological technique, which provides objective and quantitative information on the integrity and responsiveness of the corticomotoneuron and corticospinal tract [31, 32]. TMS activates the cortical motor neurons and their dendritic connections presynaptically by activation of interneurons (precortico-motoneuronal cells) projecting onto the cortical motor neuron pool. The cortical motor neuron discharges and, subsequently, corticospinal volleys are mediated via fast-conducting corticospinal connections. These connections within the corticospinal tract have direct, monosynaptic, terminations on the spinal alpha motor neurons that innervate the muscles of the hand and control independent and selective (fine manipulatory) finger movements. As a consequence, TMS is particularly effective in the

activation of distal hand muscles [33-35] in which a short-latency motor evoked potential (MEP), as an excitatory effect, can be recorded by surface electromyography (EMG) [32]. In tonically pre-activated muscles, TMS of the primary motor cortex induces a transitory suppression of the EMG-activity after the short-latency MEP, the silent period (SP), as an inhibitory effect as well (Figure 1).

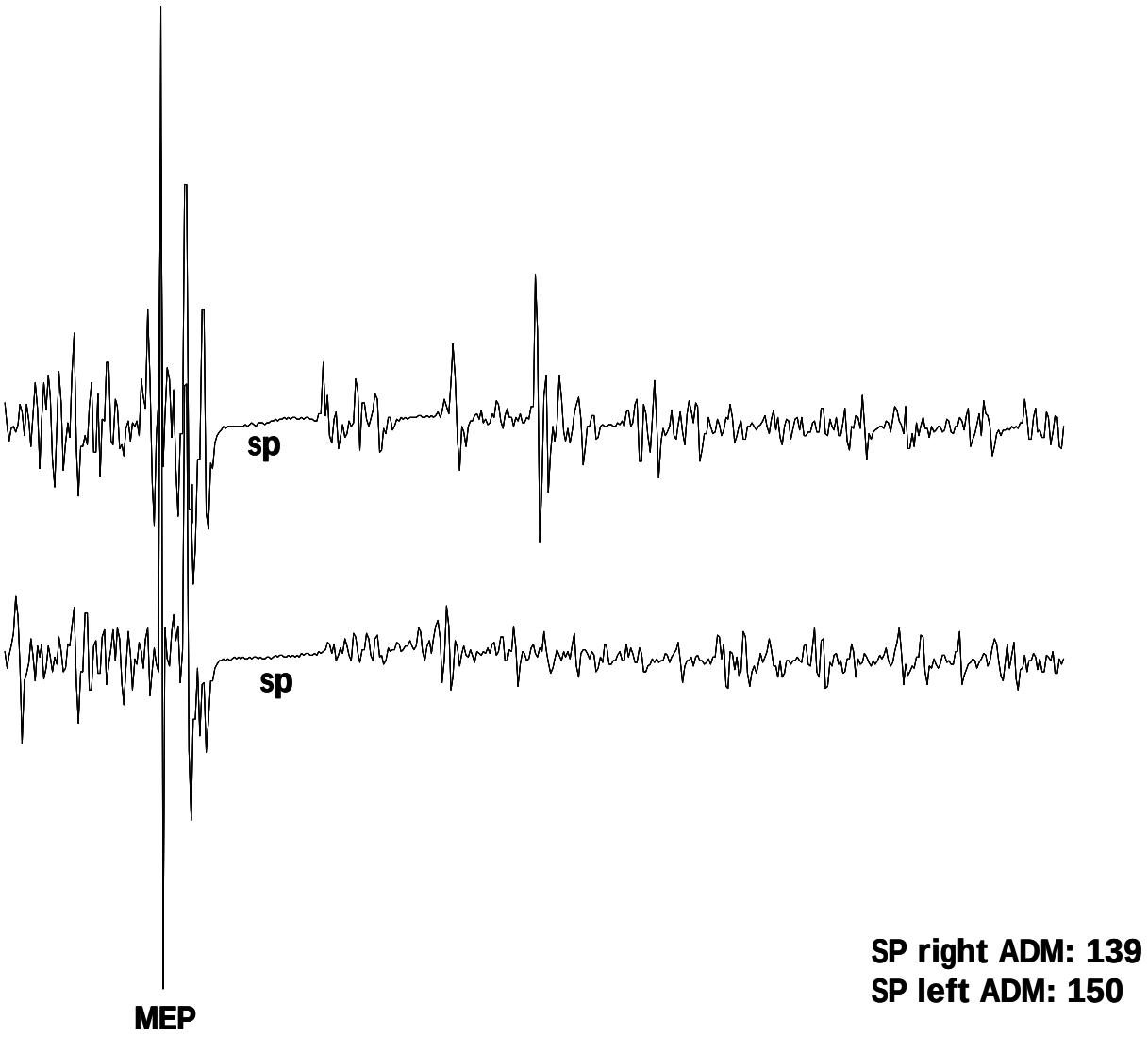

Figure 1. Example of a Motor-evoked potential (MEP) and Silent period (SP) in the abductor digiti minimi muscle (ADM).

The predictive value of the presence of a MEP with regard to motor recovery in patients with severe, middle cerebral artery stroke and an initial upper-extremity paralysis has been established previously [36, 37]. These studies consistently showed high specificity of the presence of a MEP (nearly 100%) in those patients who will show motor recovery. In

contrast, sensitivity was lower and more variable (62-94%), indicating that not all patients who will show motor recovery can be identified by the presence of an early MEP. In this perspective, the SP has been proposed as an additional parameter (to MEP) for predicting hand motor recovery. It has been suggested that the degree of shortening of the SP during the sub-acute phase after stroke correlates with the amount of hand function recovery [38-40]. There is also a possibility that the SP may be of value in predicting the development of post-stroke spasticity [40-42]. However, only few, well designed, TMS-studies on the prognostic of the SP with regard to both post-stroke motor recovery and spasticity have been performed with rather inconsistent results [38-41].

In the case of severe post-stroke cognitive deficits, the additional value of neurophysiological assessment (including TMS) to clinical assessment is anticipated to be substantial with regard to early prediction of both motor recovery and spasticity. However, the routine clinical application of TMS to predict motor recovery or the development of spasticity in individual stroke patients is still controversial [43]. There is some concern about the practical, clinical consequences of TMS in terms of improved prognostication in stroke patients [43]. At present, there is no consensus on the preferred methodology, because the precise technique and TMS characteristics used have not been standardized. Moreover, “evidence” is often based on cross-sectional studies that do not account for the non-linear nature of stroke recovery, which makes it difficult to validly generalize this information to longitudinal recovery processes. Because the results of relatively few well-designed prognostic studies are available to be integrated in stroke rehabilitation programs, a gap still remains between prognostic research and rehabilitation practices. In this perspective, there is a need for valid data on the predictive value of both MEP and SP for both motor and functional recovery from stroke (including the development of spasticity) to better substantiate the place that neurophysiological assessment deserves in making a functional prognosis in individual patients.

Objective of this thesis

This PhD-thesis should be viewed against the gradually increasing acceptance that neurorehabilitation is in need for studies that can bridge the gap between “fundamental” and “clinical” research, particularly in the fields of basic and clinically applied neurophysiology. The pathophysiological processes underlying motor recovery after stroke and the development of spasticity are not well understood. It seems essential to enhance our knowledge of (cortical) reorganization processes to ultimately improve the effects of various treatment approaches on motor recovery in stroke patients. In this study, both clinical

examinations and neurophysiological techniques will be used to investigate the importance of the integrity of the corticospinal pathways for upper-extremity functioning.

This thesis focuses primarily on long-term hand motor recovery of the hemiplegic upper extremity in a homogeneous group of stroke survivors with a severe, supratentorial, ischemic stroke. The aim of this thesis is to investigate the predictive value of TMS characteristics for functional prognostication of the upper extremity in patients with a severe, middle cerebral artery stroke. More specifically, the additional value of MEP and SP will be compared to clinical examination with regard to both recovery of hand motor function and the development of spasticity in these severe stroke patients.

Outline of this thesis

This thesis is organized in 4 sections. Besides this introductory chapter, the first part ("*Introduction*"), provides an important rationale for studying post-stroke motor recovery and the development of spasticity. Chapter 2 contains a systematic review of the literature focusing on the treatment of upper-extremity spasticity in stroke patients by focal neuronal or neuromuscular blockade.

The second part ("*Prognostic studies*") focuses on the prediction of long-term hand motor recovery (Chapters 3 and 4) and the development of spasticity (Chapters 5 and 6) in the upper extremity in severe stroke patients. It contains a review addressing the question whether the SP can be of additional value (compared to MEP) with regard to post-stroke hand motor recovery (Chapter 3), as well as three cohort studies performed in a homogeneous group of stroke survivors with a supratentorial, middle cerebral artery stroke. The first cohort study (Chapter 4) focuses on the added value of the presence of a MEP to early clinical assessment with regard to predicting long-term hand motor function. In the second cohort study (Chapter 5), the incidence and time course of spasticity is reported, as well as the predictive value of clinical assessment with regard to the development of post-stroke spasticity. In the last cohort study (Chapter 6), the prognostic value of neuroradiological and neurophysiological parameters with regard to the development of upper-extremity spasticity is addressed.

The third part (*"Neurophysiological studies"*) starts with an investigation of secondary changes in the peripheral nervous system as a consequence of stroke (Chapter 7), followed by some important methodological considerations concerning TMS. Chapter 8 focuses on the question whether TMS characteristics differ between proximal and distal upper-extremity muscles in healthy subjects.

The last part (*"Conclusion"*) is the general discussion (Chapter 9), which elaborates on the reported findings of the above-mentioned studies in a more comprehensive manner. It also addresses the most important limitations of the studies included. Last but not least, implications for clinical practice and future studies will be discussed.

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Chapter 2

Treatment of upper-extremity spasticity in stroke patients by focal neuronal or neuromuscular blockade:

a systematic review of the literature

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Journal of Rehabilitation Medicine 2002; 34: 51-61

Abstract

Objective: The primary aim of this study was to reveal the clinical effects of focal neuronal and neuromuscular blockade in post-stroke upper-limb spasticity.
Methods: Systematic review of studies published from January 1966 until October 2000 on the clinical effects of focal neuronal and neuromuscular blockade in post-stroke upper-limb spasticity. Twelve studies were included and evaluated on 13 methodological criteria.
Results: Ten studies on Botulinum toxin type A (BTX-A) treatment were found (of which 4 RCTs and 6 uncontrolled observational studies), as well as one uncontrolled observational study on phenol blockade of the subscapular muscle and one on alcohol blockade of the musculocutaneous nerve. The homogeneity of the patient groups with regard to diagnosis and their comparability with regard to functional prognosis and other sources of bias were generally unsatisfactory. Only two RCTs met the predetermined criteria of minimal validity.
Conclusions: There is evidence of effectiveness of BTX-A treatment on reducing muscle tone and improving passive range of motion at all arm-hand levels in chronic stroke patients for approximately 3 to 4 months. Effectiveness of BTX-A treatment on improving functional abilities could not be convincingly demonstrated, although two subgroups were identified that might specifically benefit at a functional level: 1) patients with mild spasticity and a potential for voluntary extensor activity, and 2) patients with severe spasticity suffering from problems with positioning and taking care of the affected arm and hand.

Introduction

Spasticity is a characteristic component of the upper motor neuron syndrome that complicates the rehabilitation process of many stroke patients. It is usually defined as a velocity-dependent increase in muscle resistance against passive lengthening due to a supraspinal disinhibition of both tonic and phasic stretch reflexes [1]. However, spasticity is also characterised by delayed and disrupted muscle synergies (e.g., co-contractions) or remote involuntary (associated) muscle activity during active movements, as well as by massive flexion or extension reactions to touch or pain stimuli [2, 3]. Spasticity can interfere with the functional use of the affected body parts, in particular when spastic antagonists counteract selective voluntary muscle activity. In the long term, untreated spasticity may lead to secondary complications such as muscle stiffness, contractures, and pain. In the upper extremity of stroke patients, spasticity most frequently emerges in a predominant flexion pattern. It may cause great difficulty with arm or hand positioning in space, grasping, self-care, and many other activities of daily living (ADL) [4, 5].

The management of spasticity remains a major challenge in rehabilitation medicine. The available treatment options include various physical methods (e.g., muscle lengthening, splinting, electrostimulation), systemic use of spasmolytic drugs, soft-tissue surgery (e.g., muscle-tendon lengthening or transposition, tenotomy, neurectomy), as well as several invasive procedures for focal neuronal or neuromuscular blockade [4-13]. The ideal treatment strategy would be to achieve a long-lasting relief of disabling hypertonia in selected groups of muscle fibres without causing impairment of sensation, deterioration of motor skills, or other local or systemic side-effects [14]. Because spasticity is a variable phenomenon in time and apparent only in certain muscle groups, the application of low-threshold and "reversible" focal treatment techniques seems to be the preferable first option. Besides peripheral and intramuscular neurolysis (e.g., with phenol), intramuscular administration of Botulinum toxin type A (BTX-A) is increasingly applied in stroke patients.

Phenol has two different actions on nerve tissue. The first, immediate and reversible effect is a local anaesthetic nerve conduction blockade [15, 16]. The second, long-term effect is demyelination and axonal degeneration by denaturation of proteins [17-21]. Through the same mechanism, phenol causes atrophy within muscle tissue [22, 23]. Although phenol blocks act non-selectively across nerve fibres, the extent of the blocks may depend on the injection technique (e.g., perineural or intraneural) and the phenol concentration used. The reported duration of neurolytic blocks with phenol varies between 6 weeks and 6 months, depending on the technique, as well as on the time required for remyelisation and axonal regeneration. Dysaesthesia and neuralgia are among the most frequently reported side-effects of neurolytic blocks [21, 24-40].

Recently, neuromuscular blockade with BTX-A has been introduced as an alternative to focal neurolysis in the management of spasticity [41-43]. BTX-A weakens the activation of spastic muscles by selectively blocking the release of acetylcholine at the neuromuscular junction of both extrafusal and intrafusal muscle fibres. Its effect seems to be to some extent dose-dependent and usually lasts 2 to 4 months [44-49]. An important advantage of motor-point blockade over neurolysis is the absence of sensory disturbances.

At present, there is no consensus about the preferred strategy, precise method of administration, and optimal dosage in the focal treatment of upper-limb spasticity following stroke. Valid comparisons of studies concerning the efficacy of different methods for focal neuronal or neuromuscular blockade in stroke are complicated because of differences in selected patients, treatment goals, and functional evaluations. The goal of this study was to provide preliminary clinical guidelines and suggestions for future research through conducting a systematic review of the literature.

Methods

Study selection

Material for the review was selected from a systematic search in the databases of Medline (January 1966-October 2000), Current Contents (January 1996-October 2000), Cinahl (January 1982- October 2000), and the Cochrane Library. This search was conducted using the following combinations of search terms: spasticity, chemical neurolysis, intramuscular neurolysis, chemical denervation, neuromuscular blockade, nerve block, motor point block, phenol, alcohol / ethanol, Botulinum toxin, thermo-coagulation, cryotherapy, and neurotomy / neurectomy. Identifying relevant references from the retrieved articles extended the search. Only studies concerning the treatment of upper-extremity spasticity by focal neuronal or neuromuscular blockade in adult stroke patients and published in the English, German, French, or Dutch languages were considered. After the primary search, the papers were subjected to a preliminary screening based on the following exclusion criteria: (1) studies not primarily addressing aspects of clinical efficacy, (2) reviews, (3) comments or letters to the editor, (4) preliminary reports or abstracts, (5) heterogeneous patient samples in which the stroke patients could not be identified, (6) sample sizes smaller than 10 patients, (7) papers not available in medical libraries in the Netherlands. Ultimately, the remaining studies were selected for detailed methodological evaluation.

Methodological evaluation

Both internal validity (V) and data extraction (D) were assessed. We established adapted V and D criteria based on a system that was originally developed for evaluating randomised controlled trials (RCTs) [50]. Adaptation of these criteria was necessary to be able to evaluate other study designs than RCTs. Each criterion was scored according to three levels: sufficient (+) (all subcriteria fulfilled), moderate (+/-) (all but one subcriterion fulfilled), or insufficient (-) (other). When a specific criterion was not applicable, it was scored as such (0). Criteria V5, D3, D5, and D6 had no subcriteria. Hence, these were scored only with sufficient (+) or insufficient (-). All selected studies were independently assessed by 3 referees (AK, AG, BB). In the case of disagreement between referees, consensus was established in second instance.

Internal validity

V1: The homogeneity of the study sample with regard to stroke and spasticity was tested. (1) A diagnosis of stroke by clinical standards was accepted, preferably confirmed by CT or MRI scanning. (2) Spasticity, being a velocity-dependent increase in muscle resistance on passive stretching, should clearly be distinguished from other types of hypertonia, muscle stiffness, and contracture.

V2: Control of bias related to functional prognosis *before* exposure to the therapeutic intervention was judged for the controlled trials. Based on the literature, three such potential confounders were identified: (1) the severity of stroke judged by its sensorimotor and cognitive consequences, (2) the chances of neurological recovery based on the time after stroke [51, 52], and (3) co-morbidity with a possible effect on the outcome of the therapeutic event (e.g., concomitant rheumatic or neuromuscular disease). As for the observational studies, the homogeneity of the (sub)group(s) with respect to these factors was judged. Furthermore, a minimal time interval after stroke of 6 months was considered appropriate to assume a relatively stable clinical situation [51, 52].
V3: This criterion tested whether there had been sufficient control for potential confounding *during* the study. More specifically, (1) paramedical co-interventions (e.g., physiotherapy) and (2) concurrent use of medication (e.g., spasmolytic drugs) should have been reported and taken into account. As for the observational studies, all co-interventions should have been kept stable during the follow-up period.
V4: Adequacy of technical aspects of the therapeutic intervention was assessed. Studies should have indicated: (1) concentration and volume of substance applied, (2) whether a fixed or individualised treatment algorithm was used, and (3) how target muscles were localised. Only injections guided by internal electrical stimulation or electromyography were considered appropriate [53-55].
V5: The selected study design was evaluated in relation to the study aim. Randomised controlled trials were accepted as was any other design with the ability to control for confounding, for instance, a cohort study making within-subjects comparisons of experimental and control interventions allowing sufficient wash-out periods.
V6: The (1) reliability, validity, and responsiveness of the selected outcome measures were assessed in relation to the study aim [56]. Also, (2) blinding of the outcome assessor was considered an absolute prerequisite for unbiased observations.

Data extraction
D1: This criterion tested (1) whether the inclusion and exclusion criteria were sufficiently reported, as well as (2) whether the base population was identified from which the study sample was selected.
D2: It was judged whether treatment effects were adequately reported in terms of (1) statistical (e.g., *F*- and *p*-values or confidence intervals) and (2) quantitative measures (e.g., absolute or relative differences).
D3: The length of the total follow-up period was assessed.
D4: This criterion tested the numbers of patients lost to follow up.
D5: It was determined whether intention-to-treat analysis was done in the case of any loss to

follow up, non-compliance, or unplanned crossovers.
D6: Description of adverse effects was assessed.
D7: The total number of included stroke patients at baseline was determined.

Criteria of minimal validity
Based on the scores for all criteria mentioned above, those studies were identified that were able to meet the following minimal criteria of validity: (1) no negative scores on the internal validity items, and (2) at least half of the items scored positive (+). These studies were primarily used for establishing clinical evidence. All other studies were considered to yield merely secondary evidence.

Results

The primary search yielded 116 papers, including preliminary reports and abstracts. After the preliminary assessment, 12 studies were included for detailed methodological evaluation [57-68]. Ten studies focused on the treatment of upper-limb spasticity with BTX-A [57-66], one focused on alcohol neurolysis [67], and one study dealt with phenol neuromuscular blockade [68]. No studies were found concerning the treatment of upper-limb spasticity with neuromuscular blockade using thermocoagulation or cryotherapy. Studies addressing neurectomy consisted of combined treatment procedures including soft-tissue surgery. For this reason these studies were excluded from further evaluation. The BTX-A treatment studies included 4 RCTs and 6 uncontrolled observational studies. Both the study on alcohol neurolysis and the one dealing with phenol nerve blockade were observational studies. The results of the assessment of both V- and D-criteria for all 12 studies are given in Table 1. Here, the RCTs will first be critically reviewed in more detail, whereas some of the methodological issues related to the observational studies will only be globally highlighted.

Randomised controlled trials
Three trials [57-59] studied the efficacy (and safety) of different dosages of BTX-A in the reduction of upper-limb spasticity in stroke patients using a randomised, triple-blind (patient, physician, and outcome-assessor), placebo-controlled design. Both Simpson et al. [57] and Bakheit et al. [58] presented multi-centred studies. Only Smith et al. [59] included two patients with head injury. Although Smith et al. [59] claimed to have excluded patients with fixed contractures, the reported results on joints range of motion (ROM) suggested the existence of contractures in their study sample. No study explicitly differentiated between spasticity and other types of increased muscle tone. The control for the influence of sensorimotor and cognitive functioning on outcome was considered insufficient in all three

Table 1. *Methodological evaluation*

		Randomised controlled trials				Observational studies							
		Hesse 1998	Simpson 1996	Bakheit 2000	Smith 2000	Lagalla 2000	Reiter 1996	Sampaio 1997	Bhakta 1996	Rodriquez 2000	Pierson 1996	Kong 1999	Hecht 1992
	Internal validity												
V1	Homogeneity with regard to definition of stroke and spasticity	+/-	+/-	+/-	-	+/-	-	+/-	-	+/-	-	+/-	-
V2	Control of bias related to functional prognosis before intervention	+/-	+/-	-	+/-	+/-	+/-	+/-	+/-	+/-	-	-	-
V3	Control for confounders during the study	+	+/-	+/-	-	+	-	+/-	-	+/-	-	+/-	+/-
V4	Description and adequacy of technical aspects of the therapeutic intervention	+	+	+/-	-	+	+	+/-	-	+	+	+	+
V5	Adequacy of study-design	+	+	+	+	+/-	+/-	-	-	-	-	-	-
V6	Adequacy of effect parameters	+	+	+	+	+/-	+/-	+/-	-	+	-	+/-	-
	Data extraction												
D1	Description of in- and exclusion criteria	+	+/-	+/-	+/-	+	+/-	+/-	+/-	+	+/-	+	+
D2	Adequacy of statistical and quantitative analysis	+/-	+/-	+	+/-	+	+/-	+	+	+/-	-	+/-	+
D3	Length of follow up	12 weeks	16 weeks	16 weeks	12 weeks	2 years	6 months	3 months	4-47 weeks	variable	4-24 months	6 months	none
D4	Loss to follow up	0	2	1	0	6	?	0	6	12	7	0	0
D5	Intention to treat analysis	0	-	+	0	-	-	0	-	-	-	0	0
D6	Description of adverse effects	+	+	+	+	+	+	+	+	-	+	+	+
D7	Sample size	24	37	83	19 2 TBI	34	15 2 TBI	19	17	14	11	20	11 2 TBI
	Minimal criteria of validity	yes	yes	no	no	no	no	no	no	no	no	no	no

TBI = traumatic brain injury

studies. In the study of Bakheit et al. [58], the control for the influence of spontaneous recovery was also considered moderate, because patients were allowed to enter the study already 3 months after their stroke, whereas the other RCTs used minimal post-stroke intervals of 9 [57] and 12 months [59]. As for co-morbidity, only Simpson et al. [57] explicitly excluded other neuromuscular diseases. Ongoing spasticity treatments (e.g., medication, physiotherapy) were maintained during the trial by Simpson et al. [57], but could differ between patients. Bakheit et al. [58] did not allow de novo treatment with spasmolytic drugs, whereas Smith et al. [59] did not control for any type of concurrent intervention. Bakheit et al. [58] determined the injection sites only by using anatomical landmarks. Smith et al. [59] used a partially individualised treatment algorithm, which was insufficiently specified. Moreover, no specifications of the localisation technique or of injected volumes were given.

In none of the three RCTs mentioned above, the base populations from which the study samples had been selected were clearly identified. Both Simpson et al. [57] and Smith et al. [59] primarily analysed within-group changes from baseline for different aspects of spasticity, where the preferable analysis should have consisted of between-group comparisons of changes from baseline. No statistical corrections were made for multiple testing of similar hypotheses. Although Bakheit et al. [58] mentioned a follow-up period of 16 weeks, the main analysis was performed using changes from baseline at 4 weeks after the intervention. Simpson et al. [57] lost 2 patients to follow up without specifying the precise reasons for drop out, or the group to which these patients had been allocated. Although Smith et al. [59] had no dropouts, 4 patients (of which 3 stroke patients) crossed over who had been originally allocated to placebo treatment.

These patients were re-randomised to one specific dosage of BTX-A. As a result, there was a source of selection bias for which the analysis was not adjusted. Considering the small sample sizes in the four parallel groups, there should be a major concern about lack of statistical power in the studies by Simpson et al. [57] and Smith et al. [59].

Hesse et al. [60] conducted a randomised, triple-blind, placebo-controlled trial on the efficacy of combining BTX-A with electrical stimulation (ES) in the reduction of upper-limb spasticity in stroke patients compared to single treatments using a four-arm parallel design (BTX-A + ES, BTX-A, placebo + ES, placebo). All patients received additional treatment consisting of physiotherapy and home exercises. There was no explicit differentiation between spasticity and other types of increased muscle tone. The possible influence of sensorimotor and cognitive functioning, and the influence of co-morbidity on outcome were not controlled for. As for the data analysis, the primary outcome measures at 2, 6, and 12 weeks were averaged and the mean post-injection value was used to determine the treatment effect on

different aspects of spasticity. As a result, no adjustments were made for the (small) differences in outcome measures at baseline. Moreover, by averaging effects over time, relatively small and temporary effects may have been obscured by false negative statistical tests (type II error) especially in view of the small group sizes (n=6) and the correction of alpha (chance of type I error) to 1%.

Observational studies

No study explicitly differentiated spasticity from other types of increased muscle tone. In (almost) all observational studies the study samples were heterogeneous with regard to patient characteristics related to diagnosis, severity of stroke, chance of neurological recovery, and co-morbidity. Only few studies controlled for ongoing spasticity treatments [61, 64-67]. Small sample sizes were common and in some studies [63, 64, 66] loss to follow up was unacceptable (> 33%). Therefore, no detailed methodological evaluation of the observational studies will be given. Instead, the reader is referred to Table 1.

Discussion

Although focal neuronal and neuromuscular blocks are increasingly used in clinical practice for the treatment of post-stroke upper-limb spasticity, the number and quality of the traced publications investigating the efficacy of these treatments is as yet limited. Four randomised controlled trials were identified [57-60], whereas other studies reported uncontrolled observations [61-68]. Of all selected studies, only two met the predetermined criteria of minimal validity [57, 60]. These studies will be primarily used for discussing clinical effectiveness. Nevertheless, the outcomes of several other studies will still be considered because they may yield secondary (supportive) evidence of effectiveness and safety, and provide important perspectives for further research. The treatment goals and outcome measures of each selected study are given in Table 2. The applied treatment protocols and main clinical outcomes are summarised in Table 3.

Alcohol or phenol

Kong et al. [67] reported a case series on the effectiveness of neurolysis of the musculocutaneous nerve with alcohol on post-stroke elbow flexion spasticity. Although patients with fixed elbow flexion contractures were included, significant improvements in tone and PROM were found with effects lasting up to 6 months. Hecht [68] reported a case series of patients with therapy resistant shoulder pain due to spasticity. Patients were given a motorpoint block of the subscapularis muscle with phenol and the immediate post-injection effects were determined. Although immediate improvements in PROM were seen, the

authors did not use an adequate measure for determining shoulder pain (patient observation during passive shoulder examination). In both studies the most common reported side effect was a transient soreness over the injection side. In the study on alcohol neurolysis [67], three patients (15%) suffered from temporary dysesthetic pain, which could be reasonably treated with amitriptyline or non-steroidal anti-inflammatory drugs. The only conclusion one can draw based upon these uncontrolled studies is that phenol or alcohol may be used as a potential agent for reducing spasticity and improving PROM in the upper extremity of stroke patients by neuronal or neuromuscular blockade, but that controlled comparative studies (e.g., with BTX-A) are urgently needed. Particular attention should be paid to comparing side effects and cost-effectiveness. This conclusion seems to be supported by the literature on the treatment of post-stroke spasticity with phenol or alcohol in general [24-40, 70-73].

Botulinum toxin

The efficacy of BTX-A treatment on tone and PROM was demonstrated by the RCT performed by Simpson et al. [57] and supported by other studies [58, 59, 61-66]. In addition, Hesse et al. [60] found evidence of a synergistic effect of ES combined with BTX-A treatment. In particular, the combined treatment of BTX-A and ES seemed superior with regard to the facilitation of hand hygiene and spasticity reduction. This synergism might be explained by a stimulating effect of ES on the uptake of BTX-A in the terminal nerve branches. Therefore, the degree of motor activity may be an important factor for the potency of BTX-A. Although Hesse et al. [60] did not find a statistically significant reduction in spasticity in the BTX-A only group compared to the placebo group, an average reduction of 0.5 Ashworth score at 6 weeks was still seen, which may not have been reached statistical significance due to the small group size (n=6) (see results).

Dosage and duration of effects. Although a clear dose-response relationship could not be demonstrated, a tendency for a dose-related improvement of the Ashworth score and PROM was seen in the studies of Simpson et al. [57], Smith et al. [59], and Bakheit et al. [58]. Their results suggest a critical dosage of BTX-A to achieve a clinically significant tone reduction. The reported doses were globally 200 MU Botox® (600 to 1000 MU Dysport®) for the biceps, 100 MU Botox® (400 to 500 MU Dysport®) in total for the wrist flexors, and 100 MU Botox® (300 MU Dysport®) in total for the finger flexors. These dosages seem to correspond with the suggested maximal dose of the dosing guidelines for adult onset spasticity by the Spasticity Study Group [69].

The duration of the reported effects varied between 10 weeks and 4 months [57-66]. The first effects of treatment became apparent not earlier than 2 to 3 days after injection [63], and the peak effects were reported between 2 to 6 weeks after injection [62, 65]. The efficacy of

repeated BTX-A injections was specifically studied by Lagalla et al. [61]. All patients exhibited a tone reduction (mean reduction in MAS 1 point) and PROM increase (mean increase at the elbow: 5 degrees, at the wrist: 19 degrees) after the first injection, which effects remained constant across repeated injections. Although the dose injected over time did not change, the intervals between injections became significantly longer, which may possibly be related to a decreasing capacity for terminal neuronal sprouting.

It is not possible to further specify the optimal dose of BTX-A for the treatment of post-stroke upper-limb spasticity from the studies included in this review, because the magnitude and duration of the spasmolytic effects are theoretically influenced by the presence of other forms of hypertonia or muscle stiffness, as well as by loss of muscle length (and thus by concomitant therapy directed at these muscle characteristics), for which influences no study adequately controlled. In addition, the products and dosages of BTX-A differed considerably between studies (Table 3).

Safety. In all selected studies, only minor side effects were seen, such as transient skin rash [58], soreness, and pain at the injection sides [57, 61, 62, 66]. Incidentally, flu-like symptoms were reported [58, 59, 65] and in one study bladder instability was observed in one patient after BTX-A treatment [57]. The most serious reported side effect seems to be an excessive muscle weakness due to an overdose of BTX-A. This seems of particular functional importance for the finger flexors. Bakheit et al. [58] found a critical dosage for preserving active movement of the finger flexors at 300 MU Dysport®. This finding was supported by Rodriquez et al. [64], who reported a critical dosage of 100 MU Botox® for preserving active finger flexion. Hence BTX-A treatment seems to be a safe treatment for upper-extremity spasticity as long as these critical dosages are appreciated.

Functional abilities. Despite the reported improvements in tone and PROM of BTX-A treatment a clear impact on functional abilities could not be convincingly demonstrated. Also, the overall reported effect on global disability scores was minimal. Nevertheless, patients in the study of Smith et al. [59] reported that the arm felt looser and appeared more relaxed particularly during walking after BTX-A injection into the biceps brachii and brachialis muscles. Subjectively, beneficial findings in gait quality and balance were reported by some ambulatory patients. Sampaio et al. [65] reported improvement in functional ability of the affected arm as assessed by the Frenchay Arm Test (FAT benefit of 1 point) in patients who were able to perform only minimal voluntary movements of the upper limb before treatment. Lagalla et al. [61] reported a FAT benefit of 2 points in a similar subgroup of 8 patients (29%). Although Reiter et al. [62] did not find a beneficial effect on the median FAT in the total treatment group, subgroup analysis gave a more discriminative picture. One subgroup

(4/17) with relatively mild spasticity and voluntary motor activity of the extensor muscles showed an increase (5%) in median FAT score after BTX-A treatment. No changes in a global disability measure (FIM) were seen, which can be explained by a ceiling effect and lack of responsiveness of this measure to functional improvement of a single arm. A second subgroup (4/17) consisted of paralytic patients with relatively severe spasticity, in which BTX-A treatment resulted in PROM increase, better passive positioning of and care for the affected limb (e.g., easier fitting of splints).

Conclusion

This review emphasizes the importance of adequate patient and goal selection when treating upper-extremity spasticity in chronic stroke patients. Since most authors used a standardised treatment protocol, the muscles selected for treatment may not have been the most optimal targets adapted to the needs of individual patients. A more individualised approach based on the distribution of spasticity, as well as on a patient's personal needs might give a better indication of the potential functional benefits of BTX-A in treating upper-extremity spasticity following stroke. Indeed, the results of Hesse et al. [60] suggest that individualised goal attainment scales may be essential to identify relevant functional changes. To identify relevant functional changes, it is of utmost importance that adequate measures to quantify functional outcome in all stages of recovery will be developed. Moreover, larger controlled studies are needed to compare the effectiveness of different and / or combined treatment approaches to reduce focal spasticity in stroke patients. In particular, adequate clinical trials are needed to compare the efficacy of BTX-A neuromuscular blockade versus phenol nerve blockade in upper-limb spasticity. The application of neurolytic techniques (chemical or thermal) to some of the (predominantly) motor branches of the upper arm seems to be a promising area of further research. Special attention should be paid to comparisons of the (duration of) functional benefits, essential co-treatment and aftercare, the (duration and severity of) side-effects, as well as cost-effectiveness. Another important issue for further research is the identification of prognostic factors in patients at risk of developing disabling upper-limb spasticity and the early institution of anti-spastic treatments before secondary complications have been developed. Two subgroups may be identified that might specifically benefit at a functional level: (1) patients with mild spasticity and a potential for voluntary extensor activity at the wrist or fingers, and (2) patients with severe spasticity suffering from problems with positioning and taking-care of the affected arm and hand.

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Table 2. *Study-goal and outcome measures*

Author	Primary goal	Outcome measures		
		Technical/Impairment	Functional	Caregiver/patient objective
Hesse et al. (60)	Efficacy of combined BTX-A and ES on spasticity and related disabilities	• MAS • Limb position at rest	• 3 ADL activities • Global pain assessment score	
Simpson et al. (57)	Efficacy of BTX-A on spasticity and related disabilities	• Ashworth Scale • Grip strength • Arm circumference • Global assessment of spasticity scale (subjective)	• Fugl-Meyer Scale • FIM • Motor task/function rating scale • Caregiver dependency scale • Function and pain assessment	Rand 36-Item Health survey
Bakheit et al. (58)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM	• Rivermead motor assessment (arm section) • Barthel Index • Caregiver/patient assessment of three functional activities • Severity of muscle pain	
Smith et al. (59)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM • Postural alignment	• Frenchay arm test • Time to dress the upper half of the body • Video assessment of gait quality	
Lagalla et al. (61)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Rest position	• Frenchay arm test • Patient/caregiver goal assessment	
Reiter et al. (62)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • MRC	• FIM • Frenchay arm test • Motricity index • VAS	Nothingham Health profile

Table 2 continued

Author	Primary goal	Outcome measures		
		Technical/Impairment	Functional	Caregiver/patient objective
Sampaio et al. (65)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Grip strength • Frequency of spasm	• Frenchay arm test • Severity of pain	Degree of satisfaction of the patient
Bhakta et al. (63)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Finger position at rest	• Patient defined ADL goal assessment • Presence and location of pain	
Rodriquez et al. (64)	Efficacy of BTX-A on spasticity	• MAS • Clonus scale • Grip strength • Videotaping finger extension		
Pierson et al. (66)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM	• Brace tolerance measure • Ambulation score • Pain rating scale	Patient satisfaction report
Kong et al. (67)	Efficacy of alcohol neurolysis on spasticity	• MAS • PROM • MRC-scale		
Hecht (68)	Efficacy of phenol neurolysis on spasticty	• PROM	• Pain subjectively rated by therapist	

BTX-A= Botulinum Toxin type A; ES= Electrical (neuromuscular) Stimulation; MAS= Modified Ashworth Scale; ADL= Activities of Daily Living; FIM= Functional Independence Measure; AROM= Active range of motion; PROM= Passive Range of Motion; MRC-scale= Medical Research Council scale; VAS= Visual Analogue Scale

Table 3. *Treatment algorithm and main outcome*

Author	Product	Treatment algorithm	Muscle/Nerve	Main outcomes
Hesse et al. (60)	Dysport	Fixed regime (4 arms): • 1000 BTX-A + ES • 1000 BTX-A • placebo + ES • placebo	• Biceps, Brachialis • FCR, FCU • FDP, FDS	• Tone reduction most prominent in group receiving BTX-A and ES; mean reduction in MAS at 6 weeks at the elbow 1.3 points, at the wrist 1.7, and at the fingers 1.5 points • Position at rest better in group receiving BTX-A and ES • Cleaning the palm of the affected hand significantly better in group receiving BTX-A and ES
Simpson et al. (57)	Botox	Fixed regime (4 arms): 75, 150, 300 MU, and placebo Biceps: 50 100 200 FCR: 15 30 60 FCU: 10 20 40 75 150 300	• Biceps • FCR, FCU	• Significant tone reduction in BTX-A treated groups compared to placebo; mean reduction in Ashworth score at 6 weeks 0.8 points at the elbow and wrist • Significant tone reduction in wrist and elbow flexors in high BTX-A dosage group; mean reduction in Ashworth score at 6 weeks 1.1 points at the elbow, and 1.2 points at the wrist • Peak effect 2-6 weeks post injection; return to baseline by 10 weeks
Bakheit et al. (58)	Dysport	Fixed regime (4 arms): 500, 1000, 1500 MU, and placebo Biceps: 200 400 600 FCR: 75 150 225 FCU: 75 150 225 FDP: 75 150 225 FDS: 75 150 225 500 1000 1500	• Biceps • FCR, FCU • FDP, FDS	• Significant tone reduction at week 4 in BTX-A treated groups compared to placebo • Significant tone reduction during 16 weeks follow up at the wrist and elbow; less clear at the fingers • Effect most prominent in high dosage group • Significant improvement in PROM at all joints, no differences between doses

Table 3 continued

Author	Product	Treatment algorithm	Muscle/Nerve	Main outcomes
Smith et al. (59)	Dysport	Individualised treatment algorithm (4 arms): 500, 1000, 1500 MU, and placebo. 2/3 above elbow; 1/3 beneath elbow If only elbow, wrist, or finger flexors: 2/3 of total dosage	• not specified	• Significant tone reduction in BTX-A treated groups compared to placebo; mean reduction in MAS at week 6 at the elbow 1 point, at the wrist and fingers 2 points • Significant improvement in PROM at wrist, and in finger curl distance at week 6 in BTX-A treated groups compared to placebo; mean increase in PROM 9 degrees at the elbow, and 14 degrees at the wrist • Significant improvement in PROM at the elbow in 1500 MU group at 6 weeks (mean increase 19 degrees); tendency for dose related tone reduction • 6/9 patients improvement in gait quality • Effects lost by 12 weeks except for PROM elbow in 1500 MU dose
Lagalla et al. (61)	Botox	Individualised treatment algorithm: Total dosages 50-300 MU. Total dosage per muscle 25-75 MU.	• Biceps, Brachialis • FCR, FCU • FDP, FDS • FPL	• Significant tone reduction after first injection; mean reduction in MAS 1 point • Significant improvement in rest position and PROM; mean increase in PROM at the elbow 5.2 degrees, at the wrist 19.0 degrees, fingers MCP 13.7 degrees, and IP 7.1 degrees • FAT increased 1 to 3 points in 8/28 patients • Steady improvement in patient and caregiver satisfaction • No changes in doses injected over time, intervals between BTX-A injections significantly lengthened • Cost of treatment solely influenced by initial Ashworth score
Reiter et al. (62)	Botox	Individualised treatment algorithm: 3-5 upper limb flexors total dosages 100-210 MU.	• Biceps • FCR, FCU • FDP, FDS • FPL	• Significant tone reduction after 1 month; mean reduction in MAS 1.2 points at the elbow, 1.4 at the wrist, and 1.0 at the fingers • Significant improvement in PROM at the elbow 36.1 degrees, at the wrist 36.5 degrees, and at the fingers 27 degrees • Increased wrist and finger extension force in 4/12 patients • VAS score changed significantly • Effect apparent after 1 week; peak effect within 30 days; steady for an average of 3.6 months

Table 3 continued

Author	Product	Treatment algorithm	Muscle/Nerve	Main outcomes
Sampaio et al. (65)	Botox	Individualised treatment algorithm: 6 prior defined muscles. Max dosage 25 MU per muscle, 150 MU in total.	• FCR, FCU • FDP, FDS • FPL, FPO	• Significant tone reduction at 1 month; mean reduction in MAS 1 point • Significant improvement in passive joint mobility score at 1 month; mean improvement 1 point • Improvement of mean FAT value from 0 to 1 point • Frequency of spasm decreased in 4 patients to 0 • Severity of pain decreased in 2 patients to 0 • Effect apparent after 1 week; peak effect 1 month post-injection; persisted up to 3 months
Bhakta et al. (63)	Dysport Botox	Individualised treatment algorithm: Allergan 100 MU/2.5 ml Dysport 500 MU/2.5 ml Total dosages 130-1000 MU	• Biceps • FCR, FCU • FDP, FDS	• Significant tone reduction post injection; mean reduction in MAS 2 points at the elbow and 1 point at the fingers • Significant PROM improvement post injection; mean increase of PROM at the shoulder 17 degrees, at the elbow 16 degrees, and at the wrist 31 degrees • Functional benefit reported in 14/17 patients • Shoulder pain in 9/17 patients, reduction in 6/9 patients; pain at the elbow in 3/17 patients, reduction in 3/3; at the wrist in 6/17patients, reduction in 5/6 • Effect apparent after 2-3 weeks after injection, lasting for 4-47 weeks • Beneficial effects on distance
Rodriquez et al. (64)	Botox	Fixed regime: 50 MU into long finger flexors	• FDP, FDS	• Significant reduction in tone; mean reduction in MAS 1 point • Significant reduction of clonus; improvement in finger extension • Significant decrease in grip strength • Changes between two injections in tone and clonus not significant; finger extension increased significantly

Table 3 continued

Author	Product	Treatment algorithm	Muscle/Nerve	Main outcomes
Pierson et al. (66)	Botox	Individualised treatment algorithm	• Biceps • FCR, FCU • FDP, FDS, FPL • abductor digiti minimi quinti	• Significant reduction in tone; mean reduction in MAS 1 point • Significant improvement in AROM (mean 17 degrees), PROM (mean 18.4 degrees), and brace wear • Beneficial effect on pain, subjective functional improvement, satisfaction with treatment outcome • Duration of effect lasted up to 4-5 months
Kong et al. (67)	Alcohol	Until abolition of muscle contracture	• n. musculocutaneous	• Significant reduction in tone at 4 weeks; mean reduction in MAS 1 point • Significant improvement in PROM (mean 17 degrees) at 4 weeks • Improved walking balance in 7/14 patients • Relief of shoulder pain reported • Effect lasted up to 6 months
Hecht (68)	Phenol	Motor point block subscapularis muscle	• m. subscapularis	• Immediate improvements ROM in flexion, abduction, and exorotation. Largest improvement in exorotation (42%), next flexion (22%) and abduction (12%) • Pain diminished in original arc of motion, but still present at extremes of end range • Effect lasted for 3-6 months

FCR= flexor carpi radialis; FCU= flexor carpi ulnaris; FDP= flexor digitorum profundus; FDS= flexor digitorum superficialis; FPL= flexor pollicis longus; FPO= flexor pollicis opponens; BTX-A= Botulinum toxin type A; ES= Electrical (neuromuscular) Stimulation; MU= Mouse Units; ROM= Range of Motion; PROM= Passive Range of Motion; AROM= Active Range of Motion; FAT= Frenchay Arm Test; VAS= Visual Analogue Scale; MAS= Modified Ashworth Scale

Chapter 3

How salient is the Silent Period?

The role of the silent period in the prognosis of upper-extremity motor recovery after severe stroke

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Abstract

Objective: The primary aim of this study was to reveal the additional value of the silent period (SP) to the motor evoked potential (MEP) with regard to the prediction of motor recovery in acute stroke patients with an initially severe paresis or paralysis of the upper extremity.
Methods: Narrative review of the literature and a case series focusing on the additional value of the SP to the MEP for predicting post-stroke hand motor recovery. *Results:* Studies that have analyzed the SP for predicting post-stroke motor recovery have rather inconsistent results and suffer from heterogeneity in technical methods, methodology, and patient characteristics. In most studies prolonged SPs have been found immediately after stroke, whereas in the (sub)acute phases thereafter, different patterns of SP duration have been found. Post-stroke reduced SPs and contraction-induced inhibitory phenomena have been associated with spasticity. However, in the majority of the patients with a severe, middle cerebral artery stroke the voluntary contraction of the hand muscles was so severely impaired that no SP could be recorded.
Conclusions: In acute stroke patients with an initial severe paresis or paralysis, the SP seems to have no additional value to MEP for predicting post-stroke hand motor recovery. Although the relation between the SP, recovery-related intracortical phenomena, and spasticity remains as yet unclear, the SP has been proposed as a prognostic factor for post-stroke spasticity.

Introduction

Motor impairments of the upper extremity are among the most common and therapeutically challenging sequellae of stroke. In stroke patients with initially severe motor impairments, the prognosis with respect to motor recovery and subsequent functional recovery is usually poor [1-4]. Most patients will end up with a non-functional arm [5-10], although some patients may show partial or even complete motor recovery [1-4]. Early prediction of motor recovery based on clinical and radiographic findings in severe stroke patients is, however, very difficult, particularly when patients suffer from aphasia, apraxia, or sensorimotor neglect. In these patients neurophysiologic assessment may be of additional value in providing objective, reliable, and quantitative data on the integrity of the corticospinal pathways [11-12].

Transcranial magnetic stimulation (TMS) of the motor cortex is a non-invasive neurophysiological technique in which motor potentials are evoked by magnetical stimulation of the motor cortex. TMS activates the cortical motor neurons and their dendritic connections presynaptically [11, 13-15] by activation of interneurons (precortico-motoneuronal cells)

projecting onto the cortical motor neuron pool. The cortical motor neuron discharges and, subsequently, corticospinal volleys are mediated via fast-conducting corticospinal connections [11, 13, 15, 16]. These connections within the corticospinal tract have direct, monosynaptic, terminations on spinal alpha motor neurons that innervate, for example, the intrinsic muscles of the hand and control independent and selective (fine manipulatory) finger movements. As a consequence, TMS is particularly effective in the activation of distal hand muscles [17-21].

In stroke patients with initially severe paresis or paralysis of the upper extremity, the observed specificity of motor evoked potentials (MEPs) was consistently high (nearly 100%), indicating that all MEP-positive patients will show some degree of motor recovery [22, 23]. In contrast, the sensitivity of MEP in severe stroke patients is lower (62-94%) [22, 23]. In this perspective, the silent period (SP) has been proposed as an additional factor to the MEP for predicting motor recovery [24-26].

This article is primarily a literature review focusing on whether the SP can be of additional prognostic value to MEP with regard to post-stroke hand motor recovery. It also integrates a case series on the prognostic value of the SP in a homogeneous sample of acute stroke patients with initial paralysis of the upper extremity.

Silent period

In tonically (pre)activated muscles, TMS of the primary motor cortex induces a short-latency MEP in the electromyogram as an excitatory effect followed by a transitory suppression of electromyographic (EMG) activity, the SP, as an inhibitory effect [11, 17, 19, 20, 27-37]. At subthreshold stimulus intensities (SI) and in single motor unit registrations, however, the SP can occur even without a preceding MEP [17, 18 36, 38-40]. In healthy volunteers, the MEP and the SP share a number of features. In both MEP and SP, optimal responses can be obtained when the primary motor cortex is stimulated, and the responses are more pronounced in distal hand muscles than in proximal arm muscles [17, 19, 20, 41]. Furthermore, the threshold for eliciting both MEP and SP in the biceps brachii and abductor digiti minimi muscles at the dominant side in healthy volunteers is lower than the threshold at the non-dominant side [42-44]. This physiological hemispheric threshold asymmetry is different for subjects of different ages. In elderly subjects (aged 61 to 82 years), the threshold asymmetries are less pronounced than in younger subjects, probably because of less functional dominance [42]. Although the stimulation thresholds at one body side in one particular individual are almost identical for both MEP and SP [31, 36, 45], with increasing SI

the amplitude of the MEP reaches a plateau [17, 20, 29, 31], whereas a near linear increase in the SP duration can be observed [17, 19, 20, 27, 28, 30, 31, 35, 37, 39, 46-49]. At constant SI, no correlation was found between the amplitude of the MEP and the SP duration among different individuals [37, 48, 49].

TMS performed during voluntary muscle contraction evokes MEPs with shorter latency and higher amplitude than when the muscle is at rest [25, 26, 29, 50]. It has been assumed that this facilitation phenomenon is due to recruitment of a larger number of active corticospinal neurons [51, 52]. In contrast to the MEP, there is no correlation between the SP duration and the level of tonic muscle preactivation in healthy volunteers [17, 19, 20, 25, 26, 30, 33, 34, 37, 40, 47- 49, 53-56]. The inhibitory mechanisms involved in the initiation and maintenance of the SP are normally uninfluenced by the recruitment of a larger number of active corticospinal neurons [25, 26]. Based on these different characteristics of the MEP and the SP, the SP is regarded as a phenomenon that is physiologically distinct from the MEP [17, 19, 35, 36, 45, 48, 49, 53].

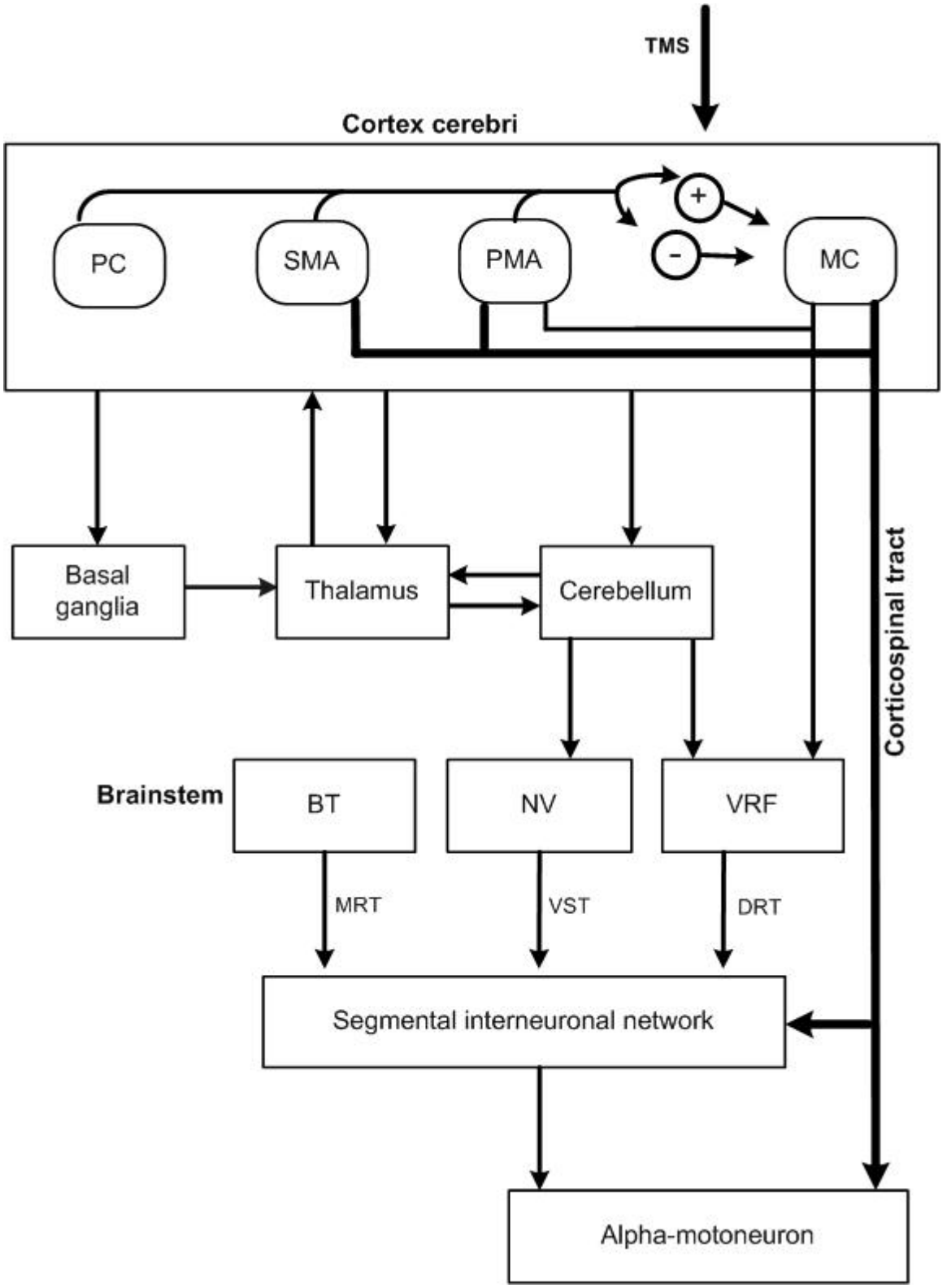
Although the exact mechanisms for the TMS-induced SP are poorly understood, both spinal and supraspinal factors appear to be involved. During the early part of the SP, up to approximately 50 ms, a marked decrease in spinal alpha motor neuron excitability has been found with concomitant inhibition of the H-reflex [17, 19, 20, 27, 28, 30, 40, 48, 55, 57, 58]. Inhibition of the H-reflex during this early part, however, was submaximal [20, 39], which suggests that both spinal inhibitory phenomena and supraspinal inhibitory pathways descending from the motor cortex may interact. During the late part of the SP (>50 ms), the spinal alpha motor neuron excitability returns to normal, so that supraspinal inhibition is thought to be responsible for the continuing suppression of EMG-activity [28, 31, 39, 49, 59]. This supraspinal inhibition has been attributed to intracortical inhibitory interneurons [17, 19, 20, 28, 35, 37, 57].

In healthy volunteers, studies concerning the quantification of the SP revealed a high inter-individual variability of its duration. The SP duration reaches its minimal variability and maximal length after cortical stimulation with maximal stimulator output (1.5 to 2.4 Tesla) and when facilitated by a slight tonic contraction of the test muscle (20 to 30% of maximum voluntary contraction) [17]. Even with such maximal stimulator output, the SP duration in a hand muscle of healthy volunteers may range between 100 and 300 ms [17, 19, 20, 24-26, 28, 40, 49, 54, 60-65]. Despite this high inter-individual variability (100 to 300 ms), a low intra-individual variability with a high inter-side symmetry (mean inter-side differences <10 ms, range 0 to 26 ms) of the SP duration has been reported [20, 24].

Silent period in stroke patients

In stroke patients, the SP has been proposed as a prognostic factor for motor and functional recovery besides the MEP. These studies that have analyzed the SP have provided rather inconsistent results (Table 1). Comparison of the results from these studies is difficult owing to variability in their technical methods, methodology, and patient characteristics. The lack of uniformity with regard to the definition of the SP and the subsequent use of different onsets and offsets for the SP (Table 2) may easily have influenced the observed SP duration [34]. If manual methods are used to assess the SP duration, inter-rater inconsistencies will further add to its variability [66]. Indeed, using a visually guided manual method, both Nilsson et al. [67] and Garvey et al. [68] found an inter-observer variability of the SP duration of as much as 20 to 22 ms. Also, different SI have been used to elicit the SP in stroke patients, which may partially account for the variability in the SP duration found in stroke patients.

Clinical heterogeneity may be another factor contributing to the inconsistencies in the literature. In previous TMS studies, stroke patients have been included with lesions located in different arterial territories, with different degrees of motor deficits, and at different times after stroke (Table 2). Von Giessen et al. [69] found a relation between stroke localization and the SP duration. In their study, shortened or even absent SPs were found despite the presence of a clear MEP response in stroke patients with infarctions located in the primary motor cortex. In addition, Schnitzler and Benecke [65] reported two patients with acute focal ischemic lesions of the primary motor cortex, who despite the presence of clear MEP responses, showed complete loss of the SP. These results suggest that in focal lesions of the primary motor cortex selective damage of cortical inhibitory interneurons and subsequent shortening or even complete loss of the SP may occur. In contrast, in acute strokes with lesions outside but anatomically projecting to the primary motor cortex, only prolonged or normal SPs have been found [62, 63, 69-71]. Afferents from the primary sensory cortex and from the premotor and supplementary motor areas bilaterally project to the primary motor cortex through cortico-cortical or transcallosal connections (Figure 1). Apart from these cortical connections, the thalamus projects to the primary motor cortex through thalamo-cortical connections [72]. These cortical and sub-cortical projections can modulate both inhibitory and excitatory interneurons within the primary motor cortex [62]. Lesions within these projections might, therefore, result in a partial deafferentiation of the primary motor cortex and a subsequent change in the balance between excitatory and inhibitory influences on the intracortical motor neurons. The prolonged SPs may result from a decreased inhibitory influence on the inhibitory interneurons that mediate the SP (cortical disinhibition) (Figure 1).



+ = excitatory
PC = Parietal Cortex (incl. primary sensory area)
MC = Primary Motor Cortex
BT = Bulbopontine Tegmentum
VRF = Ventromedial Reticular Formation
VST = Vestibulospinal Tract

- = inhibitory
SMA = Supplementary Motor Area
PMA = Pre-Motor Area
NV = Vestibular Nucleus
MRT = Medial Reticulospinal Tract
DRT= Dorsal Reticulospinal Tract

Figure 1. *Visual approach to the pathophysiology of TMS and spasticity*

The duration of the period after stroke may also be a relevant factor in determining the SP duration. In the post-acute phase after stroke, a decrease in the SP duration has been found in parallel with clinical improvement [62], whereas normalization and shortening of the SP have been reported in the chronic phases [49, 56, 62, 70, 73]. Cruz-Martinez et al. [73] performed TMS in 10 chronic stroke patients (6 months to 4 years after stroke) and in 10 healthy volunteers. In the four patients without spastic hands, the mean absolute SP did not differ from the SP found in their unaffected hands. Shortened SPs were observed mainly in patients with spastic hands (n=6), and the amount of shortening was associated with the degree of spasticity as assessed by the Ashworth scale. The authors hypothesized that in the course of the development of spasticity, cortical inhibition decreases and the SP subsequently shortens. However, the authors did not provide any information about the methods of their TMS, nor about infarct localization. Moreover, they gave no specifications of the motor, cognitive, and functional problems in their stroke sample.

Lastly, the degree of motor deficit may also be of influence on the reported SP after stroke, because the level of voluntary contraction used to elicit a SP may easily be affected by the degree of paresis. Although in healthy volunteers the inhibitory mechanisms involved in the SP are not clearly influenced by the recruitment of a larger amount of active corticospinal neurons, in the acute stage of stroke, a contraction-induced reduction in the SP duration has been observed. Catano et al. [25] performed TMS in 49 acute stroke patients (less than 5 to 10 days after stroke) with a focal ischemic lesion in the territory of the middle cerebral artery and partial motor deficit of the first dorsal inter-osseous muscle. Whether the cortical lesions involved the primary motor cortex was not delineated. To elicit a SP, patients were instructed to sustain a steady voluntary isometric contraction (VIC) of 10% and 100% of maximal strength, respectively. At 10% VIC, the mean absolute SP was prolonged in all stroke patients compared with the SP in healthy volunteers. At 100% VIC, two different patterns in SP duration were observed; in 34 patients the SP was stable and not influenced by the increased muscle contraction (pattern 1), whereas in 15 patients the SP decreased with increasing muscle contraction (pattern 2). The differences in mean absolute SPs between stroke patients with pattern 1 responses and those with pattern 2 responses at 100% VIC were significant. Ninety days after stroke, the same pattern of responses was still found. Moreover, pattern 2 responses were associated with poorer functional outcomes and increased Ashworth scores at day 90, whereas pattern 1 responses were associated with relatively good functional outcomes. The authors extended their study with 24 acute stroke patients (4 to 9 days after stroke) with a middle cerebral artery infarction and partial motor deficit of the flexor digiti minimi muscle (MRC 2 to 3) and six patients with long-standing spasticity [26].

Again, whether the cortical lesions involved the primary motor cortex was not delineated. Two more levels of muscle contraction force were added, i.e., the weakest contraction necessary to induce recordable EMG-activity (VICmin) and 50 % VIC. At VICmin, the mean absolute SP did not differ between stroke patients and healthy volunteers, whereas at the other levels of background contraction the same response patterns were found as in the first study. In five acute stroke patients and all patients with long-standing spasticity, the mean absolute SP duration decreased with increasing muscle contraction, whereas in the other 15 acute stroke patients and in healthy volunteers the SP remained stable and uninfluenced by the increased muscle contraction. Again, the differences in mean absolute SP duration between stroke patients with pattern 2 responses and both patients and healthy volunteers with pattern 1 responses were significant. The authors stated that in acute stroke patients with initially moderate to mild paresis, the relative inefficacy of the inhibitory mechanisms as indicated by a contraction-induced reduction in SP could be a negative prognostic factor for motor and functional recovery.

Case series

In a period of 1.5 years, we studied 40 acute stroke patients with initial paralysis of the upper extremity (stage I according to Brunnstrom within 7 days after stroke), admitted to the department of neurology at the Radboud University Nijmegen, Medical Centre. The diagnosis of stroke was made clinically on admission and confirmed by computed tomography (CT) scanning. In each patient a CT scan was performed twice; first on admission and second at 1 week after stroke. Patients with poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity), and patients with preexisting impairments of the upper extremity of any type were excluded. Patients with a history of craniotomy, epilepsy, cardiac prosthetic valve, pacemaker implantation, or severe polyneuropathies were excluded as well. The local ethical committee approved the study protocol and written informed consent was obtained from all patients before study entry.

Each patient received a standard medical treatment according to the guidelines of the Dutch Society of Neurology, including a multidisciplinary team approach. From post-stroke day 1, each patient received physiotherapy treatment to maintain optimal range of (joint) motion and to regulate muscle tone of the upper extremity; however, no specific therapy was initiated to improve motor recovery.

Neurophysiologic assessment

In each patient TMS of the motor cortex was performed twice, first within 1 week (mean 6.8, median 7 days) after stroke (t1), and second after 3 weeks (mean 27.8, median 25) post stroke (t2) by the same researcher. Patients were positioned comfortably in a supine position. TMS was performed through a 90-mm circular coil placed in a tangential plane above the vertex and powered by a Magstim 200 magnetic stimulator. The SI was set at maximum stimulator output (= 2.0 Tesla). To obtain a preferential activation of each hemisphere, a clockwise inducing current flow was used for the right hemisphere and a counter-clockwise current for the left hemisphere. MEPs and SPs were recorded at t1 and t2 from the abductor digiti minimi (ADM) muscle on the affected and the unaffected side. The ADM was regarded as representative of distal motor functions of the upper extremity. EMG recordings were made using an Oxford Synergy electromyograph with filter settings of 20 Hz and 3 kHz (amplifier range 100 mV, recording sensitivity of 0.5 mV / bit). A 500-ms post-stimulus period was analyzed. The MEPs were recorded when facilitated by a slight voluntary muscle contraction (20% of max VIC of the unaffected side). If the patient could not perform a contraction of the contralateral muscle (i.e., the muscle under investigation), he or she was told to activate the corresponding muscle on the healthy side [29]. The patients were asked to maintain the constant isometric contraction during the TMS performance. Because our patients lacked the ability to apply different degrees of voluntary contraction in the acute phase after stroke, the phenomenon of contraction-induced reduction in SP could not be assessed.

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 microVolts. The SP length was measured from MEP onset until the return of uninterrupted voluntary EMG-activity. The ADM responses were studied separately for both the affected and the unaffected side. Responses with the highest MEP amplitude and the shortest SP were used for analysis. Data from the unaffected side were compared with normative data and used as controls.

Outcome assessment

The motor functions were assessed using the separate hand motor score within the upper-limb subset of the Brunnstrom / Fugl-Meyer Motor Assessment (FMA) [74-76] on admission, at both the first (t1) and the second (t2) MEP registration, and at 26 weeks after stroke. The hand motor score concerns the seven original hand items of the FMA with a maximum score of 14 points. Clinical follow-up was performed by a physiatrist, who was not aware of the MEP results or the CT findings.

Analysis

In this study, the electrophysiological data from the ADM MEP were used and correlated with hand motor deficits as assessed by the FMA. The differences of the MEP amplitudes and SP durations between the first and second MEP investigation were assessed and correlated with the FMA hand score.

Results

Only the SP results will be discussed; the MEP results have been presented elsewhere [77]. In only 5 out of 40 patients, a SP could be elicited at t2 (Table 3). This small number of patients is probably due to the patient selection. In stroke patients, the amount of voluntary contraction varies with the degree of paresis. The voluntary contraction of the hand muscles in the majority of our patients was so severely impaired that no SP could be recorded [60]. The occurrence of a SP in our patients was always accompanied by the presence of motor recovery sufficient to voluntarily move the hand (FMA hand score > 3). In concordance with former studies on the SP in acute stroke patients [24-26, 54, 60-64, 71], SPs were prolonged (4 patients), reduced (1 patient), or normal (1 patient), and if any difference was found, increased inter-side differences were also found (Table 3). The mean absolute SP duration at the affected side was 349.4 (range 237 to 487) ms versus 199.2 (range 126.5 to 243.5) ms at the unaffected side. The mean absolute inter-side difference in SP duration was 150.2 (range 5 to 283) ms.

All of our patients had massive ischemic strokes located in the territory of the middle cerebral artery with involvement of both cortical and subcortical areas. In four of the five patients with a SP on the affected side at t2 the primary motor cortex was involved in the infarct area. In the acute post-stroke phase (t1), two of these four patients showed decreased or absent SP, whereas all four patients showed prolonged SPs in the sub-acute phase (t2). In two patients, one patient with a SP at t2 and involvement of the primary motor cortex, and in one patient with a SP at t2 without involvement of the primary motor cortex, SP data at t1 were missing. Although these limited data seem to support the primary versus non-primary motor cortex dichotomy by Von Giessen et al. [69] and Schnitzler and Benecke [65], they should be interpreted very carefully. In contrast to these authors, most of our patients had severe strokes involving both the primary and non-primary motor cortices.

All patients with a SP present at t2 showed full recovery of hand motor function at the 26-week motor assessment. These patients, however, could also be identified by the presence of a MEP response at t2. The SP could not identify patients with only partial recovery of hand motor function at the 26-week motor assessment, whereas the presence of a MEP response at t2 could identify these patients. Three patients showed partial recovery of hand motor function during follow-up, without a SP in the affected ADM both at t1 and t2. In one patient,

the SP could not be determined at t2 despite a present MEP response (amplitude 1.5 amplitude ratio[1]= 0.1). This patient did not show any motor recovery at t1 or t2, but had a near full hand motor recovery (FMA 12) at 6 months after stroke. In 2 additional patients the SP could not be elicited at t2 despite a MEP response (MEP amplitude = 0.2 with amplitude ratio[1]= 0.04 and MEP amplitude = 1.1 with amplitude ratio[1] = 0.16, respectively). Both patients showed recovery of hand motor function at 6 months after stroke (FMA 4). They could flex and extend their fingers in gross synergies with only minimal dexterity. Therefore, the SP in our patients (i.e., patients with initial complete paralysis of the upper extremity) seems to have no additional prognostic value to MEP with regard to hand motor recovery. These results are in agreement with Nardone and Tezzon [64]. In their study on acute stroke patients with variable degrees of upper-extremity paresis, changes in the inhibitory motor cortical circuits proved to be of little prognostic value, whereas early reductions in intrinsic excitatory properties, i.e., increased motor threshold intensity to TMS at rest, were associated with poor motor recovery.

Discussion

In stroke patients, the SP has been proposed as a possible prognostic factor for motor recovery. However, only few TMS studies have been performed on the role of the SP in motor recovery after stroke with rather inconsistent results. Comparison of these results is difficult because of the variability in the methodology, technical methods, and patient characteristics. In most studies prolonged SPs have been found immediately after stroke. In the first hours immediately after stroke, there might be a generalized decrease in intracortical inhibition in order to optimize the intracortical excitatory processes, thus, supporting motor output (MEP). As a consequence, intra-cortical inhibition of the inhibitory interneurons that mediate the SP also decreases, resulting in prolonged SPs. In some lesions of the primary motor cortex, however, the inhibitory interneurons mediating the SP may become selectively damaged, leading to a decreased or even lost SP [65]. In the (sub)acute phases thereafter, different patterns of SP duration have been found, i.e., normal, prolonged, as well as shortened SPs. These different patterns are also thought to be related to stroke localization; however, contraction-induced reduction phenomena and recovery-related intracortical phenomena may also be responsible for the different SP durations found.

[1] Amplitude ratio= MEP amplitudes relative to the maximal M-response recorded from the ADM muscle on the affected side

Although in acute stroke patients the SP might be of value to identify clinically silent or minor strokes [69], in acute stroke patients with initial paralysis or severe paresis the SP seems to have no additional prognostic value for post-stroke motor recovery when compared with TMS-induced excitatory phenomena (increased motor thresholds and decreased amplitudes) [22, 64, 70, 77]. Therefore, in the acute phase of severe stroke, merely the evaluation of motor cortex excitability provides prognostic information about both the likelihood and the extent of motor recovery [23, 64, 70, 77].

Nevertheless, in acute stroke patients with initially moderate to mild paresis and in chronic stroke patients with long-standing (more than 3 months) spasticity, Catano et al. [25, 26] observed a contraction-induced reduction in SP. The authors stated that the relative inefficacy of the inhibitory mechanisms as indicated by a contraction-induced reduction in SP could be a negative prognostic factor in post-stroke motor recovery and a positive prognostic factor in the development of spasticity. Uozumi et al. [49] and Cruz-Martinez et al. [73] also found a possible association between the SP and the development of spasticity. The authors observed shortened SPs mainly in chronic stroke patients with spastic hands [49, 73], and the amount of shortening was associated with the degree of spasticity as assessed by the Ashworth scale [73]. Both authors hypothesized that in the course of the development of spasticity, cortical inhibition decreases and the SP subsequently shortens.

Yet, from a neurophysiologic point of view, the proposed relationship between TMS-induced SP and spasticity is not evident. TMS primarily assesses the corticomotoneuron and corticospinal tract. These corticospinal pathways are generally believed not to be responsible for spasticity [78]. Selective damage to the corticomotoneuron or the corticospinal tract does not result in spasticity but in hypotonia and loss of fine, manipulatory hand movements. Spasticity is generally thought to result from concomitant damage to para-pyramidal motor pathways, such as the reticulospinal tract [78]. Damage to these para-pyramidal motor pathways results in a loss of the cortical drive to several inhibitory centers in the brainstem, resulting in disinhibition of spinal and bulbar reflexes [78, 79]. Although the para-pyramidal motor pathways cannot be directly assessed, they might be indirectly assessed by the TMS. Loss of cortical drive to the inhibitory centers in the brainstem may be due to lesions within areas projecting to the primary motor cortex (Figure 1). Indeed, the primary sensory area, supplementary motor area, premotor area, basal ganglia, thalamus, and cerebellum all provide important modulatory inputs to the primary motor cortex. Lesions within these areas might, therefore, result in a partial deafferentiation of the primary motor cortex and lead to a subsequent change in the balance between excitatory and inhibitory influences on the intracortical motor neurons that project to both the reticulospinal tract and to the corticospinal tract.

Conclusion

The exact relation between TMS-induced, contraction-induced reduction phenomena and recovery-related intracortical phenomena and spasticity remains unclear. More research is needed to identify the prognostic value of the SP in relation to post-stroke spasticity. Furthermore, to identify relevant prognostic changes in SP, a standardized approach to elicit, define, and measure the SP should be developed first.

The SP duration reaches its minimal variability and maximal length after cortical stimulation using maximal stimulator output and when facilitated by a slight tonic contraction of the test muscle (20 to 30% of maximal voluntary contraction) [17]. We therefore, recommend the use of at least this SI and level of muscle pre-activation. A proper recommendation of the definition of the SP is more difficult. Although the time-interval between the end of the M-wave and the first burst of uninterrupted EMG-activity is the most proper definition of the SP, it is also the most difficult method to visually assess. Both the end of the M-wave and the first burst of uninterrupted EMG-activity are inconsistent and difficult to interpret in the EMG-tracings. The time of stimulus delivery and even MEP onset used as the onset marker, may be easier to interpret. However, both include also the MEP-duration that could affect the duration of the SP. It seems worthwhile to study SP onset and offset markers to determine which is the most valid, precise, and applicable method. The development of graphical methods [68] may further add to more precision in this process and to less inter-rater variability.

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Table 1. *Studies on the Silent Period in stroke patients; Results*

Author	Silent period duration (SPD)	Results
Nardone and Tezzon (2002)	Normal: 247.6 ms (range 184.8-288.6) Unaffected: 222.7 ± 19.9 ms (range 196.6-250.8) Affected: 332.55 ± 52.07 ms (range 250.5-406.2)	1. Reduced intracortical inhibition in all patients at stroke onset 2. SPD in the affected hemisphere prolonged in 15/20 patients at stroke onset 3. SPD proved to be of little additional (functional) prognostic value
Byrnes et al. (2001)	SP-Ratio non-dominant/dominant side Normal: 1.02 ± 0.12 (range 0.89-1.23) Patients: 1.05 ± 0.12 (range 0.79-1.32)	1. No correlation between changes in MEP amplitude, motor threshold, and SPD 2. SP normal in all patients, except in 1 patient (prolonged SPD) 3. Rearrangements of corticomotor maps with diverse patterns of cortical reorganisation in chronic stroke patients
Liepert et al. (2000)	Normal: 149.2 ± 18.7 ms Unaffected 172.3 ± 32.7 ms Affected: 294.9 ± 77.5 ms	1. Cortical disinhibition in all patients 2. SPD in the affected hemisphere prolonged in all patients 3. Cortical disinhibition in the affected hemisphere in acute cerebral infarction which spared the primary motor cortex occurred simultaneously with prolongation of the SP
Ahonen et al. (1998)	Normal: 215 ± 63 ms; ID 13 ± 10 ms Unaffected: 210 ± 70 ms; Affected: 400 ± 177 ms; ID: 196 ± 63 ms unimpaired hand function 284 ± 96 ms impaired hand function: 508 ± 168 ms	1. Mean SPD in the affected hemisphere prolonged in 25/29 at stroke onset; SPD also prolonged in subgroup of 14 patients with normal hand function 2. No significant difference between SPD between the unaffected hemisphere and the control group
Cruz-Martinez et al. (1998)	Normal: 167.9 ± 25.9 ms (range 150-209) Unaffected: 153.1 ± 21.9 ms (range 125-180) Affected: 101 ± 26.6 ms (range 66.4-160) Spastic: 68.5 ± 15.9 ms (range 66.4-105)	1. SPD significantly shorter in chronic stroke patients with spasticity. SPD correlated with the Ashworth scale 2. SPD not significantly different (only slightly shorter) from control and/or unaffected hemisphere in chronic stroke patients without spasticity

Table 1 continued

Author	Silent period duration (SPD)	Results
Catano et al. (1997)	Normal: 145 ± 16 ms at VIC 10%; 148 ± 17 ms at VIC 100%; SPI 102 ± 6% Unaffected: 146 ± 16 ms at VIC 10%; 147 ± 16 ms at VIC 100%; SPI 100 ± 6% Affected: 165 ± 12 ms at VIC 10%; 158 ± 21 ms at VIC 100%; SPI 96 ± 11% Day 7 Pattern 1: 165 ± 11 ms at VIC 10%; 169 ± 12 ms at VIC 100%; SPI 110 ± 6% Day 7 Pattern 2: 163 ± 12 ms at VIC 10%; 131 ± 10 ms at VIC 100%; SPI 81± 2% Day 90 Pattern 1: 165 ± 12 ms at VIC 10%; 165 ± 17 ms at VIC 100%; SPI 100 ± 9% Day 90 Pattern 2: 165 ± 10 ms at VIC 10%; 146 ± 22 ms at VIC 100%; SPI 89 ± 11%	1. Mean SPD in the affected hemisphere prolonged in patients at stroke onset 2. Reduction of SPD with increasing VIC in 15 patients with chronic spastic hemiplegia and patients with poor recovery 3. Pattern 1 responses associated with better functional recovery. Pattern 2 responses with poor functional outcome and the eventual occurrence of spasticity 4. In normal subjects the SP, albeit augmented with SI, was not influenced by voluntary contraction
Catano et al. (1997)	Normal and unaffected side: SPD at min. VIC increased from 64 to 137 ms with rising SI, uninfluenced by facilitation Affected side: SPD at min. VIC increased from 68 to 139 ms with rising SI, uninfluenced by facilitation in group 1. Group 2: SPD increased relatively less with augmented SI; mean SPD reduced from 127 at min VIC to 111 ms at 100%VIC and SI 100% Spastic: SPD increased relatively less with augmented SI; mean SPD reduced from 128.8 at min VIC to 80.3 ms at 100%VIC and SI 100%	1. Reduction of SP during increasing VIC in 6 patients with chronic spastic hemiplegia and 5 patients with poor recovery in the long run 2. Pattern 1 responses associated with better functional recovery (subgroup 1) and pattern 2 with poor functional outcome (subgroup 2) at D90. Pattern 2 responses associated with the occurrence of spasticity at D90. 3. In normal subjects the SP, albeit augmented with SI, was not influenced by voluntary contraction

Table 1 continued

Author	Silent period duration (SPD)	Results
Classen et al. (1997)	Normal: 181 ± 11 ms Acute stroke patients, unaffected side: 233 ± 28 ms Acute stroke patients, affected side: 922 ± 563 ms Chronic stroke patients, unaffected side: 202 ± 40 ms Chronic stroke patients, affected side: 253 ± 81 ms	1. SPD prolongation in acute stroke in patients with and without hemiplegia in both the affected and unaffected hemisphere compared to controls 2. Clinical improvement was accompanied by a shortening SP over time; normalisation completed at 6-12 weeks
Faig and Busse (1996)	At 1.2 RT: Unaffected: 99.7 ± 20.7 ms (range 63-128) Affected: 124 ± 31.3 ms (range 73-187) At 2 RT: Unaffected: 173.78 ± 34.7 ms (range 102-275) Affected: 248. 1 ± 44.1 ms (range 186-352)	1. SPD prolonged on the affected side; effect more pronounced with high than with low SI 2. No differential effects of different thalamic lesions observed
Braune et al. (1996)	Normal: 155 ± 41.4 ms (range 57-250); ID: 8.9 ± 6.4 ms (range 0-26) Patients: 158 ± 44.1 ms (range 72-226); ID 44.7 ± 39.2 ms (range 8-179)	1. Significant inter-side difference in SPD and high inter-individual variation in stroke patients; in 8 patients inter-side differences within normal range 2. Inter-side difference correlated with SPD and degree of motor impairment in patients 3. SP-ratio (longer SP/shorter SP) more sensitive tool ($p<0.001$; 84% abnormal values) for quantification of UMN deficit compared to inter-side difference ($p<0.01$; 68% abnormal values)
Braune et al. (1995)	Normal: 114 ms (range 100-219); ID: 10.5 ms (range 0-60.5) Group 1: al prolonged SPD; ID: 33.2 ms (range 11-68.5) Group 2: prolonged in 15 / reduced in 7; ID: 58.3 ms (range 8-251) Group 3: prolonged in 16 / reduced in 5; ID: 104.7 ms (range 9-280)	1. Only small inter-side differences in healthy controls; in patient group increasing inter-side differences according to the degree of motor impairment 2. 12/50 patients exhibited a reduction of SP; no constant pattern of SP reduction or prolongation found
Haug et al. (1994)	Normal: 81 ± 20 ms Unaffected: 119 ± 50 ms Affected: 153 ± 63 ms	1. SPD prolonged on the affected side, more pronounced with intra-individual side comparison; SPD prolonged in 7/9 patients; inter-side differences in 8/9 patients

Table 1 continued

Author	Silent period duration (SPD)	Results
Von Giessen et al. (1994)	SPD not quantified, only ratio's (affected/unaffected) given	1. In patients with lesions MC the SPD decreased as compared to the healthy side; most pronounced in patients with severe clinical motor abnormalities and abnormal MEP findings 2. In patients with lesions of the internal capsule, thalamus, premotor cortex, and temporal/parietal lobes the SPD was either prolonged or normal
Haug et al. (1992)	No quantitative data	1. SPD prolonged on the affected side; more pronounced with intra-individual side comparison 2. In controls a near linear increase of SPD with SI; no relationship between SPD and amount of voluntary muscle activity or contraction force 3. Slight decrease in SPD with age
Kukowski and Haug (1992)	Normal: 81.2 ms (SD 19.6 ms); ID :0.6 ms (SD 7.6 ms) Unaffected: 93.6 ms (SD 29.3 ms) Affected: 145.8 (SD 49.4 ms); ID: 52.2 ms (SD 35.4 ms) Normal SP latency: 48.4 ms (SD 5.2 ms) Unaffected SP latency: 46.7 ms (SD 6.3 ms) Affected SP latency: 49.7 ms (SD 4.5 ms)	1. In controls vertex optimum side for evoking a SP from FDI muscle 2. SP appeared with low SI (30-45%), insufficient to evoke a visible muscle twitch 3. Linear increase in SPD with increasing SI. No correlation between different innervation forces and both onset latencies and SPD. Small inter-side differences 4. In stroke patients onset latency of the SP related to the duration of the excitatory response. No inter-side differences in onset latency 5. SPD prolonged and increased inter-side differences in patients
Uozumi et al. (1992)	Normal: 126.6 ± 29.5 ms Affected: 75.5 ± 41.3 ms	1. Linear increase in SPD with increasing SI in normals 2. SPD does not depend on MEP amplitude 3. SPD after single coil stimulation shorter than after twin coil stimulation 4. SPD shortened in patients with spastic hyperreflexia and correlated with the amplitude of the F-wave
Uozumi et al. (1991)	Normal: 126.6 ± 29.5 ms Affected: 73.9 ± 41.7 ms (range 28.8-149.7)	1. SPD shortened in stroke patients

ID = inter-side differences; SD = standard deviation; MC = primary motor cortex; SI = stimulus intensity; SPI = SP index= SPD (VIC100%) / SPD (VIC10%); SPD = silent period duration; MEP = motor evoked potential; UMN = upper motor neuron; FDI= flexor digitorum indices muscle; RT = resting threshold

Table 2A. *Studies on the Silent Period in stroke patients; Patient characteristics*

Author	Patients	Stroke type	Patient Characteristics	Muscle
Nardone and Tezzon (2002)	20 patients within 24 h after stroke	First-ever, ischemic, stroke in MCA territory	post-stroke day 1: Hemiparesis, hemiplegia excluded NIH 12.3 ± 2.41 (range 7-18)	FDI
Byrnes et al. (2001)	10 patients 6 mo to 15 y after stroke	First-ever, ischemic, subcortical stroke 6 int. capsule; post limb 5 basal ganglia 3 thalamus 4 corona radiata	4-6 wk after stroke: 8 full recovery (MRC 5; MAS 18) 2 slight paresis (MRC 4+; MAS 17) impaired finger dexterity BI 20/20 in all	APB
Liepert et al. (2000)	11 patients within 14 d after stroke	Ischemic stroke, MC not affected 6 MCA territory 4 striatocapsular 1 lacunar	Post-stroke day 1; mild-moderate paresis NIH 8.4 ± 4.9 (range 2-17) BI 56.4 ± 35 (range 15-100)	FDI
Ahonen et al. (1998)	29 patients within 4 d after stroke	First-ever, ischemic stroke 14 fronto-temporo-parietal 4 temporo-parieto-occipital 7 corona radiata 3 int. capsule 1 thalamus	20 normal pinchgrip; >50% of unaffected side 9 moderately reduced pinchgrip; 10-50% of unaffected side 14 normal hand motor function* 15 impaired hand motor function*	Thenar
Cruz-Martinez et al. (1998)	10 patients 6 mo to 4 y after stroke	Ischemic stroke	Canadian neurological scale: 0.95 ± 0.43 (range 0.5-1.5) modified Ashworth: 2.15 ± 1.2 (range 1-4)	?

Table 2A continued

Author	Patients	Stroke type	Patient Characteristics	Muscle
Catano et al. (1997)	49 patients within 10 d after stroke	First-ever, ischemic, cortical stroke in MCA territory	Post-stroke day 7: MRC 2.31 ± 0.47 Ashworth: 0.55 ± 0.54 BI: 46 ± 8	FDI
Catano et al. (1997)	24 patients within 9 d after stroke 6 patients with spasticity for at least 3 mo	First-ever, ischemic stroke in MCA territory	Post-stroke day 7: MRC: 2.5 ± 0.51 Ashworth: 0.63 ± 0.71 BI: 43.1 ± 7.6	FDI
Classen et al. (1997)	16 patients within 7 d after stroke	Ischemic and haemorrhagic, subcortical stroke; MC and PT spared 14 MCA territory 1 basal ganglia 1 vasculitis	SP affected at least two times the unaffected side No fractionated finger movements 7 complete hemiplegia 2 severe paresis 7 moderate paresis 6 normal tendon reflexes 9 increased tendon reflexes 1 decreased tendon reflexes	FDI
Faig and Busse (1996)	9 patients within 20 d after stroke; 2 unknown	First-ever, ischemic, thalamic stroke	6 no motor impairments 2 ataxia 1 paresis	Thenar
Braune et al. (1996)	25 patients within 7 d after stroke	First-ever, ischemic stroke MCA territory (confirmed by CT)	10 slight hemiparesis 15 moderate hemiparesis	ADM
Braune et al. (1995)	50 patients within 7 d after stroke	First-ever, ischemic stroke MCA territory	7 no motor deficits 22 slight hemiparesis 21 moderate hemiparesis	ADM

Table 2A continued

Author	Patients	Stroke type	Patient Characteristics	Muscle
Haug et al. (1994)	9 acute stroke patients	Ischemic stroke	Incomplete paresis	FDI
Von Giessen et al. (1994)	19 patients 24 h to 2 y after stroke 6 TIA	First-ever ischemic (11) or haemorrhagic (2) stroke 5 focal lesion SMA 7 int. capsule/thalamus 1 premotor cortex	7 normal hand function; 1 increased tendon reflexes 3 clumsiness without paresis 4 slight spastic paresis (MRC 4) 3 moderate spastic paresis (MRC 3) 1 severe spastic paresis (MRC 2-1)	FDI
Haug et al. (1992)	12 patients before dismissal	Ischemic, cortical or subcortical stroke	Nearly full recovery	APB
Kukowski and Haug (1992)	10 patients 4 to 12 mo after stroke	First-ever, ischemic stroke MCA territory	Minor residual motor disturbances normal muscle tone	FDI
Uozumi et al. (1992)	17 patients 5 wk to 16 mo after stroke	Ischemic stroke; multiple cerebral infarctions in 5 patients	Chronic spastic paresis, hemiplegia excluded	APB
Uozumi et al. (1991)	12 chronic stroke patients	Focal ischemic stroke	Moderate-severe paresis thenar muscle	APB

MCA = Middle Cerebral Artery; SMA = supplementary motor area; MC = primary motor cortex; PT = pyramidal tract; APB = abductor pollicis brevis muscle; FDI = flexor digitorum indices muscle; TIA = transient ischemic accident

BI = Barthel index; MAS = motor assessment scale for stroke; MRC = Medical Research Council scale; NIH = National Institute of Health stroke scale

* = hand motor function evaluated following principles presented by Elliot and Connolly; 0= normal function, 24= total paresis

Table 2B. *Studies on the Silent Period in stroke patients; Technical methods*

Author	Coil	Stimulus localization	Stimulus Intensity	Preactivation	Silent Period Definition
Nardone and Tezzon (2002)	Figure of eight	?	150% RMT	Max. voluntary contraction (uncontrolled)	Time interval from end of M-wave to first burst of reappearing EMG-activity
Byrnes et al. (2001)	Figure of eight	Motor hand area	AMT + 20%	VIC: 10 ± 3% of max rms-EMG (controlled)	Time interval from MEP onset to resumption of voluntary EMG-activity
Liepert et al. (2000)	Figure of eight (8 patients) Circular (3 patients)	Motor hand area C3 C4	150% RMT	VIC: 30% of max. force (controlled)	Time interval from MEP onset to resumption of on-going EMG-activity
Ahonen et al. (1998)	Circular	Motor hand area	90% max. stimulator output (2.2 Tesla)	Max. voluntary contraction (controlled)	Time interval from MEP onset to resumption of voluntary EMG-activity
Cruz-Martinez et al. (1998)	?	?	Fixed at 30% above threshold	Max. tonic activation (uncontrolled)	?
Catano et al. (1997)	Circular	Motor hand area	130% RMT	Max. VIC and 10% max. VIC (controlled)	Time interval from MEP latency to resumption of EMG-activity
Catano et al. (1997)	Circular	Motor hand area	100% and 80% max. stimulator output (2.4 Tesla), RMT, and RMT – 10%	Min VIC, max VIC, 10% max. VIC, and 50% max. VIC (controlled)	Time interval from end of M-wave to first reappearing bursts of EMG-activity
Classen et al. (1997)	Circular	Vertex	150% RMT	VIC: 20% of max. force	Time interval from stimulus delivery to resumption of voluntary EMG-activity

Table 2B continued

Author	Coil	Stimulus localization	Stimulus Intensity	Preactivation	Silent Period Definition
Faig and Busse (1996)	Circular	Vertex	120% and 200% RMT	VIC: 50-75% max. force (controlled)	Time interval from stimulus delivery to reappearance of uninterrupted tonic EMG-activity
Braune et al. (1996)	Circular	Vertex	150% ST	Constant isometric contraction (controlled, not quantified)	Time interval from MEP onset to reappearance of uninterrupted voluntary EMG-activity
Braune et al. (1995)	Circular	Vertex	150 % ST	Constant isometric contraction (controlled, not quantified)	Time interval from MEP onset to reappearance of uninterrupted voluntary EMG-activity
Haug et al. (1994)	Circular	Vertex	1.5 ST	VIC: 50% of max. force	Not mentioned: Time interval from the end of M-wave to resumption of tonic voluntary EMG-activity
Von Giessen et al. (1994)	Circular	Vertex	1.5 RMT	VIC: 10% of max. force	Time interval from MEP onset to resumption of tonic voluntary EMG-activity. Long latency responses <25 ms duration neglected.
Haug et al. (1992)	Circular	Vertex	ST + 30% max. stimulator output	VIC: 50% of max. force	Time interval from the end of M-wave to resumption of tonic voluntary EMG-activity
Kukowski and Haug (1992)	Circular	Vertex	150% ST	VIC: 50% of max force	Time interval from the end of M-wave to resumption of tonic voluntary EMG-activity
Uozumi et al. (1992)	Circular Figure of eight	Vertex Motor hand area	80-90% max. stimulator output (800-900 V)	Max voluntary contraction (controlled)	Time interval from the end of M-wave and the first reappearing bursts of EMG-activity

Table 2B continued

Author	Coil	Stimulus localization	Stimulus Intensity	Preactivation	Silent Period Definition
Uozumi et al. (1991)	Circular	Vertex	80-90% max. stimulator output (800-900V)	Max voluntary contraction (controlled)	Time interval from the end of M-wave and the first reappearing bursts of EMG-activity

RMT= resting motor threshold; AMT= active motor threshold, ST= silent period stimulation threshold; RMS= root mean square; VIC= voluntary isometric contraction

Chapter 4

Predicting hand motor recovery in severe stroke;

The role of motor evoked potentials in relation to early clinical assessment

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Abstract

Objective: The primary aim of this study was to compare the predictive value of motor evoked potentials (MEPs) and early clinical assessment with regard to long-term hand motor recovery in severe stroke patients.
Methods: Inception cohort of 39 stroke patients with an acute, ischemic, supratentorial stroke and an initial upper-extremity paralysis admitted to an academic hospital. Hand motor function recovery was defined at 26 weeks post stroke as a Fugl-Meyer motor assessment (FMA) hand score >3 points. The following prognostic factors were compared at week 1 and week 3 post stroke: motor functions as assessed by the FMA upper-extremity and lower-extremity subscores, and the presence of a MEP in the abductor digiti minimi (ADM) and biceps brachii (BB) muscle.
Results: Both the presence of an ADM-MEP and any motor recovery in the FMA upper-extremity subscore showed a positive predictive value of 1.00 at week 1 and 3. The FMA lower-extremity subscore showed the best negative predictive value (0.90; 95%-CI 0.78-1.00 at week 1, and 0.95; 95%-CI 0.87-1.00 at week 3).
Conclusions: In stroke patients with an initial paralysis of the upper extremity the presence or absence of a MEP has similar predictive value compared to early clinical assessment with regard to long-term hand motor recovery.

Introduction

Nearly one third of all stroke survivors initially shows severe motor impairments in the upper extremity [1-3]. Although 30-66% of these severe patients will regain no motor function of the upper extremity at all, 25% will show partial motor recovery and 5-20% will even regain full motor function of the upper extremity [2-5]. Because both motor recovery and the development of complications such as shoulder subluxation, spasticity [6], and contractures already take place very early after stroke onset, the preferred time window for the institution of rehabilitation strategies is shifting from the subacute phase (6 weeks to 6 months) into the acute phase (within the first 6 weeks) after stroke.

In patients with a potential for motor recovery it is important to focus on the restoration of motor function as early as possible [7]. In these patients, repeated failures to use the paretic arm and hand in the acute and subacute phases after stroke can lead to negative reinforcement, the so-called ‘learned non-use’, complicating the rehabilitation process later on [7]. On the other hand, focusing on the restoration of motor function in stroke patients

without a potential for motor recovery will lead to frustration and disappointment in both patients and therapists, and delays a shift of therapy focus towards learning compensation strategies. To proactively apply appropriate rehabilitation strategies in individual patients, it is important to differentiate those with a potential for motor recovery from those without such potential as early as possible and with a high degree of accuracy.

The initial grade of paresis and the early patterns of motor improvement are well known clinical predictors of functional recovery [2, 3]. At the end of week 4 after stroke, Kwakkel et al. [3] found a probability of 94% for regaining dexterity at 6 months after stroke in patients with an initially flaccid arm who had achieved at least 19 points on the upper-extremity subscore of the Fugl-Meyer motor assessment (FMA). However, at 1 week after stroke the predictive value of clinical assessment was substantially lower. A probability of only 74% for regaining dexterity at 6 months after stroke was found in those patients who had reached some voluntary movement over the hip, knee, and/or foot. Moreover, clinical assessment of motor functions can sometimes be difficult, particularly in patients suffering from concomitant cognitive deficits, such as aphasia, apraxia, or sensorimotor neglect. Hence, in the first week post stroke and in patients with cognitive deficits, neurophysiological assessment might add to the predictive value of early clinical assessment with regard to upper-extremity motor recovery.

Indeed, transcranial magnetic stimulation (TMS) has been proven successful in the prediction of motor recovery of the upper extremity in patients within the first 3 weeks after stroke [8, 9]. It offers an objective evaluation of the integrity of the corticospinal pathways, responsible for the primary motor functions. In stroke patients with an initial paralysis of the upper extremity, the specificity of the presence of a motor evoked potential (MEP) in the abductor digiti minimi muscle (ADM) for hand motor recovery has consistently been shown to be high (nearly 100%) [8, 9], indicating that at 3 weeks after stroke all MEP-positive patients will show some degree of hand motor recovery at 6 months after stroke. However, the sensitivity of the MEP in these patients was lower and more variable (62-94%) [8], indicating that not all patients who will show hand motor recovery can be identified by the presence of an early MEP. Therefore, the clinical value of TMS in terms of improved prognostication in stroke patients is still debated.

There are no studies available, however, that have made a direct comparison between early clinical assessment and TMS with regard to predicting long-term hand motor recovery in stroke patients with an initial paralysis. Moreover, studies focusing on the predictive value of either clinical assessment or TMS are difficult to compare due to the variability in patient characteristics and time-post stroke. The primary aim of this study was, therefore, to

compare the predictive value of clinical assessment and motor evoked potentials at one and at three weeks after stroke with regard to long-term hand motor recovery in a homogeneous group of patients with severe stroke.

Materials and Methods

Patients

Patients with a first-ever, ischemic, supratentorial stroke and admitted to the Department of Neurology at the Radboud University Nijmegen, Medical Centre during a 3,5 years' period (2002-2006) were eligible. The diagnosis of stroke was made clinically by a neurologist according to the World Health Organisation clinical criteria [10] and confirmed by CT scan. In each patient, a CT scan of the brain was made twice: at first on the day of admission and, second, at 1 week after stroke to delineate the structural lesion.

Only patients presenting with no voluntary muscle activity and no muscle tone at the elbow, wrist, or finger flexors (Brunnstrom stage I [11]) on the day of admission were included within the first 7 days after stroke. Patients with a poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity), as well as patients with severe pre-existing impairments of the upper extremity of any type (e.g., rheumatic deformities, contractures) were excluded. Patients with a history of craniotomy, epilepsy, cardiac prosthetic valve or pacemaker implantation, or severe polyneuropathy were excluded as well. The local ethics committee approved the study protocol and written informed consent was obtained from all patients before study entry.

All patients received a 'best medical treatment' according to the guidelines of the Netherlands Society of Neurology, ensuring that each patient was given physiotherapy to maintain optimal passive and active range of motion of all upper-extremity joints from the first day after stroke. However, for the first 3 weeks after stroke, no specific therapy was initiated specifically aimed at facilitation of hand function recovery. Thereafter, patients were discharged to their private homes, rehabilitation centres, or nursing homes, dependent on their functional status, implicating that the total amount of rehabilitation given was not controlled.

Neurophysiological assessment

TMS of the motor cortex was performed twice in each patient; at first, at 1 week after stroke (t1) and, secondly, at 3 weeks after stroke (t2) by the same experienced clinical neurophysiologist (JP). This clinical neurophysiologist was blinded with regard to the results

of the clinical assessments. Patients were positioned comfortably in a supine position. TMS was performed through a 90 mm circular coil placed in a tangential plane above the vertex and powered by a Magstim 200 magnetic stimulator. The stimulus intensity was set at maximum stimulator output (100% = 2.0 Tesla) to ensure maximum stimulation of the MEP [12]. To obtain a preferential activation of each hemisphere, a clockwise inducing current flow was used for the right hemisphere and a counter-clockwise current for the left hemisphere.

MEPs were recorded at week 1 (t1) and at week 3 (t2) post stroke from the biceps brachii muscle (BB) and the ADM on both the paretic and non-paretic sides. These muscles were regarded as representatives of proximal and distal motor functions of the upper extremity. Because it has been suggested that early, proximal movements of the arm are predictors for upper-extremity motor recovery [13], we performed a BB MEP as well. Two self-adhesive recording surface electrodes were placed on the ADM and BB on both the paretic and non-paretic side. The active electrode was placed on the muscle belly and the reference electrode was placed on the tendon approximately 3 cm distal from the position of the active electrode. Recordings were made using an Oxford Synergy electromyograph with filter settings of 20 Hz and 3 kHz (amplifier range 100 mVolts and recording sensitivity of 0.5 mVolts / bit). A 500-ms post-stimulus period was analysed in search for a MEP response.

The MEPs were preferably recorded when facilitated by a slight voluntary muscle contraction. If the patients could not perform a contraction of the affected hand or arm muscle, they were asked to activate the corresponding muscle on the non-paretic side [14, 15]. The patients were instructed to maintain the constant isometric contraction during the TMS performance. Although muscle preactivation facilitates enlargement of the MEP amplitudes, preactivation is not a prerequisite to elicit a MEP-response. Three responses were obtained to assess the reproducibility. The presence of a MEP was defined as the presence of at least two responses out of three with a minimal peak-to-peak amplitude of 200 microVolts.

Clinical assessment

Within the first 24 hours after stroke the treating neurologist assessed all patients with regard to initial motor functions, muscle tone, and level of consciousness (Mini-Mental State Examination [16]). Thereafter, an experienced rehabilitation physician who was not aware of the MEP results performed the clinical assessments. The motor functions of the upper extremity were assessed at week 1 (t1), 2, 3 (t2), 6, and 12, and at 26 weeks (t3) after stroke using the motor part of the upper-limb subset of the FMA [11]. Motor functions of the lower extremity were assessed on admission, at week 1 (t1), and at week 3 (t2) using the motor part of the lower-limb subset of the FMA [11]. This cumulative numerical scale is based on

the sequential motor recovery stages that can be observed in hemiparetic patients and is scored under standardised test conditions. For the upper extremity, 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.

Data Analysis

In the prediction model, the FMA hand subset was used as the primary outcome. Because particularly achieving voluntary extension of the wrist and fingers is critical for regaining dexterity [17], the optimal dichotomization point was, based on the literature [3, 18], set at ≤ 3 versus > 3 points.

As potential prognostic factors were tested at week 1 (t1) and at week 3 (t2):
1) the presence of an ADM-MEP, 2) the presence of either a BB-MEP or ADM-MEP, and 3) the presence of any motor recovery of the upper extremity. In addition, we tested the presence of any voluntary movements of the affected lower extremity at week 1 (t1), and a FMA lower extremity subscore of at least 10 points at week 3 (t2). This latter dichotomization point was also based on existing data in severe stroke patients with an initially flaccid arm [3].
In second instance, we investigated whether the combination of early clinical assessment and the presence of a MEP offered a better prediction of long-term hand motor recovery than that offered by any single determinant.

To investigate the possible association between hand motor recovery at 26 weeks (t3) after stroke and the selected prognostic factors, both a positive (PPV) and negative predictive value (NPV) were calculated for each factor with corresponding 95% confidence intervals.

Results

Forty-four patients with an initial paralysis of the upper-extremity were screened for inclusion in this study. Five patients did not met the inclusion criteria because of poor prognosis for survival, none refused to participate in this study. Of the initially included 39 patients, 4 patients (2 men and 2 women) died during the first 3 weeks after stroke. These patients were excluded from the analysis. Thus, 35 patients, 18 male and 17 female patients, completed the study. Their mean age was 59.8 years (standard deviation 15 years; range 20-86 years). All patients had extensive lesions located in the territory of the middle cerebral artery. The patient characteristics are described in Table 1.

Table 1. C*haracteristics of the 35 patients*

		number
Gender	Female	18
	Male	17
Stroke history	First ever	35
Lesion side	Left	20
	Right	15
Lesion characteristics	Single, extensive, mixed cortical / subcortical lesions affecting multiple brain areas	
Mean age, years (range; SD)	58 (20-86; 15)	
FMA upper-extremity subscore at day 1	0 (0)	
Median Barthel Index on admission (inter-quartile range)	0 (0)	
Median MMSE on admission (range 0-30)	25 (21-28)	
Aphasia	present	22
	absent	13
Hemi-inattention	present	20
	absent	15

SD = standard deviation; FMA = Fugl Meyer Motor Assessment; MMSE = Mimi-Mental State Examination

Upper-extremity Motor Recovery

In 21 patients (60%) the upper extremity did not show any motor recovery throughout the 26-week follow-up period, whereas in 14 patients (40%) upper-extremity motor recovery was present at 26 weeks after stroke. These patients are depicted in Figure 1. At 6 months post stroke, 6 patients (17%) achieved complete motor recovery of the upper extremity (FMA= 44), whereas 8 patients (23%) showed partial motor recovery of various degrees. At one week post stroke (t1), motor recovery was present in 4 patients (10%) of which 2 progressed to complete recovery at the 26 weeks. At 3 weeks post stroke (t2), motor recovery was present in 9 patients (26%) of which 5 patients eventually reached complete motor recovery. Two patients with partial motor recovery showed only gross motor functions of the arm, not of the hand, implicating that 12 patients (34%) achieved hand motor recovery at 26 weeks post stroke. In all these patients, hand motor recovery was always accompanied by arm motor recovery. Twenty-three patients (66%) did not show any hand motor recovery at 6 months.

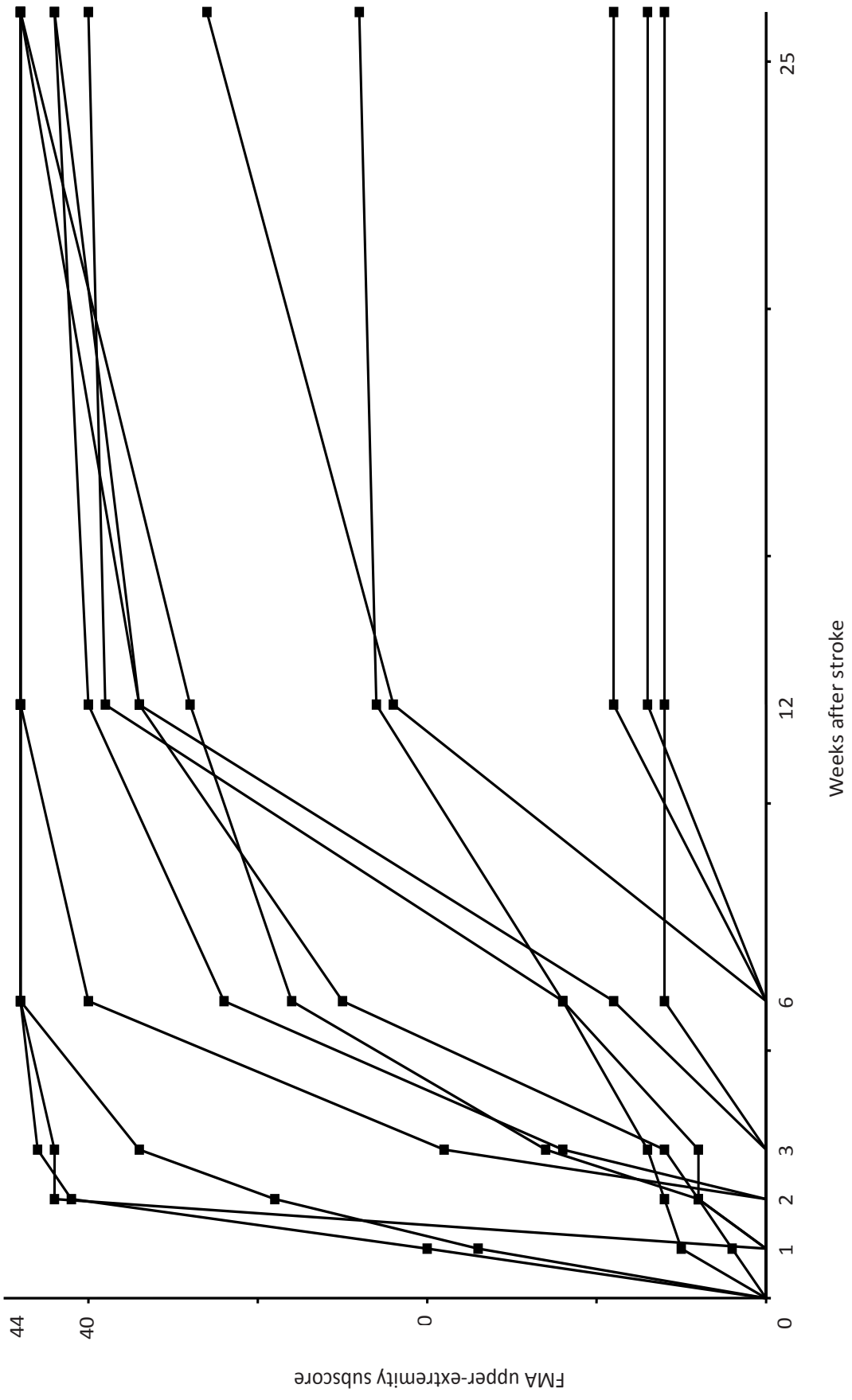

Figure 1. *Motor-recovery profiles of the 14 patients who showed upper-extremity motor recovery (assessed by the Fugl-Meyer motor assessment (FMA) upper-extremity subscore) during the first 6 months post stroke*

Motor Evoked Potentials

Five patients refused the second MEP assessment. Three patients reported discomfort during the first TMS assessment as the primary reason, whereas 2 patients where too ill to attend the second TMS assessment (both suffered from pneumonia). These patients did not differ from the other participants with regard to their neuroradiological or clinical assessment. Two of these patients showed hand motor recovery at 6 months. Therefore, the neurophysiological data set was complete for 30 patients. In 17 patients, no MEP response could be elicited after maximal stimulation of the affected hemisphere, neither at week 1 (t1), nor at week 3 (t2). A MEP of the ADM or BB muscle was obtained in 10 patients (34%) at week 1 (t1) and in 13 patients (43%) at week 3 (t2) post stroke.

Prediction of hand motor recovery

Table 2 shows the contingency tables and the PPVs and NPVs for each prognostic factor. PPVs varied from 0.62 to 1.00 and NPVs from 0.74 to 0.95.

At t1, both the FMA upper-extremity subscore and the presence of an ADM-MEP showed PPVs of 1.00. Both factors identified 4 patients who regained hand motor function at t3. However, only 2 of these patients were identified by both the FMA upper-extremity subscore and the ADM-MEP. The highest NPVs were found for the FMA lower-extremity subscore (0.90, 95%-CI 0.78-1.00) and the presence of any MEP (BB and /or ADM) (0.80, 95%-CI 0.64-0.96). At t2, the NPVs increased with the highest values for the FMA lower-extremity subscore of at least 10 points (0.95, 95%-CI 0.87-1.00) and the presence of any MEP (BB and/or ADM) (0.94, 95%-CI 0.83-1.00). Again, the highest PPVs were found for the upper-extremity subscore and the presence of an ADM-MEP (PPV 1).

In addition, table 3 shows the PPVs and NPVs for the selected combinations of the potential prognostic factors. At t1, the presence of a FMA upper-extremity subscore or a positive ADM-MEP identified 2 additional patients (6 instead of 4) with hand motor recovery at t3, whereas at t2 this combination of factors identified 1 additional patient (10 instead of 9). As a result the NPVs slightly increased from 0.74 to 0.79 at t2 and from 0.88 to 0.91 at t2. Only when the FMA upper-extremity subscore was combined with any MEP (BB and / or ADM) a NPV of 1.00 was reached at t2.

Table 2. *Positive and negative predictive values for different prognostic factors with regard to hand motor recovery (FMA hand score > 3) at 6 months after stroke*

		Number of patients with hand motor recovery at 6 months (t3)	Number of patients without hand motor recovery at 6 months (t3)	Positive (PPV) and negative predictive values (NPV) (95% confidence intervals)
Week 1 post-stroke (t1)				
Any MEP (BB and / or ADM)	Present	7	3	PPV 0.70 (0.42-0.98)
	Absent	5	20	NPV 0.80 (0.64-0.96)
ADM-MEP	Present	4	0	PPV 1.00 (1)
	Absent	8	23	NPV 0.74 (0.59-0.90)
FMA upper-extremity subscore	Present	4	0	PPV 1.00 (1)
	Absent	8	23	NPV 0.74 (0.59-0.90)
FMA lower-extremity subscore	Present	10	4	PPV 0.71 (0.48-0.95)
	Absent	2	19	NPV 0.90 (0.78-1.00)
Week 3 post-stroke (t2)				
Any MEP (BB and /or ADM)	Present	8	5	PPV 0.62 (0.35-0.88)
	Absent	1	16	NPV 0.94 (0.83-1.00)
ADM-MEP	Present	6	0	PPV 1.00 (1)
	Absent	3	21	NPV 0.88 (0.74-1.00)
FMA upper-extremity subscore	Present	9	0	PPV 1.00 (1)
	Absent	3	23	NPV 0.88 (0.76-1.00)
FMA lower-extremity subscore of at least 10 points	Present	11	2	PPV 0.85 (0.65-1.00)
	Absent	1	21	NPV 0.95 (0.87-1.00)

BB= biceps brachii muscle; ADM= abductor digiti minimi muscle; MEP= motor evoked potential; FMA= Fugl-Meyer motor assessment.

Discussion

To our knowledge, this is the first study that made a direct comparison between early clinical assessment and TMS with regard to predicting hand motor recovery after stroke. A well-selected, homogeneous, sample of patients with an initial paralysis of the upper extremity caused by a first-ever, ischemic, supratentorial stroke was included, because particularly in this subgroup early prediction of motor recovery is considered both clinically relevant and difficult at the same time. As a consequence, the results of this study are applicable only to the severely affected stroke survivors with an initial paralysis of the upper extremity. At six months after the initial stroke, 12 patients (34%) developed some hand function as assessed by the FMA hand subscore. Six of these patients (17%) even regained complete hand motor function. These figures are consistent with those reported in the literature on motor recovery after severe stroke [3, 5].

Thirty-four percent of the patients had a positive MEP response in either proximal or distal upper-extremity muscles at the first TMS assessment, which increased to 43% at the second assessment. Most muscles that generated motor evoked potentials at week 1 showed motor recovery at 6 months after stroke. The presence of an ADM-MEP was able to accurately identify hand motor recovery at 6 months post stroke in patients with an initial upper-extremity paralysis (PPV = 1). Indeed, all patients with a MEP response in the ADM muscle at either week 1 (t1) or week 3 (t2) showed hand function recovery at 6 months after stroke, whereas for the BB muscle a positive MEP response did not result in any hand motor recovery at 6 months in 3 patients at week 1 and in 5 patients at week 3. In all 3 patients at week 1 post stroke and in 4 patients at week 3, a positive MEP-response in the BB muscle did not result in any recovery of arm motor function at 6 months as well.

This discrepancy between positive predictive values of ADM and BB may be due to differences in the physiology of motor control between proximal and distal upper-extremity muscles [19, 20]. In contrast to proximal muscles, the motoneurons that innervate the intrinsic muscles of the hand and govern independent and fractionated (fine manipulatory) finger movements, receive direct, monosynaptic inputs from the corticospinal tract [21-23]. Therefore, the integrity of the corticospinal pathway is considered a prerequisite for normal hand function rather than for arm function.

However, the selected neurophysiological parameters did not yield better predictive values compared to clinical assessment. At week 1 after stroke, both early hand motor recovery and the presence of an ADM-MEP showed a good positive predictive value (PPV = 1) with regard to recovery of hand motor functions at 6 months.

Table 3. *Positive and negative predictive values for selected combinations of prognostic factors with regard to hand motor recovery (FMA hand score > 3) at 6 months after stroke*

		Number of patients with hand motor recovery at months (t3)	Number of patients without hand motor recovery at 6 months (t3)	Positive (PPV) and negative predictive values (NPV) (95% confidence intervals)
Week 1 post-stroke (t1)				
FMA upper-extremity subscore or any MEP (BB and / or ADM)	Present	8	3	PPV 0.73 (0.46-0.99)
	Absent	4	20	NPV 0.83 (0.68-0.98)
FMA upper-extremity subscore or ADM MEP	Present	6	0	PPV 1.00 (1)
	Absent	6	23	NPV 0.79 (0.65-0.94)
Week 3 post-stroke (t2)				
FMA upper-extremity subscore or any MEP (BB and / or ADM)	Present	12	5	PPV 0.71 (0.49-0.92)
	Absent	0	16	NPV 1.00 (1)
FMA upper-extremity subscore or ADM-MEP	Present	10	0	PPV 1.00 (1)
	Absent	2	21	NPV 0.91 (0.80-1.00)

BB= biceps brachii muscle; ADM= abductor digiti minimi muscle; MEP= motor evoked potential; FMA= Fugl-Meyer motor assessment.

Early leg motor recovery had a lower predictive value (PPV = 0.71). This pattern of results differs to some extent from the results reported by Kwakkel et al. [3]. Yet, Kwakkel et al. [3] did not include the presence of hand motor recovery at 1 week in their prediction model. Prediction of hand function at 6 months after stroke in their study was best identified by leg motor recovery in the first week after stroke with a probability of 74%. This discrepancy with the results of the present study may be due to the different populations of severe stroke patients studied. In the study of Kwakkel et al. [3], only 76 % of the patients had a paralysis of the upper extremity at onset, whereas in our study all patients had an initial paralysis.

Although both early hand motor recovery and the presence of an ADM-MEP were highly predictive with regard to hand motor function at 6 months after stroke, only 4 and 6 out of 12 patients with hand function at 6 months were identified at week 1 and week 3 respectively, implicating a rather poor NPV for both prognostic factors. By combining these factors a few more recovering patients could be identified, but the NPV just slightly increased. Only when the FMA upper-extremity subscore was combined with any MEP of the BB or the ADM a NPV of 1.00 was reached at 3 weeks after stroke. Compared to the NPV of the FMA lower-extremity subscore at 3 weeks post stroke (NPV = 0.95), this difference is small and attributable to merely 1 false-negative patient for the leg score.

In severe stroke patients with a potential for motor recovery it is generally important to focus rehabilitation efforts on the restoration of motor function. In this perspective, one wants to treat as many of these patients as early as possible after stroke, accepting the chance of treating some patients without potential for motor recovery unsuccessfully. From this point of view, false-negative classifications must be prevented and prediction of hand motor recovery can best be based on early motor recovery of the leg, which has a good NPV at 1 week (0.90) and at 3 weeks (0.95) post stroke. Only the combination of an absent upper-extremity FMA subscore and an absent MEP in BB and ADM at 3 weeks post stroke may provide more certainty (NPV = 1.00). However, if one considers vigorous treatment strategies that impose an unacceptable burden on non-responders, one should strive for as few false-positives as well. From this perspective, a positive leg motor score is certainly informative, but one might want to rely on a positive upper extremity-motor score or a positive ADM-MEP for excluding false positives.

Our results show that, apparently, critical residual sparing of corticospinal connections cannot be detected by TMS in all cases during the acute and sub-acute phases post stroke. This might be due to insufficient cortical stimulation of functionally depressed, but undamaged corticomotoneurons. Another explanation is that restoration of motor function may be due to cortical reorganization involving brain systems that cannot be recruited by

TMS, because these are not directly connected to the corticospinal pathways [24]. In these cases, adding neuroimaging studies to TMS may provide valuable additional information about the residual function of the cortical sensorimotor system [25].

Our TMS protocol was restricted to TMS assessment at 100% stimulator output. Several authors have reported that at this stimulus intensity, maximum values of the MEP amplitude with minimal variability can be obtained [12, 26]. In this study, we were merely interested in the question whether the intactness of the corticospinal tract is predictive of hand motor function recovery. For this purpose, both TMS characteristics (presence or absence of a MEP) and hand function (FMA hand score > 3) have been dichotomized. Thus, we were able to minimize the time taken and effort needed to perform TMS measures in the patients suffering from severe stroke.

Another limitation of our study is the still relatively small number of patients included, which affects the accuracy of the estimated PPVs and NPVs. Many more patients would be needed to reduce the estimated confidence intervals. Yet, we deliberately restricted the inclusion to patients with an initial paralysis. This subgroup of severely affected stroke patients comprises only 19-30% of the stroke population at large, and has a high risk of post-stroke death (62%) and a relatively small chance of motor recovery [2-5]. As a result, the inclusion rate and the incidence of motor recovery were relatively low. However, as we argued in the introduction, accurate prediction of hand motor recovery is particularly relevant in these severe patients, because the appropriate rehabilitation strategy depends on the probability of motor recovery and the chance of developing complications secondary to paralysis or spasticity. Patients with residual arm and hand function at the time of stroke onset will always show some motor recovery, which warrants a treatment strategy promoting such recovery [27].

Conclusion

In stroke patients with an initial paralysis of the upper extremity the presence or absence of a MEP seems to have no additional predictive value compared to early clinical assessment with regard to long-term hand motor recovery. Based on the FMA, accurate prediction of long-term hand function recovery can be made 3 weeks after stroke using the upper-extremity subscore to predict motor recovery and the lower-extremity subscore to predict the absence of recovery. In individual patients that are difficult to examine, for instance due to severe cognitive deficits or loss of consciousness, TMS may still provide more reliable results than clinical examination. In the future, stimulus-response curves of the MEP amplitude might be used to assess corticospinal function in patients with mild to moderate strokes. By

combining such TMS techniques with modern imaging techniques, we may be able to distinguish the restorative cortical mechanisms from those of the descending corticospinal tract.

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Chapter 5

Are clinical characteristics associated with upper-extremity hypertonia in severe ischemic supratentorial stroke?

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Abstract

Objective: The primary aim of this study was to identify clinical risk factors, in addition to muscle weakness, for upper-extremity hypertonia in patients with severe, ischemic, supratentorial stroke. The secondary goal was to investigate the time course of upper-extremity hypertonia in these patients during the first 26 weeks after stroke.
Methods: Inception cohort of forty-three consecutive patients with an acute ischemic supratentorial stroke and an initial upper-extremity paralysis. Primary outcome: Hypertonia assessed by the Ashworth scale at week 26 after stoke. Potential risks factors: Motor functions assessed by the upper-extremity subscore of the Fugl-Meyer motor assessment, Barthel Index at week 1, consciousness, sensory disturbances, apraxia, neglect, and hyperreflexia. Secondary outcome: time course of upper-extremity hypertonia by assessing its prevalence at 6 consecutive moments after stroke during a follow-up period of 26 weeks.
Results: Twenty-five patients (63%) developed hypertonia during the follow-up period of 26 weeks. During this period, the prevalence of hypertonia followed a rather dynamic course, with cases of early, transient, and late hypertonia. Univariate analyses yielded none of the selected clinical characteristics as significantly associated with hypertonia.
Conclusions: Despite the high incidence of hypertonia (63%) observed, none of the selected clinical characteristics could be identified as a risk factor for hypertonia.

Introduction

Spasticity is a characteristic component of the upper motor neuron syndrome in the post-acute and chronic phases of stroke. Spasticity develops in about 20 to 40% of all stroke survivors, usually within 3 months after stroke [1-5]. In the upper extremity, spasticity may cause difficulty with basic arm and hand abilities, such as reaching and grasping, as well as with many more complex activities of daily living (ADL) [6-8]. In the acute and post-acute phases after stroke, recurrent negative reinforcement in attempts to use the affected arm can lead to so-called ‘learned non-use’, in particular when spastic antagonists counteract selective voluntary muscle activity [9]. Moreover, in the long-term, untreated spasticity can lead to secondary complications, such as changes in the visco-elastic properties of the musculo-tendinous apparatus (stiffness), loss of muscle length (contractures), and pain, which may further impede the functional use of the upper extremity [3, 10].

The precise relationship between spasticity elicited by passive tendon or muscle stretch and the active movement capacity, however, remains unclear. As a consequence, it is not clear

whether reduction of spasticity will always improve active motor functions and dexterity. A systematic review of the treatment of post-stroke upper-extremity spasticity by focal neuronal or neuro-muscular blockade revealed the potential efficacy of such treatments in reducing hyperreflexia, muscle tone, and in improving passive range of joint motions [11], yet, functional benefits could not be convincingly demonstrated. Generally, functional effects of spasticity treatment seem to depend highly on a critical selection of subjects, individualized goal setting, and appropriate selection of outcome measures [12, 13]. Patients after severe stroke with a low potential for motor recovery in particular may profit from a pro-active treatment approach to prevent disabling spasticity and the functional consequences of secondary complications, such as muscles stiffness, contractures, and pain. Benefits can be achieved with regard to activities such as dressing, bathing and grooming, as well as with regard to limb positioning, cosmetic appearances, and comfort [12, 13]. Against this background, it seems clinically relevant to assess, besides the probability of motor recovery, the risk of developing spasticity in the individual patient early after stroke.

However, although motor recovery can be predicted reasonably well by clinical assessment [14], early recognition of the risk of developing spasticity based on clinical characteristics is much more difficult and the literature does not really support clinical reasoning. Because the clinical assessment of spasticity measures resistance against passive stretch (hypertonia), it cannot distinguish between the neural (reflexive) mechanisms, and the secondary (intrinsic) changes in muscle properties. Studies on the risk factors for post-stroke hypertonia are also scarce. Besides a recently published cohort study by Leathly et al. [4], no other studies are available in (sub) acute stroke patients. In stroke survivors, Leathly et al. [4] found a moderate association of both muscle weakness and a low Barthel Index (BI) [15] on day 7 after stroke with hypertonia at 12 months after stroke. Based on clinical experience, some authors have suggested the importance of sensory impairments, visuospatial deficits, and apraxia for developing hypertonia [16, 17]. However, these disorders were not identified as risk factors in the study by Leathly et al. [4], which might have been due to the relatively low number of cases with hypertonia (36%).

Against this background, we conducted a cohort study including only patients with an initial paralysis of the upper extremity after supratentorial ischemic stroke to maximize the likelihood of observing hypertonia and, thus, to optimize the chance of identifying additional risk factors for post-stroke upper-extremity hypertonia. As a secondary goal, we studied the time course of upper-extremity hypertonia by assessing its prevalence at 6 consecutive moments after stroke during a follow-up period of 26 weeks.

Materials and Methods

Patients

As part of a larger study on the value of motor-evoked potentials (MEPs) in predicting motor and functional outcome after stroke [18], 43 consecutive acute patients with an ischemic supratentorial stroke were recruited during a 1.5-years' period. These patients were admitted to the Department of Neurology at the Radboud University Nijmegen, Medical Centre. The diagnosis of stroke was made clinically by a neurologist according to the World Health Organization (WHO) clinical criteria [19] and confirmed by computerized tomography (CT) scan.

Only patients presenting with stage I of the upper extremity according to Brunnstrom [20] (i.e., no tone and no voluntary muscle activity at the elbow, wrist, or finger flexors) at day 1 were included within 7 days after stroke. Patients with a poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity) as well as patients with severe pre-existing impairments of the upper extremity of any type (e.g., rheumatic deformities, contractures) were excluded. Because all patients had to undergo transcranial magnetic stimulation to record MEPs, those with a history of craniotomy, epilepsy, cardiac prosthetic valve or pacemaker implantation, or severe polyneuropathy were also excluded. The local ethics committee approved the study protocol and written informed consent was obtained from all patients before study entry.

Each patient received 'best medical treatment' according to the guidelines of the Netherlands Society of Neurology, including a multi-disciplinary initial rehabilitation approach. This approach ensured that each patient received physiotherapy to maintain optimal passive and active range of motion of all upper-extremity joints from day 1 after stroke. However, for the first 3 weeks after stroke, no specific therapy was initiated aimed at facilitation of hand function recovery.

Potential risk factors

Within the first 24 hours after stroke the treating neurologist assessed all patients with regard to initial motor functions, muscle tone, and level of consciousness. All consecutive clinical assessments of motor, sensory, and cognitive functions were performed at weeks 1, 2, 3, 6, 12, and 26 after stroke by a rehabilitation physician (HH). Motor functions were assessed according to the upper-limb subset of the Fugl-Meyer Motor Assessment (FMA) [20]. A selected hand motor score was derived from the FMA, which consisted of the 7 original hand items of the FMA with a maximum score of 14 points. Early hand motor function recovery was defined as any change in the FMA hand score within the first 3 weeks after stroke.

Sensory deficits were assessed by clinical examination of light touch, pinprick, and vibration sense of the hemiparetic arm. Proprioception was assessed by the 'thumb-finding test' [21]. Sensory deficit was ultimately recorded on a binary scale as either 'absent' or 'present' based on reproducible differences in at least 2 sensory modalities compared with the non-paretic arm. Biceps and triceps tendon reflexes were quantified according to the Mayo Clinic scale for tendon reflex assessment (range -4 to +4) [22]. Hyperreflexia was considered present if the tendon reflex on the paretic side was ≥ +1.

Neglect was defined as the inability to detect, attend to, or respond to stimuli located on the contra-lesional side of body or action space [23]. Apraxia was defined as the inability to perform previously learned skilled acts, despite sufficient comprehension, motor capacity, and sensation. Both the existence of neglect and apraxia were based on clinical observations of the patient's ADL performances by the nursing staff, the treating neurologist, and the consulting rehabilitation physician within the first 3 weeks after stroke. Neglect and apraxia were considered present if symptoms were witnessed by at least 2 of these 3 observers.

Finally, ADL performances were assessed with the Barthel Index (BI) [15]. Consistent with Leathly et al. [4], the BI score at the first week after stroke was considered as a potential risk factor.

Outcome assessment

Hypertonia was clinically assessed by grading muscle tone through the Ashworth scale (AS) [24]. Muscle tone was assessed within the first 24 hours after stroke and consecutively at weeks 1, 2, 3, 6, 12, and 26 after stroke under standardized test conditions by a rehabilitation physician (HH). The patients lay supine or sat in a comfortable sitting position with their forearms supinated and resting on a horizontal plane. Patients were instructed to completely relax while their affected elbows and wrists were passively moved throughout the maximal range in both flexion and extension directions. Passive extension of the patient's elbow was performed during approximately one second by counting "one thousand and one" while the forearm was held just proximal to the wrist. When the elbow was extended, the upper arm was stabilized just proximal to the elbow. Passive extension of the patient's wrist was also performed during approximately one second while the hand was held just proximal to the metacarpo-phalangeal joints and the forearm just proximal to the wrist. Muscle tone was quantified according to the criteria outlined by Ashworth [24] (grades 0-4). Clinically relevant hypertonia was operationally defined as an AS score equal to or greater than 2 in at least one joint.

Data analysis

From 2x2 contingency tables, positive and negative predictive values for each of the potential risk factors with their 95% confidence interval were calculated. In addition, to test the association of gender with hypertonia, Pearson's chi-square analysis was performed. The required 2-tailed significance level was set at 0.05. For the ordinal outcome measure BI at week 1 after stroke, the Mann- Whitney *U* test was performed to assess the association between the BI and hypertonia. Again, the required 2-tailed significance level was set at 0.05.

In case of positive outcome of the univariate analysis, multiple backwards logistic regression was planned to determine the explained variance by each characteristic with regard to hypertonia, independent of its possible association with other characteristics.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS® version 11).

Results

Patients characteristics and time course of post-stroke hypertonia

Two patients died within the first 2 weeks after stroke. Both continued to have a flaccid paralysis of the upper extremity from clinical presentation. Another patient was excluded from the study at week 13 because of a poor prognosis for survival after he had a recurrent stroke. Thus, 40 patients, 20 women and 20 men, completed the study. The clinical characteristics of these 40 patients are shown in Table 1. Sixteen (40%) patients had had a previous stroke, whereas 24 (60%) patients had had a first-ever stroke.

The highest estimated AS scores in our patients were 0 (n=9), 1 (n=6), 2 (n=8), 3 (n=12), and 4 (n=5). If clinical hypertonia was defined as AS equal to or more than 2, 25 (63%) patients developed hypertonia at any time after stroke. In 20 patients hypertonia developed within the first 6 weeks after stroke, and in 10 (25%) patients even within the first 3 weeks after stroke. This 'early' (within 3 weeks) hypertonia was not correlated with previous stroke (Fisher's exact p = 0.48). We identified 16 hypertonic patients at 6 months who were not initially hypertonic, as well as 3 patients with normal muscle tone at 6 months who were initially hypertonic. Figure 1 illustrates how the prevalence of hypertonia evolved in our study sample.

In 12 patients, recovery of hand motor function was present at week 26 after stroke. In the group with persistent hypertonia, 7 (33%) patients showed any recovery of hand motor function, whereas in the group without hypertonia 5 patients showed such recovery (26%). Figure 2 illustrates the FMA-hand scores at week 26 after stroke in both the patients with and those without persistent hypertonia.

Table 1. C*haracteristics of the 40 patients*

		number
Gender	Female	20
	Male	20
Stroke history	First ever	24
	Previous	16
Lesion side	Left	22
	Right	18
Median age, years (interquartile range)	68 (59-77)	
Median Barthel Index on admission (interquatile range)	0 (0)	

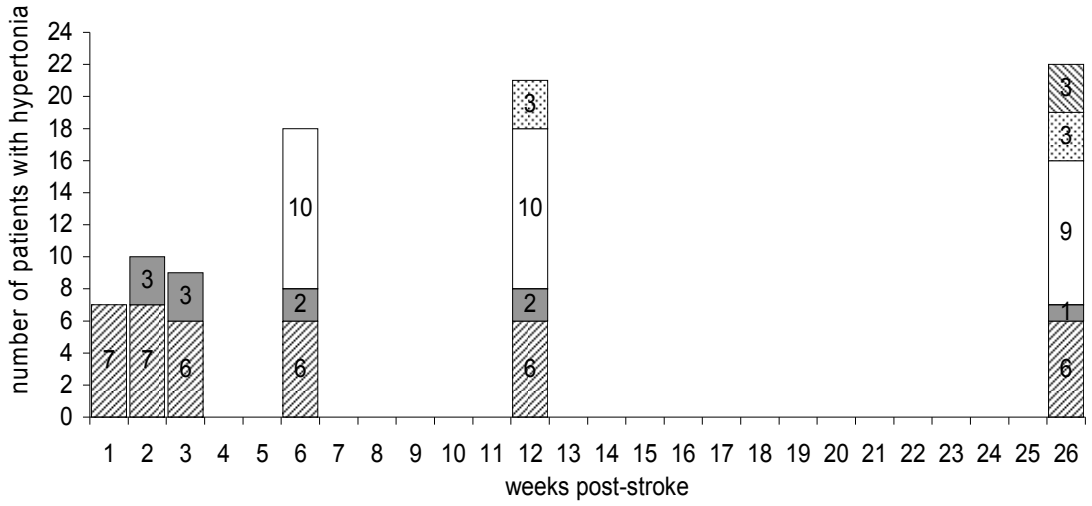

Figure 1. *Prevalence of post-stroke hypertonia during the first 26 weeks post-stroke. Patients developing hypertonia at week 1 (▨), week 2 (■), week 6 (□), week 12 (⁘), and week 26 (▧) post-stroke*

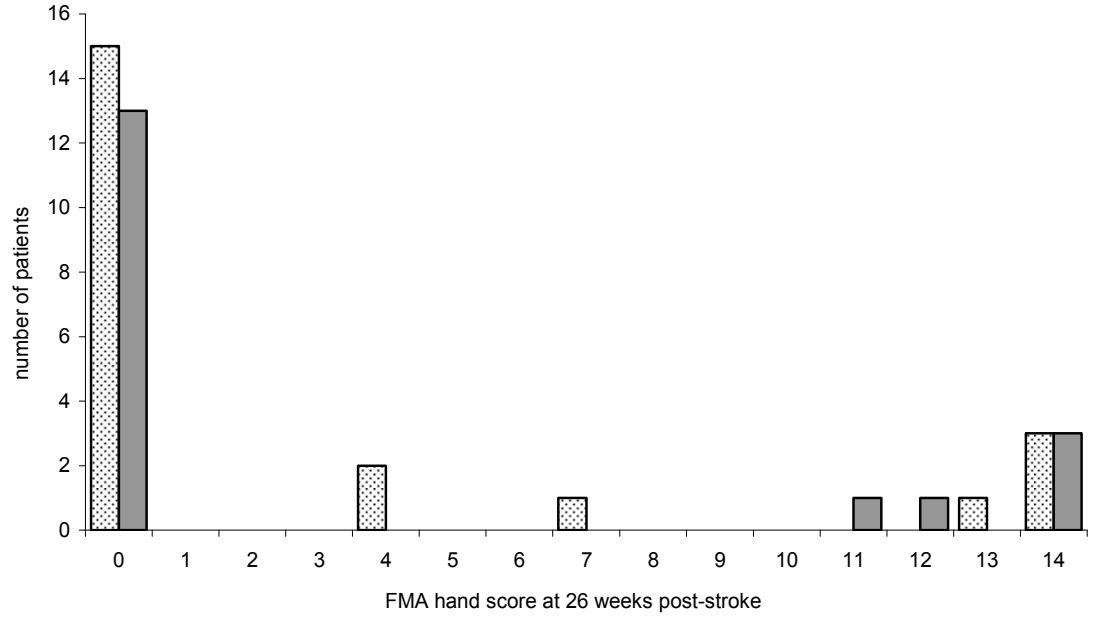

Figure 2. *Fugl-Meyer Motor Assessment (FMA) hand score at 26 weeks post-stroke in patients with ( ) and those without ( ) persistent hypertonia*

Potential risk-factors for post-stroke hypertonia

Because, from a clinical point of view, we were most interested in predicting *persistent* hypertonia, we considered hypertonia at week 26 after stroke as the primary outcome. In univariate analyses, all associations between hypertonia at week 26 and the potential risk factors were low and statistically not significant. Table 2 shows the positive and negative predictive values with their 95% confidence intervals for all factors. Positive predictive values varied from 0.52 to 0.68 and the negative values from 0.33 to 0.62.

In addition, 10 females and 12 men suffered from hypertonia at 26 weeks after stroke. In both patients with and those without hypertonia the median BI at week 1 after stroke was 2 (inter-quartile range 0 to 4). There was no association between gender and hypertonia (χ^2 0.404; p = 0.525) and neither between the BI at week 1 and hypertonia (p = 0.93). Changing the definition of *persistent* hypertonia into AS equal to or more than 2 at week 12 or week 6 after stroke yielded similar results. Even if clinically relevant hypertonia was defined as AS equal to or more than 1, or if hypertonia at *any* time after stroke was used as the primary outcome, no association with the potential risk factors could be demonstrated.

Table 2. *Association between potential risk factors and hypertonia at 26 weeks post-stroke*

		Number of patients with hypertonia	Number of patients without hypertonia	Positive (PPV) and negative predictive values (NPV) and 95% confidence intervals
Unconsciousness at stroke	Present	18	14	PPV 0.56 (0.38-0.74)
	Absent	4	4	NPV 0.50 (0.35-0.97)
Sensory disturbances	Present	16	15	PPV 0.52 (0.34-0.70)
	Absent	6	3	NPV 0.33 (0.07-0.59)
Hyperreflexia	Present	17	13	PPV 0.57 (0.40-0.74)
	Absent	5	5	NPV 0.50 (0.19-0.81)
Apraxia	Present	11	7	PPV 0.68 (0.49-0.87)
	Absent	11	11	NPV 0.50 (0.28-0.72)
Neglect	Present	19	13	PPV 0.58 (0.41-0.75)
	Absent	3	5	NPV 0.62 (0.33-0.91)
Early hand motor recovery	Absent	19	16	PPV 0.54 (0.37-0.71)
	Present	3	2	NPV 0.40 (0.05-0.75)

Discussion

In this study a sample of patients with initial paralysis of the upper extremity caused by ischemic supratentorial stroke was included to optimize the chance of identifying risk factors, additional to muscle weakness, for early, persistent hypertonia. The observed overall incidence of hypertonia within 6 months after stroke in this group was 63%. In comparison, Sommerfeld et al. [5] found a 24% overall incidence of hypertonia within 3 months in a hospital-based cohort of patients with an acute, first-ever, ischemic stroke. Other studies on stroke-related hypertonia mainly reported prevalences instead of incidences, varying from 19 to 39% of the hospitalized stroke population at large [4-6]. Hence, our patient sample was clearly different from those in previous studies. It was restricted to a homogeneous subgroup of the most severely affected survivors from ischemic, supratentorial stroke, i.e., those with an initial paralysis of the upper extremity. The severity of stroke is also evident from the finding that all patients had an initial BI of 0. Based on the observed incidence in this study, this subgroup of stroke patients with initial paralysis of the upper extremity apparently has a substantial chance of developing hypertonia within 6 months after stroke.

Yet, even in this severely affected group, we could not identify any of the selected clinical characteristics as a significant risk factor for early or persistent hypertonia. Even hyperreflexia, which is regarded by many clinicians as a sign of “spasticity”, was not significantly associated with the AS in this study. This finding is corroborated by several electrophysiological studies that have shown dissociations between hyperreflexia and hypertonia, indicating that phasic and tonic stretch reflexes are controlled differently by the central nervous system [2, 5]. However, it might also reflect the fact that the AS is unable to distinguish between neural mechanisms (hyperreflexia) and secondary intrinsic changes of muscle properties (contracture). As for sensory or cognitive deficits, our data do not underscore the clinical notion that loss of sensibility, neglect, or apraxia may increase the risk of developing post-stroke upper-extremity hypertonia. These findings are consistent with those of Patano et al. [25], who could not find any differences in sensory disturbances, aphasia, or visuospatial neglect between patients with prolonged muscular flaccidity and those with hypertonia in the sub-acute phase (2 to 6 months) after stroke. Hence, as yet, only a modest association between early muscle weakness and chronic hypertonia has been found by Leathly et al. [4].

The secondary goal of this study was to explore the time course of upper-extremity hypertonia during the first 26 weeks after stroke in patients with initial paralysis. Although it is generally assumed that muscle tone increases from flaccidity in the acute phase of stroke to various degrees of hypertonia in the long term [1, 2, 26], the patients with early (25% within 3

weeks after stroke), transient (10%), or late (15%) hypertonia in our cohort did not fit within this general idea. Sommerfeld et al. [5] reported hypertonia within the first week after stroke in 21% of their acute hospitalized patients as well. In contrast to the opinion of others [27], in our study early hypertonia was not correlated with previous stroke. In 3 patients who developed hypertonia within 6 weeks after stroke, muscle tone had normalized at 26 weeks, perhaps related to neural plasticity. At 26 weeks we identified another 6 patients in which hypertonia developed only after the third month post-stroke. It seems likely that secondary intrinsic changes of muscle properties contributed to this late hypertonia [28].

At 26 weeks after stroke, we did not find any difference in motor or functional recovery between patients with and those without hypertonia, which may be due to the fact that the majority of our patients ended up with a non-functional paralytic arm and hand. The unique influence of hypertonia on motor impairments and ADL performances is, no doubt, difficult to assess in a subgroup of patients with initial paralysis with such a poor chance of motor recovery. In addition, specifically patients with severe stroke may suffer from various other problems of, for example, mood, cognition, vision, and sensation, which may contribute to their overall disability. Lastly, the BI is probably not the best measure to assess ADL performances related to arm and hand function. When, for instance, hypertonia causes pain or discomfort or problems with arm positioning, dressing, or hygiene control, treatment that reduces hypertonia and prevents secondary complications may greatly benefit the patient on a functional level [12, 13], although such benefit does not need to be reflected in a change in the BI score.

One of the possible limitations of this study is that upper-extremity hypertonia was clinically assessed using the AS, whereas instrumented analysis of electromyographic (EMG) and force signals from the upper-extremity muscles on passive stretching might have allowed better discrimination between active (i.e., contractions) and passive (i.e., stiffness) contributions to muscular resistance [3, 29]. However, instrumented tests are not yet available for routine clinical application, which is the reason that the AS and modified AS are still the most commonly used measures of adult spasticity in clinical practice. The AS is most frequently used as the primary outcome measure in intervention studies as well, and other scales, such as the tone assessment scale, can be regarded as modifications of the AS. All these measures are equally reliable regarding muscle tone assessment of the upper extremity [30]. Overall, there is a reasonable association between the (modified) AS and EMG responses in patients with hemiparetic stroke [31], which does not preclude a significant contribution of passive muscle properties to (particularly late) hypertonia.

Another limitation of our study may have been a lack of power to identify risk factors for upper-extremity hypertonia due to the still limited number of patients. We included merely patients with initial paralysis to optimize the risk of post-stroke hypertonia. This subgroup comprises only 19 to 30% of the stroke population at large and has a high risk of post-stroke death (62%) [32]. As a result, the inclusion rate was relatively low in just one academic hospital. However, 40 patients would have been sufficient to discriminate a moderate from an 'absent' association between hypertonia and any clinical determinant (setting alpha at 0.05 and 1-beta at 0.80). Hence, larger studies of high-risk patients will be needed to include the number of subjects to identify "weak" but significant associations.

Conclusion

The present study showed that a subgroup of patients with an initial paralysis of the upper extremity apparently has a substantial chance of developing hypertonia at any time after stroke. The observed incidence over the 26-week follow-up period was 63%. The prevalence of upper-extremity hypertonia during the first 26 weeks after stroke followed a rather dynamic course, with cases of early, transient, and late hypertonia. Even in this selected study sample with a high incidence of hypertonia, we could not identify any of the selected clinical characteristics as a risk factor for transient or persistent hypertonia. Unlike the stroke population in general, in patients with severe stroke and initial upper-extremity paralysis, hypertonia appeared not to be associated with motor or functional recovery of the affected arm.

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Chapter 6

Are neuroradiological or neurophysiological characteristics associated with upper- extremity hypertonia in severe ischemic supratentorial stroke?

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Abstract

Objective: The primary aim of this study was to identify the neuroradiological and neurophysiological risk factors for upper-extremity hypertonia in patients with severe, ischemic, supratentorial stroke.
Methods: Inception cohort of forty-three consecutive patients with an acute, ischemic, supratentorial stroke and an initial upper-extremity paralysis. Primary outcome: Upper-extremity hypertonia was assessed by the Ashworth scale and clinically relevant hypertonia was defined as an Ashworth score equal to or more than 2. Any association of (clinically relevant) hypertonia with neuroradiological (lesion side, extent of lesion, and stroke history), and neurophysiological (motor-evoked potential and silent period) characteristics was investigated.
Results: Associations between hypertonia and the selected neuroradiological and neurophysiological risk factors were generally low. Univariate analyses yielded none of the selected neuroradiological or neurophysiological characteristics as significantly associated with hypertonia.
Conclusions: Despite the high incidence of hypertonia in these patients, we could not identify any of the selected neuroradiological or neurophysiological characteristics as a risk factor for hypertonia.

Introduction

Spasticity is a characteristic component of the upper motor neuron syndrome in the post-acute and chronic phases of stroke. The precise relationship between spasticity elicited by passive tendon or muscle stretch and the active movement capacity, however, remains unclear. In the upper extremity, spasticity may cause difficulty with basic arm and hand abilities, such as reaching and grasping, as well as with many more complex activities of daily living [1-5]. Functional effects of spasticity treatment seem to depend highly on a critical selection of subjects, individualized goal setting, and appropriate selection of outcome measures [6-9]. In particular, patients after severe stroke with a low potential for motor recovery may profit from a pro-active treatment approach to prevent disabling spasticity and the functional consequences of secondary complications, such as muscles stiffness, contractures, and pain. Against this background, it seems clinically relevant to assess, besides the probability of motor recovery, also the risk of developing spasticity in these patients early after stroke.

Studies on risk factors for post-stroke spasticity are, however, scarce and complicated by the inability of clinical measures to distinguish between the neural mechanisms and the secondary intrinsic changes of muscle properties. Indeed, the clinical assessment of spasticity incorporates both neural and non-neural mechanisms by grading resistance against passive stretch (hypertonia). As for clinical risk factors, as yet, only modest associations of early muscle weakness and a low initial Barthel Index (BI) with chronic hypertonia have been found [10]. In a companion paper describing the same selected study population of patients after stroke with an initial paralysis of the upper extremity and a BI of 0, we were unable to identify any clinical characteristic as an additional risk factor for early or persistent hypertonia, despite the high incidence of hypertonia observed in these patients [11]. In this perspective, it is a logical step to investigate whether specific neuroradiological or neurophysiological characteristics might be associated with early or persistent hypertonia.

Neuroradiological assessments (magnetic resonance imaging or computerized tomography (CT) scan) in patients after acute stroke are performed on a routine basis to confirm diagnosis and differentiate lesion type. Some neuroradiological characteristics (lesion type, size, and site) have been associated with motor recovery and functional outcome, however, as yet, there remains much debate on whether stroke location or size are associated with hypertonia [12-15]. Clinical heterogeneity with regard to both patient-groups and time post-stroke may be an important factor contributing to these inconsistencies in the literature.

Transcranial magnetic stimulation (TMS) has also become appreciated as a diagnostic and prognostic tool in patients after stroke [16]. In tonically pre-activated muscles, TMS of the primary motor cortex induces a short-latency motor-evoked potential (MEP) in the electromyogram as an excitatory effect, followed by a transitory suppression of the electromyographic activity, the silent period (SP), as an inhibitory effect. Although motor recovery can be predicted reasonably well by TMS [17,18], early prediction of hypertonia based on TMS is much more difficult. In patients with sub-acute and chronic strokes due to focal vascular brain lesions an association has been found between shortening of the SP and hypertonia as assessed by the Ashworth scale (AS) [19-21]. Studies regarding these neurophysiological characteristics as potential risk factors for hypertonia in patients with acute stroke are, however, lacking.

Against this background, we conducted a prospective cohort study including only acute stroke patients with an initial paralysis of the upper extremity to maximize the likelihood of observing hypertonia and, thus, to optimize the chance of identifying additional risk factors for post-stroke upper-extremity hypertonia. We investigated the association of neuroradiological (lesion side and extent) and neurophysiological characteristics (MEP and

SP) with early and late hypertonia, since these laboratory measures can be easily obtained in most hospitals with an acute stroke unit.

Materials and Methods

Patients

As part of a larger study on the value of MEP in predicting motor and functional outcome after stroke [18], 43 consecutive acute patients with an ischemic supratentorial stroke were recruited during a 1.5-years' period. These patients were admitted to the Department of Neurology at the Radboud University Nijmegen, Medical Centre. The diagnosis of stroke was made clinically by a neurologist according to the World Health Organization (WHO) clinical criteria [22] and confirmed by CT scan.

Only patients presenting at day 1 after stroke with no voluntary muscle activity and no muscle tone at the elbow, wrist, or finger flexors (Brunnstrom stage I [23]) were included within the first 7 days after stroke. Patients with a poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity) as well as patients with severe pre-existing impairments of the upper extremity of any type (e.g., rheumatic deformities, contractures) were excluded. Patients with a history of craniotomy, epilepsy, cardiac prosthetic valve or pacemaker implantation, or severe polyneuropathy were also excluded. The local ethics committee approved the study protocol and written informed consent was obtained from all patients before study entry.

Each patient received 'best medical treatment' according to the guidelines of the Netherlands Society of Neurology, ensuring that each patient received physiotherapy to maintain optimal passive and active range of motion of all upper extremity joints from day 1 after stroke. However, for the first 3 weeks after stroke, no specific therapy was initiated aimed at facilitation of hand function recovery.

Potential risk factors

Neuroradiological assessment

In each patient, a CT scan of the brain was made twice; the first time on the day of admission and, the second time, at week 1 after stroke to delineate the structural lesion. Both an independent neuroradiologist and a neurologist assessed the CT scans of all patients, independently of one another. Evidence of previous stroke ('present' or 'absent') as well as the extent of the (structural) vascular lesions ('extensive' or 'focal') were recorded. Extensive stroke was defined as lesions with a diameter equal to or more than 5 cm and / or located in both subcortical and cortical areas. Stroke lesions with a diameter less than 5 cm and

restricted to the subcortical areas (subcortical white matter, or basal ganglia, or internal capsule) were regarded as focal. Both assessors were blinded with regard to the neurophysiological and clinical assessments. In the case of disagreement between the assessors, consensus was established afterwards.

Neurophysiological assessment

TMS of the motor cortex was performed twice in each patient; at first, within 1 week after stroke (t1) and, secondly, at 3 weeks after stroke (t2) by the same experienced clinical neurophysiologist. This clinical neurophysiologist was blinded with regard to the results of the clinical and neuroradiological assessments. Patients were positioned comfortably in a supine position. TMS was performed through a 90 mm circular coil placed in a tangential plane above the vertex and powered by a Magstim 200 magnetic stimulator. The stimulus intensity was set at maximum stimulator output (100% = 2 Tesla). To obtain a preferential activation of each hemisphere, a clockwise inducing current flow was used for the right hemisphere and a counter-clockwise current for the left hemisphere. MEPs were recorded at t1 and t2 from the biceps brachii muscle (BB) and the abductor digiti minimi muscle (ADM) on both the affected and the unaffected side. SPs were recorded at t1 and t2 from the ADM, as a representative muscle for distal motor function of the upper extremity. Recordings were made using an Oxford Synergy electromyograph with filter settings of 20 Hz and 3 kHz (amplifier range 100 mV and recording sensitivity of 0.5 mV / bit). A 500-ms post-stimulus period was analysed. The MEPs and SPs were preferably recorded when facilitated by a slight voluntary ADM contraction. When patients could not elicit a contraction of the affected hand muscle, they were asked to activate the non-paretic ADM [24]. At least two responses were obtained to assess the reproducibility. The presence of a MEP was defined as any reproducible response with minimal peak-to-peak amplitude of 200 μV. The absence of a positive MEP at 3 weeks after stroke was regarded as a potential risk factor for post-stroke hypertonia. Responses with the highest MEP amplitude were used for analysis. The SP length was measured from ADM-MEP onset until the return of uninterrupted voluntary electromyography activity. Responses with the shortest SP length were used for analysis. Data from the non-paretic arm were compared with normative data and used as a reference. Finally, the BB and ADM responses (mean MEP amplitude and SP duration) were studied separately for both the paretic and the non-paretic side.

Outcome assessment

Hypertonia was clinically assessed by grading muscle tone through the AS [25]. Muscle tone (grade 0 to 4) was assessed within the first 24 hours and consecutively at weeks 1, 2, 3, 6, 12, and 26 after stroke under standardized test conditions by a rehabilitation physician. The precise technique of assessment has been described in a companion paper [11]. Clinically

relevant hypertonia was operationally defined as an AS score equal to or greater than 2 in at least one joint.

Data analysis

The MEP amplitude and SP duration obtained from the ADM and the BB on the paretic side were compared with the corresponding values obtained from the non-paretic side using Student's *t*-test.

In addition, from 2x2 contingency tables, positive and negative predictive values for each of the potential risk factors with their 95% confidence intervals were calculated. In case of positive outcome of the univariate analysis, multiple backwards logistic regression was planned to determine the explained variance by each characteristic with regard to hypertonia, independent of its possible association with other characteristics.

Results

Neuroradiological and TMS characteristics

Three patients were excluded from the study; 2 patients died within the first two weeks after stroke and another patient suffered from a recurrent stroke at week 13 resulting in a poor prognosis for survival. All 3 patients continued to have a flaccid paralysis of the upper extremity from clinical presentation. Thus, 40 patients, 20 women and 20 men, completed the study. The median age was 68 years (interquartile range 59 to 77 years). The neuroradiological characteristics of these 40 patients are shown in Table 1. Sixteen (40%) patients had had previous stroke, whereas 24 (60%) patients had had a first-ever stroke. Twenty-nine patients had extensive lesions that were located in the territory of the middle cerebral artery, involving cortical (n=2), subcortical (n=1), or both cortical and subcortical areas (n=26). Eleven patients had a focal, subcortically located lesion. In 4 of these patients the lesion was restricted to the basal ganglia.

TMS of the motor cortex was performed in all patients, however, 4 patients refused the second MEP assessment. Two of these patients developed hypertonia, 1 patient within the first week after stroke. In the other patient, hypertonia was observed from the 6th week after stroke. Thus, the complete MEP dataset was available for only 36 patients. The quantitative aspects of the TMS recordings are summarized in Table 2 for the subgroups of patients in which a positive MEP was obtained at t1 and t2. At both times, the MEP amplitudes in the BB and the ADM were significantly lower on the paretic than on the non-paretic side.

Table 1. *Neuroradiological characteristics of the 40 patients*

		Number (n)
Stroke history	First ever	24
	Previous	16
Lesion side	Left	22
	Right	18
Infarct size	Small (<2cm)	1
	Moderate (2-5 cm)	16
	Extensive (>5 cm	23
Infarct localisation	Cortical	2
	Subcortical	12
	Cortical/subcortical	26
Extent of stroke lesion	Focal	11
	Extensive	29

TMS of the motor cortex was performed in all patients, however, 4 patients refused the second MEP assessment. Two of these patients developed hypertonia, 1 patient within the first week after stroke. In the other patient, hypertonia was observed from the 6th week after stroke. Thus, the complete MEP dataset was available for only 36 patients. The quantitative aspects of the TMS recordings are summarized in Table 2 for the subgroups of patients in which a positive MEP was obtained at t1 and t2. At both times, the MEP amplitudes in the BB and the ADM were significantly lower on the paretic than on the non-paretic side.

Potential risk-factors for post-stroke hypertonia

From a clinical point of view, we were most interested in predicting persistent hypertonia. Therefore, we considered hypertonia at the 26th week after stroke as the primary outcome. Both at t1 and at t2 no differences in MEP amplitude on the paretic side could be found between patients with and those without hypertonia (Table 3). At t1 no SP could be elicited at the paretic side in any of our patients, whereas at t2 only in 4 patients a SP could be determined: 2 patients with and 2 without hypertonia. No difference in SP duration between these small patient groups was found.

Table 2. *Transcranial magnetic stimulation characteristics for both the biceps brachii (BB) and abductor digiti minimi (ADM) muscle in patients obtaining a positive motor-evoked potential (MEP) at week 1 and week 3 post stroke*

			Paretic side	Non-paretic side	Number of patients (n)	Paired sample t-test p-value
BB	Amplitude in mV	Week 1	1.47 (1.27)	5.46 (5.26)	9	0.05
	mean (standard deviation)	Week 3	1.59 (1.74)	6.11 (3.28)	15	0.00
ADM	Amplitude in mV	Week 1	2.22 (1.97)	6.68 (2.52)	6	0.00
	mean (standard deviation)	Week 3	2.28 (2.41)	7.51 (1.63)	10	0.00
	Silent period in msec	Week 1		-	0	-
	mean (standard deviation)	Week 3	336.75 (106.90)	202.50 (29.46)	4	0.11

Table 3. *Transcranial magnetic stimulation characteristics in both the biceps brachii (BB) and abductor digiti minimi (ADM) muscle at week 1 and at week 3 post-stroke in relation to hypertonia*

			Patients with hypertonia	number (n)	Patients without hypertonia	number (n)	Indept. sample t-test p-value
BB	Amplitude in mV	Week 1	1.20 (1.31)	7	2.4 (0.71)	2	0.266
	mean (standard deviation)	Week 3	1.11 (1.44)	10	2.56 (2.04)	5	0.132
ADM	Amplitude in mV	Week 1	2.15 (2.10)	4	2.35 (2.48)	2	0.921
	mean (standard deviation)	Week 3	2.28 (2.91)	6	2.27 (1.50)	4	0.993
	Silent period duration	Week 1	-	0	-	0	-
	in msec	Week 3	327.00†	2	237.00†	2	*
			487.00†		296.00†		

*: Not calculated; †: individual data (data per patient) at week 3

In univariate analyses, all associations between hypertonia at week 26 and the selected potential risk factors were low and statistically not significant (Table 4). Table 4 shows the positive and negative predictive values with their 95% confidence intervals for all factors. The positive predictive values varied from 0.52 to 0.68 and the negative values from 0.36 to 0.61. Changing the definition of *persistent* hypertonia into AS equal to or more than 2 at the 12th week or at the 6th week after stroke yielded similar results. Even if clinically relevant hypertonia was defined as AS equal to or more than 1, or if hypertonia at any time after stroke was used as the primary outcome, no association with the selected potential risk factors could be demonstrated.

Discussion

This study aimed to investigate to what extent selected neuroradiological and neurophysiological characteristics can be considered as risk factors for developing upper-extremity hypertonia in patients with severe, ischemic, supratentorial stroke. With regard to the neuroradiological assessments, the observed lack of association between the extent of the vascular lesion and hypertonia is consistent with the study of Patano et al. [12], who also found no correlation between lesion volume and muscle tone. Having had a previous stroke or the side of the lesion was also not significantly associated with hypertonia. In general, the lack of association between stroke location and hypertonia in our study may have been influenced by the fact that the majority of our patients suffered from extensive lesions on CT involving both the cortical and subcortical areas. In the literature, there also remains much debate on the influence of stroke location on the occurrence of hypertonia [12-15], which may well be related to the fact that the applied methods to localize and measure the lesions lack sufficient sensitivity.

The selected neurophysiological measures obtained by TMS did not show a significant association with the occurrence of hypertonia either. Although it has been shown that muscle weakness is a clinical risk factor for post-stroke hypertonia, the absence of an ADM-MEP at the third week after stroke was not associated with hypertonia. This negative result can be explained by the fact that hypertonia may not directly result from damage to the corticospinal pathways, but from concomitant damage to the para-pyramidal pathways [26].

At the cerebral level, there may be a loss of the cortical drive to several inhibitory centres in the brainstem, e.g., the origin of the lateral reticulospinal tract, resulting in disinhibition of bulbar and spinal reflexes [26-28]. This loss of cortical drive may be due to lesions within areas projecting to the primary motor cortex, such as the primary somatosensory area,

supplementary motor area, the premotor area, basal ganglia, thalamus, and cerebellum. These brain areas provide important modulatory inputs to the primary motor cortex and lesions within these areas might, therefore, lead to a subsequent change in the balance between excitatory and inhibitory influences on the intra-cortical motor neurons that project to inhibitory centres at the level of the brainstem. Although these para-pyramidal pathways cannot be directly assessed, they might be indirectly assessed by TMS. Nevertheless, the results of this study do not support this clinical reasoning.

In chronic stroke patients, Uozumi et al. [19] and Cruz-Martinez et al. [20] found a possible association between TMS-induced inhibitory phenomena (SP) and hypertonia. The authors hypothesized that in the course of the development of hypertonia, cortical inhibition decreases and, subsequently, the SP shortens. In patients with a subacute stroke (within 2 weeks post-stroke) with a focal ischemic lesion in the territory of the middle cerebral artery, Catano et al. [21] observed a decrease in SP duration with increasing muscle contraction. This contraction-induced reduction of the SP was associated with hypertonia. Although this (relative) inefficacy of the inhibitory mechanisms might be a risk factor for hypertonia, the phenomenon of contraction-induced reduction of the SP could not be assessed in our study. The voluntary contraction of the hand muscles in the majority of our patients was so severely impaired that often no SP could be recorded. Even patients in whom a SP could be elicited lacked the ability to elicit different degrees of voluntary contraction. As a result, in only 4 out of 40 patients (10%) a SP could be determined at 3 weeks after stroke. The mean duration of the SP in 2 patients with hypertonia did not differ from the mean SP duration in 2 other patients without hypertonia. However, due to these small numbers of patients, the finding that the SP was not related to hypertonia in this acute-phase study must be interpreted with care.

It is important to note that this study was restricted to a homogeneous group of patients with acute stroke with initial paralysis of the upper extremity and a BI of 0. Predicting hypertonia using neuroradiological and neurophysiological characteristics as potential risk factors in such a severe subgroup restricts generalization of the outcomes to less severely affected patients. Moreover, this severe subgroup is probably not the most appropriate group to study the value of TMS-induced inhibitory phenomena.
These patients lack the ability to move their affected limb voluntarily and selectively, which is necessary to generate a MEP and a subsequent SP.

Table 4. *Associations between potential risk factors and hypertonia at 26 weeks post stroke*

		Number of patients with hypertonia	Number of patients without hypertonia	Positive (PPV) and negative predictive values (NPV) and 95% confidence intervals
Lesion Side	Left	15	7	PPV 0.68 (0.49-0.88)
	Right	7	11	NPV 0.61 (0.39-0.84)
Previous stroke	Present	14	10	PPV 0.58 (0.38-0.78)
	Absent	8	8	NPV 0.50 (0.25-0.75)
Extensive stroke	Present	15	14	PPV 0.52 (0.34-0.71)
	Absent	7	4	NPV 0.36 (0.03-0.69)
ADM-MEP	Absent	18	12	PPV 0.60 (0.43-0.78)
at week 3	Present	4	6	NPV 0.60 (0.30-0.90)

ADM-MEP= Abductor Digiti Minimi- Motor Evoked Potential

Another possible limitation of this study may still be a lack of power due to the limited number of patients. We included merely patients with initial paralysis to optimize the risk of post-stroke hypertonia (approximately 62%). This subgroup comprises however, only 19 to 30% of the stroke population at large [29]. As a result, the inclusion rate was relatively low in just one academic hospital. Still, 40 patients should be a sufficient number to distinguish a 'moderate' from an 'absent' association between hypertonia and any clinical determinant (setting alpha at 0.05 and 1-beta at 0.80). Larger studies of high-risk patients are needed to identify "weaker", but significant, associations.

Conclusion

As yet, the association of neuroradiological stroke characteristics as well as TMS-induced excitatory and inhibitory phenomena with hypertonia seems to be weak, even in patients with severe stroke and an upper-extremity paralysis. In addition, TMS characteristics, such as the contraction-induced inhibition of the SP, are not applicable in these patients during the acute and sub-acute phases after stroke.

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Chapter 7

Supratentorial ischemic stroke: More than an upper motor neuron disorder

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Abstract

Objective: The primary aim of this study was to identify secondary functional changes in the peripheral motor units of the paretic upper extremity in patients with severe ischemic stroke and to determine how these changes develop during the first weeks.
Methods: An inception cohort of 27 consecutive patients with an acute ischemic supratentorial stroke and an initial upper-extremity paralysis was compared to 10 healthy control subjects. The ulnar nerve was electrically stimulated proximal to the wrist and electromyographic recordings were obtained from the abductor digiti minimi (ADM) muscle. Hemiparetic side mean values of the compound muscle action potential (CMAP) at 1 and at 3 weeks after stroke were compared with the non-paretic side and with CMAP values obtained from healthy controls.
Results: The mean CMAP amplitude in patients was significantly lower on the paretic side compared with both the non-paretic side and with controls. Decrease in CMAP amplitude was observed in more than half of the stroke patients, sometimes as early as 4 days after stroke, and persisted in most cases. Whenever present, it was accompanied by absence of motor recovery at that specific time after stroke.
Conclusions: Decreased CMAP amplitude in the ADM muscle can be seen already in the very acute phases after stroke unrelated to peripheral neuropathy, radiculopathy, or plexopathy, and it is accompanied by absence of upper motor neuron recovery. This knowledge is important for interpreting electrophysiological data in stroke patients.

Introduction

In stroke patients, transcranial magnetic stimulation (TMS) is enjoying increased use as a tool for studying cortical plasticity and subsequent reorganization processes in the case of paresis or paralysis after stroke. In TMS studies focusing on plasticity after upper motor neuron (UMN) lesions, it is assumed that the lower motor neuron (LMN) has not been affected and hence, no attention has been directed to nerve function distal to the level of the brain lesion. However, it is well known that injuries to the peripheral nerves lead to changes in the functional organization of the sensori-motor cortices [1-4]. From animal studies, we know that this cortical plasticity already occurs within hours after the primary lesion of the peripheral nervous system [2, 4]. Given this strong relationship between the central and peripheral nervous system, it seems possible that UMN lesions lead to functional changes in the LMN as well.

In UMN lesions, the LMN may become functionally depressed or undergo transsynaptic degeneration through loss of synaptic input and lack of activation. Hara and associates [5, 6] observed a decreased number of functional motor units already in the second week after stroke by F-wave motor unit number estimation (MUNE). This decrease was related to the severity of paresis; in general the loss was greater and more prolonged in patients with severe than in those with mild paresis. Because Hara et al. [6] included patients who had a supratentorial stroke at least 9 days (on average 19 days) after stroke, it remains unclear if these LMN changes already occur in the very acute phase after stroke.

The motor unit decrease secondary to UMN lesions in the acute phase after stroke might be a confounding factor in studying cortical plasticity by TMS because the induced motor evoked potential (MEP) depends on the conductivity of the peripheral structures as well. Peripheral dysfunction may prevent axons from responding appropriately after TMS. To validly study neuronal plasticity in the acute and subacute phases after stroke, we should understand the underlying mechanisms of both UMN and LMN changes and their time course. In addition, and probably more clinically relevant, motor unit decrease secondary to UMN lesions might be a confounding factor in interpreting electrophysiological data in (sub) acute stroke patients as well. EMG or nerve conduction studies in acute stroke patients with considerable muscle weakness may lead to diagnostic errors, suggesting a peripheral neuropathy when none might exist.

Hence, the primary aim of this study was to determine whether secondary changes in peripheral motor units are present in the very acute (< 1 week) and in the subacute (≥3 weeks) phases after stroke. Against this background, we conducted a cohort study including only patients with an initial paralysis of the upper extremity after a supratentorial stroke to maximize the likelihood of changes in LMN function. Changes in LMN function were studied through recording compound motor action potential (CMAP) characteristics in the abductor digiti minimi (ADM) muscle after distal stimulation of the ulnar nerve in both the paretic and nonparetic arms of stroke patients and by comparing these results with CMAP characteristics from healthy control subjects.

Materials and Methods

Patients

As part of a larger study on the value of MEP in predicting motor and functional outcome after stroke [7], 27 consecutive acute patients with an ischemic supratentorial stroke in whom electromyographic (EMG) recordings were made using an Oxford Synergy electromyograph were included in this study. These patients were admitted to the department of neurology at the Radboud University Nijmegen, Medical Centre. The diagnosis of stroke was made clinically on admission by a neurologist according to the WHO clinical criteria [8] and confirmed by computed tomography scanning.

Only patients presenting with stage I of the upper extremity according to Brunnstrom (i.e., no tone and no voluntary muscle activity at the elbow, wrist, or finger flexors) [9] at day 1 were included within 7 days after stroke. Patients with a poor prognosis for survival (loss of consciousness, severe CT abnormalities, and severe co-morbidity) as well as patients with severe pre-existing impairments of the upper extremity of any type (e.g., rheumatic deformities, contractures) were excluded. Patients were screened to ensure that they had no contraindication for TMS (e.g., history of craniotomy, epilepsy, cardiac prosthetic valve or pacemaker implantation, or severe polyneuropathy). From day 1 after stroke, each patient received a standard medical treatment according to the guidelines of the Dutch Society of Neurology, including a multidisciplinary team approach. Each patient received physiotherapy treatment to maintain optimal range of (joint) motion and to regulate muscle tone of the upper extremity; however, no specific therapy was initiated to improve hand motor recovery.
A total of 10 healthy volunteers were similarly investigated to establish reference values. Volunteers were recruited among the relatives of patients participating in an amyotrophic lateral sclerosis study [10]. All control subjects were free from central and peripheral nervous system diseases and did not use any medications with possible effects on the nervous system.
After a detailed explanation, all subjects gave written informed consent to participate in this study, which was approved by the local ethics committee.

Clinical assessment

Within the first 24 hours after stroke, the treating neurologist assessed all 27 patients with regard to their initial motor functions, muscle tone, and level of consciousness. All consecutive clinical assessments of motor and sensory functions, muscle tone, and stretch reflexes were performed at weeks 1, 2, 3, 6, 12, and 26 after stroke by a rehabilitation physician. Motor functions were assessed according to the upper-limb subset of the Fugl-Meyer Motor Assessment (FMA) [9]. Sensory deficits were assessed by clinical examination

of light touch and pinprick of the hemiparetic arm. Biceps and triceps tendon reflexes were quantified according to the Mayo Clinic scale for tendon reflex assessment (range, -4 to +4) [11]. Hyperreflexia was considered present if the tendon reflex on the paretic side was ≥ +1. Hypertonia was clinically assessed by grading muscle tone through the Ashworth scale (AS) under standardized test conditions [12]. Clinically relevant hypertonia was operationally defined as an AS score equal to or greater than 2 in at least one joint [13].

The diagnostic criteria following physical examination of Kingery et al. [14] were used to diagnose plexopathy, radiculopathy, or neuropathy. All three of the following criteria had to be observed:

1. A focal weakness in the distribution of the suspected nerve injury greater than the weakness observed in the rest of the paretic upper extremity.
2. At least one of the following findings present only in the distribution of the suspected nerve injury:
    a. Diminished stretch reflexes relative to the rest of the hemiparetic upper extremity.
    b. Objective sensory loss.
    c. Muscle atrophy on visual inspection.
3. An absence of hyperreflexia or rigidity in the distribution of the suspected nerve.

Electrophysiological assessment

In 27 patients, electrophysiological assessment of the ADM CMAP was performed twice, at first within 1 week (mean, 6.8, median, 7 days) after stroke (t1) and second, at 3 weeks (mean, 28.7, median, 25 days) after stroke (t2) by the same experienced clinical neurophysiologist. In addition, in the 10 healthy control subjects electrophysiological assessment of the ADM CMAP was performed once, using the same technique as in stroke patients.

The ADM muscle was selected for this study because it was regarded as representative of distal motor functions of the upper extremity. CMAPs were recorded at t1 and t2 from the ADM on both the paretic and nonparetic side. CMAPs were recorded using surface electrodes placed in a tendon belly montage. EMG electrodes had parallel detection surfaces (1 cm in diameter) and were located 3 cm apart. The active electrode was positioned over the belly of the ADM. The inactive electrode was positioned on the tendon of the ADM. The ground electrode was positioned between the recording and the stimulus sites at the wrist over the head of the ulna. Electromyographic recordings were made using an Oxford Synergy electromyograph with filter settings of 20 Hz and 3 kHz (amplifier range 100 mV and recording sensitivity of 0.5 mV / bit). The ulnar nerve was stimulated just proximal to the wrist

both on the paretic and on the nonparetic side. CMAPs were evoked with supra-maximal stimulation using single square electrical pulses of 0.2-ms duration. Amplitude of CMAPs as well as distal motor latencies were determined over a standardized distance of 80 mm. The ADM responses were studied separately for both the paretic and the nonparetic side, and both responses were related to the ADM responses in healthy control subjects. Responses with the highest CMAP were used for analysis. Finally, CMAP amplitude ratios (CMAP-amplitude paretic / nonparetic side) were determined in stroke patients and related to the amplitude ratios in healthy control subjects (CMAP-amplitude nondominant / dominant side).

Statistical analysis

Shapiro-Wilks tests of normality ensured the appropriateness of applying parametric statistics. Paired-sample *t*-tests were used to determine whether differences in CMAP characteristics were evident between the paretic and nonparetic side in stroke patients and between the dominant and nondominant side in the healthy control subjects. Paired-sample *t*-tests were also used to determine whether CMAP characteristics at both the paretic and nonparetic side differed between the first and the second electrophysiological assessment. Independent-sample *t*-tests were used to determine if these differences were significant between stroke patients and healthy control subjects. The Mann-Whitney test was used to compare amplitude ratios between stroke patients and healthy control subjects. The required 2-tailed significance level was set at 0.05. All analyses were performed using the Statistical Package for the Social Sciences (SPSS® version 11).

Results

Patient Characteristics

Twenty-seven stroke patients, 12 women and 15 men, were enrolled in the study. Although none of our patients had any pre-existing impairments of the upper extremity, radiological assessment showed a previous stroke in 12 patients (44%), whereas 15 patients (56%) had had a first-ever stroke. Seventeen patients had stroke lesions located in the left hemisphere, whereas 10 patients had lesions located in the right hemisphere. Twenty-one patients had extensive lesions that were located in the territory of the middle cerebral artery involving cortical (n=2), or both cortical and subcortical areas (n=19). Six patients had a focal, subcortically located lesion. In 3 of these patients, the lesion was restricted to the basal ganglia.

Table 1. *Clinical characteristics at physical examination of the hemiparetic arm*

		Number (n)
Motor recovery	present	8
	absent	19
Sensory disturbances	present	20
	absent	7
Hyperreflexia	present	22
	absent	5
Spasticity	present	18
	absent	9

The mean age of the stroke patients was 69.5 years (standard deviation, 10.0; range, 46 to 84 years). Clinical assessment failed to identify stroke patients who met the diagnostic criteria for a brachial plexus injury, radiculopathy, or neuropathy both in the initial and in the follow-up examinations. None of our patients showed evident proximal or distal muscle atrophy or edema within the first week after stroke. If present, areflexia, flaccidity, sensory loss, and muscle weakness were not limited to, or more profound in the distribution of a specific nerve, root, trunk, or cord. Results of the clinical assessments are summarized in Table 1.

The control group consisted of 9 women and 1 man. The mean age of the control group was 61.8 years (standard deviation, 10.9; range, 38 to 80 years).
The electrophysiological assessment was performed in all patients and control subjects, however, 2 patients refused the second assessment and 2 other patients died in the first weeks after their stroke. Thus, the electrophysiological assessment at 3 weeks after stroke was available for only 23 patients.

Electrophysiological outcomes
In the healthy control subjects, no significant differences in CMAP characteristics between the dominant and nondominant upper extremity were found. Therefore, these data were pooled for comparison with the stroke patients.

The quantitative aspects of the CMAP recordings are summarized in Table 2 for all participants. The CMAP amplitude was significantly smaller on the paretic side compared to the nonparetic side of the stroke patients ($t = -7.72$, $p = 0.000$ at t1, and $t = -7.80$, $p = 0.000$ at t2) and compared with healthy control subjects ($t = -4.862$, $p = 0.000$ at t1, and $t = -6.13$, $p = 0.000$ at t2).

Table 2. *CMAP amplitude and distal motor latency of the ADM in all participants*

	Number (n)	Paretic side	Non-paretic side	(Healthy) Control subjects
CMAP amplitude				
week 1	27	8.75 ± 2.76 mV	12.00 ± 2.77 mV*	12.53 ± 2.33 mV**
week 3	23	7.62 ± 2.77 mV	11.05 ± 2.68 mV*	12.53 ± 2.33 mV**
CMAP latency				
week 1	27	2.59 ± 0.51 ms	2.48 ± 0.46 ms	2.63 ± 0.32 ms
week 3	23	2.78 ± 0.40 ms	2.77 ± 0.45 ms	2.63 ± 0.32 ms

Values are mean ± SD
Legend: symbols refer to significant differences:
* significantly different from paretic side (paired t-test)
** significantly different from paretic side (independent samples t-test)

Table 3. *CMAP amplitude ratio in stroke patients and in healthy control subjects*

	Number (n)	Stroke patients	Healthy control subjects	P value*
CMAP ratio				
week 1	27	0.73 ± 0.17 (range 0.42-1.00)	0.85 ± 0.08 (range 0.75-1.00)	0.013
week 3	23	0.69 ± 0.18 (range 0.29-0.99)	0.85 ± 0.08 (range 0.75-1.00)	0.002

Values are mean ± SD; * Mann Whitney test

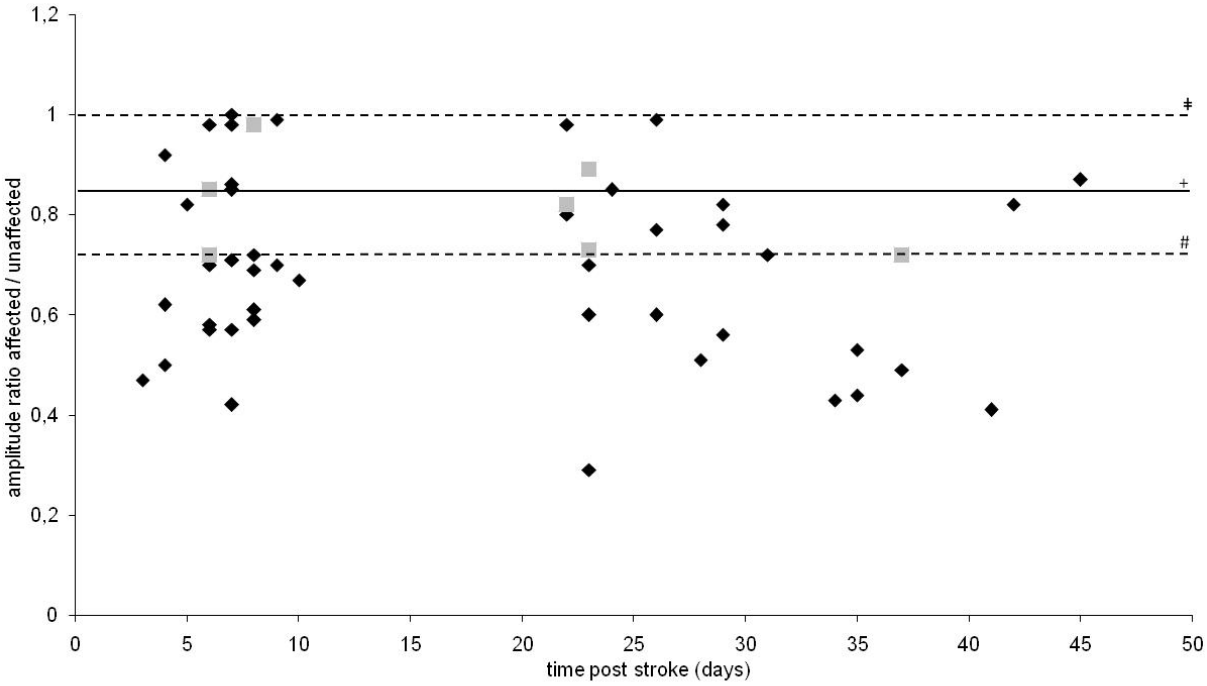
Overall, there was no statistical difference between the mean CMAP values of the control subjects and those obtained from the nonparetic arm of the stroke patients, neither at t1 nor at t2. Overall, the CMAP amplitude at t1 did not differ from the amplitude at t2 at the nonparetic side ($t = 1.76$, $p = 0.92$) and at the paretic side ($t = 1.94$, $p = 0.70$). As for distal motor latencies, no statistical differences were found between the paretic and nonparetic sides, or between the stroke patients and the healthy control subjects. CMAP amplitude ratios in stroke patients were significantly different from those in healthy control subjects both at t1 and at t2 (Table 3). Correcting the analysis for motor recovery by excluding the patients with some degree of motor recovery at either t1 or t2 yielded similar results.

More than half of the stroke patients showed an abnormally decreased CMAP amplitude ratio at t1, lying outside the range of amplitude ratios found in healthy control subjects. In 3 patients decreased CMAP amplitude ratios were seen as early as 4 days after stroke (Figure 1). Three patients showed upper-extremity motor recovery already one week after stroke onset at which time their CMAP amplitude ratio fell within the range of amplitude ratios found

in healthy control subjects. One of these 3 patients refused the second assessment. Two other patients without motor recovery at week 1 showed motor recovery 3 weeks after stroke.

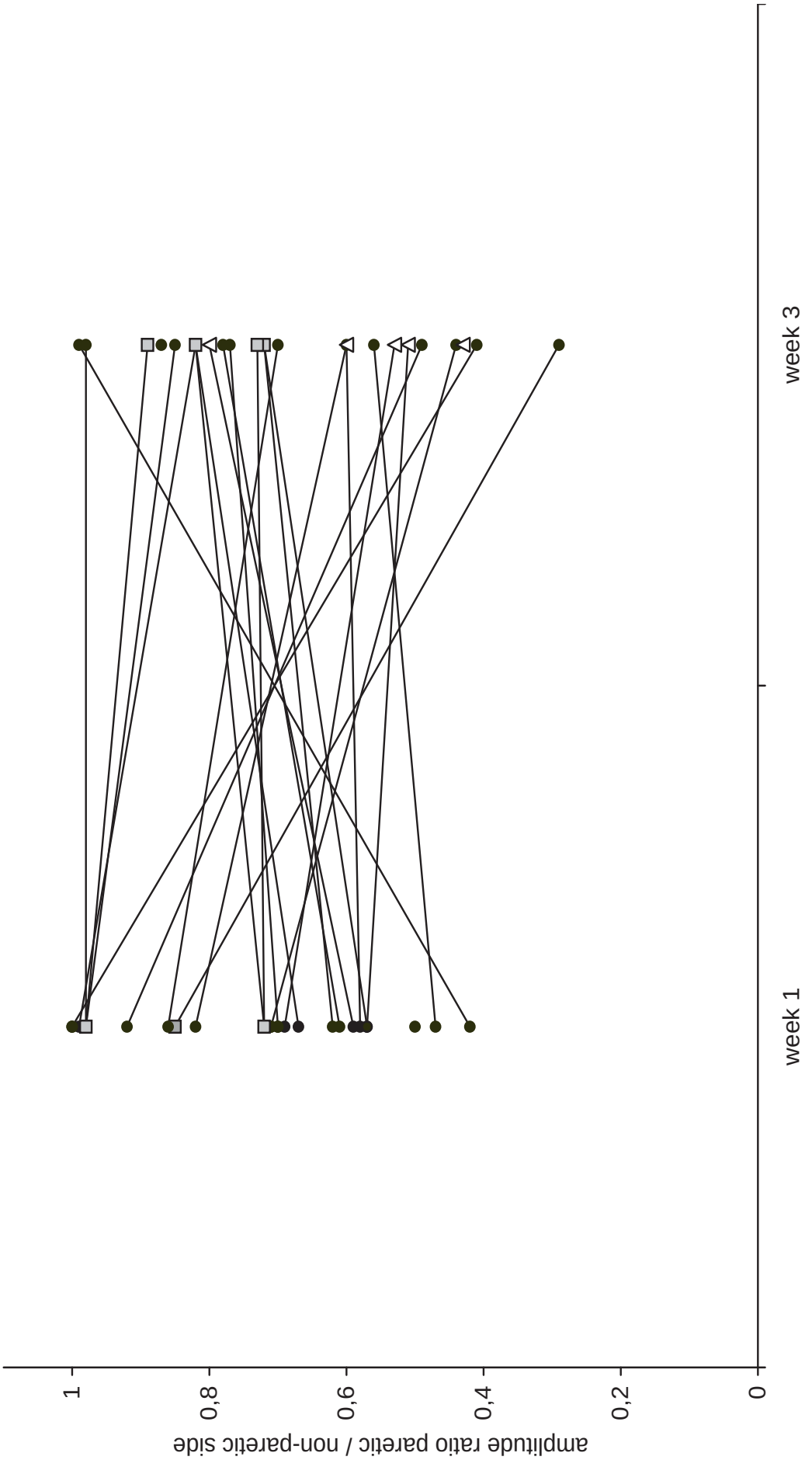
Hence, a decreased CMAP amplitude ratio was always accompanied by absence of motor recovery at that specific time after stroke (Figure 1). During the follow-up period, the individual amplitude ratios followed a rather variable course with cases showing a decrease, stabilization, or an increase in the paretic ADM CMAP over time (Figure 2)

Figure 1. *Compound motor action potentials (CMAP) amplitude in relation to time post stroke*



(∓) maximum, (+) mean, and (#) minimum amplitude ratio in healthy control subjects

paralysis ◆ , motor recovery ■



□ Motor recovery at time of EMG; ● no motor recovery; △ motor recovery in the long term

Figure 2. Time course of amplitude ratio in stroke patients with and those without motor recovery

Discussion

In this longitudinal study, a homogeneous sample of patients with initial paralysis of the upper extremity caused by ischemic supratentorial stroke was included to identify secondary functional changes in LMN. Decreased CMAP amplitudes in the ADM muscle on the paretic side were present in the majority of patients who had no signs of motor recovery on average 1 week after stroke and persisted in the subacute phase (after the third week post stroke) in patients without motor recovery. Hara [5, 6] and Lukacs [15] and their associates have reported decreased CMAP amplitudes in the ADM muscle on the paretic side at least 9 days after stroke onset in a more heterogeneous sample of patients who had various degrees of paresis. This is the first longitudinal study reporting decreased CMAP amplitudes as early as 4 days after stroke in paralytic patients without clinical signs of peripheral neuropathy.

Some authors have suggested that the decrease in CMAP amplitude in the paretic upper extremity reflects a reduction in functional motor units, i.e., the number of units that can be excited by electrical stimulation [15, 16]. Hara et al. [5, 6] demonstrated a decrease in functional motor units by the F-wave MUNE. This decrease in functional motor units was accompanied by fibrillation potentials and positive sharp waves in the needle EMG observed at least 9 days after stroke. Other studies have recorded a high incidence of fibrillation potentials and positive sharp waves in the needle EMG from the second week after stroke as well [5, 6, 14, 15, 17, 18], remaining on a nearly constant level up to 3 to 4 months thereafter [6, 14]. Fibrillation potentials and positive sharp waves were never observed before 9 days after the initial stroke. Because these fibrillation potentials and positive sharp waves did not depend on denervation of the LMN, Spaans and Wilts [18] introduced the term pathologic spontaneous muscle fiber potentials (SMFP). In general, the incidence of SMFP was closely related to the severity of the paresis with greater and more prolonged occurrence in patients with severe than in those with mild paresis [6, 14, 15, 19].

Considering the data available in the literature and those provided by the present study, the functional changes in the LMN after stroke might take place in a specific sequence. McComas et al. [16] first reported the concept of “dying back” neuropathy of the LMN as a result of UMN lesions. UMN lesions may cause loss of synaptic input and lack of activation of the spinal alpha motor neurons, which become functionally inactive or undergo transsynaptic degeneration [16, 17]. Dysfunction of these anterior horn cells results in a disturbance of the axonal flow, leading to axonal degeneration which starts proximally and extents to distal (Wallerian degeneration). Impaired axonal transport secondary to functional disturbance of spinal alpha motor neurons may then lead to a dysfunction of the neuromuscular transmission at the motor end plate and a subsequent decrease in the CMAP amplitude [19,

20] and pathological SMFP. Maintaining a sufficient axonal flow in a long neuron seems to require more energy from the anterior horn cells than maintaining sufficient flow in a short neuron [17]. Therefore, the distal upper-extremity muscles show the most prominent functional changes [17]. The SMFP found in the subacute phase after stroke tended to disappear after 6 weeks; however, motor unit loss neither progressed nor improved [6, 15, 17, 18]. Apparently, once it occurs, motor unit loss persists for a long time. In the chronic phase of stroke, a slight enlargement of active motor units can be seen that can be explained by restoration of axonal function or by collateral reinnervation. Both mechanisms of recovery may lead to an increased number of muscle fibers that can be activated and may explain the recovery of the CMAP seen in the chronic stage after stroke [15].

From this point of view, it is important to realize that one should be informed about both UMN and LMN changes when using TMS to study neuronal plasticity in the acute and subacute phases in severe stroke patients. Motor unit decrease secondary to UMN lesions might be a confounding factor because the observed MEP depends on the conductivity of the peripheral structures as well. In future studies it is necessary to look at changes in motor unit structure and function over a longer time period to determine how these changes in LMN function influence motor recovery following stroke.

Perhaps the most important clinical implication of this study, however, is that a decrease in CMAP amplitude and SMFP both may be caused by an UMN lesion and need not be related to an associated neuropathy, radiculopathy, or plexopathy of the paretic limb. Hence, studies relying solely on electrophysiological data to identify plexopathy, radiculopathy, or neuropathy in stroke patients may lead to diagnostic errors because of the high incidence of EMG abnormalities, which could mimic a plexopathy, radiculopathy, or neuropathy [14, 18]. Because of these EMG abnormalities, EMG has limited validity in diagnosing concomitant peripheral neuropathy in case of stroke, unless physical examination fails to demonstrate UMN symptoms in the paretic extremity. In that case, measuring the conduction latencies across the plexus and determining the CMAP amplitudes in the distribution of the suspected injury are recommended [14, 18].

Conclusion

As a direct consequence of the stroke lesion and subsequent loss of central drive, adjustment of peripheral structures takes place. Spinal alpha motor neurons may become functionally depressed but may still survive after stroke. A decreased CMAP amplitude in the ADM muscle can be seen already in the very acute phases after stroke unrelated to

peripheral neuropathy, radiculopathy, or plexopathy. Whenever present, it was accompanied by absence of motor recovery at that specific time after stroke. This knowledge is important for interpreting electrophysiological data in stroke patients. Longitudinal studies are needed that look at these changes in motor unit structure and function over a longer time period to determine how these changes in LMN function develop and how they influence motor recovery following stroke.

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Chapter 8

Stimulus-response characteristics of motor evoked potentials and silent periods in proximal and distal upper-extremity muscles

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Abstract

Objective: The primary aim of this study was to compare stimulus-response characteristics of both motor evoked potentials (MEPs) and silent periods (SPs) induced by transcranial magnetic stimulation (TMS) in proximal and distal upper-extremity muscles.
Methods: Stimulus-response curves of MEPs and SPs were obtained from the biceps brachii (BB) and abductor digiti minimi (ADM) muscles in 15 healthy participants. A non-linear mixed model was used to fit the stimulus-response curves to a sigmoid Boltzmann function.
Results: Small residuals of the function were found for MEPs and SPs in both muscles. Higher maximal MEP amplitudes were found for the BB compared to the ADM ($p < 0.01$). The active motor threshold to obtain a SP was less for the ADM compared to the BB ($p < 0.01$). The slope parameter of the function of the SP duration was steeper and more variable in the ADM than in the BB ($p < 0.01$). For the MEP amplitude no difference in active motor threshold and slope of the function was found between both muscles.
Conclusions: Excitatory (MEP) and inhibitory (SP) effects of TMS differ between proximal arm and distal hand muscles in healthy participants. The adequate fit of our model suggests that this model can be used to study between and within subject changes in future studies.

Introduction

Transcranial magnetic stimulation (TMS) of the human motor cortex is a noninvasive technique to assess the integrity of the corticospinal motor pathways. TMS elicits a short-latency motor evoked potential (MEP) as an excitatory effect that can be recorded by surface electromyography (EMG) in the target muscles. In pre-activated muscles, TMS of the primary motor cortex also induces a transitory suppression of the EMG-activity after the short-latency MEP as an inhibitory effect, referred to as the silent period (SP) [1-4]. The SP has been proposed as a measure of the excitability of the cortical inhibitory circuits, whereas the MEP has been proposed as a measure of the excitability of the facilitatory circuits [2].

Both the MEP amplitude and the SP duration depend on the stimulus intensity. With increasing stimulus intensities both the MEP amplitude and the SP duration increase until they reach plateau values [2, 5-8]. The plateau phase of the MEP amplitude, however, seems to be achieved at lower stimulus intensities compared to the plateau phase of the SP duration [8]. The MEP and the SP differ in their response to muscle (pre)activation as well. TMS performed during voluntary muscle contraction evokes MEPs with a shorter latency and a higher amplitude than when the muscle is at rest [5], whereas the SP duration is relatively unaffected by the *level* of muscle pre-activation [2, 3, 5]. Partly because of these differences,

it has been suggested that the facilitatory mechanisms involved in the MEP are physiologically different from the inhibitory mechanisms contributing to the SP [1, 2, 4, 5, 9].

Both the MEP and the SP have been used to predict post-stroke motor recovery [10-16]. In stroke patients with an initial paralysis of the upper extremity, the presence of an early MEP within the first weeks after stroke showed good positive predictive value (PPV = 1, 35 patients) for regaining hand motor function at 6 months after stroke. The negative predictive value, however, was substantially lower (NPV = 0.88, 35 patients). Not all patients with hand motor recovery could be identified by the presence of an early MEP [17]. With regard to the SP, Traversa et al. [18] discovered that in stroke patients with a moderate paresis of the upper extremity the SP shortened during recovery and that the amount of shortening correlated with the degree of hand function recovery [18, 19]. However, a review on the role of the SP in predicting post-stroke motor recovery showed rather inconclusive results, which may be due to methodological differences between the studies [20].

TMS studies on post-stroke motor recovery show considerable heterogeneity in patient characteristics, time of evaluation after stroke, stimulation procedures, and methodology, which could all be responsible for the differences between studies [20, 21]. MEP and SP are usually elicited at stimulus intensities corresponding to a certain percentage of the corticomotor threshold or the stimulator output. Due to their dependency on the stimulus intensity, changes in motor threshold have implications for the interpretation of MEP and SP characteristics. And it should be noted that an altered motor threshold (e.g., as observed during the subacute phases of stroke) might itself indicate an abnormality.

With regard to the upper extremity, several TMS studies revealed differences in corticomotor thresholds for eliciting MEPs and the SPs between proximal and distal upper-extremity muscles [5, 7, 22]. In addition, distal muscles seem to be more sensitive to TMS-induced inhibitory phenomena compared to proximal muscles, probably due to their larger cortical representation and greater dependency on corticospinal tracts [5, 23]. As a consequence, it is necessary to have knowledge of the TMS characteristics in both proximal and distal upper-extremity muscles.

Stimulus-response curves have been constructed to study MEP amplitude and SP duration independently from their corticomotor threshold [6-9, 24-26]. Only few studies, however, have been conducted that have focused on the MEP amplitude or SP duration in both distal and proximal upper-extremity muscles over a wide range of stimulus intensities [7, 25]. Ray et al. [25] performed stimulus response-curves of the MEP amplitude exclusively from the biceps brachii and the abductor pollicis brevis muscles at rest in 8 healthy volunteers. Taylor et al. [7] constructed stimulus-response curves of MEP area and SP in both the biceps

brachii and adductor pollicis muscles in only 4 healthy volunteers at different levels of voluntary muscle contraction. Comparison of the results of these studies is difficult due to their variability in methodology (e.g., degree of muscle pre-activation used) and technical aspects (e.g., figure of eight versus round coil). Moreover, both studies did not apply stimuli over the full range of stimulus intensities from threshold to 100% stimulator output.

The primary aim of this study was to explore the differences between proximal arm and distal hand muscles in stimulus-response characteristics of both MEP and SP in healthy volunteers. To construct reliable stimulus-response curves for both the MEP amplitude and the SP, these curves will be constructed over the full range of stimulus intensities ranging from threshold to 100% stimulator output.

Materials and Methods

Subjects

Eighteen healthy individuals participated in this study. Because it has been reported that the threshold for eliciting both MEP and SP in the BB and ADM muscles at the dominant side is lower than at the non-dominant side [27], and because left handed subjects show larger MEP amplitudes compared to right handed subjects [28, 29], only right-handed subjects were included. Handedness was tested with the Edinburgh Handedness Inventory [30]. Subjects with a history of epilepsy, cardiac disorders, pacemaker implantation, craniotomy, psychiatric or neurological diseases were excluded. Pregnant women or individuals using medications with possible effects on the nervous system were excluded as well. Approval of the local ethics committee was obtained and all participants gave written informed consent.

General Procedure

Participants were comfortably seated in a chair with their right forearm and hand pronated and supported by a custom built device. The elbow was positioned in 90 degrees of flexion. The device restricted movement of the upper arm, forearm, wrist, and fingers, but allowed right isometric forearm flexion and digit V abduction. Bipolar EMG-recordings were obtained using 2 pairs of self-adhesive surface electrodes placed in a standard tendon belly montage. EMG-signals were recorded using a CED data acquisition and amplifier system (Cambridge Electronic Design Ltd) with a bandpass filter of 20 to 3000 Hz at a recording sensitivity of 0.5 microVolt/bit (amplifier range 100 mV), using a recording time of 150 ms before and 850 ms after each stimulus. The EMG data were collected using Spike2 laboratory software (Cambridge Electronic Design Ltd).

First, EMG-activity was recorded from the abductor digiti minimi muscle (ADM). To obtain isometric muscle contractions, right digit V abduction was performed against a fixed frame, while digits II-IV were immobilized by Velcro straps. Secondly, the forearm and hand were supinated and EMG-activity in the biceps brachii muscle (BB) was recorded while participants performed elbow flexion against a fixed frame. For measurements in both proximal and distal muscles, participants were instructed to exert maximum force for 3 seconds during 3 trials. Visual feedback of rectified EMG-activity was provided through a computer screen placed 1 meter in front of the participants. The EMG target level was presented as a vertical line.
The maximal voluntary EMG-activity was taken as the mean EMG-amplitude achieved during these 3 trials. The 50% maximal voluntary EMG-activity, being the target level during the trials, was calculated from the maximal voluntary EMG-activity.

Transcranial Magnetic Stimulation
TMS of the motor cortex was performed through a 90 mm circular coil powered by a Magstim 200 magnetic stimulator (Magstim Company Limited). The circular coil was used, because this type of coil evokes larger MEPs compared to a figure of eight coil during strong contractions [7]. The vertex was located and marked directly on the scalp. The coil was positioned in a tangential plane near the vertex at approximately 45 degrees to the sagittal line (Mid-central - Cz according to the international 10-20 system of electrode placement) and fixed in this position through a mechanical arm. A counterclockwise inducing current flow was used to activate the left hemisphere.

During the TMS sessions, the participants performed constant isometric muscle contractions at 50% of their maximal voluntary EMG-activity to ensure maximal facilitation of motoneurons [7, 31]. The computer monitor displayed this target level. The participants were instructed to increase muscle activity to the target level, and to maintain muscle activity as close as possible to this level, until they were instructed to relax. TMS was delivered 2 seconds after the target level was obtained.

TMS was applied with increasing intensities ranging from 20% to 100% (in 5% increments) maximum stimulator output (100% = 2 Tesla). To avoid serial order effects, the different stimulus intensities were applied in random order. At each stimulus intensity, 5 consecutive trials were performed with an inter-stimulus interval of approximately 5 seconds. Within such a single session, participants were instructed to relax for 2 seconds after each stimulus was delivered. The MEP amplitudes and SP durations in the BB and ADM were recorded. To avoid the occurrence of fatigue, consecutive sessions of different stimulus intensities were separated by at least 30 seconds rest.

Experimental methods

The baseline (BL) EMG-activity was calculated as the mean value of the rectified and filtered EMG-activity over the 150 ms time-segment prior to stimulus delivery. At each stimulus intensity, the mean MEP amplitude and SP duration were determined from the average of five trials. The active motor threshold was defined as the minimum stimulus intensity needed to elicit a recordable MEP (≥100 microVolts) from the target muscle in at least 3 out of 5 trials. The MEP amplitude was calculated by subtracting the baseline activity from its maximum. The SP duration was defined as the latency between MEP onset and SP offset in the rectified EMG-data. The SP offset was determined as the return of continuous EMG-activity to baseline values. If no SP could be detected in the averaged data, a duration of 0 seconds was assigned.

Next, the mean MEP amplitude and SP duration were plotted against stimulation intensity for each participant. Visual inspection of the stimulus-response curves revealed that the relation between these variables could have a sigmoid shape. Hence, the data were fitted with the following three-parameter sigmoid statistical model (Boltzmann equation):

$$y_{ij} = \frac{a_i}{1 + e^{(b_{1i} - S_j) \,/\, b_{2i}}} + \varepsilon_{ij}$$

Where the three parameters of the function are:

1) a_i ,reflecting the plateau phase of participant *i*,
2) b_{1i} ,reflecting the active motor threshold of participant *i*, and
3) b_{2i} ,reflecting the slope parameter (steepness) of participant *i*,

and where

y_{ij} is the MEP amplitude or the SP duration of participant *i* at stimulus intensity *j*,
S_j is the stimulus intensity *j*, and ε_{ij} is the normal distributed residual with mean zero and variance σ^2 of participant *i* at stimulation intensity *j*.

Statistical methods

A non-linear mixed model was used to fit the individual data to this regression model. The dependent variables were the MEP amplitude and the SP duration of the ADM and BB muscles (*y*), respectively, and the independent (regression) variable was the stimulus intensity (*S*). The plateau phase (*a*) and the active motor threshold (b_1) of the function were treated as random effects, to allow subject-specific regression coefficients. The “slope”-parameter (b_2) was treated as a fixed (here: subject independent) regression coefficient. The differences between the models with random effects and models with fixed effects were

tested for statistical significance, using the likelihood ratio test. Note that this test is based on the full likelihood function of the hierarchical models [32]. All parameters are estimated simultaneously, using maximum likelihood methods of the model used.

The fit of the data to the final model was visualized in the observed and estimated stimulus-response curves of the MEP amplitude and SP duration of the ADM muscle in two typical participants. Moreover R-square statistics have been performed.

The estimated regression variables with standard error are presented. Paired-sample *t*-tests were used to determine whether differences in stimulus-response characteristics were evident between the ADM muscle and the BB muscle for MEP and SP. The required 2-tailed significance level was set at 0.05. All analyses were performed using the Statistical Package SAS version 8.2.

Results

Seven men and eleven women between 23 and 49 years of age (mean 32 years, standard deviation 9 years) were included. Three subjects failed to complete the experiment due to severe discomfort during the TMS assessment. These 3 individuals were excluded from the data analysis. The MEP and SP data of the remaining 15 right handed participants were used to construct the stimulus-response curves.

Motor Evoked Potentials

Figure 1 (a, b) shows the individual stimulus-response curves for the MEP amplitude of the BB and ADM muscles. The amplitudes in both muscles increased with increasing stimulus intensity until they reached a plateau. This figure also revealed that there was considerable inter-individual variation in both the active motor threshold and the maximum MEP amplitude. The variability in maximum MEP amplitude was largest for the BB muscle. These inter-individual variations had to be taken into account when modeling the stimulus-response curves. Figure 2 visualized the fit of the data to the model. The upper part of this figure (a, b) shows the observed and the estimated stimulus-response curves of the MEP amplitude of the ADM muscle in two typical participants. The goodness of fit (R-square) for the BB was 0.97 and for the ADM 0.93 (Table 1).

Table 1 shows the estimated parameters with standard error (SE) of the Boltzmann function for both the BB and ADM muscles of an average participant of our population, as well as the goodness of fit. Residuals of the function were small for both the BB and ADM muscles.

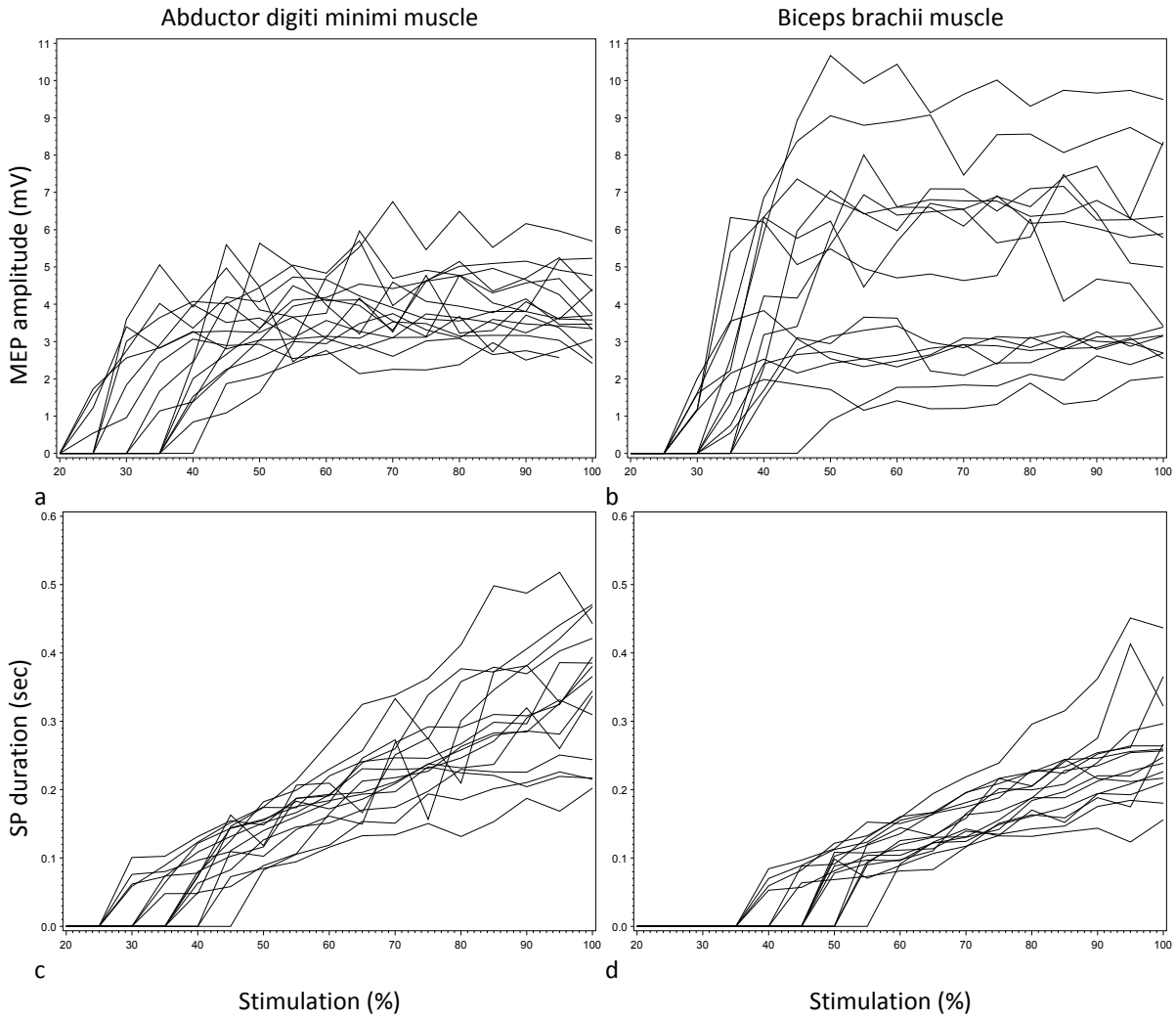

Figure 1. Stimulus/response curves of the motor evoked potentials (MEP amplitudes) and the silent periods (SP durations) of the abductor digiti minimi muscle and biceps brachii muscle of all participants in the study.

The larger SE of the maximal amplitude (a) of the BB compared to the ADM reflects the larger inter-individual variability of the maximal amplitude in the BB ($p < 0.01$). Figure 2 (a, b) shows the observed and the estimated stimulus-response curves of the MEP amplitude of the ADM muscle in two typical subjects. Because the individual curves were simultaneously estimated in our model, we were able to estimate the percentage of participants having reached their plateau values. Table 2 shows the number of subjects that are closer than 1 SE near the estimated plateau of the function at different stimulation intensities. As can be observed from table 2, all participants were near the plateau value at a stimulus intensity of 70% stimulator output.

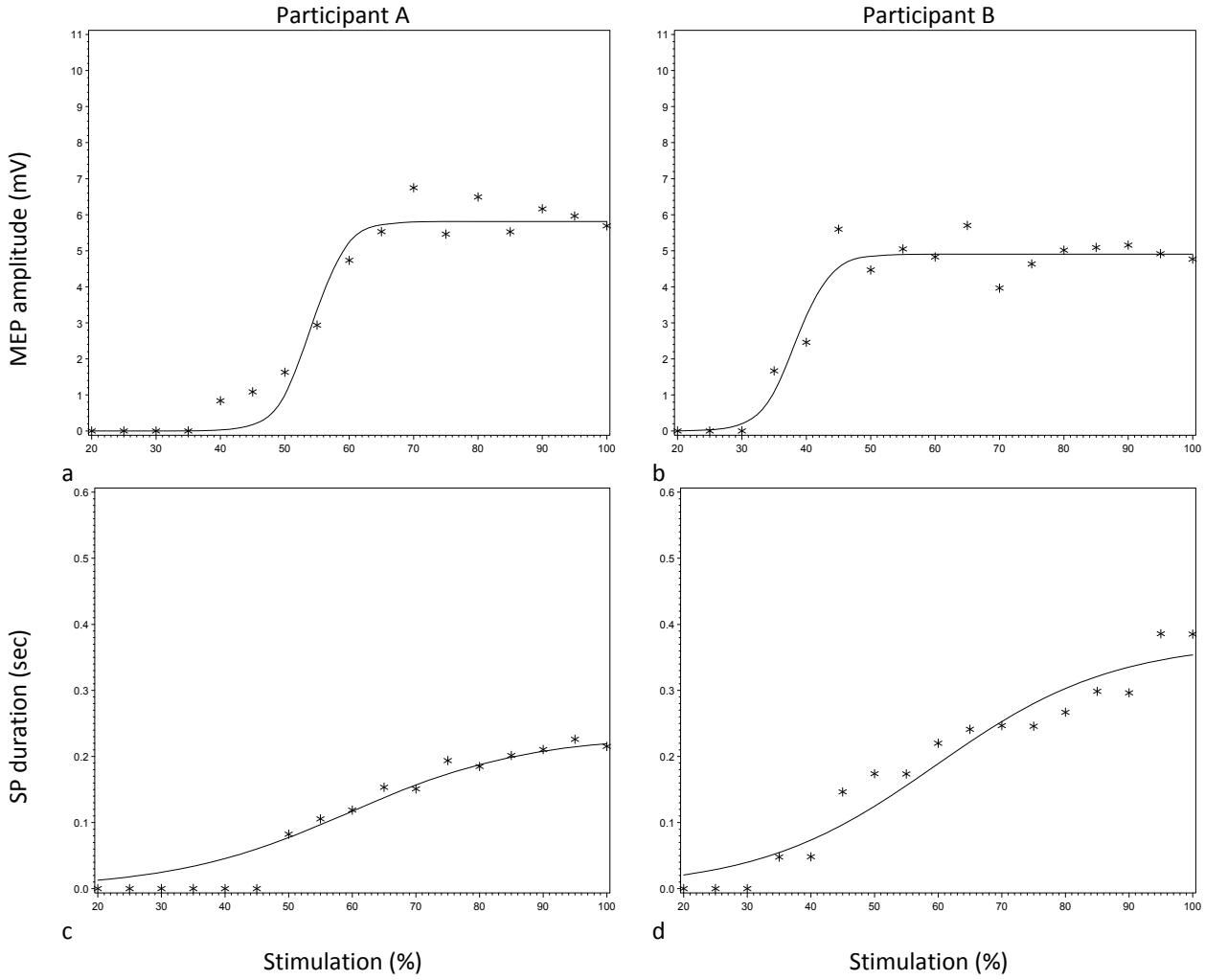

Figure 2. *The observed (*) and estimated (line-graph) stimulus-response curves of the motor evoked potentials (MEP amplitude) and the silent periods (SP duration) of the abductor digiti minimi muscles in two typical participants*

SP duration

In the BB small bursts of EMG-activity occurred before the resumption of continuous EMG-activity, especially at higher stimulation intensities. These burst were not observed in the ADM, not even at maximum stimulator output. Figure 1 (c, d) shows the individual stimulus-response curves of the SP duration of the BB and ADM muscles. The SP durations in both ADM and BB muscle increased with increasing stimulus intensities. The individual stimulus-response curves of the SP did not reach a plateau before maximum stimulator output (Figure 1 and Table 2). The relation between stimulus intensity and the SP duration in both muscles could also be described by a sigmoid function as given by the Boltzmann equation. The fit of the data to the model is visualized in figure 2 and table 1. The lower part of this figure (c, d) shows the observed and the estimated stimulus-response curves of the SP duration of the ADM muscle in two typical participants.

Table 1 shows the estimated parameters with standard error (SE) of the Boltzmann function

for both the BB and ADM muscles of an average participant of our population. The residuals of the function were small for both the BB and the ADM muscles. The active motor threshold of the function was less for the ADM compared to the BB ($p < 0.01$). The SE of the slope parameter of the function was larger for the ADM compared to the BB muscle ($p < 0.01$). Table 2 shows the number of subjects that are closer than 1 SE near the estimated plateau of the function at different stimulation intensities. As can be observed from table 2, none of the participants reached their plateau value before 100% stimulator output.

Discussion

The aim of this study was to explore the differences in stimulus-response characteristics of the MEP amplitude and SP duration between proximal and distal upper-extremity muscles. Overall, the form of the stimulus-response curves of the MEP and SP did not differ between proximal and distal muscles. Above active motor threshold, the MEP amplitude increased until it reached a plateau, whereas the SP duration in most participants did not reach a plateau value in the Boltzmann function before maximum stimulator output. As previously reported [6, 8], both curves could be quantitatively described by a sigmoid Boltzmann function.

MEP amplitudes and SP durations, shown as a function of the stimulus intensity, varied substantially between individual participants. Across subjects there was considerable variability in active motor threshold of both the MEP and the SP in proximal and distal upper-extremity muscles as well. Because both MEP and SP are related to the intensity of stimulation [2, 33], the inter-individual variability in active motor threshold makes it hard to compare the stimulus-response characteristics such as the maximum MEP or SP at a given stimulus intensity. Therefore, the stimulus-response curves had to be adjusted to the inter-individual variability in motor threshold using a non-linear mixed model. The Boltzmann function described the data accurately when considering both the plateau of the function (a) and the active motor threshold (b_1) as random effects, allowing subject specific regression coefficients. This is best illustrated by figure 2, which shows the observed and estimated stimulus response curves of 2 typical participants of our study. It is also illustrated by the small residuals of the function for both MEP and SP in the BB and ADM muscles.

Table 1. *The estimated parameters of the Boltzmann function of the motor evoked potentials and silent periods in the biceps brachii and abductor digiti minimi muscles, using a nonlinear mixed model (n=15)*

	MEP amplitude			SP duration		
	Biceps brachii mean (SE)	Abductor digiti minimi mean (SE)		Biceps brachii mean (SE)	Abductor digiti minimi mean (SE)	
Plateau value (a)	4.92 (0.63) mV	3.89 (0.22) mV	p< 0.01	0.26 (0.06) sec	0.35 (0.08) sec	ns
Active motor threshold (b2) (% stimulator output)	36.97 (1.40)	35.89 (2.16)	n.s	65.24 (1.19)	59.65 (1.17)	p< 0.01
Slope parameter of the function (b3) (%)	2.49 (0.19)	2.65 (0.27)	n.s	12.38 (0.07)	13.97 (0.74)	p< 0.01
SD_{res}	0.53	0.48		0.03	0.03	
R square (%)	97	93		94	94	

SE = standard error, SD_{res} = within subject (residual) standard deviation, MEP = motor evoked potential, SP = silent period, R-square = percentage explained variance by the model, ns = not significant.

Table 2. *The number (percentage; 95% confidence interval) of the participants (n=15) that is closer than one SE near the estimated plateau (a1) of the Boltzmann function at differen stimulation intensities, using a nonlinear mix model.*

Stimulation	MEP amplitude		SP duration	
	Biceps brachii n (%: 95%CI)	Abductor digiti minimi n (%: 95%CI)	Biceps brachii n (%: 95%CI)	Abductor digiti minimi n (%: 95%CI)
50	12 (80%: 52 – 96%)	11 (73%: 45 – 92%)	0 (0%: 0 – 22%)	0 (0%: 0 – 22%)
60	15 (100%: 78 – 100%)	14 (93%: 68 – 100%)	0 (0%: 0 – 22%)	0 (0%: 0 – 22%)
70	15 (100%: 78 – 100%)	15 (100%: 78 – 100%)	0 (0%: 0 – 22%)	0 (0%: 0 – 22%)
80	15 (100%: 78 – 100%)	15 (100%: 78 – 100%)	0 (0%: 0 – 22%)	0 (0%: 0 – 22%)
90	15 (100%: 78 – 100%)	15 (100%: 78 – 100%)	0 (0%: 0 – 22%)	0 (0%: 0 – 22%)

SE = standard error, MEP = motor evoked potential, SP = silent period, CI = confidence interval.

Motor evoked potential

Although there was considerable variability in active motor threshold between individuals, no systematic differences were seen between the BB and ADM muscles in the active motor threshold and the slope parameter of the function. The active motor threshold of the stimulus-response curve reflects the stimulus intensity required to activate the corticospinal cells and spinal alpha motor neurons [26] that are near their threshold. The slope of the stimulus-response curve provides a general estimate of the excitability of the corticospinal pathway [26]. The recruitment characteristics of both corticospinal cells and spinal alpha motor neurons will influence the steepness of the slope [34]. Our results suggest that at least during an isometric muscle contraction of 50% of the maximal voluntary EMG-activity, the corticospinal cells and spinal alpha motor neurons in proximal and distal upper-extremity muscles behave similar in response to TMS. This is in agreement with the study of Taylor et al. [7]. These authors hypothesized that isometric contraction levels of 50 % MVC resulted in the recruitment of almost all available motoneurons in both the distal hand and proximal arm muscles [7]. However, at these high contraction levels changes in cortical excitability may also have contributed to the facilitation of the MEP in both muscles [35, 36].

A high inter-individual variability in the maximal MEP amplitude of the function in the BB was found, with individual cases of higher and lower plateau levels in the BB compared to the ADM. The plateau value of the stimulus-response curve represents the balance between excitatory and inhibitory components of the corticospinal volley [26]. The plateau level depends on the inherent recruitment and discharge properties of both the corticomotor neuron and the spinal alpha motor neurons [21, 26]. With high levels of muscle contraction, Wu et al. [3] discovered that the inherent recruitment and discharge properties of the spinal alpha motor neurons are more important for the differential excitatory effects of TMS on the proximal arm and distal hand muscles than the cortical mechanisms. The recruitment and discharge properties of the spinal alpha motor neurons are different for the small hand muscles compared to the proximal arm muscles [3, 22]. In distal hand muscles most motoneurons are recruited at voluntary contraction forces below 30% MVC and a further increase in muscle contraction results in an increase in the firing rate of the motoneurons. In contrast, in the BB additional motoneurons are recruited up to 90% MVC. Rate coding plays a more prominent role in force modulation in distal hand muscles, whereas recruitment plays a more dominant role in proximal arm muscles [3]. These differences in recruitment and discharge properties might be responsible for the differences in variability of the plateau values found between the ADM and BB muscles in our study.

Silent period

The stimulus-response curves of the SP had similar forms in the ADM and BB muscles. The threshold intensity to obtain a SP, however, was less for the ADM than for the BB muscle. The active motor threshold of the stimulus-response curve reflects the stimulus intensity required to activate the corticospinal and spinal alpha motor neurons. Distal hand muscles seem to be more sensitive to the inhibitory effects of TMS compared to proximal arm muscles, probably due to their greater cortical representation [5]. The slope of the function was steeper and more variable in the ADM compared to the BB. The increase in SP duration with increasing stimulation intensities reflects the activity of a greater number of inhibitory neurons activated during voluntary contraction [7]. As a consequence, the recruitment of intracortical inhibitory neurons by TMS must be different for distal hand muscles compared to proximal arm muscles. The difference in the recruitment properties between distal and proximal upper-extremity muscles might be due to their task specificity. Small hand muscles are mainly involved in fine, controlled motor tasks, in which fast modulation of the force is required. A strong inhibitory control, therefore, is necessary for the small hand muscles [5, 37].

Another difference between proximal and distal upper-extremity muscles observed in our study population was the small burst of EMG-activity interrupting the SP. These small bursts of EMG-activity before return to the mean pre-stimulus EMG-activity were most commonly seen in the BB. These EMG bursts may be due to fluctuations in contraction force in the period immediately after TMS, such that some responses might have been evoked when the contraction force produced was less than the target level [6]. Because inhibitory inputs to corticofugal neurons are stronger in the distal hand muscles compared to proximal muscles [7], these bursts may also be due to non-cortical sources of motoneuron excitation, interrupting the SP in proximal muscles.

Stimulus-response curves most likely reflect the excitability of the cortical circuitry, the corticospinal cells, as well as of the spinal alpha motor neuron pool [26]. The sigmoid shape of these curves is most likely related to a combination of the way cortical elements are recruited by TMS, the multiple components of the corticospinal volley, the recruitment of spinal alpha motor neurons with progressively larger motor unit potentials [38], and perhaps a greater tendency for synchronization of motor units discharges with increasing stimulus intensities [26]. The facilitatory mechanisms involved in the MEP, however, seem to differ from the inhibitory mechanisms eliciting the SP. The differences in stimulus-response characteristics between MEP and SP observed in this study underline this distinction.

It has previously been assumed that the MEP reflects the excitability of corticospinal cells, as well as of the spinal alpha motor neuron pool. The SP mainly reflects the cortical circuitry [7], although the early part of the SP, up to approximately 50 ms, might be due to both cortical and spinal inhibitory phenomena [3-5, 23]. If the SP would be generated by segmental inhibitory phenomena due to muscle twitches, the form of the stimulus-response curves of the SP would mimic that of the MEP. However, in our study the MEP amplitude reached a plateau in both distal and proximal upper-extremity muscles at a stimulation intensity of approximately 70% of the maximum stimulator output, whereas the SP duration did not reach its plateau value before 100% stimulator output. Although recruitment of inhibition (SP) and excitation (MEP) might correlate, they are thought to represent different neurophysiological systems within the cortex [9].

In some participants TMS at the higher stimulation intensities (90 to 100%) was not well tolerated. Although several authors have reported that the maximum values for both MEP amplitude and SP duration are obtained only at 100% stimulator output [5], our data indicate that it is not necessary to perform TMS at intensities above 70% of the maximum stimulator output to obtain a maximum MEP amplitude in healthy participants at a pre-activation level of 50% of maximum EMG-activity. However, at 70% stimulator output a linear increase in SP duration was still observed in most patients. TMS at high stimulus intensities is therefore still necessary to obtain maximum values for the silent period.

In our study isometric contraction levels of 50% of maximal voluntary EMG-activity have been used to ensure maximal facilitation of the MEP [7, 31]. Especially in the BB muscle, the strong muscle twitches associated with high stimulus intensities occasionally interfered with the subject's effort to keep the force constant. This has been reported in previous TMS studies as well [8]. Moreover, 23% of the healthy participants experienced fatigue during the TMS assessment and almost all participants had difficulty maintaining the target EMG-level. In patients with upper motor neuron disorders it will be even more difficult to maintain this high level of muscle contraction due to paresis. Although it is well known that voluntary pre-activation of the target muscles provides an optimal facilitation to obtain maximal MEP amplitudes with minimum stimulation intensities compared to muscles at rest, there is still controversy on the most effective level of pre-activation [39-42]. Hence, more research is needed to define this optimal pre-activation level in patients with upper motor neuron disorders.

After constructing stimulus-response curves in healthy participants, the question arises if these stimulus response-characteristics differ for patients with upper motor neuron diseases.

For instance, changes in motor threshold due to restorative mechanisms will have implications for the interpretation of the TMS data. Knowledge of the stimulus-response relations in various stages after upper motor neuron lesions will give more insight in the (disease specific) changes in excitation or inhibition of the corticomotor neuron and corticospinal pathways.

Conclusion

Differences in central inhibitory (SP) and excitatory (MEP) mechanisms induced by TMS have been observed between proximal and distal muscles. Variations in discharge and recruitment properties at high levels of muscle contraction, as well as differences in the physiology of muscle control seem to be responsible for these differences. Knowledge of the stimulus-response relations in various upper-extremity muscles will give more insight in the (muscle specific) differences in excitation or inhibition of the corticomotor neuron and corticospinal pathways. The adequate fit of the non-linear Boltzmann function suggests that this model can be used to study between and within subjects changes in future studies.

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Chapter 9

General Discussion

Adapted version of an invited review for "Brain hypoxia-ischemia research progress", Océane M. Roux, eds. Nova science publishers, Inc 2008 entitled "Predicting hand motor recovery and spasticity in patients with an acute, severe, middle cerebral artery stroke. The role of early clinical assessment and transcranial magnetic stimulation". Annette A van Kuijk, Gert Kwakkel, Machiel J Zwarts, and Alexander CH Geurts.

A major goal of this thesis was to investigate the predictive value of transcranial magnetic stimulation (TMS) for functional prognostication of the upper extremity in patients with a severe, middle cerebral artery stroke. More specifically, the additional value of motor evoked potentials (MEPs) and silent periods (SPs) was compared with regard to both hand motor recovery and the development of spasticity in patients with an initial paralysis of the upper extremity due to supratentorial stroke. In this section we will elaborate on the current, as well as on the future clinical value of TMS with regard to predicting hand motor recovery and spasticity. The most important strengths and limitations of the studies included will be addressed, as well as implications for future studies.

Current clinical value of TMS to predict upper-extremity motor recovery from stroke

In stroke patients with an initial paralysis of the upper extremity, the presence or absence of a MEP or SP seems to have no additional predictive value compared to early clinical assessment with regard to long-term hand motor recovery and spasticity. Accurate prediction of long-term hand motor recovery in these patients can be made 3 weeks after stroke, using the Fugl-Meyer motor assessment (FMA) upper-extremity subscore to predict recovery and the lower-extremity subscore to predict the absence of recovery [1]. With regard to spasticity, as yet, only modest associations of early muscle weakness and a low initial Barthel index with long-term hypertonia have been found [2].

Predicting Motor Recovery

In the cohort of severe stroke patients with an initial paralysis of the upper extremity presented in chapter 4, similar positive predictive values (PPV = 1) with regard to long-term hand motor recovery have been found for the presence of a MEP in the abductor digiti minimi muscle (ADM) and early clinical assessment of the upper-extremity, as assessed by the FMA upper-extremity subscore. Both the presence of a MEP in the biceps brachii muscle (BB) and any degree of early leg motor recovery, as assessed by the FMA lower-extremity subscore, were less accurate in identifying hand motor recovery (PPV = 0.70 and 0.71, respectively). The discrepancy between the PPVs for the presence of an ADM-MEP on the one hand, and the presence of a BB-MEP on the other hand, is probably due to differences in the physiology of motor control [3, 4]. In contrast to proximal muscles, the spinal alpha motor neurons that innervate muscles of the hand receive direct, unilateral, monosynaptic input from the primary motor cortex [5, 6]. The integrity of these monosynaptic inputs from the corticospinal pathway is considered a prerequisite for normal hand function. As for the BB-MEP and lower-extremity motor function, these determinants most likely reflect stroke

severity in general and are less specific for recovery of hand motor function.

Although both early motor recovery and the presence of an ADM-MEP were highly predictive with regard to hand motor function 6 months after stroke, less than half of the patients with hand function at 6 months could be identified within the first 3 weeks, implicating a poor negative predictive value (NPV) for both factors. Only if the absence of any motor recovery in the upper-limb was combined with an absent MEP in both the BB and the ADM muscle, a NPV of 1.0 was reached at 3 weeks after stroke. Still, the absence of a FMA lower-extremity subscore at 3 weeks post stroke approached this prediction rather well with a NPV of 0.95. This latter criterion is easier to apply in daily clinical practice.

Apparently, critical residual sparing of corticospinal function cannot be detected by TMS in all cases during the acute and subacute phases post stroke. This might be the result of insufficient cortical stimulation of functionally depressed, but undamaged corticomotoneurons. Another explanation is that restoration of motor function may be due to cortical reorganization involving brain systems that cannot be recruited by TMS, because these are not directly connected to the corticospinal pathways [7, 8]. In these cases, neuro-imaging studies might add valuable information about the residual function of the sensorimotor system [9].

Besides the TMS-induced excitatory mechanisms (MEP), the inhibitory mechanisms (SP) have been proposed as parameters to predict hand motor recovery. The review in chapter 3 showed that only few, well designed TMS-studies on the prognostic value of the SP with regard to post-stroke motor recovery have been performed, which yielded rather inconsistent results. Comparison of the results is difficult because of the variability in patients' characteristics and time post-stroke, methodology (e.g., definition of SP offset and onset), and the technical methods used. In most studies, prolonged SPs have been found in the first hours, immediately after stroke. This may be due to a generalized decrease in intracortical inhibition in order to optimize the intracortical excitatory processes, thus, supporting the motor output [10-12]. As a consequence, intra-cortical inhibition of the inhibitory interneurons in the primary motor cortex (that mediate the SP) decreases as well, resulting in prolonged SPs. In focal lesions of the primary motor cortex, however, the inhibitory interneurons mediating the SP themselves may become selectively damaged, leading to a decreased or even absent SP [13] (Fig. 1).

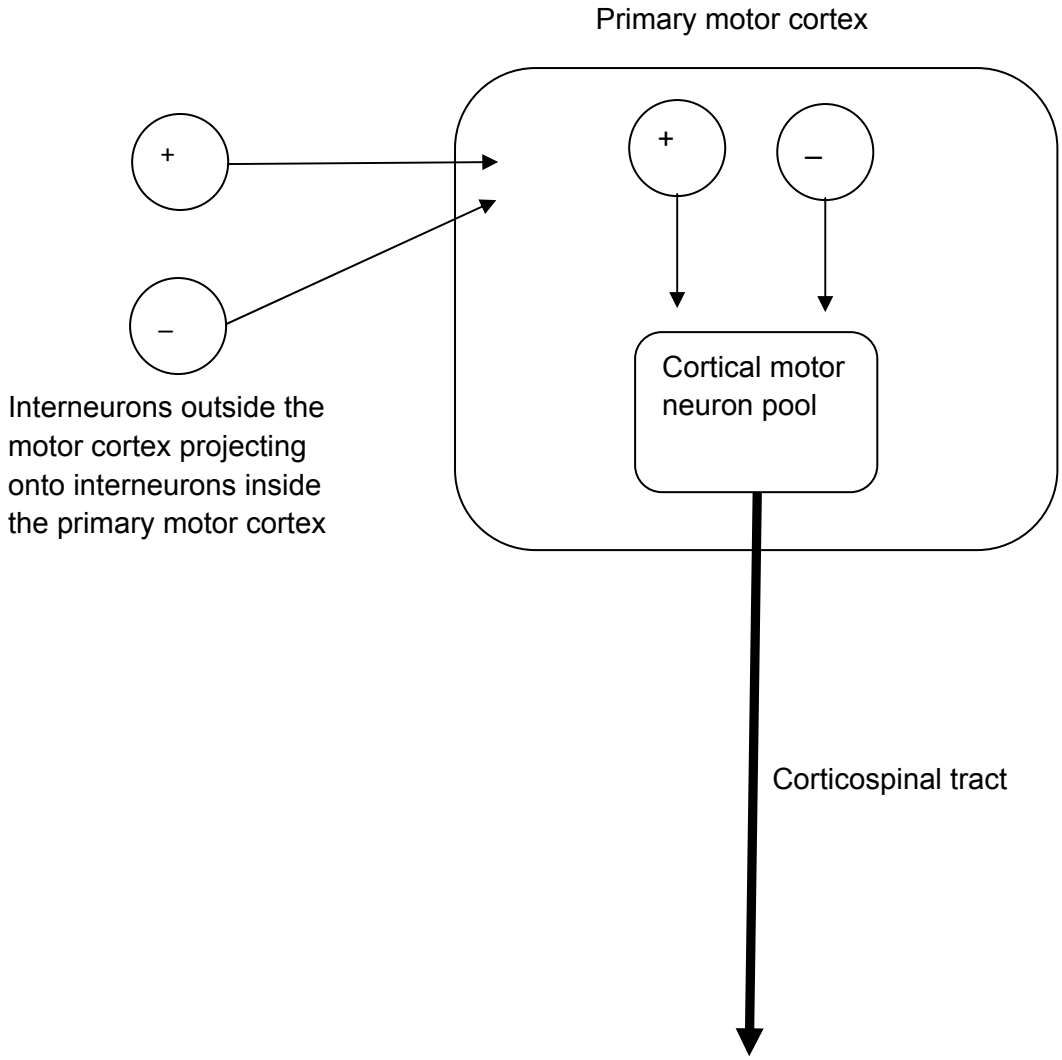

Figure 1. Visual approach to the different effects of stroke lesions within the primary motor cortex compared to lesions outside the motor cortex on the SP duration

Predicting Spasticity

In the (sub)acute phases thereafter, different patterns of SP duration have been found, i.e. normal, prolonged, as well as shortened SPs. These different patterns are thought to be related to stroke location (primary versus non primary motor cortex). Because in patients with mild to moderate middle cerebral artery strokes the degree of normalization of the SP seems to correlate with the amount of hand function recovery [10, 14, 15], recovery-related intracortical phenomena may also be responsible for these different patterns. To differentiate these recovery-related mechanisms in patients with mild to moderate strokes from the influence of stroke location, neuro-imaging studies might add valuable information to TMS. In patients with severe, middle cerebral artery strokes and an initial upper-extremity paralysis,

however, the SP seems to have no additional predictive value for post-stroke motor recovery when compared with TMS-induced excitatory phenomena (MEP).

In the cohort of patients with a severe, middle cerebral artery stroke and an initial upper-extremity paralysis, we observed an overall incidence of 63% for hypertonia within the first 6 months (chapter 5). Moreover, in a substantial amount of these patients (25%) the presence of hypertonia was observed already within the first 3 weeks after stroke. Apparently, these patients have a substantial chance to develop hypertonia in an early phase post stroke as well. As a consequence, by studying this subgroup we were able to maximize the likelihood of observing post-stroke hypertonia and, thus, to optimize the chance of identifying risk factors for hypertonia.

Even in this selected population of severe stroke patients, we were unable to identify any clinical or neuroradiological characteristic as a risk factor for early (onset ≤ 1 week post stroke) or long-term hypertonia (> 3 months post stroke) (chapters 5 and 6). Clinical characteristics such as hyperreflexia, sensory impairments, visuospatial deficits and apraxia, which are often associated with spasticity based on clinical experience, were not associated with hypertonia (chapter 5). These findings are consistent with the literature [16]. The lack of association between stroke location and hypertonia in our study may have been influenced by the fact that the majority of our patients suffered from extensive lesions on CT-scans involving both cortical and subcortical areas in the brain.

Reviewing the role of the SP in predicting motor recovery in chapter 3, there was some evidence that TMS might also be of value in predicting the development of post-stroke spasticity. In both subacute (≤ 2 weeks post stroke) and chronic stroke patients with initially mild to moderate paresis and a focal ischemic lesion in the territory of the middle cerebral artery, the relative inefficacy of the inhibitory mechanisms as indicated by a contraction-induced reduction in SP might have a positive predictive value with regard to spasticity [15]. In severe stroke patients with an initial upper-extremity paralysis, however, none of the neurophysiological characteristic (the presence of a MEP or SP) could be identified as a risk factor for early or long-term hypertonia (chapter 6). Yet, due to the small numbers of patients, the finding that the SP was not related to hypertonia must be interpreted with care. In addition, the voluntary contraction of the hand muscles was so severely impaired in the majority of the patients that often no SP could be recorded. Even patients in whom a SP could be elicited (nearly 10%) lacked the ability to elicit different degrees of voluntary contraction.

To elaborate on the predictive value of neurophysiological characteristics and cortical inhibitory mechanisms, longitudinal studies in patients with mild to moderate paresis and focal brain lesions should be conducted. From a neurophysiological point of view, the proposed relationship between TMS-induced inhibitory mechanisms and spasticity is not evident. TMS primarily assesses the corticomotoneuron and the corticospinal tract. Selective damage to the corticomotoneuron or the corticospinal tract does, however, not primarily result in spasticity, but rather in muscle weakness and a loss of fine, manipulatory hand movements [17]. Spasticity is generally thought to result from concomitant (in)direct damage to para-pyramidal motor pathways, such as the reticulo- and vestibulospinal tracts [17]. Stroke lesions within areas projecting to both the primary motor cortex and the brainstem might lead to a subsequent change in the balance between excitatory and inhibitory influences on the intra-cortical motor neurons that project to both the bulbospinal and the corticospinal tracts [8]. As a result, there may be a loss of the cortical drive to several inhibitory centres in the brainstem, resulting in disinhibition of bulbar and spinal reflexes as well [17, 18]. Although the para-pyramidal pathways cannot be directly assessed, they might be indirectly assessed by TMS. Nevertheless, as yet, the literature and the current results of this thesis do not support this idea.

TMS as a future tool to study and predict upper-extremity motor recovery from stroke

TMS as a future tool to predict upper-extremity motor function

The results of the prognostic studies in this thesis do, however, not preclude the future clinical value of TMS in individual patients. In severe stroke patients that are difficult to examine due to, for instance, cognitive deficits or loss of consciousness, TMS may still provide more reliable results than clinical examination. These patients lack the ability to move the arm and hands selectively, whereas clinical scores such as the FMA rely on the patients' ability to voluntarily and selectively move their extremities. As a result, early motor assessment can be biased by severe cognitive deficits. Particularly in these patients, neurophysiological assessment might be of additional value to provide objective, reliable, and quantitative data on the integrity of the corticospinal pathways. This hypothesis, however, would require prognostic studies in an even more selected subgroup of severe stroke patients than included in the studies presented in this thesis. As a result, the inclusion rate and the incidence of motor recovery will both be very low in this population, which would require large, multi-centred studies to include a sufficient number of subjects to identify significant associations.

This thesis primarily focused on the question whether the *intactness* of the corticospinal tract is predictive of the occurrence of hand motor function. For this purpose, both TMS characteristics (presence or absence of a MEP) and hand function (FMA hand score greater than 3) have been dichotomized. Thus, we were able to minimize the time taken and effort needed to perform TMS measurements in the selected patients. Patients with severe stroke are, however, not the most appropriate group to study whether the *level* of corticospinal functioning is predictive for the *degree* of hand function recovery. These patients lack the ability to move their affected limb voluntarily, which is necessary to adequately facilitate the MEP response. To answer the question whether the level of corticospinal functioning is associated with the degree of hand motor recovery, patients with mild to moderate strokes should be studied.

In these patients, stimulus-response curves that reflect the MEP amplitude or the SP duration for a range of stimulation intensities may give more insight in the (disease specific) changes in excitation and inhibition of the corticomotorneuron and corticospinal pathways than single conventional TMS characteristics [19-21]. MEP and SP are usually elicited at stimulus intensities corresponding to a certain percentage of the corticomotor threshold or the stimulator output [22, 23]. Due to their dependency on the stimulus intensity, changes in motor threshold e.g., as observed during the subacute phases of stroke, have implications for the interpretation of conventional MEP and SP characteristics [22, 23]. Stimulus-response curves have been constructed to study MEP amplitude and SP duration independently of their corticomotor threshold [19-22, 24]. These curves are considered to provide more sensitive and meaningful reflections of the function of the corticospinal pathways than single, conventional TMS characteristics [20, 21].

When constructing stimulus-response curves, recent neurophysiological studies on upper-extremity motor function have demonstrated that it is worthwhile to study the extensor muscles as well [25, 26]. In addition, recent clinical studies have indicated that active finger extension seems to be a reliable early predictor of upper-extremity motor recovery. It may be that the function of the finger extensors is most closely related to the degree of sparing of the corticomotoneurons and corticospinal pathways [26]. To substantiate this hypothesis, however, further research is needed.

TMS as a future tool to predict upper-extremity spasticity

Although the severe stroke patients that were studied in this thesis have a substantial risk of post-stroke spasticity, it may not be the most appropriate group to investigate the predictive value of neuroradiological characteristics and TMS-induced inhibitory phenomena with

regard to spasticity. In general, these patients suffer from large, extensive stroke lesions, affecting multiple brain areas. The relation of a specific brain area with the development of spasticity is, therefore, difficult to assess. Moreover, patients with initial upper-extremity paralysis lack the ability to move their affected limb voluntarily, which is necessary to generate a SP. To reveal the prognostic value of neuroradiological and TMS-induced inhibitory phenomena with regard to spasticity, a cohort of patients with mild to moderate paresis and more restricted brain lesions should be studied. In these milder patients, however, spasticity will be less frequent, requiring a much larger study sample than included in the studies presented in this thesis.

As for using the SP in spasticity prediction, the lack of uniformity regarding its definition may influence the observed duration, even if the SP is studied relative to the corticomotor threshold [27]. In this thesis, the SP has been assessed as the time period between the onset of the MEP and the resumption of continuous tonic voluntary EMG-activity to pre-stimulus EMG-levels. Both reference points are consistent in proximal and distal upper-extremity muscles and can readily be determined by a computer, independent of the assessor, and are hence less subject to inter-rater variability. In contrast, manually assessment of the data is subject to greater inter-rater variability. MEP and SP assessment tends to be more complex in stroke patients and inter-rater reliability may be of even greater concern in this population, suggesting a more critical need for (computerized) methods.

As for predicting post-stroke spasticity, a limitation of the studies presented in this thesis is that upper-extremity hypertonia was clinically assessed using the Ashworth scale, whereas instrumented assessments including surface EMG and force registrations from the upper-extremity muscles upon passive stretching would have provided better discrimination between active (i.e., contraction) and passive (i.e., muscle stiffness and shortening) contributions to muscular resistance [28]. However, instrumented tests are not yet available for routine clinical application, which is the reason that the (Modified) Ashworth Scale is still the most commonly used measures of adult spasticity. Other clinical scales can be regarded as modifications of the Ashworth scale. All such measures show equally and limited reliability and validity regarding muscle tone assessment [29, 30]. Future studies should, therefore, implement more advanced methods to quantify spasticity.

TMS as a future tool to understand upper-extremity motor function and recovery

Apart from clinical prognostication, TMS may be used to gain valuable information about the underlying mechanisms responsible for motor recovery after stroke. A better understanding of the factors that facilitate motor recovery as well as of the time window in which restorative

mechanisms are active is needed to optimize treatment strategies in individual patients. TMS can be used to assess relevant corticospinal reorganization in response to focal ischemic damage or subsequent (functional) recovery [7, 8, 22, 31, 32]. Stimulus-response curves of MEP amplitude and SP duration may give insight in the (disease specific) changes in excitation and inhibition of the corticomotorneurons and corticospinal pathways [19-22]. These curves reflect the excitability of all components of the corticospinal pathways, i.e. cortical circuitry, corticospinal tract, the spinal alpha motor neuron pool, and spinal interneuronal relays [19, 20].

In chapter 8 considerable variability in the active motor threshold of the stimulus-response curves in both proximal (arm) and distal (hand) muscles across healthy subjects is reported. Because both MEP and SP depend on the intensity of the stimulation [22, 23], the interindividual variability in active motor threshold made it difficult to compare the stimulus-response characteristics such as the maximum MEP or SP duration at a given stimulus intensity. Therefore, the stimulus-response curves had to be adjusted to this inter-individual variability in motor threshold using a non-linear mixed model. A sigmoid Boltzmann function described the data accurately when considering both the plateau of the function and the active motor threshold as random effects, allowing subject specific regression coefficients. The adequate fit of this model suggests that the non-linear Boltzmann function can be used to study between and within subject changes due to cortical and corticospinal reorganization in future TMS studies.

Even if the non-linear Boltzmann function was used, differences in the central facilitatory mechanisms induced by TMS (maximal MEP amplitude) were present between proximal and distal upper-extremity muscles. Variations in recruitment and discharge properties at high levels of muscle activation seem to be responsible for these differences [33, 34]. In proximal hand muscles, recruitment plays a dominant role in force modulation, whereas rate coding plays a prominent role in the force modulation of distal hand muscles [34]. With regard to the inhibitory mechanisms, differences in both the maximal SP duration and the slope of the input-output curve were found between proximal arm and distal hand muscles. Distal hand muscles seem to be more sensitive to TMS-induced inhibitory phenomena than the proximal arm muscles, probably due to their larger cortical representation [35, 36]. Moreover, small hand muscles are mainly involved in fine motor tasks in which sharp, sudden modulation of the force is required. A strong inhibitory control, therefore, is necessary for the small hand muscles [3, 34], whereas non-cortical sources of motoneuron excitation may be stronger in proximal muscles [37]. Yet, proximal and distal upper-extremity motor functions are equally important in providing an adequate understanding of upper limb functioning in stroke

patients. As a consequence, it is necessary to have muscle-specific knowledge of TMS characteristics.

Although stimulus-response curves may be sensitive reflections of the function of the cortico-spinal pathway, the exact contribution of each single element of this pathway cannot be retrieved. By adding modern imaging techniques such as diffusion and perfusion weighted magnetic resonance imaging (MRI) to the TMS-induced stimulus-response curves, we may be able to better distinguish the restorative intracortical mechanisms from those of the descending tracts [38]. These MRI techniques, however, cannot assess the precise brain location in relation to functionally important motor and sensory pathways [39]. Diffusion tensor imaging (DTI) and fiber tractography offer new perspectives to assess the location and extent of focal brain lesions, as they can visualize the main fiber bundles (e.g., the corticopsinal tract) and provide information on tissue integrity [39, 40]. DTI and fiber tractography may shed light on alterations in brain connectivity resulting from neuroplasticity, as well as on Wallerian degeneration after stroke. The latter process is important because, as a consequence of the stroke lesion and the subsequent loss of central drive, adaptation of peripheral neural structures takes place.

Spinal alpha motor neurons may become functionally depressed, but may still survive after stroke. In the majority of the patients presented in chapter 7, who had no signs of motor recovery in the upper-extremity and no clinical signs of peripheral neuropathy, decreased compound motor action potentials (CMAPs) in the ADM muscle on the paretic side were present as early as 4 days post stroke on peripheral stimulation of the ulnar nerve. This decrease in CMAP amplitude in the affected upper extremity reflects a reduction in functional motor units, i.e., the number of spinal alpha motor neurons and their axons that can be excited by electrical stimulation [41-45]. In patients suffering from hand motor weakness, this reduction occurs already in the early phases post stroke [41]. UMN lesions may cause a sudden loss of synaptic input and lack of activation of the spinal alpha motor neurons, which then become functionally inactive or undergo trans-synaptic degeneration [41, 46, 47]. Dysfunction of the anterior horn cells results in a disturbance of the axonal flow, leading to axonal degeneration (Wallerian degeneration). Impaired axonal transport may then lead to a dysfunction of the neuromuscular transmission at the motor end plate with a subsequent decrease in the CMAP amplitude [46]. This concept is referred to as “dying back” neuropathy [41], and appears closely related to the severity of the paresis [42, 43, 45, 47]. Maintaining a sufficient axonal flow in a long neuron seems to require more energy from the anterior horn cells than maintaining sufficient flow in a short neuron [48]. Therefore, the distal upper-extremity muscles show the most prominent functional changes [48].

In patients without motor recovery, motor unit loss neither progresses nor improves in the sub-acute phases [42, 45, 47, 48], remaining on a nearly constant level up to 3-4 months post stroke [45, 47]. Apparently, once it occurs, motor unit loss persists for a long time. In the chronic phase of stroke, a slight enlargement of active motor units can be seen that can be explained by restoration of axonal function or by collateral reinnervation. Both mechanisms of recovery may lead to an increased number of muscle fibers that can be activated and may explain the recovery of the CMAP seen in the chronic stages after stroke [42, 43]. The adaptive changes observed in the motor units might influence muscle structure and function. As yet, however, there are no longitudinal studies that look at these changes over a longer time-period to determine how they develop and how they are associated with motor recovery following stroke. In these cases DTI and fiber tractography may add valuable information to neurophysiological studies on the association of Wallerian degeneration and damage to both the cortical motoneuron and corticospinal tract.

Coda

To better understand motor and functional recovery after stroke, longitudinal studies are needed that assess and integrate neuroplasticity at all levels of the sensorimotor system, i.e., the upper motor neuron, the lower motor neuron, as well as the musculo-tendineous apparatus. Within the 2nd stimulation program for rehabilitation research in the Netherland (funded by the Netherlands Organization for Health Research and Development (ZonMw)), a new national research consortium has recently been instituted that will conduct, besides two early-phase multi-centre randomized intervention trials, several multi-centre cohort studies using functional MRI and, the above suggested neurophysiological techniques, as well as advanced kinesiological and biomechanical measurement tools to monitor and explain the plasticity of the upper-extremity sensorimotor system after stroke (“EXPLICIT”). Hopefully, this research will bring about promising new perspectives for understanding, predicting, and promoting motor recovery and spasticity after stroke, that will support the rehabilitation of these patients worldwide.

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Summary

Chapter 1 is a general introduction and provides information on stroke epidemiology, post-stroke muscle weakness and spasticity, and the use of transcranial magnetic stimulation (TMS) for clinical prognostication. The introduction concludes by presenting the scope and structure of this thesis. The main goal of this thesis is to investigate the additional predictive value of TMS to early clinical examination with regard to long-term hand motor recovery and spasticity of the hemiplegic upper extremity. This issue is addressed in a homogeneous group of stroke survivors with a severe, supratentorial, ischemic stroke. After an *introductory systematic review* that provides an important rationale for studying and predicting post-stroke motor recovery and spasticity, *four prognostic studies* are presented that focus on the prediction of long-term hand motor recovery and hypertonia of the upper extremity in severe stroke patients. Next, *two neurophysiological studies* address some important methodological considerations for future studies. The last part of this thesis is the *general discussion*, which elaborates on the reported findings of the above-mentioned studies in a more comprehensive manner.

Chapter 2 presents an introductory systematic review that evaluates the methodological quality of intervention studies on the clinical effectiveness of focal neuronal and neuromuscular blockade in post-stroke upper-extremity spasticity. Although 12 studies were included, only 2 randomized clinical trials met the predetermined criteria of minimal validity. The homogeneity of the patient groups with regard to diagnosis, time post-stroke, and their comparability with regard to functional prognosis and other sources of selection bias were generally poor. Yet, there was sufficient evidence for the effectiveness of BTX-A treatment for reducing muscle tone and improving passive range of motion at all arm-hand levels in chronic stroke patients lasting approximately 3 to 4 months. The effectiveness of BTX-A treatment for improving functional abilities could not be convincingly demonstrated, although two subgroups were identified that might specifically benefit at a functional level: (1) patients with mild hypertonia and a potential for voluntary extensor activity at the wrist and fingers, and (2) patients with severe hypertonia and no potential for motor recovery, but who suffered from problems with positioning, handling, and taking care of the affected arm and hand. Whereas in the first subgroup improvement of active motor function can be pursued, improvement of ‘passive’ abilities is a realistic goal in the second subgroup. We concluded that functional effects of spasticity treatment depend on a critical selection of subjects and individualized goal setting with appropriate selection of outcome measures. In order to adequately select subjects and set attainable individual goals, reliable clinical prognostication of motor recovery and the development of both spasticity and hypertonia is essential.

Chapters 3 and 4 both deal with the prediction of motor recovery of the upper extremity, whereas **chapters 5 and 6** focus on the prediction of upper-extremity hypertonia in patients with severe stroke.

Chapter 3 is a narrative review and a case series addressing the question whether the silent period (SP) can be of additional value to the motor evoked potential (MEP) in predicting post-stroke motor recovery of the upper limb. Relevant studies showed rather inconsistent results and suffered from heterogeneity in technical methods, methodology, and patient characteristics. In most studies prolonged SPs have been observed immediately after stroke, whereas in the (sub)acute phases thereafter, different patterns of SP duration have been found. The majority of the patients included in the case series suffered from a severe, ischemic, middle cerebral artery stroke. As a result, the voluntary contraction of the hand muscles was so severely impaired that no SP could be recorded. It was concluded that in acute stroke patients with an initial severe paresis or paralysis, the SP seems to have no additional value to MEP for predicting post-stroke motor recovery. Still, in patients with mild to moderate strokes, (contraction-induced) reduction of the SP has been associated with spasticity. Although the relation between the SP, recovery-related intracortical phenomena, and spasticity remains as yet unclear, a neurophysiological model underlying the SP is discussed.

In **Chapter 4**, the predictive values of the presence of an early MEP and of early clinical assessment have been compared with regard to long-term hand motor recovery. A prospective cohort study of 39 patients with a first-ever, ischemic, middle cerebral artery stroke and an initial upper extremity paralysis is presented. Hand motor recovery at 26 weeks post onset was selected as the primary outcome and defined as a hand subscore of the Fugl-Meyer Motor Assessment (FMA) greater than 3 points. Motor functions as assessed by the FMA upper- and lower-extremity subscores, as well as the presence of a MEP in the abductor digiti minimi (ADM) and biceps brachii (BB) muscles at 1 and 3 weeks post stroke were considered relevant prognostic determinants. At 6 months after stroke, 12 patients (34%) had regained hand function. Both the presence of an ADM-MEP and any recovery in the FMA upper-extremity subscore (at week 1 and 3) showed a positive predictive value of 1.0 with regard to hand motor recovery at 6 months post stroke. The FMA lower-extremity subscore showed the best negative predictive values (NPV = 0.90 at week 1; and 0.95 at week 3). It was concluded that in stroke patients with an initial paralysis of the upper extremity, the presence or absence of a MEP has no additional predictive value compared to early clinical assessment with regard to long-term hand motor recovery. Based on the FMA, accurate prediction of long-term hand function can be made 3 weeks after stroke using the

upper-extremity subscore to predict recovery, and the lower extremity subscore to predict absence of recovery.

The primary goal of the study presented in **Chapter 5** was to identify possible clinical risk factors, in addition to muscle weakness, for upper-extremity hypertonia in patients with a severe, ischemic, middle cerebral artery stroke. In addition, the prevalence and time-course of upper-extremity hypertonia was assessed at 6 consecutive moments during the first 26 weeks after stroke. A prospective cohort of forty-three patients who had been consecutively admitted to an university hospital with an acute, ischemic, middle cerebral artery stroke and an initial upper-extremity paralysis was included. Clinically relevant hypertonia (defined as an Ashworth score ≥ 2) at 6 months after stoke was selected as the primary outcome. The following potential risk-factors were considered at week 1 post stroke: 1) motor functions as assessed by the upper-extremity subscore of the FMA, 2) Barthel Index, 3) consciousness, 4) sensory disturbances, 5) apraxia, 6) neglect, and 7) hyperreflexia. Twenty-five patients (63%) developed hypertonia during the follow-up period of 26 weeks. During this period, the prevalence of hypertonia followed a rather dynamic course, with cases of early, transient, and late hypertonia. Despite the high incidence of hypertonia, none of the selected clinical characteristics could be identified as a risk factor.

The primary goal of the study presented in **Chapter 6** was to identify possible neuroradiological and neurophysiological risk factors for upper-extremity hypertonia in the same cohort of severe stroke patients as presented in chapter 5. Any association of hypertonia (Ashworth ≥ 2) with neuroradiological (lesion side, extent of lesion, and previous stroke), and neurophysiological (presence of a MEP or SP) characteristics was investigated. Associations between hypertonia and the selected neuroradiological and neurophysiological characteristics were generally low. Despite the high incidence of hypertonia in the study population, none of the selected neuroradiological or neurophysiological characteristics could be identified as a risk factor for upper-extremity hypertonia.

In **chapters 7 and 8,** two studies are reported that further investigate the use of neurophysiological methods for understanding and predicting motor recovery and hypertonia in severe stroke patients.

Chapter 7 presents a cohort study aimed at identifying secondary functional changes in the peripheral motor units of the affected upper extremity in patients with severe ischemic stroke. In addition, it is investigated how these peripheral functional changes develop during the first weeks after stroke. A prospective cohort of 27 consecutive patients with an acute ischemic supratentorial stroke and an initial upper-extremity paralysis was compared to 10 healthy control subjects. Clinical assessment at admission and at 1 and 3 weeks after stroke was

performed in all patients using the criteria of Kingery to diagnose plexopathy, radiculopathy, or neuropathy. The ulnar nerve was electrically stimulated proximal to the wrist and electromyographic recordings were obtained from the ADM muscle. Mean values of the compound muscle action potential (CMAP) on the affected side were compared with those obtained from the non-affected side at 1 and 3 weeks after stroke and with the CMAP values obtained from healthy controls. The mean CMAP amplitude in patients was significantly lower on the affected side compared with the non-affected side and with the controls. A decrease in CMAP amplitude was observed in more than half of the stroke patients, in some cases as early as 4 days after stroke. Whenever present in the (sub)acute phases, it was accompanied by absence of motor recovery at that specific time after stroke. Thereafter, recovery of CMAP amplitude was strongly associated with motor recovery. We concluded that a decreased CMAP amplitude in the ADM muscle can be seen already in the very acute phase after stroke, which is unrelated to peripheral neuropathy, radiculopathy, or plexopathy, but strongly related to absence of upper motor neuron recovery. This knowledge is important for the use of neurophysiological methods in stroke patients, including the interpretation of TMS results.

In **Chapter 8** stimulus-response characteristics of both MEP and SP induced by TMS were studied and compared between proximal and distal upper-extremity muscles. Stimulus-response curves of MEPs and SPs were obtained from the BB and ADM muscles in 15 healthy participants. A sigmoid Boltzmann function was used to fit the stimulus-response curves. The Boltzmann function described the stimulus-response curves of the MEP and the SP in both muscles adequately. The parameters of the stimulus-response curves of both the MEP and the SP differed between proximal arm and distal hand muscles in healthy participants. Higher maximal MEP amplitudes were found for the BB compared to the ADM, whereas for the MEP amplitude no difference in active motor threshold and slope of the function was found between both muscles. The active motor threshold to obtain a SP was less for the ADM compared to the BB. The slope parameter of the function of the SP duration was steeper and more variable in the ADM than in the BB. The differences between proximal arm and distal hand muscles might be due to differences in motor control of the upper-extremity muscles. It was concluded that, in future research, a Boltzmann function can be used to fit stimulus-response curves of both MEP and SP in muscles of the upper extremity to study between and within subject differences. However, specific curves should be constructed for proximal and distal muscles.

In **Chapter 9**, the general discussion, the main findings are summarized and discussed in view of the importance of the integrity of the corticospinal pathways for both upper-extremity motor recovery and spasticity after stroke. The current as well as the future value of TMS

with regard to predicting and understanding hand motor recovery and hypertonia is addressed. The need for new longitudinal recovery studies is stressed. These studies should assess and integrate neuroplasticity at all levels of the sensorimotor system, i.e. the upper motor neuron, the lower motor neuron, as well as the musculo-tendineous apparatus in order to better monitor, explain, and predict motor recovery and both spasticity and hypertonia of the upper-extremity after stroke.

Samenvatting

Hoofdstuk 1, de algemene inleiding, bespreekt de epidemiologie van het cerebrovasculair accident (CVA) en het daarbij optredende verlies aan spierkracht en spasticiteit. Daarnaast worden de basisprincipes van transcraniële magneetstimulatie (TMS) uitgelegd. De inleiding eindigt met de doelstelling en de opbouw van dit proefschrift. Een belangrijke doelstelling van dit proefschrift is het bepalen van de toegevoegde waarde van TMS ten opzichte van het vroege standaard klinisch onderzoek bij het voorspellen van herstel van handfunctie en het ontstaan van spasticiteit. Deze toegevoegde voorspellende waarde wordt onderzocht in een homogene groep patiënten met een supra-tentorieel gelokaliseerd, ernstig ischemisch CVA. Na een inleidende *systematische literatuurstudie,* die belangrijke argumenten geeft voor het bestuderen en het voorspellen van herstel van spierkracht en spasticiteit na CVA, worden *vier prognostische studies* gepresenteerd die zich richten op het voorspellen van het herstel van handkracht en het ontstaan van musculaire hypertonie op de lange termijn. Hierna volgen *twee neurofysiologische studies* die zich richten op enkele belangrijke methodologische overwegingen voor toekomstige TMS studies. Het laatste deel van dit proefschrift, de *algemene beschouwing*, plaatst de gerapporteerde bevindingen in een breder perspectief.

In **Hoofdstuk 2** wordt een systematische literatuurstudie besproken, waarin de methodologische kwaliteit wordt onderzocht van interventiestudies gericht op de effectiviteit van behandeling van spasticiteit in de bovenste extremiteit door middel van focale neurolyse of neuromusculaire blokkade bij CVA patiënten. Hoewel 12 studies werden geïncludeerd, voldeden slechts 2 gerandomiseerde studies aan de vooraf bepaalde criteria van minimale validiteit. De homogeniteit van de onderzochte patiëntgroepen met betrekking tot zowel de diagnose, het tijdstip na CVA, als hun functionele prognose en de controle voor andere mogelijke bronnen van vertekening was over het algemeen laag. Desondanks kon bij chronische CVA-patiënten voldoende bewijskracht gevonden worden voor de effectiviteit van de behandeling met botulinetoxine A voor het verminderen van musculaire hypertonie en het verbeteren van de passieve bewegingsuitslagen van de bovenste extremiteit. Deze effecten hielden tot 3 à 4 maanden na behandeling aan. De effectiviteit van de botulinetoxine A behandeling voor het verbeteren van de gebruiksmogelijkheden van de bovenste extremiteit kon niet overtuigend worden aangetoond, hoewel twee subgroepen werden geïdentificeerd die op functioneel niveau zouden kunnen profiteren van de behandeling: (1) patiënten met milde musculaire hypertonie en het vermogen tot actieve strekking van de pols en/of vingers, en (2) patiënten met forse musculaire hypertonie, zonder vooruitzicht op herstel van spierkracht of actief bewegingsvermogen, en met problemen bij het (passief) positioneren en verzorgen van de aangedane arm en hand. Daar waar in de eerste subgroep verbetering van het actieve bewegingsvermogen kan worden nagestreefd, is in de tweede subgroep

verbetering van de passieve verzorgingsmogelijkheden en contracturen een meer realistische doelstelling van behandeling. Geconcludeerd werd dat de functionele resultaten van spasticiteitsbehandeling afhangen van een kritische selectie van patiënten en van op het individu toegesneden doelstellingen met een juiste selectie van uitkomstmaten. Om tot een juiste selectie van patiënten te kunnen komen en haalbare, individuele, doelen te kunnen stellen, is een betrouwbare voorspelling van zowel het herstel van actief bewegingsvermogen, als van het ontstaan van spasticiteit en musculaire hypertonie noodzakelijk.

In de **Hoofdstukken 3 en 4** wordt het voorspellen van actief bewegingsvermogen besproken, terwijl in de **hoofdstukken 5 en 6** de nadruk ligt op het voorspellen van musculaire hypertonie in de bovenste extremiteit bij patiënten met een ernstig CVA.

Hoofdstuk 3 geeft een overzicht van de bestaande literatuur (narrative review) en bevat tevens een cohort studie. Beide richten zich op de vraag of de “silent period” (SP), naast de motore opgewekte potentialen (MEPs), van toegevoegde waarde is bij het voorspellen van herstel van actief bewegingsvermogen van de arm en hand na CVA. Relevante literatuurstudies toonden inconsistente resultaten. Er werd een grote verscheidenheid gezien aan gebruikte TMS technieken, methodologie, en aan patiëntkenmerken. Direct na het CVA werd in het meeste studies een verlenging van de SP duur waargenomen, terwijl in de subacute fase zowel verkorting, normalisatie, als verlenging van de SP duur werd vermeld. In de cohort studie kon bij de meeste patiënten met een ernstig, ischemisch CVA (gelokaliseerd in het stroomgebied van de arteria cerebri media) geen SP worden geregistreerd. Deze patiënten hadden een dusdanig ernstig verlies van spierkracht in de handspieren dat geen SP kon worden opgewekt. Geconcludeerd werd dat in de acute fase na CVA de SP geen toegevoegde waarde heeft ten opzichte van MEP bij het voorspellen van het herstel van actief bewegingsvermogen bij patiënten met een fors of volledig krachtsverlies van de bovenste extremiteit. Bij patiënten met een mild CVA werd een mogelijke associatie gevonden tussen de (door spiercontractie geïnduceerde) verkorting van de SP en spasticiteit. Hoewel de precieze relatie tussen de SP, cerebrale plasticiteit, en spasticiteit onduidelijk is, wordt een mogelijk neurofysiologisch verklaringsmodel voor de SP besproken.

In **Hoofdstuk 4** wordt de voorspellende waarde van (de aanwezigheid van) een MEP in de vroege fase voor het actief bewegingsvermogen van de hand 6 maanden na het CVA vergeleken met de voorspellende waarde van het vroege klinisch onderzoek. Dit werd onderzocht in een prospectief cohort van 39 patiënten met een eerste, ischemische CVA gelokaliseerd in het stroomgebied van de arteria cerebri media en een volledig krachtsverlies

van de bovenste extremiteit direct na het CVA. Herstel van handfunctie 26 weken na het ontstaan van het CVA werd beschouwd als de belangrijkste uitkomst maat. Herstel werd gedefinieerd als een score van meer dan 3 punten op de hand subschaal van de Fugl-Meyer Motor Assessment (FMA). Actief bewegingsvermogen van de bovenste en onderste extremiteit, beoordeeld middels de daarbij behorende subschalen van de FMA, en de aanwezigheid van een MEP in de abductor digiti minimi (ADM) en/of de biceps brachii (BB) werden beschouwd als relevante prognostische determinanten en geregistreerd in de eerste en derde week na het CVA. Zes maanden na CVA was er bij 12 patiënten (34%) sprake van herstel van handfunctie. Zowel de aanwezigheid van een ADM-MEP als een score groter dan 0 op de bovenste extremiteit subschaal van de FMA in de eerste en derde week na het CVA hadden een positief verspellende waarde van 1.0 voor het herstel van handfunctie op de lange termijn. Een score van tenminste 10 punten op de onderste extremiteit subschaal van de FMA had de beste negatief voorspellende waarde (week 1 NPV = 0.90, week 3 NPV = 0.95). Er werd geconcludeerd dat bij patiënten met een volledig krachtsverlies van de arm en hand direct na CVA de aan- of afwezigheid van een MEP geen toegevoegde voorspellende waarde heeft ten opzichte van vroege klinische beoordeling voor het herstel van handfunctie op de lange termijn. Gebruikmakend van de FMA bovenste extremiteit subschaal kan 3 weken na het CVA een accurate voorspelling van herstel worden gedaan van handfunctie op de lange termijn. De onderste extremiteit subschaal kan gebruikt worden om de afwezigheid van herstel te voorspellen.

De belangrijkste doelstelling van de studie die gepresenteerd wordt in **Hoofdstuk 5** was om bij patiënten met een ernstig, ischemisch CVA in het stroomgebied van de arteria cerebri media naast spierzwakte, mogelijke andere klinische risicofactoren te identificeren voor het ontstaan van musculaire hypertonie in de bovenste extremiteit. Ook werd gedurende 6 opeenvolgende momenten tijdens de eerste 26 weken na het CVA de prevalentie van hypertonie in de bovenste extremiteit bestudeerd. Hiertoe werd een prospectief cohort bestaande uit 43 patiënten, verwezen naar een academisch ziekenhuis in verband met een acuut, ischemisch CVA en een volledig krachtsverlies van de bovenste extremiteit geïncludeerd. Als primaire uitkomstmaat werd de aanwezigheid van klinisch relevante musculaire hypertonie 6 maanden na CVA geselecteerd. Klinische relevante hypertonie werd daarbij gedefinieerd als een Ashworth score groter of gelijk aan 2. Als mogelijke risicofactoren werden beschouwd de aanwezigheid van één van de volgende determinanten 1 week na het CVA: 1) gebrek aan bewegingsvermogen gemeten met de bovenste extremiteit subschaal van de FMA, 2) lage Barthel Index, 3) laag bewustzijn, 4) sensibiliteitsstoornissen, 5) apraxie, 6) neglect, en 7) hyperreflexie. Vijfentwintig patiënten (63%) ontwikkelden hypertonie gedurende de onderzoeksperiode van 26 weken. Gedurende

deze periode wisselde de prevalentie van musculaire hypertonie sterk, waarbij er sprake was van patiënten met vroeg, tijdelijk, en laat optredende hypertonie. Ondanks de hoge incidentie van musculaire hypertonie kon geen van de geselecteerde klinische determinanten worden geïdentificeerd als een risicofactor voor hypertonie.

De doelstelling van de studie gepresenteerd in **Hoofdstuk 6** was mogelijke neuroradiologische en neurofysiologische risicofactoren te identificeren voor het ontstaan van musculaire hypertonie in de bovenste extremiteit in hetzelfde cohort van patiënten als genoemd in hoofdstuk 5. Er werd gekeken naar mogelijke associaties tussen klinisch relevante hypertonie (Ashworth ≥ 2) van de bovenste extremiteit en neuroradiologische (infarctzijde, uitgebreidheid van het infarct, en een eventueel eerder infarct), en neurofysiologische (aanwezigheid van een MEP of SP) determinanten. De gevonden associaties tussen hypertonie en de geselecteerde neuroradiologische en neurofysiologische determinanten waren laag. Ondanks de hoge incidentie van musculaire hypertonie in deze patiëntengroep kon geen van de geselecteerde neuroradiologische of neurofysiologische karakteristieken worden geïdentificeerd als een risico factor voor musculaire hypertonie.

In de **Hoofdstukken 7 en 8** worden 2 studies besproken die een aantal methodologische aspecten onderzoeken van het gebruik van neurofysiologische methoden bij het verklaren en voorspellen van het herstel van actief bewegingsvermogen en musculaire hypertonie bij ernstige CVA patiënten.

In Hoofdstuk 7 wordt een cohort studie gepresenteerd die zich richt op het vaststellen van secundaire veranderingen in de functie van de perifere motor units van de aangedane bovenste extremiteit bij patiënten met een ernstig, ischemisch CVA. Daarnaast wordt onderzocht hoe deze veranderingen zich gedurende de eerste weken na het CVA ontwikkelen. Een prospectief cohort bestaande uit 27 patiënten met een acuut, ischemisch, supratentorieel gelokaliseerd CVA en een initiële paralyse van de bovenste extremiteit werd vergeleken met een controlegroep van 10 gezonde personen. Bij opname en na respectievelijk 1 en 3 weken na het CVA vond bij alle patiënten een lichamelijk onderzoek plaats. De klinische criteria van Kingery werden toegepast om perifere neuropathie, radiculopathie, of plexopathie te diagnosticeren. Electromyografische reacties van de ADM werden verkregen door de nervus ulnaris proximaal van de pols elektrisch te stimuleren. In de eerste en derde week na CVA werden de aldus verkregen gemiddelde waarden van de spierreactie, de compound muscle action potential (CMAP), aan de aangedane zijde vergeleken met de waarden aan de niet aangedane zijde en met CMAP waarden van de controle groep. Bij patiënten was de gemiddelde CMAP amplitude significant lager aan de aangedane dan aan de niet aangedane zijde, en tevens ten opzichte van de controle groep.

In meer dan de helft van de CVA patiënten werd een verlaging van de CMAP amplitude gezien, soms al 4 dagen na het CVA. Wanneer in de (sub)acute fase sprake was van een verlaging van de CMAP, ging dit altijd gepaard met de afwezigheid van actief bewegingsvermogen op dat specifieke moment. Na de acute fase was het herstel van de CMAP amplitude sterk geassocieerd met het herstel van actief bewegingsvermogen. Geconcludeerd werd dat in de ADM een verlaging van de spierreactie (CMAP amplitude) al in een zeer vroege fase na CVA kan worden gezien. Deze verlaging is niet gerelateerd aan perifere neuropathie, radiculopathie, of plexopathie, maar is sterk gerelateerd aan de afwezigheid van herstel van het centrale motorische (corticospinale) neuron. Hiermee dient bij het gebruik van neurofysiologische methoden bij CVA patiënten rekening gehouden te worden.

In **Hoofdstuk 8** worden de stimulusrespons karakteristieken van de door TMS opgewekte MEP en SP bestudeerd. De stimulusrespons curven van zowel proximale armspieren (BB) als distale handspieren (ADM) van 15 gezonde vrijwilligers werden met elkaar vergeleken. De stimulusresponse curven werden beschreven door middel van een sigmoïdale Boltzmann functie. Deze Boltzmann functie bleek de stimulusrespons curven van zowel MEP als SP in beide spieren goed te beschrijven. Bij de gezonde vrijwilligers verschilden de parameters van de beschreven stimulusrespons curven van zowel MEP als SP tussen de proximale arm- en de distale handspieren. Bij de MEP werden in de BB in vergelijking met de ADM hogere maximale MEP amplitudo's gevonden. Er werd geen verschil in de actieve drempelwaarde en de helling van de Boltzmann functie tussen beide spieren gevonden. Bij de SP was de actieve drempelwaarde in de ADM lager dan in BB, terwijl de helling steiler en meer variabel was. De geobserveerde verschillen in de parameters van de Boltzmann functie tussen de proximale arm- en de distale handspieren worden mogelijk veroorzaakt door verschillen in de centrale aansturing van de betreffende spieren. Er werd geconcludeerd dat de Boltzmann functie in toekomstig onderzoek gebruikt kan worden om de stimulusresponse curven van MEP en SP in spieren van de bovenste extremiteit te beschrijven. Wanneer bij de interpretatie van de parameters rekening gehouden wordt met de verschillen tussen proximale en distale spieren, kunnen met de Boltzmann functie verschillen binnen en tussen patiënten bestudeerd worden.

In **Hoofdstuk 9**, de algemene discussie, worden de belangrijkste bevindingen samengevat en besproken in het licht van het belang van de integriteit van de corticospinale banen voor het herstel van actief bewegingsvermogen en voor het ontstaan van spasticiteit in de bovenste extremiteit na een CVA. De huidige en toekomstige waarde van TMS voor het voorspellen en het begrijpen van herstel van handfunctie en spasticiteit wordt bediscussieerd. Ook wordt de noodzaak voor verder longitudinaal onderzoek naar de

herstelmechanismen optredend na een CVA benadrukt. In toekomstige studies zou de plasticiteit op alle niveaus van het sensomotorische systeem, dat wil zeggen zowel in het centrale zenuwstelsel, als in het perifere zenuwstelsel en het spier-pees apparaat, meegenomen moeten worden om het herstel van actief bewegingsvermogen en het ontstaan van spasticiteit en musculaire hypertonie na een CVA beter te kunnen begrijpen en voorspellen.

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Curriculum Vitae

Annette van Kuijk was born on January 18th, 1971, in Sittard, the Netherlands. After attending secondary school at the Serviam Lyceum in Sittard, she studied medicine at the Radboud University in Nijmegen. During her study she became interested in research and fulfilled scientific internships at the department of Orthopedics of the Radboud University Nijmegen Medical Centre, and at the department of Rehabilitation Medicine of the Sint Maartenskliniek in Nijmegen. In 1996 she finished her medical training, after which she worked for 18 months as a senior house officer at the department of Neurology of the Erasmus University Medical Centre in Rotterdam. From 1998 to 2000 she was employed as a resident in Rehabilitation Medicine at the Sint Maartenskliniek in Nijmegen, and from 2000 to 2002 at the Jeroen Bosch Hospital and at Tolbrug Rehabilitation Centre in 's-Hertogenbosch. In October 2002 she was awarded the "TOS-AGIO" trophy for her scientific work as a resident. In 2002 she was registered as a physiatrist.

During a fellowship from 2002-2003 at the department of Rehabilitation Medicine of the Radboud University Nijmegen Medical Centre, she started her research project entitled: "Predicting and monitoring upper-extremity motor recovery after severe stroke", which resulted in the work presented in this thesis. In 2006 she pursued a master degree in Clinical Epidemiology at the Vrije Universiteit Amsterdam, Institute for Research in Extramural Medicine (EMGO-institute).

Currently, she is working as a paediatric physiatrist at Tolbrug Rehabilitation Centre and as a senior researcher at the department of Rehabilitation of the Radboud University Nijmegen Medical Centre. She is also the scientific coordinator of Tolbrug Rehabilitation Centre and a member of the scientific board of the Jeroen Bosch Hospital.