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DEVELOPMENT AND EVALUATION OF A NEW METHOD TO OBJECTIVELY MEASURE SPASTICITY

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To my family

ABSTRACT

Spasticity is a neurological symptom that can occur after stroke and traumatic brain injury due to a lesion of the motor pathways descending from the brain to the brainstem and spinal cord. Spasticity is characterised by a velocity-dependent increase in resistance when muscles are passively stretched. There is a lack of valid measures of spasticity, which creates difficulties both in following the development of symptoms and in evaluation of potential treatment interventions.

The overall aim of this thesis was to develop and evaluate a new objective measure able to separately quantify spasticity and other components of passive muscle resistance in the wrist and finger flexor muscles. A biomechanical model was developed and adopted into a measurement instrument that performs passive isokinetic movements extending the wrist and finger flexor muscles. The model estimates three different components of the measured resistance to passive movement: neural (spasticity, NC) and non-neural (elastic, EC and viscous, VC) components.
The aim of Study I was to evaluate the new measurement model and to examine its validity. The model was adopted into a measurement instrument, the NeuroFlexor. The aim of Study II was to investigate the reliability and measurement error of the method. The aim of Study III was to investigate the method's sensitivity to change, which was examined in the context of treatment with botulinum toxin type A. In Study IV, the NeuroFlexor was used to explore the relationship between spasticity and other measures of upper limb body functions and activity. In all four studies, the participants were all adults in the chronic stage after stroke or traumatic brain injury.

The results from Study I showed that there was a strong association between the NC (spasticity) and the stretch reflex measured with surface electromyography (EMG). This was clearly shown in a nerve block test. The results also showed that the NC but not the EC and VC increased with increasing velocity of the muscle stretch. These results are in accordance with the definition of spasticity, and therefore constitute evidence of the method's validity. The results from Study II showed a high reliability of the NeuroFlexor method both within and between raters. In Study III sensitivity to change was demonstrated. The results from this study showed that the method is sensitive enough to detect change on a group level; however, its sensitivity to change on the individual level needs to be explored further. In Study IV, the results showed that spasticity had only weak to moderate assocations with other measures of function and activity.

The overall clinical implications and conclusions from this thesis are that this new method to measure spasticity is valid and is able to distinguish between spasticity and other components of passive muscle resistance in the wrist and finger muscles. The new method shows good psychometric properties making it a suitable alternative for more accurate clinical measurement of spacticity.

LIST OF PUBLICATIONS

I. Lindberg PG, Gäverth J, Islam M, Fagergren A, Borg J, Forssberg H. Validation of a new biomechanical model to measure muscle tone in spastic muscles. Neurorehabil Neural Repair 2011; 25: 617–625.

II. Gäverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson A-C. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. J Rehabil Med 2013;45:630-636.

III. Gäverth J, Eliasson A-C, Kullander K, Borg J, Lindberg PG, Forssberg H. Sensitivity of the NeuroFlexor method to measure change in spasticity after treatment with botulinum toxin A in wrist and finger muscles. (Submitted)

IV. Gäverth J, Krumlinde-Sundholm L, Borg J, Lindberg PG, PT, Forssberg H, Eliasson A-C. Associations between the NeuroFlexor measure of spasticity and other measures of upper limb function and activity after stroke. (In manuscript)

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LIST OF ABBREVIATIONS

Ad-AHA Stroke	Adult or adolescent version of the Assisting Hand Assessment for persons with stroke
ANOVA	Analysis of variance
CI	Confidence interval
CV%	Coefficient of variation expressed as percentage
EC	Elastic component of passive movement resistance
EMG	Electromyography
ICC	Intraclass correlation coefficient
iEMG	Integrated electromyography
M	Mean
MAS	Modified Ashworth Scale
Mdn	Median
NC	Neural component of passive movement resistance
N	Newton (SI unit)
PROM	Passive range of movement
r	Repeatability coefficient
RM-ANOVA	Repeated measures analysis of variance
sEMG	Surface electromyography
VC	Viscous component of passive movement resistance

1 INTRODUCTION

1.1 GENERAL INTRODUCTION

Her arm was twisted into an abnormal position, the fist clenched and the fingernails were digging into the flesh of the palm. The arm was numb and she felt like the whole limb was dead. This sentence would not feel out of place in a crime novel but it is in fact a description of some of the symptoms occurring after stroke or traumatic brain injury as a result of lesions in the central nervous system. These symptoms include paresis, change or loss of sensation, contractures, and different aspects of muscle hypertonia. The main focus of this thesis is spasticity, which is one aspect of muscle hypertonia that may restrict passive movement by involuntary reflex-mediated muscle contractions. In clinical rehabilitation and research, spasticity has been considered problematic and as a cause of disability although the association between spasticity and functioning is not clear.

The severity of spasticity is commonly rated according to the Modified Ashworth Scale (MAS) where spasticity is subjectively rated on a six-point ordinal scale during rapid manual muscle stretch. The MAS has however been criticized with regard to validity and many agree that it should not be used as an outcome measure. The main critique of the scale is that it is not able to separate spasticity from other causes of increased resistance to passive movement such as soft tissue contractures, which often occur in parallel. Consequently, there is a need for an objective and valid measure of spasticity that can be used in research and in clinical practice. The rationale of this thesis was to present a new method that is quick and easy to use and that still provides a valid and reliable quantitative measurement of spasticity. This should help the clinical management of spasticity by improving both diagnosis and follow-up.

The overall aim of this thesis was to describe and evaluate the NeuroFlexor, a new method to quantify wrist and finger spasticity. The NeuroFlexor is an instrumented measure which records resistance to movement during passive wrist extensions. It uses a computerised biomechanical model to estimate both spasticity and passive muscle resistance caused by structural changes in muscle and connective tissue. In this thesis and the associated articles, the biomechanical model will be described and the psychometric properties of the method including validity, reliability and sensitivity to change will be discussed. Spasticity is generally the same across different diseases or conditions. However, the aetiology (or rather the location) of the lesion or if the lesion occurred in the mature or developing nervous system, may have an impact on the manifestation of the muscle contractions and the parallel changes in muscle and connective tissue. Therefore, in this thesis we have chosen to focus mainly on spasticity after stoke but also to some extent on spasticity after acquired brain injury.

1.2 FRAME OF REFERENCE

1.2.1 International Classification of Functioning Disability and Health

How a person is affected by a disease or injury is dependent on what parts of the body are affected, what activities the person wants or needs to do, the context or environment in which the person is situated and previous experiences and personality traits. This is a dynamic relationship which forms the basis of the International Classification of Functioning Disability and Health (ICF). The ICF provides a worldwide standardised language for health and health-related states, as well as a scientific basis for understanding and studying health health-related states, outcomes, and determinants (World Health Organization, 2001). It complements the International Classification of Diseases (ICD-10) by enabling a standardised description of how an individual's functioning is affected by a disease. The ICF is comprised of two parts. Part one covers functioning and disability, including body functions and structures, activity, and participation. Part two covers contextual factors, including environmental factors and personal factors. The interactions between the different components of the ICF are shown in Figure 1. Body functions are the physiological functions of body systems (including psychological functions). Body structures are anatomical parts of the body such as organs, limbs, and their components. Impairments cover problems in body function or structure, such as a significant deviation or loss.

Activity is the execution of a task or action by an individual, and participation is involvement in a life situation. Difficulties in these components are described as activity limitations and participation restrictions. Environmental factors make up the physical, social, and attitudinal environment in which people live and conduct their lives, and can be both facilitating and hindering. Personal factors are the particular background of an individual's life and living, and comprise features of the individual that are not part of a health condition or health states. Personal factors are not classified within the ICF, but are included in the model described in Figure 1 to show their impact on the other domains.
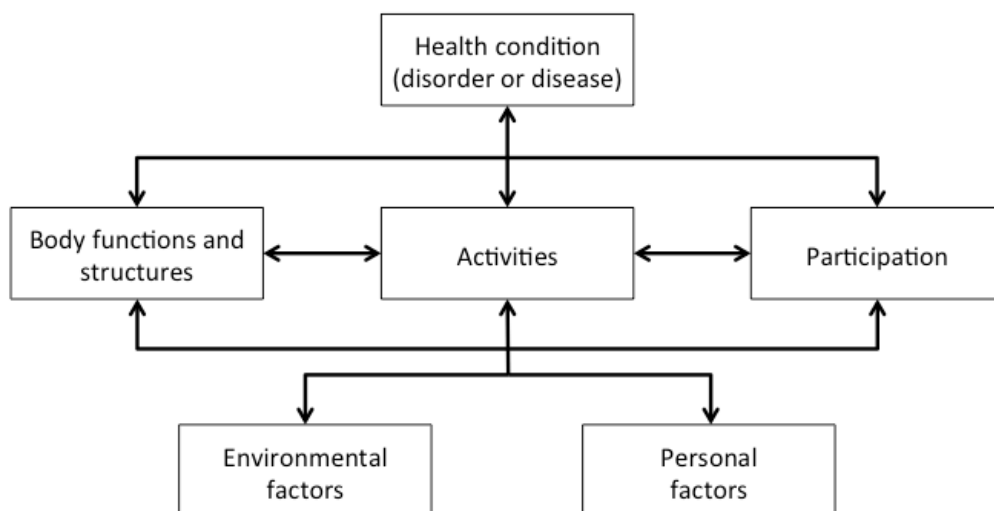

Figure 1. The interaction of the components of the ICF. Adapted from The World Health Organization (World Health Organization, 2001).

Spasticity is not classified as a body function in the ICF but is associated with the following categories within the domain of body functions: muscle tone functions (b735), motor reflex functions (b750) and involuntary movement reaction functions (b755). The non-neural component of the passive movement resistance (caused by structural changes in the muscle and connective tissue) is found in the domain of body structures, under the category of structures related to movement (s710-s799).

1.3   THE DEVELOPMENT OF A NEW MEASUREMENT INSTRUMENT

The process of developing a measurement instrument contains several important stages (Standards, 1999). In the first stage, it is important to determine what knowledge is lacking about a specific health condition. For spasticity, a need has already been recognised for a measure free from subjective ratings. The measure should also be able to distinguish between spasticity and the other components of passive movement resistance caused by changes in muscle and connective tissue.

In the second stage, it is necessary to determine the type of output that is required. A measure of spasticity could, on the one hand, be a classification answering the question of whether spasticity is present. On the other hand, it could be an ordered variable, like the MAS, giving information about the magnitude of spasticity from absent to extreme. In this type of scale, the distances between the scale steps are not necessarily equal and the ratings may be more or less subjective. This makes it difficult to compare ratings between different individuals. We saw the need for a continuous linear variable with the distance between each scale step. This was important for a number of reasons. We wanted an objective and sensitive measure which would be able to detect even small differences in the state, but also to allow objective comparison of the output both between repeated measurements in the same individual and between different individuals.

In the third stage, is important to determine how easy it is to perform the measurements, the estimated time consumption, and the comfort/discomfort for the patient in relation to the output. The optimal relationship is when the effort and discomfort are at a minimum and the output is at a maximum. An example of this is taking a blood sample and being able to determine whether an illness is present. In the case of measuring spasticity, we aimed for a non-invasive measure that could be used in a clinical setting after a minimal amount of training for the medical staff. The output should also be sensitive, easy to interpret, and easy to explain to the patient.

The quality of a measure can be described by its psychometric properties: validity, reliability, and sensitivity to change. Knowledge about the psychometric properties of a measure can help the clinician or the scientist to decide whether that measure should be used in a specific situation. It also helps the recipient of clinical information or the reader of a scientific report to evaluate the quality of the results. In the following sections, the concepts of validity, reliability, and sensitivity to change will be presented in more detail using the measurement of spasticity as an example.

1.3.1 Validity

Validity refers to the degree to which evidence and theory support the interpretations of test scores entailed by proposed uses of the tests (Standards, 1999). In plain language, a test is valid if it measures what it is intended to. The *Standards for Educational and Psychological Testing* describe five sources of validity, two of which are important for this thesis: evidence based on test content, and evidence based on relationships with other variables (Standards, 1999). Evidence based on internal structure, response processes, and consequences of testing will not be covered in this thesis.

Evidence based on test content. This has also been referred to as face validity, and means that a test *appears* to measure what it is intended to measure. In the case of measuring spasticity, it may seem reasonable to measure resistance to passive movement during rapid passive stretch, since this is one of the hallmarks according to Lance's definition (Lance, 1980) (see section 1.4). Similarly, it may seem reasonable to measure the resistance caused by a muscle's elastic properties during a very slow passive stretch when no stretch reflex is likely to be elicited. Both of these measures could therefore be said to have evidence of validity based on the content. Evidence from this source of validity may not be considered strong, since it is largely based only on common sense or common knowledge within a field; however, it forms the fundamental basis for a test.

Evidence based on relationships with other variables. This source of evidence is based on the fundamental assumptions of the construct the test is intended to measure. The output of the test is compared with other measures of the same construct (preferably including a gold standard) in order to establish the extent to which they are associated. The basic construct of spasticity is a motor disorder expressed by a velocity-dependent increase in passive movement resistance caused by hypersensitive stretch reflexes. Evidence based on relationships with other variables could therefore be obtained by exploring the associations between the spasticity measure and the expression of hypersensitive stretch reflexes given by the amplitude and duration of electromyogram across different stretch velocities. It could also be obtained by investigating changes in test results after an intervention with a known effect. Evidence of validity is present in this case if the test result changes in relation to the intensity of the intervention.

It must be remembered that the generalizability of the aspects of validity of a test should not be assumed. As an example, a measurement of spasticity in two individuals with stroke may result in one valid and one invalid measure. The basic construct of spasticity is not different between the two persons, but one of them lacks the ability to relax the muscles during testing. If the test is not designed to measure spasticity in randomly contracting muscles, the results from that measurement will not be valid. It is therefore important that written instructions for performing the test should be accompanied by information on the current evidence of validity.

1.3.2 Reliability and measurement error

Reliability refers to the degree to which test scores for a group are consistent over repeated applications of a measurement procedure (Standards, 1999). Two

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measurements on the same person may yield different results for a number of reasons, including variability in what is being tested, in the person being tested, in the person administering the test, and in the test itself. A test with little variation between measurements or a low level of measurement errors is described as being reliable. Knowledge about the magnitude of the variability between measurements is important in both clinical and research settings, whether the goal is to follow the development of a condition or to evaluate the effect of an intervention.

Reliability is often reported in terms of the intraclass correlation coefficient (ICC), which gives an indication of the relationship between the measurement error and the true or "error-free" estimation of the quantity (Shrout & Fleiss, 1979; Bartlett & Frost, 2008). The ICC takes a value ranging from 0 to 1, where 1 indicates perfect reliability. To give one example of the interpretation of the ICC, a value of 0.90 means that 90% of the variability is due to genuine differences between the persons being measured whereas 10% is due to the measurement process.

The ICC is dependent on the population heterogeneity; if the between-subject variability is low in relation to the within-subject variability, the ICC tends to be low. A hypothetical example of this is given by Bartlett and colleagues showing a dramatic reduction in ICC when comparing a heterogeneous and homogenous sample (Bartlett & Frost, 2008).

The ICC is a relative estimation of the reliability and should therefore not be reported alone, but always accompanied by an absolute estimation of the measurement error. An example of this is the standard error of measurement (SEM) (Lexell & Downham, 2005), which Bland and Altman call "the within-subject standard deviation". The SEM represents the standard deviation of the differences between a test result and a theoretically "true" or "error-free" value (Bland & Altman, 1996). The SEM can be expressed in the same units as the measure, and is then easily interpreted. In some cases, the measurement error increases with the magnitude of what is being measured. In these cases, the raw scores are log transformed and the SEM is therefore also expressed as a logarithmic value; the interpretation of the SEM then becomes very difficult. This transformation was necessary in Study II in this thesis. Still, the logSEM provides important information which can be used to determine whether a change is indeed greater than the measurement error after, for example, an intervention.

1.3.3 Measuring change

Some consider the ability to measure change as a form of evidence of validity based on the relationship with other variables (Streiner & Norman, 2003), while others consider it important enough to be considered a third psychometric property, equal with validity and reliability (Kirshner & Guyatt, 1985). Whatever one's opinion on this point, it is imperative that a test within evidence-based medicine should be able to detect a change between two assessments in order to evaluate the effect of an intervention or monitor the development of a condition.

In this thesis, a distinction is made between two approaches to measuring change: sensitivity and responsiveness. The two approaches are related, but form different concepts to describe change. Sensitivity to change is defined as any degree of change,

while responsiveness is concerned with clinically meaningful change (Liang, 2000). Responsiveness is often preferred, but is sometimes not easily obtained. The problem lies in defining what is a meaningful clinical change, since this is sometimes based on subjective opinions. One example is the use of a questionnaire with the question "How would you rate the change after the intervention?" with response alternatives ranging from "no effect" to "extremely large effect". Another way of defining a meaningful clinical change could be to relate the change to a change in another variable associated with the desired effect. An example of this is a decrease of 5 mmHg in systolic blood pressure, which is associated with a significantly reduced mortality rate in persons at risk of having a myocardial infarction.

Neither of the approaches described above is directly applicable in a new measure of spasticity. The sensitivity approach does not take into account the magnitude of the measurement error, and the consequence that a measured change could just be normal variability of the condition. The responsiveness approach is also not possible, since there are no established limits for a meaningful change in spasticity. Therefore, in this thesis we combined the sensitivity approach with the measurement error determined in Study II. By doing this, a measure of repeatability was obtained (see Formula 1) (Bland & Altman, 1996).

Formula 1. Repeatability

$$Repeatability = \sqrt{2} \times SEM \times 1.96$$

Repeatability means that the difference between two measurements for the same subject is expected to be less than $\sqrt{2} \times SEM \times 1.96$ for 95% of pairs of observations, and so a larger difference indicates a real change. If the measurement error is uniform across the scale, repeatability can be expressed in the same units as the original measure. We found that this was not the case for spasticity; instead, the measurement error was greater when the spasticity was more severe. In this case, Bland and Altman recommend log transformation of the raw data (Bland & Altman, 1997). When using log-transformed data, repeatability is no longer expressed in the units of the original scale but as a coefficient. This coefficient is then used to calculate how great a real change is for a specific measured value. A detailed description of this method is given in section 3.5.2.

1.4 DEFINITION OF SPASTICITY

The first descriptions of treatment of spasticity were published in the late 1880s by Abbe and Bennet respectively (Abbott, 1996). Ten years later, Sherrington published a famous series of experiments where he induced spasticity in a cat and was later able to reduce the spasticity by dorsal rhizotomy (Sherrington, 1898). However, it would take almost 90 years for spasticity to be properly defined.

At the beginning of the 1980s, Lance published the definition of spasticity we use today: *"Spasticity is a motor disorder characterized by velocity-dependent increase in tonic stretch-reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyperexitability of the tonic stretch reflex, as one component of the upper motor neuron*

syndrome". Unfortunately, despite this definition, spasticity is sometimes used interchangeably with other symptoms associated with muscle overactivity such as spasms (flexor, extensor, and adductor), associated reactions, mass movements, clonus, action-induced spastic dystonia, static spastic dystonia, and spastic co-contraction (Sheean & McGuire, 2009). It is however clear that these symptoms can exist independently of each other and do not necessarily share a common pathophysiology (Nielsen et al., 2007).

There has been some debate about Lance's definition, and Pandyan et al. have questioned its validity (Pandyan et al., 2005). Other definitions have been proposed, but to date, no other definition has been given international recognition. It is imperative that there is a consensus on the matter in order to allow clear clinical communication and to ensure that spasticity can be measured according to the same construct, even if by different means. The new objective measure of spasticity described in this thesis is based on the key points of Lance's definition: "motor disorder", "velocity-dependent increase in tonic stretch-reflexes", and "resulting from hyperexcitability of the tonic stretch reflex". This would not have been possible if we had chosen a definition that did not include the pathophysiological aspect of spasticity, as this could have led to confusion with other symptoms of muscle overactivity (Sanger et al., 2003; Pandyan et al., 2005; Bakheit et al., 2011).

1.5 DEFINITION OF STROKE AND TRAUMATIC BRAIN INJURY

This thesis uses the World Health Organization's broad definition of stroke: *"rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting 24 hours or until death, with no apparent non-vascular cause"* (The World Health Organization, 1988).
There is no consensus on the definition of traumatic brain injury (TBI). However, in a recent position statement from the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, TBI was defined as: *"an alteration in brain function, or other evidence of brain pathology, caused by an external force"* (Menon et al., 2010).

1.6 PATHOPHYSIOLOGY OF SPASTICITY

Knowledge about the mechanisms behind spasticity may provide important clues to its treatment (Nielsen et al., 2007). It is known that spasticity occurs distally to a lesion in the pathways descending from the brain to the brainstem and spinal cord, and it is recognised that this leads to altered supraspinal drive and plastic changes in the spinal cord. However, despite decades of research, the exact mechanisms are not fully understood (Pierrot-Desseilligny & Burke, 2005). Excitation of the Ia afferents originating in the muscle spindle is the main contributor to the excitation of the stretch reflex (Nielsen et al., 2007), but there are also numerous spinal pathways that may increase or decrease the effect of this monosynaptic excitation. A summary based on two reviews of the possible causal factors of increased excitability of the stretch reflex by Burke et al. and Nielsen et al. (Nielsen et al., 2007; Burke et al., 2013) is given below in Table I.

Table I. The possible central mechanisms causing spasticity. A summary of reviews by Burke et al., and Nielsen et al. (Nielsen et al., 2007; Burke et al., 2013).

Factor	Comment	Probable causal relationship with spasticity after stroke
Changes in the input to spinal motor neurons		
Increased fusimotor drive	Increased sensitivity of the muscle spindle through central activation of gamma efferent fibres	**-** (Wilson et al., 1999)
Decreased presynaptic inhibition of Ia afferents	Decreased activity in interneurons mediating presynaptic inhibition	**-** (Faist et al., 1994)
Decreased homosynaptic depression (post-activation depression)	Decrease in the normal habituation (reduced transmitter release) when Ia afferents from the muscle spindle are activated at low frequencies (< 10 Hz)	**+** (Aymard et al., 2000)
Changes in reflex circuits affecting motor neuron excitability		
Recurrent inhibition	Mediated by Renshaw cells. Interneuron producing negative feedback to the alpha motor neuron.	**-** (Katz & Pierrot-Deseilligny, 1982)
Decreased reciprocal Ia inhibition	Mediated via disynaptic reciprocal Ia inhibitory pathway.	**+** (Yanagisawa et al., 1976)
Nonreciprocal group I inhibition (Group Ib inhibition)	Absent or replaced by facilitation after stroke.	**-/+** (Delwaide & Oliver, 1988)
Group Ib facilitation	Mediated via reciprocal group Ib afferents from Golgi tendon organs.	**-/+** (Crone et al., 2003)
Group II facilitation	Mediated via group II afferents from secondary spindle endings.	**-/+** (Marque et al., 2001)
Changes in the intrinsic properties of the motor neuron		
	Input to the motor neuron pool by a central lesion can activate voltage-dependent channels causing persistent inward Ca^{2+} and Na^+ currents. These currents are important since they can prolong and amplify the response of the motor neurons to synaptic excitation. It can also lead to a self-sustained discharge in response to sudden input.	**-/+** (McPherson et al., 2008)

There is evidence for some plausible candidates for the physiological mechanism of spasticity, such as decreased homosynaptic depression and decreased reciprocal Ia inhibition, while other factors need further research. It seems evident that no single spinal pathway is responsible for causing spasticity, but rather the cause is a combination of many. There is also some evidence emerging that the spinal pathways can be modulated by brain stimulation (Mori et al., 2009). Findings from these studies may in the future cast new light on the pathophysiology of spasticity.

1.6.1 Prevalence and time course of development of spasticity

Due to methodological difficulties, there is no exact information on the development of post-stroke spasticity. Only a few studies have used neurophysiological methods to study the development of spasticity. Thilmann et al. showed that the stretch reflex threshold decreased and the amplitude increased in a sample of post-stroke patients during the first month after stroke, and the EMG response reached its maximum between 1 - 3 months (Thilmann et al., 1991).

The majority of studies are performed with manual rating scales such as the MAS and the Tone Assessment Scale (TAS). Wissel et al. (Wissel et al., 2013) recently compiled current knowledge into a systematic review including a number of studies performed by two independent groups in Sweden (Sommerfeld et al., 2004; Welmer et al., 2006; Lundström et al., 2008; 2010; Welmer et al., 2010). They reported that the prevalence of spasticity was 4–27% in the early time course (1–4 weeks), 19–26.7% in the post-acute phase (1–3 months), and 17–42.6% in the chronic phase (>3 months) (Wissel et al., 2013). This indicates that spasticity develops during the first weeks after stroke and seems to remain stable or diminish after 3 months.

There is a large variability within and a significant overlap between the different time frames in the studies included in the review. This can partly be explained by the inability of manual rating scales to distinguish between spasticity and soft tissue contractures. Wissel et al., also point out that the studies included in the review had small sample sizes, and were heterogeneous with regard to the time the assessments were made within the abovementioned time frames. Furthermore, many of the studies were conducted at rehabilitation centres, meaning that only the more severely affected patients were included, thus limiting their representation of the population (Wissel et al., 2013).

1.7 CHANGES IN MUSCLE AND CONNECTIVE TISSUE IN ADULTS AFTER BRAIN INJURY

Paresis after a lesion in the motor areas of the brain, brainstem, or spinal cord may leave the affected muscles in a shortened position because of immobilisation and disuse and over time, contractures may form. The process starts within hours after a lesion, but clinical manifestations in the form of reduced passive range of movement may appear after days, weeks, or months (Gracies, 2005). In a small study, Pandyan et al. compared two groups of patients in the subacute phase after stroke. One group had some motor function in the affected hand and the other group had no motor function (Pandyan et al., 2003). The findings from this study indicate that poor motor function is a predictor of contracture formation, but no associations were found between spasticity and either increased muscle stiffness or reduced passive range of movement. There is no evidence of a direct causal relationship between spasticity and changes in muscle and connective tissue. It is however not unlikely that spasticity may often be partly responsible for muscles being kept in a shortened position, thus aggravating contracture formation.

Post-stroke paresis causes several changes on the molecular level in the muscle and surrounding tissue. Gracies provides a comprehensive review of these structural changes (Gracies, 2005), summarised below in Table II.

The increased stiffness in the muscle may result in an increase in the mechanical muscle spindle stimulation by stretch, hence creating a vicious circle (Williams, 1980). Ada et al. measured contracture development in elbow flexor muscles over 52 weeks in a group of stroke patients (Ada et al., 2006). Contractures were defined as the difference in passive range of motion between the intact and the affected side. Spasticity explained 23% of the variance in the contractures during the first 4 months. In the later stages, weakness explained the majority of loss in passive range of movement. One explanation for this shift could be the fact that spasticity reaches its maximum around 3 months and then partly subsides (Thilmann et al., 1991).

Table II. Structural changes occurring in skeletal muscle after onset in post-stroke paresis. A summary of the review by Gracies, (Gracies, 2005).

Structural change	Comment	Relationship with increased passive movement resistance
Muscle atrophy	In non-paretic humans, immobilisation causes reduction in fibre diameter and reduced cross-sectional area of the whole muscle. In hemiparetic patients, the atrophy is more pronounced in the arm than in the leg. In animal models, there is less atrophy if the muscle is kept in a lengthened position.	Not likely to increase muscle stiffness
Loss of sarcomeres	Muscles adapt to their resting length and loose sarcomeres until those remaining overlap optimally to enable maximal tension at the immobilised length. This also applies to immobilisation in lengthened position.	Not likely to increase muscle stiffness but reduces muscle extensibility
Accumulation of intramuscular connective tissue	Immobilised rat muscle has increased endo- and perimysial connective tissue. There is an overall increase in the ratio of collagen to muscle-fibre tissue in the muscle. Collagen is a major component of the extracellular matrix.	Likely to both reduce extensibility and increase stiffness
Increased fat content	Fat accumulates in both spastic and flaccid muscles. This is more pronounced in the arm than in the leg in hemiparetic patients.	Not likely to cause increased stiffness
Degenerative changes in the myotendinous junction	Vascular density decreases and degenerative changes occur in the myotendinous junction, decreasing its tensile strength.	Likely to reduce extensibility

These structural changes in the muscle have implications for measuring spasticity. As mentioned earlier, the most commonly used measure claiming to measure spasticity, the MAS, does not distinguish between the stretch-induced reflex resistance and the mechanical resistance caused by increased stiffness in muscle and connective tissue. An objective measure of spasticity should be able to single out spasticity as a specific component of the passive movement resistance. An overview of current measurement methods is given in section 1.9.

1.8 FUNCTIONING AFTER BRAIN INJURY

Direct damage to cortical and subcortical areas including neurons originating in the sensory and motor areas of the cerebral cortex and the brain stem, such as that occurring after stroke or traumatic brain injury, may cause impaired sensory and motor functions (Lang et al., 2013). The severity of the impairment is often, but not always,

related to the size, location, and severity of the lesion. Paresis is the most common upper limb impairment, and as many as 50–70% of stroke survivors still experience weakness and disuse in the upper limb after several years (Wade et al., 1983; Broeks et al., 1999; Faria-Fortini et al., 2011; Lang et al., 2013). Changed muscle tone is also common, and spasticity occurs in almost 50% of those with paresis (Sommerfeld et al., 2012). Other impaired functions may include various somatosensory modalities (light touch, proprioception, temperature, and pain), control of voluntary movements, and joint range of movement (Jørgensen et al., 1995; Geyh et al., 2004).

The relationship between upper limb functions and activity may seem obvious. However, Burridge et al. showed that not all impaired functions were related to the ability to grasp and move objects in the Action Research Arm Test (ARAT) activity assessment (Burridge et al., 2009). For individuals in the chronic phase after stroke, only the loss of functions such as isometric force generation and active range of movement were associated with the ARAT, and not the overactive functions such as hyperreflexia measured with EMG and the non-neural muscle stiffness. These findings are similar to those of others (Zackowski et al., 2004; Ada et al., 2006; Harris & Eng, 2007) although there are also studies with conflicting results. Lin and Sabbahi showed that hyperreflexia was associated with activity measured with the Box and Block Test and active range of movement, but also with grip strength and the Fugl-Meyer motor assessment (Lin & Sabbahi, 1999).

Relationships between reduced spasticity and measures of activity were investigated in a large multi-centre study (Shaw et al., 2011). The effect on activity limitations was explored in patients with upper limb spasticity in the chronic phase after stroke, treated with intramuscular injections of botulinum toxin type A. The findings in this study showed that although the group had reduced spasticity measured with the MAS, the result on the ARAT did not change.

1.9 MEASUREMENT TECHNIQUES FOR SPASTICITY

The most commonly used measure of spasticity is the Modified Ashworth Scale (MAS) (Bohannon & Smith, 1987). Resistance to rapid passive movements is rated on a six-point ordinal scale ranging from "no increased resistance" to "limb fixed in flexion or extension". Although the MAS gives a fair approximation of spasticity as a screening instrument, there is more or less a consensus that the validity of the MAS is flawed, and it should not be used as an outcome measure to evaluate interventions aimed at reducing spasticity (Burridge et al., 2005; Fleuren et al., 2010; Sunnerhagen et al., 2013).

There are alternatives to the MAS, with greater evidence of validity, but translation of basic science knowledge back to the clinical domain has been lacking in the field. Some measures combine recordings of passive movement resistance and EMG, such as the method described by Voerman et al. which enables separated quantification of spasticity and passive muscle resistance in the wrist. (Voerman et al., 2007). The problem is that this type of measure is too complicated to use in a clinical setting, and may not be commercially available. Availability is indeed an issue which favours the clinical scales with low evidence of validity over the more advanced methods. This is a problem that could be overcome in larger studies with greater available recourses, but

the MAS remains the outcome of choice, probably because the results are easy to interpret and to compare with other studies.

Burridge et al. list a number of requirements that a valid spasticity measure should fulfil (Burridge et al., 2005): it should i) have a clearly defined protocol, ii) use variable velocities, iii) record resistance to passive movement and EMG simultaneously, and iv) be able to test response during both active and passive conditions. The last of these conditions is somewhat controversial, since some believe that spasticity by definition only occurs in resting muscles The increased resistance during active movements may rather be a result of action-induced spastic dystonia, associated reactions, or mass movements (Sheean & McGuire, 2009). An overview of different measures of spasticity and their benefits and limitations is given in Table III.

Table III. Overview of clinical scales and quantitative measures of spasticity

	Description	Benefits	Limitations
Clinical scales using an externally imposed stretch			
Modified Ashworth Scale (Ashworth, 1964; Bohannon & Smith, 1987)	Rapid manual stretch Rates passive movement resistance on a six-point ordinal scale.	Written guidelines. Easy to use. No equipment.	Questionable validity. Not standardised. No separation between spasticity and passive muscle resistance.
Tardieu Scale (Tardieu et al., 1954; Boyd & Graham, 1999; Gracies et al., 2000)	Manual stretch, two velocities rapid and very slow. Rates passive movement resistance on a six-point ordinal scale. Defines the spasticity angle. Passive range of movement is measured.	Written guidelines. Stretch reflex sensitivity is estimated by the spasticity angle, i.e. when marked resistance is felt during rapid movement.	Questionable validity. Poor reliability in angle measurements with goniometer. More difficult in adults than in children because of the size of limbs.
Tone Assessment Scale (Gregson et al., 1999)	Twelve-item questionnaire covering posture at rest (Q1-Q3), resistance to passive movement (Q4-Q9), and associated reactions (Q10-Q12).	Combines several aspects of increased muscle tone.	Questionable validity. Not confined to measuring spasticity. Unclear guidelines.
Neurophysiological			
H-reflex, Hmax/Mmax-ratio	Classical neurophysiological method. Measures the amplitude of the Hoffman reflex and the motor response to an electrical stimulus as a proxy for the excitability of the stretch reflex.	Standardised procedure.	Poor correlation with clinical scales. Requires specific equipment and training. Difficult to interpret.
Stretch reflex threshold (Calota & Levin, 2009)	Manual passive stretch of muscles in combination with EMG. Mathematical algorithm determining the stretch reflex threshold as a proxy for excitability of the stretch reflex.	Standardised procedure.	Not commercially available. Requires specific equipment and training. Difficult to interpret.
Hybrid (a combination of neurophysiological and biomechanical)			
Torque-EMG recordings during passive stretch (Voerman et al., 2007; Turk et al., 2008; Lorentzen et al., 2012)	Controlled ramp or sinusoidal perturbations in a small or large range of passive movements in combination with EMG. Mathematical algorithms for separation of active (reflex) and passive components.	Possible to standardise. Possible to separately quantify spasticity and passive muscle resistance.	Not commercially available. Requires specific equipment and training. Difficult to interpret.

1.10 DEVELOPMENT OF A NEW METHOD FOR QUANTIFICATION OF SPASTICITY

The rationale for the method was that it should be able to separately quantify spasticity and passive muscle resistance in an objective and standardised way. We wanted it to have similarities with the clinical MAS, to more easily allow comparisons and to facilitate interpretation of the measurement. In developing this, we needed to understand the biomechanical properties of passive movement resistance, and hence used knowledge gained from previous studies performed by Fagergren during his doctoral studies (Fagergren, 2003), complemented by the general assumptions made by Koo and Mak (Koo & Mak, 2006)

Using the methodology employed in another study, we converted a wrist rig designed to perform passive wrist extension in an MR scanner (Lindberg et al., 2009). The rig was complemented with the ability to simultaneously record passive movement resistance and surface EMG at different velocities, in order to meet the recommendation of Burridge et al. (Burridge et al., 2005). The experimental setup used in Study I is shown in Figure 2.
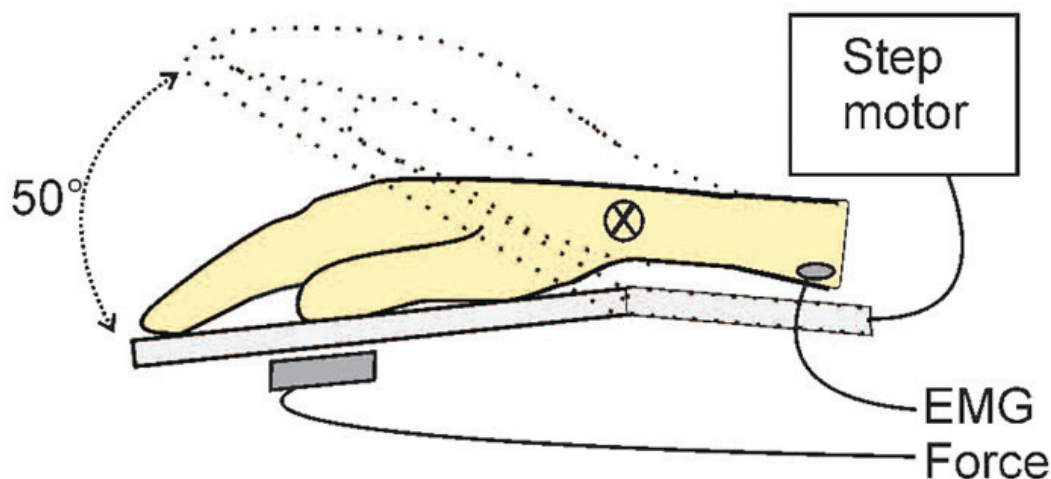
Figure 2. A schematic figure of the experimental setup used in Study I for the validation of the biomechanical model used for quantification of spasticity and non-neural components of passive movement resistance.

1.10.1 Basic assumptions

There is a basic assumption that whenever human muscle and connective tissue such as tendons and fasciae are stretched, the resistance is built up of four components: inertia, viscous resistance, elastic resistance, and reflex resistance. Koo and Mak (Koo & Mak, 2006) described the model in Formula 2.

Formula 2. Basic assumptions of passive movement resistance

$$T_m(\theta) = T_p(\theta) + T_y(\theta) + T_r(\theta) + T_{in}(\theta)$$

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where θ denotes a specific angle, T_m is the total resistance, T_p is the length dependent resistance (elastic resistance), T_v is velocity dependent resistance (viscous resistance), T_r is the reflex resistance and T_{in} is the inertia.

1.10.2 Model input

To allow calculation of the different components of the model, passive movement resistance is recorded during rapid isokinetic wrist extensions. The movement velocity is fast enough to ensure that a stretch reflex response is elicited. The model additionally requires recordings of a very slow movement, where it is very unlikely that a stretch reflex response is elicited. Finally, the following information is also required: acceleration rate, mass of the hand, and mass of the mechanical construction being moved during the measurements.

Offline, force data are extracted from three different defined locations on the force recordings. First, in order to provide an estimate of the viscosity, the highest amplitude during the acceleration phase is extracted (P1). This peak amplitude contains the inertia and also what is called the initial viscosity or short-range stiffness attributed to the properties of the cross bridges (Rack & Westbury, 1974). The viscous resistance during the isokinetic movement is a defined fraction of the initial viscous force. The second force required in the model is the force at the end of the fast movement when the wrist is fully extended (P2). The end of the movement was chosen in order to allow the stretch reflex to propagate in the muscle and cause a reflex-mediated muscle contraction. In order to capture the elastic length-dependent resistance, the force is extracted 1 s after the end of a slow movement while the wrist is still extended (P3), in order to ensure that no reflex activity is occurring. A graphic description of P1, P2, and P3 is shown in Figure 3.
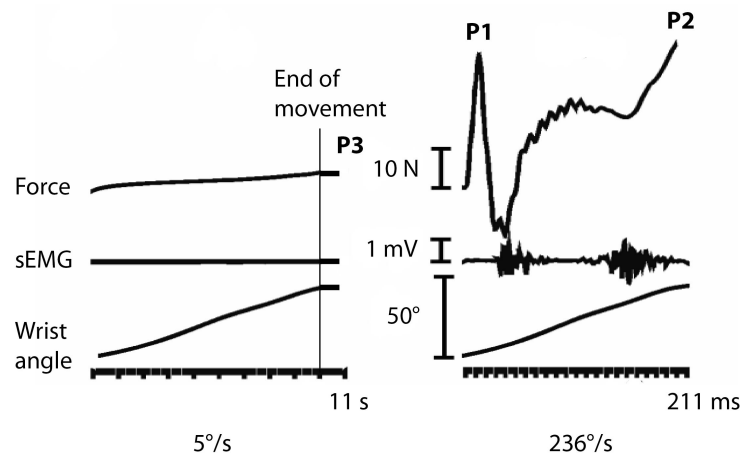

Figure 3. Model input. The figure shows force, EMG, and position data from one slow (5°/s) and one fast (236°/s) isokinetic passive wrist extension in a custom-built device. The acceleration phase is too early for a stretch reflex to occur; instead, inertia and initial viscosity are captured in the first force peak (P1). This force data is used in the biomechanical model for the estimation of the viscous resistance during the isokinetic movement (the viscous component). At the end of the fast movement, the force P2 is recorded. This force data is a sum of all the components of passive movement resistance, and is used to estimate the reflex-mediated resistance (the neural component). No EMG occurs during slow movement, which allows for measurement of the passive length-dependent component of passive movement resistance (the elastic component). This force is recorded 1 s after the end of the passive movement (P3).

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1.10.3 Model output

The biomechanical model translated from Koo and Mak's generic model is shown in Formula 3 where IC = 0 at P2 due to constant velocity (Koo & Mak, 2006). The different components are explained in detail below.

Formula 3. Adapted biomechanical model

$$Total\ force_{P2} = EC + VC + NC + IC$$

1.10.3.1 Inertial component (IC)

Inertia is the resistance of any physical object to change in its state of motion or rest (Özkaya, Nordin, Goldsheyder, & Leger, 2012*a*). It is the product of the mass of the moving object (*m*) and the acceleration of the movement (*a*); in our case, m is the mass of the hand in kg and *a* is the acceleration in m/s^2 (see Formula 4). Note that 1 kgm/s^2 = 1 N. Inertia is only present during the acceleration phase. In our model, the mass of the moving platform is ignored, since the force produced when the platform is moved without the hand being attached is subtracted from the force recordings with the hand on the platform.

Formula 4. Inertia

$$IC = m{\times}a$$

1.10.3.2 Elastic component (EC)

Elasticity is defined as the ability of solid materials to return to their original shape and size after any deforming forces have been removed (Özkaya, Nordin, Goldsheyder, & Leger, 2012*b*). In biomechanical models, elasticity is often represented by a linear spring. According to Hooke's law, elasticity is proportional to the length change of the spring: *F = kx*, where *x* is the length change and *k* is a stiffness constant dependent on the properties of the spring. In our model, elasticity gives rise to the force when the muscles in the forearm are extended, and is recorded 1 s after the end of the passive movement; that is, at P3 (see Figure 3 and Formula 5).

Formula 5. Elastic component

$$EC = P3$$

1.10.3.3 Viscous component (VC)

Viscosity can be informally described as a fluid's resistance to flow or the resistance of a moving object in a fluid (Özkaya, Nordin, Goldsheyder, & Leger, 2012*b*). In practice, this means that the faster and harder one tries to move an object in a fluid, the more resistance is experienced. Therefore, in biomechanical models, the viscous resistance is often represented by a dashpot which acts as a damper when tissue is extended. Human tissue has fluid-like qualities, and we therefore treated it accordingly. In our biomechanical model, the assumption is that the viscosity of the muscles and connective tissue gives rise to a velocity-dependent resisting force.

The viscous resistance is at its highest during the acceleration phase, and can be calculated by subtracting the inertia from the highest amplitude during the acceleration

phase; that is, $VC_{initial} = (P1-IC)$. However, in our model we were interested in the viscous resistance at the end of the movement ($P2$). At this point it is not possible to calculate the viscous resistance, and so it has to be estimated. By studying individuals with post-stroke spasticity participating in a nerve block test (Study I), we learned that the viscous resistance at the end of the movement ($P2$) was approximately 20% of the initial viscosity ($VC_{initial}$); see Figure 3 and Formula 6.

Formula 6. Viscous component

$$VC = (P1 - IC) \times 0.20$$

1.10.3.4 Neural component (NC)

As shown in Formula 2, the resistance at a given angle is the sum of the elastic, viscous, and reflex (spasticity) resistance. In order to estimate the resisting force components at the end of a rapid movement, the equation was translated into the following: P2 = $EC + VC + NC$, where P2 is the force measured at the end of the fast movement (see Figure 3). Hence, NC is calculated according to Formula 7:

Formula 7. Neural component

$$NC = P2 - (EC + VC)$$

1.10.4 Verification of the biomechanical model

The method described in this thesis estimates the EC, VC and NC through simple calculation steps based on unique data points, P1, P2 and P3 recorded during slow and rapid passive wrist extensions. To verify the accuracy of the calculations we used the knowledge from previous studies performed by Fagergren et al. (Fagergren 2003). In his studies Fagergren studied the precision grip where he was able to estimate how much force was produced dependent on the neural activity during the precision grip (Fagergren, Ekeberg, & Forssberg, 2000). These estimations were obtained by biomechanical simulations based on a nonlinear Hill based lumped-parameter model (Winters & Stark, 1985; Winters & Stark, 1987).

In Study I, we inverted the model in order to estimate how much neural activity was needed to produce a certain amount of force during a passive muscle stretch. By loading the force data recorded during passive movements (P1, P2 and P3) into the simulation model we were able to estimate the neural activity and verify the calculations used in this thesis to extract EC, VC and NC. We found very strong associations between the EC, VC and NC and the simulated parameters describing the elastic, viscous and reflex mediated resistance (unpublished data). These experiments formed the basis for the continued validation of the new method to measure spasticity.

1.10.4.1 Development of the NeuroFlexor measurement instrument

The biomechanical model developed for Study I was incorporated into a compact and portable measurement system, the NeuroFlexor. This was done in close collaboration between researchers at Department of Women's and Children's Health at Karolinska Institutet, and students at The Royal Institute of Technology (KTH) under the supervision of Professor Mats Hansson. The prototype of the measurement system including both hardware and software was later refined in collaboration with Devex

Mekatronik AB, Uppsala, Sweden. The version of the NeuroFlexor shown in Figure 4 was used in Studies II–IV.

Figure 4. The NeuroFlexor measurement device used in Studies II–IV. A PC is connected to the device to control the measurements, store the data, and perform the analyses. Photo: Ola Gäverth.

2 AIMS OF THE THESIS

The overall aim of this thesis was to develop a new objective method to investigate and describe spasticity after lesions in the central nervous system. The method was given the name NeuroFlexor. The specific aims of the included studies were:

Study I
To develop and validate a new model, easy to apply clinically, that allows estimation of the relative contribution of the neural and the non-neural components of spasticity.

Study II
To describe the reliability of the NeuroFlexor measurements in persons with chronic stroke. The aim was also to determine the limits for the smallest difference that indicates a real change, both at a group and an individual level.

Study III
To investigate whether the NeuroFlexor is sensitive enough to monitor changes induced by anti-spasticity treatment with Botulinum toxin type A. The aim was also to explore the relationship between change in spasticity as measured with the NeuroFlexor and change in passive range of movement, grip strength and perceived manual ability.

Study IV
To explore the association between spasticity measured with the NeuroFlexor and other outcomes of upper limb body functions such as range of movement, grip strength and sensory impairments as well as activity level outcome measures. A second aim was to evaluate the strength of the association between spasticity and the ability to use the affected hand in bimanual activities in relation to other measures of upper limb function and activity.

3 METHODS

3.1 STUDY OUTLINES

In Study I we examined different aspects of validity of a new biomechanical model for objective quantification of neural and non-neural contributions to passive movement resistance in wrist and finger flexor muscles after stroke. A custom-built device was used to perform isokinetic ramp movements in wrist extension and resistance to passive movement was recorded. The model separately estimates the neural (spasticity), elastic and viscous components of passive movement resistance and the model is based on three fundamental assumptions:

I.   The neural component is a reflex-mediated resistance; that is, spasticity. One of the main features of spasticity is velocity-dependence according to Lance's definition (Lance, 1980). We therefore hypothesised that the neural component should increase with increasing movement velocity. Our second hypothesis was that the neural component should correlate with objective measures of the stretch reflex; that is, surface electromyography. Our third and final hypothesis in relation to the neural component was that the NC should be significantly reduced during an ischemic nerve block test.

II.   The elastic component is a length-dependent component of the passive movement resistance, which is independent of the movement velocity, (se section 1.10.3.2). Our hypothesis was therefore that this component could be captured during a condition in which no stretch reflex was elicited and when the muscle and connective tissue was stretched out to the test's maximum range.

III. The viscous component is a velocity-dependent factor independent of the passive movement resistance, (see section 1.10.3.3). We therefore hypothesised that the viscous component should increase with increasing movement velocity when no stretch reflex was present.

Table IV shows the different aspects of evidence of validity of the biomechanical model, and the means with which the hypotheses were tested in Study I.

Table IV. The different aspects of evidence of validity of the biomechanical model for quantification of neural (spasticity; NC), elastic (EC), and viscous (VC) resistance to passive movement.

Model component	Hypothesis	Means of testing the hypothesis	Research questions	Main aspect of evidence of validity
NC	Velocity dependence	Different movement velocities	Does the NC increase with increasing movement velocity?	Test content and relation to other variables
	NC quantifies the passive movement resistance caused by stretch reflex	Surface EMG	Does the NC correlate with surface EMG across the different velocities?	Relation to other variable
	There is a close association between the NC and the stretch reflex response, surface EMG	Ischemic nerve block test	Does the NC change at the same rate as the surface EMG during an ischemic nerve block test?	Relation to other variable
EC	Length dependence	Visual inspection of force recordings during very slow movement velocities	Does the resistance increase with increasing joint angle?	Test content and relation to other variables
	Independence of the stretch reflex	Surface EMG	Does EMG activity occur during the slow passive movements?	Relation to other variable
		Ischemic nerve block test	Does the EC change at the same rate as the surface EMG during an ischemic nerve block test?	Relation to other variable
VC	Velocity dependence	Different movement velocities	Does the VC increase with increasing movement velocities	Test content and relation to other variables
	Independence of the stretch reflex	Ischemic nerve block test	Does the VC change at the same rate as the surface EMG during an ischemic nerve block test?	Relation to other variable

EMG: electromyography.

The biomechanical model described in Study I was applied in a measurement instrument (the NeuroFlexor) developed in collaboration with the Department of Machine Design, Division of Mechatronics and Embedded Control Systems, at the Royal Institute of Technology in Stockholm. In Study II we used a test-retest and inter-rater design to explore the reliability and the measurement error of this instrument.

In Study III we examined the sensitivity of the NeuroFlexor measurements. Patients with stroke or traumatic brain injury and with spasticity were examined before and after treatment with intramuscular injections of botulinum toxin type A. The hypothesis in this study was that reduction in the NC would be associated with a higher treatment dose and that changes greater than the measurement error would be detected.

In Study IV, we explored the relationship between spasticity and other measures of upper limb functions and activity such as muscle power, sensory function, passive range of movement, the ability grasp and the ability to perform two-handed activities. We also explored the impact of spasticity on the effectiveness of the affected hand as an assisting hand.

Table V. Summary of the aims, design, number of participants, and methods of the four studies

Study	Aim	Design	Participants	Principal methods
I	To develop and validate a new model allowing estimation of the relative contribution of the neural and non-neural components of spasticity.	Cross-sectional design	Persons with chronic stroke (n=31) and non-neurologically-impaired persons of comparable age (n=13). Total n=44	sEMG PMR MAS
II	To describe the reliability of the NeuroFlexor measurements in persons with chronic stroke.	Test-retest and inter-rater design	Persons with chronic stroke or traumatic brain injury (n=34)	NeuroFlexor
III	To investigate whether the NeuroFlexor is sensitive enough to monitor changes induced by anti-spasticity treatment with Botulinum toxin type A.	Prospective observational design	Persons with chronic stroke and traumatic brain injury (n=24)	NeuroFlexor MAS
IV	To explore the association between spasticity measured with the NeuroFlexor and other outcomes of upper limb body functions such as range of movement, grip strength, and sensory impairments as well as activity level outcome measures.	Cross-sectional design	Persons with chronic stroke and traumatic brain injury (n=26)	NeuroFlexor Ad-AHA-Stroke MAS PROM Sensory function (2PD) BB test Grip strength

sEMG: surface electromyography, PMR: passive movement resistance, MAS: modified Ashworth scale, BB test: Box and Block Test, PROM: passive range of movement, Ad-AHA Stroke: Adult/adolescent version of the Assisting Hand Assessment, 2PD: two point discrimination

3.2 PARTICIPANTS AND DATA COLLECTION

3.2.1 Study I: participants

The participants in Study I comprised a convenience sample of 31 persons (age: $M = 61.3$, $SD = 10.0$ years) in the chronic phase after stroke (time: $M = 5.3$ $SD = 4.5$ years since stroke). They were recruited through the Department of Rehabilitation Medicine, Danderyd University Hospital, in the Stockholm greater area. The inclusion criteria were: i) stroke with right side hemiparesis > 6 months prior to inclusion; ii) a minimum of 40 degrees of passive wrist extension; and iii) ability to understand information about the study. The exclusion criteria were: i) neurological disorder other than stroke, or stroke more than once; and ii) current pharmacological treatment of spasticity. A reference group of 13 non-neurologically-impaired persons of comparable age was also recruited from among the staff at Danderyd Hospital and the acquaintances of the authors, in order to give an indication of whether the components of the model were different in persons with and without neurological impairments.

3.2.2 Study I: data collection

The data collection took place at the Department of Neurophysiology, Karolinska University Hospital, Solna, Sweden. First, a test battery was administered consisting of motor and sensory assessments (see Table VII). The order of the assessments was the same for all participants. The second part of the data collection was measurement of passive movement resistance and sEMG of wrist and finger muscles. Measurements were taken with the participant in a sitting position with the hand securely fastened in a custom-built device incorporating a computer-controlled step motor. Four different velocities in an ordered sequence were used to produce passive isokinetic wrist extensions. Passive movement resistance and sEMG data were recorded and stored for offline analysis. On average, the whole test procedure lasted for approximately 90 minutes. The non-neurologically-impaired reference group did not perform the motor and sensory function tests. A sub-sample of stroke participants was also examined during an ischemic nerve block test to explore changes in passive movement resistance, specifically NC, over time (25 minutes). A tourniquet placed on the participant's upper arm was inflated to 30 mm Hg above systolic blood pressure and sustained for 25 minutes. Passive movement resistance and sEMG were recorded before inflation at baseline, every five minutes during inflated tourniquet, and after the pressure was released (see Figure 5). This procedure took place on a separate day and lasted approximately 45 minutes.
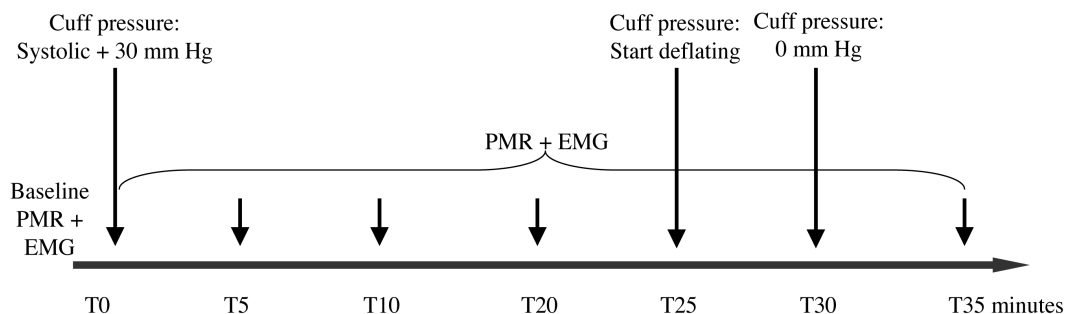

Figure 5. Nerve block test procedure. PMR: Passive movement resistance, EMG: surface electromyography, T: time.

3.2.3 Study II: participants

The participants in Study II comprised a convenience sample of 34 persons (age: $M = 53.8$, $SD = 12.1$ years) in the chronic phase after stroke or traumatic brain injury (time: $M = 5.0$, $SD = 3.6$ years). The mode of recruitment and exclusion criteria were the same as in Study I, except that there was no restriction with regard to side of hemiparesis. The test-retest examinations were performed by two raters (authors JG and MS) who had received training in the NeuroFlexor method.

3.2.4 Study II: data collection

The data collection took place at the Department of Rehabilitation Medicine, Danderyd University Hospital, in the greater Stockholm area. First, background information, grip strength, and passive range of movement were assessed by author MS. Second, test-retest of NeuroFlexor assessments was performed by two trained physiotherapists, authors JG (A) and MS (B). There were two ordered sequences between the therapists — ABAB or BABA — which were used consecutively. There was a 10-minute interval between each NeuroFlexor assessment, during which the device was restored to a default. The individual settings of the NeuroFlexor from the first assessment (test) were reused in the second assessment (retest).

3.2.5 Study III: participants

The participants in Study III comprised a clinical sample of 24 persons (age: $M = 50.8$, $SD = 11.3$ years) in the chronic phase after stroke or traumatic brain injury (time: $M = 5.0$, $SD = 3.6$ years since incident), scheduled for treatment with botulinum toxin type A. They were identified by the staff at an outpatient clinic for spasticity management at the Department of Rehabilitation Medicine, Danderyd University Hospital, in the greater Stockholm area. The inclusion criteria were: i) stroke or traumatic brain injury > 6 months prior to inclusion, ii) spasticity in wrist and finger flexors with MAS $\geq$ 1, iii) considered suitable for treatment with BoNT-A, iv) no fixed contractures of the wrist, and v) the ability to understand and comply with instructions.

3.2.6 Study III: data collection

The data collection took place at the Department of Rehabilitation Medicine, Danderyd University Hospital, and the Huddinge site of Karolinska University Hospital, both in the greater Stockholm area. Repeated measurements were made at baseline, at the time when the treatment had maximum effect (4 weeks after treatment), and at the time when the effect of the botulinum toxin type A was considered to have subsided significantly (12 weeks). On each occasion, the test procedure started with an assessment battery consisting of clinical measures of spasticity, range of movement, grip strength, and manual dexterity followed by a NeuroFlexor measurement.

3.2.7 Study IV: participants

Study III and IV consist of data from the same data collection; 19 persons are common in the two studies. The 26 participants (age: $Mdm = 55.0$, IQR 45.7 - 62.3 years) were all in the chronic stage after stroke or traumatic brain injury (time: $Mdn = 40.5$, IQR

16.0 - 119.3 months since injury). Inclusion criteria were i) stroke > 6 months prior to inclusion, ii) adequate passive range of movement for NeuroFlexor measurements, that is a minimum of 30 degrees of wrist extension and iii) ability to understand and comply with instructions.

3.2.8 Study IV: data collection

The data collection in Study IV was the same as in Study III, but 5 participants did not perform the Ad-AHA Stroke because of time restrictions. Therefore 7 additional persons with spastic hemiparesis after stroke were assessed on one occasion with the same test battery as in Study III. For these participants, the data collection took place at the Department of Rehabilitation Medicine, Danderyd University Hospital.

3.3 OVERALL PARTICIPATION IN THE STUDIES

A total of 75 individuals took part in at least one of the studies. One person participated in all four studies, 7 in three, 23 in two, and 44 in just one. Table VI shows how the participants overlapped between studies.

Table VI. Number of participants with stroke or traumatic brain injury overlapping between studies.

	Study I ($n = 31$)	Study II ($n = 34$)	Study III ($n = 24$)	Study IV ($n = 26$)
Study I	**31**	10	2	3
Study II	10	**34**	9	7
Study III	2	9	**24**	19
Study IV	3	7	19	**26**

3.4 ASSESSMENTS

The methods used in this thesis will be presented in detail in the following section, and are summarized in Table VII.

3.4.1 Passive movement resistance (Studies I-IV)

In Study I, a custom-built device was used which simultaneusly recorded resistance to passive movement, position (joint angle) and surface electromyography. The device was orignally designed to be used in an magnetic resonance imageing environment and was used in a previous study (Lindberg et al., 2009). During measurement of passive movement resistance, force recordings were sampled at 400 Hz Data were stored and analysed in SC/ZOOM, a dedicated signal analysis computer system (Department of Physiology, Umeå University, Umeå, Sweden). The force recordings were adjusted for by subtracting the baseline offset (average of 500 ms before start of movement). The force recordings also included an angle-dependent variation of the gravitational force exerted on the hand (which was largest in the horizontal plane at zero degrees). The total force trace was corrected to compensate for this angle-dependent gravitational variation (Lindberg et al., 2011). The average of three force recordings from three movements were used in the analyses.

In Studies II - IV the NeuroFlexor was used. I is an instrumented measurement device where the wrist joint is passively extended at two different isokinetic velocities and the resistance to passive movement is registered, (See Figure 4). The participant is seated comfortably with the elbow in 90 degrees of flexion, and the hand is placed in the device with the wrist axis of rotation aligned with the device and then securely fastened. The instrument performs slow and fast movements (5 and 236 degrees/s, respectively) in a 50 degree range of movement with a starting angle of 20 degrees of palmar flexion. For each participant, one value of NC, EC, and VC, respectively, is calculated in dedicated software using recordings from nine fast and four slow passive movements (NeuroFlexor Scientific, Release 0.0.6, Aggero MedTech AB, Solna, Sweden).

3.4.2   Surface electromyography (Study I)

Bipolar circular Ag-AgCl surface EMG electrodes with an interelectrode distance of 15 mm and an inbuilt amplification (MYO 115, Liberty Technology, Hopkinton, Massachusetts) were placed on the muscle belly aligned with the muscle fibres of the flexor carpi radialis (FCR). To make sure there was no co-contraction, activity of the extensor carpi radialis (ECR) was also recorded but not used in the analysis. sEMG was sampled at 800Hz. Data were stored and analysed in SC/ZOOM, a dedicated signal analysis computer system (Department of Physiology, Umeå University, Umeå, Sweden). The program rectified the EMG by converting the signal to a root mean square using a 2 ms moving-window averaging technique. The area under the curve from start to end of movement was calculated by integrating the EMG signal amplitude * time (mVs). The average of three EMG recordings from three movements were used in the analyses.

3.4.3   Upper limb Motor Assessment Scale (UL-MAS) (Study I)

The UL-MAS is a subscale of the Motor Assessment Scale designed to measure the functional movement in adults (Loewen & Anderson, 1988; Lannin, 2004). It consists of three items: Upper Arm Function, Hand Movements, Advanced Hand Activities. Each upper limb item contains six tasks, with hierarchical scoring for each item ranging from 0 (unable to perform task 1) to 6 (optimal performance as patient can perform all six tasks). Sabari et al. (Sabari et al., 2005) examined the validity of the hierarchical scoring system using Rasch analysis, finding some inconsistencies, and therefore suggested changes in the scale. We used the scale in such a way that each participant performed all tasks. Each successful task was awarded 1 point, giving a range of scores from 0-18.

3.4.4   Modified Ashworth Scale (Studies I-III)

The Modified Ashworth Scale is probably the most common rating scale for spasticity. With this instrument, the rater rapidly stretches the participant's muscles by moving (for example) the wrist in flexion or extension. The scale has six ordered steps ranging from 0: "no increase in muscle tone" to 4: "affected part(s) rigid in flexion or extension". In this thesis, the participants were tested in a sitting position. (Bohannon & Smith, 1987). The validity of the scale has been questioned (Fleuren et al., 2010),

but we chose to use it anyway due to a lack of other options. The main purpose was to compare the MAS ratings with the components of passive movement resistance (NC, EC, and VC).

3.4.5 Sensory function (Study I)

Sensory functions light touch and the ability to distinguish between dull and sharp was assessed according to Fugl-Meyer on a ordinal scale: 0, 1, and 2, where 2 is normal sensation and 0 is no sensation (Fugl-Meyer et al., 1975).

3.4.6 Grip strength (Studies I-IV)

Two aspects of grip strength were used to describe the level of upper limb impairment, namely maximal grip strength and grip strength ratio (Grip%). The latter of these is calculated as [(grip strength$_{imp}$ / grip strength$_{unimp}$)*100]. In Study I the Grippit digital hand dynamometer was used (AB Detektor, Göteborg, Sweden), and in Studies II-IV the Jamar analogue hand dynamometer was used (Jamar hand grip dynamometer, Sammons-Preston, Bolingbrook, Ill, USA) (Hammer & Lindmark, 2003; Trutschnigg et al., 2008). Verbal encouragement was given, and the best of three attempts was used in the final analyses.

3.4.7 Passive range of movement (Studies I-IV)

Passive range of movement was primarily measured to avoid discomfort or injury to muscle or connective tissue during measurement of passive movement resistance both with the custom-built device and the NeuroFlexor. This is the reason why the exclusion criteria were set to 40 degrees (Studies I-III) and 30 degrees (Study IV). Wrist extension with the fingers extended was measured using a 18 cm plastic goniometer according to Clarkson (Clarkson, 2000).

3.4.8 Box and Block Test (Studies I and IV)

The Box and Block Test was used to assess manual dexterity (Mathiowetz et al., 1985; Platz et al., 2005). This test counts the number of wooden blocks (2.5 x 2.5 x 2.5 cm) that can be transported from one compartment of a box to another over a partition within 1 minute. In Study IV a dichotomous variable was created: ability to move at least one block (yes or no). This variable was used in the ordinal regression model as a proxy for ability to perform voluntary movements in the upper limb.

3.4.9 ABILHAND (Study III)

The ABILHAND questionnaire was used to assess manual ability as perceived by the participant (Penta et al., 2001). Each participant's own opinion on how difficult they found it to perform an activity was scored for 23 items on a three-point ordinal scale: easy, difficult, or impossible. The option "do not know" was marked when no other option was applicable. The score on the 23 items was converted into a linear measure of manual ability through online Rasch measurement model analysis, giving a score between approximately -3.5 and 3.5 logits (www.rehabscales.org).

3.4.10 Adult/ adolescent version of the Assisting Hand Assessment for stroke (Study IV)

The adult/adolescent Assisting Hand Assessment for Stroke (Ad-AHA Stroke) was used to assess bimanual performance (Swedish version 1.0) (Krumlinde-Sundholm & Hoare 2013). The Ad-AHA is a criterion-referenced test for use with adolescents and adults who have unilateral upper limb impairment following a stroke. It aims to measure how effectively a person uses the affected hand in a bimanual activity. The Ad-AHA is conducted by video observation of the participant during a 10-15 minute session where a task that requires both hands is performed; for example, unwrapping a gift box tied with string, opening an envelope containing a greeting card, and then wrapping up the gift again. The task requires a number of actions important for bimanual performance, such as stabilizing, reaching, holding, releasing, and coordinating. A total of 19 items defining different actions are scored on a 4-point scale rating the quality of the performance. The Ad-AHA Stroke was developed by use of Rasch measurement model analysis that converts ordinal level data to a continuous measure, giving a range between 0 (low ability) and 100 AHA units (high ability).

3.4.11 Two-point discrimination (Study IV)

The finger pulp of finger III was tested using a metal paper clip with a distance of 7 mm between the prongs, according to the method described by Krumlinde-Sundholm & Eliasson (Krumlinde-Sundholm & Eliasson, 2002). Being able to discriminate two stimuli 7 mm apart is considered as important for fine motor function. The participant passed the test if five correct answers were given consecutively.

Table VII. Summary of the different assessments of body functions, activity capacity, and performance used in the four studies.

Assessment	Study I	Study II	Study III	Study IV
PMR	X*	X**	X**	X**
sEMG	X			
UL-MAS	X			
MAS	X	X	X	X
Sensory function (dull/sharp or light touch)	X			
Grip strength	X	X	X	X
PROM	X	X	X	X
BB test	X			X
ABILHAND			X	
Ad-AHA Stroke				X
2PD (7 mm)				X

PMR: passive movement resistance, sEMG: surface electromyography, UL-MAS: upper limb subscale of the Motor Assessment Scale, PROM: passive range of movement, BB test: Box and Block Test, Ad-AHA Stroke: Adult/adolescent version of the Assistion Hand Assessment for stroke, 2PD: two point discrimination.
*Custom-built device, **NeuroFlexor

3.5 STATISTICS

A summary of the statistical methods used in this thesis is shown in Table VIII. A detailed description of the different methods in the four studies is given below.

Table VIII. Summary of the statistical methods used in the four studies in this thesis.

Statistical method	Study I	Study II	Study III	Study IV
Descriptive statistics	X	X	X	X
Friedman's ANOVA	X		X	
Wilcoxon's matched pairs test	X		X	
Mann-Whitney U test	X			
Spearman's rank order correlation	X		X	X
Repeated measures ANOVA		X	X	
Intraclass correlation (ICC)		X		
Shapiro-Wilk test		X		
Coefficient of variation CV%		X		
Repeatability		X	X	
Pared t-test			X	
Pearson's correlation			X	
Ordinal logistic regression				X

3.5.1 Study I: data analysis and statistics

The validity of the different components of passive movement resistance (NC, EC and VC) was assessed using different statistical methods. Correlation analysis was performed using the Spearman's rho to explore the relationship between the components and iEMG and MAS score. The velocity-dependence of the components was explored using Friedman's ANOVA with post hoc analysis performed using Wilcoxon's matched pairs test. The effect of the ischemic nerve block on NC, EC and VC, was also explored using Friedman's ANOVA and Wilcoxon's matched pairs test.

3.5.2 Study II: data analysis and statistics

In Study II it became apparent that the variation between test and retest was higher for participants with a high resistance to passive movement compared to those with low resistance. The problem with heteroscedasticity was solved by logarithmic transformation, and the transformed values were used in the reliability and measurement error analyses. To assess reliability, a two-way random effects model single measure was used to generate an intraclass correlation coefficient model 2.1 ($ICC_{2,1}$) (Shrout & Fleiss, 1979). This model assumes that the variance generated by both the rater and the participant is random.

The measurement error was estimated on a group level using the coefficient of variation (CV%) and on the individual level by calculating the repeatability coefficient (*r*) (Bland & Altman, 1997). The coefficient of variation is expressed as per cent and was calculated according to Formula 8 where *e* is the base of the natural logarithm and SDw is the mean square error term from a RM-ANOVA.

Formula 8. Coefficient of variation

$$CV\% = (e^{SDw} - 1) \times 100$$

The repeatability coefficient is the analogue to the Smallest real difference described by Lexell & Downham (Lexell & Downham, 2005), and was calculated according to Formula 9. This formula is the equivalent to Formula 1 with the difference that Formula 9 uses log-transformed data; SEM $= e^{SDw}$ and $\sqrt{2} \times 1.96 \approx 2.77$.

Formula 9. Repeatability coefficient

$$r = (e^{SDw})^{2.77}$$

3.5.3 Study III: data analysis and statistics

Sensitivity to change was explored in two ways. First we counted the number of participants that had a change in NC greater than the measurement error. We also calculated if the change was greater than the measurement error using the repeatability coefficient from Study II. The repeatability coefficient can be used to calculate a 95% CI around an observed measure, and then, for example, a post-intervention repeated measure which falls outside this CI can be regarded as "real"; that is, greater than the measurement error.

The upper and lower limits of the CI was calculated according to Formula 10 where X_0 is the observed baseline value and *k* is a constant unique for the three components NC, EC and VC respectively. The *k* values derived from Study II were $k_{NC} = 3$, $k_{EC} = 1$ and $k_{VC} = 1$.

Formula 10. Upper and lower limits of the smallest real difference

$$Upper\ limit = r(X_0 + k) - k$$

$$Lower\ limit = \left(\frac{X_0 - k}{r}\right) - k$$

In this study we also explored the associations between the difference in NC between baseline and 4 weeks after treatment and change in clinical tests regarding PROM, perceived manual ability (ABILHAND) and maximal grip strength using Spearman's rank order correlation.

3.5.4 Study IV: data analysis and statistics

In this study we explored the association between spasticity and unimanual upper limb function and unimanual and bimanual activity. Univariate correlation was explored

using Spearman's rank order correlations. For multivariate analysis, an ordinal logistic regression was used to explore the impact of spasticity on assisting hand functioning in relation to other measures of upper limb function and activity.

3.5.5 Interpretation of correlation coefficients

In all the studies in this thesis, a general interpretation of the correlation coefficient was made according to Taylor: ≤ 0.35 was considered a weak correlation, 0.36 to 0.67 moderate, and 0.68 to 1.0 strong (Taylor, 1990). The ICC was interpreted according to the guidelines given by Currier: 0.90–0.99 was considered to indicate high reliability, 0.80–0.89 to indicate good reliability, 0.70–0.79 to indicate fair reliability, and ≤ 0.69 to indicate poor reliability (Currier, 1990).

3.5.6 Statistical software

In Study I, the data were analysed using STATISTICA 7.0 for Windows (StatSoft Scandinavia AB, Klostergatan, Uppsala, Sweden), while in Studies II-IV, version 19.0 of IBM SPSS Statistics was used (Armonk, NY: IBM Corp).
All statistical tests were two-tailed, and the overall significance level was set to $p < .05$.

3.6 ETHICAL CONSIDERATIONS

The regional ethical review board in Stockholm approved all studies in this thesis and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

4 SUMMARY OF RESULTS

4.1 STUDY I

The aim of Study I was to investigate the validity of a model for quantification of neural (spasticity) and non-neural components of the resistance when the wrist and finger muscles are passively extended. The model defines neural, elastic, and viscous components of the passive resistance.

Evidence of validity was revealed in three ways. Firstly, the NC was significantly reduced when the stretch reflex was blocked during an ischemic nerve block, while the non-neural components remained unchanged. This is clearly in agreement with Lance's definition of spasticity (Lance, 1980). This finding was the strongest evidence that the NC reflects the stretch-reflex-mediated resistance during passive muscle stretch. Figure 6 shows a summary of the results from the nerve block test. Secondly, the NC both correlated with the integrated EMG and showed velocity dependence across the different movement velocities. Again, the correlation with EMG and velocity dependence was not present for either the EC or VC. Thirdly, the NC correlated moderately with the clinical Modified Ashworth Score.

In conclusion, strong evidence of validity for the NC was presented in this study, suggesting that it is possible to objectively quantify wrist and finger spasticity in a non-invasive way which is usable in a clinical setting.
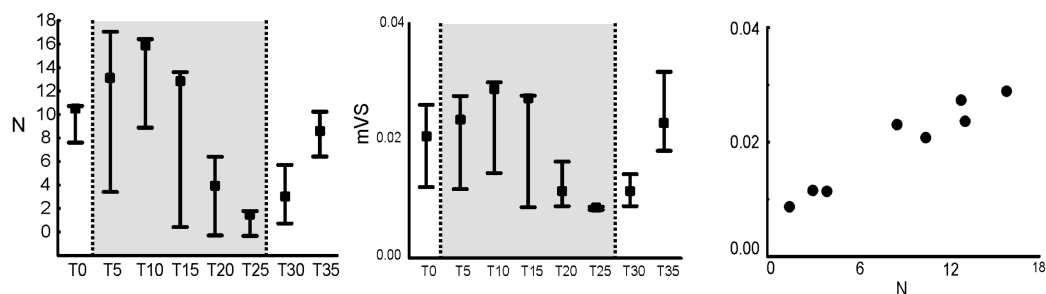

Figure 6. Results from the nerve block test. The grey shaded area represents the time when the blood pressure cuff was inflated. The first graph from the left shows the neural component (i.e. spasticity), and the second shows the integrated surface EMG. The third graph shows a scatterplot of the association between the neural component (x axis) and the integrated EMG (y axis). Each dot represents the time points T0 to T35. *Spearman's rho =* 0.86, *p* = .007.

4.2 STUDY II

In Study II, the model tested in Study I was applied in a measurement instrument, the NeuroFlexor. The aim of this study was to explore the reliability of the measurements and establish the smallest real difference.

The results showed high reliability for the NC both within and between raters, with ICCs > .90. Slightly lower reliability was found for the EC and VC components. The smallest real difference was also established for all the components on an individual level (repeatability coefficient). On a group level, the variability between measurements was reported as the coefficient of variation. The coefficient of variation (CV%) is an

estimate of the between-measurement variations on a group level. The CV% for the NC was up to 32% which, although high, is in line with other measures such as instrumented tendon taps (Dimitrijević & Nathan, 1973; Stam & Tan, 1987).

On an individual level, the repeatability coefficient (*r*) enables the possibility of calculating a 95% CI around an observed baseline value. A repeated measure which falls outside this CI can be regarded as "real"; that is, greater than the measurement error. Table IX shows the upper and lower limits for a wide range of possible observed values for the three components.

In conclusion, we found high reliability of the NeuroFlexor measurement, and established a smallest real difference which can be used to evaluate anti-spasticity treatments.

Table IX. Smallest real difference based on the repeatability coefficient (r). Upper and lower limits are given for a 95% CI showing the expected variation around an observed value. These limits can be used to measure changes in the components over time, and establish whether the changes are greater than the measurement error.

	Observed value (N)	Lower bound (N)	Upper bound (N)
NC	5	1.5	11.4
	10	4.2	20.4
	15	7.0	29.3
	20	9.8	38.3
	25	12.6	47.3
	30	15.4	56.3
	35	18.1	65.3
	40	20.9	74.3
	45	23.7	83.3
	50	26.5	92.2
	55	29.3	101.2
	60	32.1	110.2
EC	2	0.6	4.7
	4	1.6	8.5
	6	2.7	12.3
	8	3.7	16.1
	10	4.8	19.9
	12	5.9	23.7
	14	6.9	27.5
	16	8.0	31.2
	18	9.0	35.0
	20	10.1	38.8
	22	11.1	42.6
	24	12.2	46.4
VC	1	0.4	1.8
	1.5	0.8	2.5
	2	1.1	3.2
	2.5	1.5	3.9
	3	1.8	4.6
	3.5	2.2	5.3
	4	2.6	6.0
	4.5	2.9	6.7
	5	3.3	7.4

N: Newton, NC: neural component, EC: elastic component, VC: viscous component. Mean r of raters A and B was used to calculate the lower and upper bounds:
$r_{NC}= 1.798$, $r_{EC}= 1.897$, and $r_{VC}= 1.404$.

4.3 STUDY III

The aim of Study III was to explore the sensitivity of the NeuroFlexor measurements and to investigate whether the smallest real difference established in Study II is useful in a clinical setting. We followed a group of 24 adult stroke patients given individual doses of botulinum toxin in wrist and finger muscles. Doses ranged from 15 to 210 units of Botox®, dependent on the clinical indication. On a group level, there was a significant difference at 4 weeks after treatment, when the maximal effect of the treatment was expected. Only 7 of the 24 participants had a reduction in NC greater than the smallest real difference. These individuals had been treated with a mean dose of 158 units (95% CI: 120 – 196), while the remaining 19 participants had a mean dose of 98 units (95% CI: 66 – 130). It should however be noted that 8 of the 19 had been treated with doses ≤ 70 units, which is unlikely to have an effect on spasticity (Childers et al., 2004).

All participants were also assessed with the MAS, to allow comparison with the NeuroFlexor measurements. When the smallest real difference of the MAS was set to - 1, which has become a consensus limit, 19 participants showed a real difference. It is noteworthy that the 8 patients treated with ≤ 70 units of Botox® all had -1 on the MAS. We believe this to be an indication that the MAS may overestimate the effect of anti-spasticity treatments.

We also explored whether a reduction in spasticity was associated with improved function. However, no significant differences were found regarding wrist passive range of movement, maximal grip strength, and self-rated manual ability (ABILHAND) before and 4 weeks after treatment.

In conclusion, this study shows that the NeuroFlexor is sensitive enough to monitor changes on a group level after treatment with botulinum toxin. On an individual level, the NeuroFlexor is sensitive to change if higher doses of botulinum toxin are given. There is a need for studies involving more advanced laboratory measurements, to allow exploration of whether the smallest real differences of the NeuroFlexor measurements are clinically adequate.

4.4 STUDY IV

The first aim of Study IV was to explore the association between spasticity measured with the NeuroFlexor and other outcomes of upper limb body functions such as range of movement, grip strength, and sensory impairments as well as activity level outcome measures. The second aim was to evaluate the strength of the association between spasticity and the ability to use the affected hand in bimanual activities in relation to other measures of upper limb function and activity.

The participants comprised 26 persons with chronic stroke and moderate to severely impaired upper limb body functions. There was a moderate correlation between spasticity and passive range of movement, but no correlation between spasticity and any of the other measures of upper limb body functions. On the activity level, spasticity was moderately correlated to the Box and Block Test and the Ad-AHA Stroke. The results from the multivariate analysis showed that spasticity, grip strength, and passive range of movement did not contribute to the regression model predicting the ability to use the affected hand in bimanual activities. The final model included sensation (2PD) and the ability to move one block; these two variables together explained 42.6% of the

variance. The model showed that the likelihood of a moderate assisting hand (rather than poor) is 11 times higher if the person has some sensation and 12 times higher if the person is able to move one block.

In conclusion, although spasticity was associated with reduced passive range of movement and with measures of gross motor ability and bimanual performance, it was subordinate to having sensation and being able to move a small object in predicting the ability to use the affected hand as an assisting hand in bimanual activities.

5 DISCUSSION

This thesis describes a new method for objective and separate quantification of spasticity and passive muscle resistance in wrist and finger flexor muscles. The method was implemented in a measurement instrument, the NeuroFlexor and the results from the studies show that the method can be used in persons with spasticity resulting from stroke or traumatic brain injury. In the following sections the results from the individual studies will be discussed with focus on the evidence of validity, reliability and sensitivity to change.

5.1 CURRENT EVIDENCE OF VALIDITY

Validity refers to "the degree to which evidence and theory support the interpretations of test scores entailed by the proposed uses of tests" (Standards, 1999). With regards to the NeuroFlexor measurements this means that the different components of the passive movement resistance actually measure what they are intended to. Validation is a dynamic and a continuous process in a world where new knowledge is constantly emerging. The section "current evidence of validity" is intended to reflect this fact and it is recognised and acknowledged that what we know today may be either verified or falsified in the future. In particular, this may be true regarding both the neural and viscous component which are dependent on theoretical assumptions rather than solid known facts.

5.1.1 Elastic component (EC)

In the biomechanical model described in this thesis, the elastic resistance is recorded in a static position after the muscle has been slowly stretched. The EC is defined as a static resisting force at a given joint angle. It captures the static length-dependent resistance produced by several structures and mechanisms including (i) stretching stabile cross-links between the actin and myosin filaments (series elastic components), (ii) stretching non-contractile proteins within and around the sarcomeres (series elastic components) and (iii) deformation of the connective tissues located within and surrounding the muscle belly (parallel elastic component) (Gajdosik, 2001).

There may be some confusion regarding the terminology and it should therefore be pointed out that the EC is not the equivalent of elastic stiffness. Elastic stiffness is defined as the ratio of the change in the passive resistance (ΔF) to the change in the length displacement (ΔL) or $\Delta F/\Delta L$ (Gajdosik, 2001). This is difficult to measure in vivo since muscle fibres may not be aligned with the direction of the muscle stretch. Consequently, the muscle fibre length may not be directly proportional to joint angle displacement.
The term viscoelasticity is also often used to describe the properties of passive movement resistance. This term refers to a combination of elastic and viscous properties of the tissue being stretched and since viscosity is dependent on the rate of change, viscoelasticity is only captured during a dynamic stretch. See further discussion on muscle viscosity below in section 5.1.2.

Validity of the EC is based on several sources of evidence as shown in Table IV. The EC is recorded in the static stretched muscle and as stated above, it is assumed to be a length-dependent force produced by the elastic properties of the muscle and connective tissue. This assumption was not possible to verify statistically. Instead we performed visual inspection of the force trajectories recorded by the system during the slow passive movement in Study I. We saw a constant even increase in passive movement resistance in the absence of EMG above threshold throughout the range of movement, indicating that the elastic resistance was indeed captured in the EC. In the same study we also performed an ischemic nerve block test where measurements were performed every five minutes after a blood pressure cuff on the upper arm of the participant was inflated. Total time with the cuff inflated was 25 minutes. The results from this experiment showed that the EC did not change during the nerve block, indicating that it is independent of the stretch reflex. Similar results were also found in Study III where measurements were performed before and at expected maximum effect of intramuscular injections with Botulinum toxin type A. Furthermore, throughout the studies we have found strong positive correlations between the EC and passive range of movement, for example in Study IV: $r_s = .67 \ p < .01$. Based on the findings from the studies included in this thesis, there is reason to believe that there is a good amount of evidence supporting that the EC is an estimation of the passive elastic resistance of the muscle.

In the future it would be interesting to investigate the relationship between the EC and findings from analyses of muscle biopsies. As introduced earlier in section 1.7 there are a number of changes occurring in the paretic muscle and connective tissue after brain injury. It would be especially interesting to correlate the EC with the amount of collagen within and surrounding and the muscle fibres. Others have found that there is an overall increase in the ratio of collagen to muscle-fibre tissue in the muscle (Gracies, 2005). Collagen is a major component of the extracellular matrix and is a likely candidate for increased passive resistance when extending the muscle.

5.1.2 Viscous component (VC)

Viscosity is in this thesis defined as a velocity dependent resistance to passive movement/stretch, which is not caused by neural activity. Normally viscosity works as a damper on movements and is often described as a dashpot or a hydraulic piston in the biomechanical literature (Gajdosik, 2001; Lindberg et al., 2011). Although the exact mechanism is unknown it is believed that the passive viscous resistance is developed by friction between, for example, myosin and actin filaments or between the muscle-tendon unit and the surrounding tissue (Gajdosik, 2001; Ranatunga, 2001). Ranatunga et al. provided some evidence for this when they showed that by chemical compression of the filaments and thereby increasing the friction, the viscous resistance but not the elastic resistance was increased (Ranatunga, 2001).

In the biomechanical model described in this thesis, viscosity is estimated as a fraction of the initial viscosity during the acceleration phase. As described in Formula 6: $VC = (P1 - IC) \times 0.20$ where P1 is the highest amplitude during the acceleration phase and $IC = m \times a$, where m is the mass of the hand and a is the rate of acceleration. This means that the VC is dependent on a number of partly unknown factors. These

are: (i) the exact mass of the hand, (ii) the exact rate of acceleration, (iii) the exact fraction of $P1 - IC$, and (iv) the exact position of the centre of mass of the hand in relation to the force sensor.

Measuring the mass of the hand could in practice be performed using the Archimedes' principle. By lowering the hand into water and measuring the volume of the displaced water, the mass of the hand could be quantified. This would, however, not be feasible in a clinical setting and this option was therefore not considered. In theory, mass of the hand could also be measured using the NeuroFlexor device. We did not find this an attractive solution since it would be very difficult to find a position where the muscles of the hand are totally relaxed so that an accurate measure can be obtained. Since measuring the mass of the hand is a quite complicated matted, this was estimated as 0.6% of the total body weight based on results from anthropometric studies since measuring the mass of the hand is a quite complicated matter (Winters & Stark, 1985). We rely here on the literature, which is based on healthy non-impaired individuals, but are aware that small individual deviances from the standard may occur.

The rate of acceleration of the hand was determined in a series of experiments by using an accelerometer on the NeuroFlexor hand platform. These recordings may differ somewhat from the acceleration of the hand. When the hand is accelerating, the soft tissue is compressed and the distance between the hand and the hand platform is reduced. If the hand is oedematous, or if the hand is not in full contact with the surface of the platform, the acceleration may be different from a normal hand. Furthermore, if the passive movement resistance is very high, the acceleration of the step motor itself may also be slightly different from when measuring the normal hand. This has not been explored in this thesis but needs further studies.

The fraction of the initial viscosity forming the VC was determined from force recordings from nine control subjects who had no visible EMG response, suggesting that they had no or very little muscle activity induced by the stretch. In these subjects, the mean relationship between the viscosity at the end of the movement and the initial viscosity was 25% at 71°/s, 22% at 142°/s, and 17% at 236°/s. We therefore determined that our model should approximate the late viscosity at P2, to be 20% (Halaki et al., 2006; Lindberg et al., 2011). The small sample size and the fact that the participants were non-impaired may be a threat to the validity of the VC and further studies are warranted to verify the findings.

There are two major factors related to the position that may result in erroneous measurements. The first is the alignment of the rotational axis of the wrist joint in relation to the axis of the NeuroFlexor device. Even small deviations may affect the measurements and thereby reduce reliability. For example in in Study I we saw that a displacement of the centre of mass of a rectangular weight ± 1.5 cm relative to the device's rotational axis generated an error ± 0.5 N. When measuring additional errors may be introduced due to shear forces. The second factor is the position of the hand on the platform in relation to the force sensor. The placement is standardised according to the user's manual (User's Manual, Version A08, Aggero MedTech AB, Solna Sweden). Deviations from the instructions inevitably result in erroneous estimations of

the NC, EC and VC since biomechanical model assumes a certain distance from the centre of mass to the sensor.

Evidence of validity of the VC was presented in several ways in the included studies. As defined above, viscosity is velocity dependent and independent of the reflex. In Study I we showed that the VC increased with increasing movement velocity (Study I, Figure 4C). The results from both Study I and Study III also showed that while the NC was mechanically blocked or reduced after injections with Botulinum toxin, the VC did not change. We consider this indirect evidence for that the VC is being independent of the reflex. Furthermore, little is known about viscosity in spastic muscles. If if the assumptions of the mechanisms behind viscosity are true as stated above, larger and more muscle fibres should result in a higher VC. Consequently, the VC should therefore consequently be proportional to the maximal voluntary generated force. In Study I we showed that the VC was higher in the non-impaired participants with normal grip strength (Study I, Figure 4C) and in study IV we fond similar results. We reported that for the impaired participants there was a moderate positive correlation between the VC and maximal grip strength measured with a hand held dynamometer r_s = .40, p < .05. Participants with the highest VC thus showed the greatest force production.

Further research regarding the VC is warranted to refine the biomechanical model. Over- or under-estimation of the VC affects the estimation of NC but since the VC is generally small in relation to NC, sometimes more than 20 times smaller in persons with severe spasticity. The errors introduced by the VC may therefore be marginal. But, if the VC in the future is to be used as an independent variable, for instance as a proxy for the structural integrity of the muscle, it needs further validation. A study, using ultrasound or magnetic resonance imaging, of the relationship between the muscles cross sectional area in non-neurologically impaired persons may be one option. Another option could be finding a way of increasing the viscosity in vivo. Ranatunga et al. (Ranatunga, 2001) did this in a chemical way in vitro but one could consider mechanically compressing the muscles by means of a blood pressure cuff as in Study I.

5.1.3 Neural component (NC)

The NC is in this study defined as the resistance to passive movement caused by reflex mediated muscle contractions in accordance with Lance's definition of spasticity (Lance, 1980; Lindberg et al., 2011).
Evidence of validity was presented in three major ways: (i) by showing the association between the NC and the neural activity trough surface EMG, (ii) by modulating neural activity and thereby reducing the NC, and (iii) by showing velocity dependence of the NC.

In Study I we used surface EMG to record the reflex activity during rapid passive movements. We found a strong relationship between the NC and integrated EMG from forearm flexor muscles, which was the first line of evidence for the method. This led us on to explore what would happen if the EMG signal would be disrupted either by an ischemic nerve block (as in Study I) or by blocking the neuromuscular junction with

Botulinum toxin type A (as in Study III). The findings from both studies are quite clear with significantly reduced NC as an effect of the intervention.

In Study I the nerve block was performed using a standard blood pressure cuff inflated 30 mmHg above systolic pressure (Jaeger et al., 1982). A few of the participants already had significantly reduced sensation as a result of the brain lesion and it was therefore difficult to definitely determine whether the block was truly effective. After the cuff had been inflated 25 minutes all participants with initial sensation were no longer able to distinguish between a sharp and a dull object gently pressed against the back of the hand. This was in line with the findings by Jaeger et al. (Jaeger et al., 1982). There are more effective ways of blocking the nerve signalling. A nerve block using local anaesthetics would probably have been more effectively produced we found the non-invasive method more feasible and with less discomfort for the participant. Despite the methodological considerations, the results from the ischemic nerve block produced a significant reduction in both NC and EMG which we consider the as the strongest evidence of validity of the NC (see Figure 6).

The effect of Botulinum toxin type A (BoNT-A) per se is undisputed (Wissel et al., 2009) and the injections were all done by highly experienced physicians. We believe that this justifies the use of BoNT-A to explore sensitivity to change of the NeuroFlexor. There is, however, a very small number (less than 1 %) of persons who have antibodies towards BoNT-A, and this will remove the effect of the drug (Naumann et al., 2010). Furthermore, there is a possibility that the muscles causing the highest resistance to passive movement were not injected thus leaving NC unchanged despite high doses of BoNT-A. Finally, in Study III the participants received treatment according to their individual plan. This resulted in a wide variety in BoNT-A dose making the interpretation of the results from the sensitivity analysis more difficult than if all were given the same treatment. All these factors could lead to a threat to the validity of the NC by confusing the analysis. Nevertheless, in Study III, on a group level the NC was significantly reduced when BoNT-A was assumed to have maximum effect and we were also able to show a dose-dependent relationship where the larger dose generally gave a greater reduction in NC.

Further evidence of validity of the NC was shown in Study I by demonstrating velocity dependence ((Lindberg et al., 2011).

The overall aim of this thesis was to develop an objective measure of spasticity. When comparing the NC, the total resistance at the end of the fast movement in the device and the wrist flexor score on the MAS, we found a strong correlation between the NC and MAS as well as the total force and MAS $r_s > .06\ p < .001$. The correlation was, however, stronger between the total force and the MAS, indicating that MAS is indeed a measure of passive movement resistance rather than spasticity. We therefore consider these findings in favour of the evidence of validity of the NC.

Electromyography was used in Study I but not in the subsequent studies since there was evidence that the NC captured similar information. We however suggest that further experiments are performed in the future using the NeuroFlexor together with EMG to confirm previous findings.

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5.2 CURRENT EVIDENCE OF RELIABILITY

In Study II we explored the reliability of the NeuroFlexor measurements. The results showed very high intraclass correlation coefficients (ICC) for the NC and slightly lower for the EC and VC. This was found both for reliability between tests with the same person performing the measurements (test-retest) and between different persons performing the measurement (interrater). The ICC gives an indication of the reliability of the measurement but it does not give any information on the magnitude of the absolute measurement error. This is information that is required when one is studying the effect of an intervention or following the development of a symptom over time. Therefore we also calculated the repeatability coefficient (r) and the error band around a measured baseline value, see Table IX.

There are two main methodological issues that may affect reliability in this case. These are the time between the measurements and the training of the persons performing the measurements. In Study I we primarily wanted to explore the reliability of the NeuroFlexor measurements. It is known that spasticity fluctuates over time (Sköld, 2000), therefore the time between each measurement was short, that is, ≤10 minutes A longer interval between the different measurements may have resulted in a different ICC and repeatability coefficient. Training of the person performing the measurements may also affect the reliability of a measure. It is likely that a more highly trained person would induce less error related to the specific method.
Further evidence of reliability is warranted in the future. Studies with several weeks between the measurements would better correspond to clinical evaluations before and after an intervention. Studies including persons with different levels of training would also give information on the need of education and written instructions.

5.3 CURRENT EVIDENCE OF SENSITIVITY TO CHANGE

Reliability and sensitivity to change are closely related. Sensitivity of a measure may be defined as the ability to detect any change. This is not enough for a measure designed to measure changes as a result of an intervention since a "real" change must be separated from the measurement error. We therefore used the repeatability coefficient from Study II and applied it on the baseline measures in Study III, where a group of patients with spasticity were treated with intramuscular injections of Botulinum toxin. In this sample, 7 of the 26 participants had a change in NC greater than the measurement error. This may seem like a low sensitivity to change but the result is affected by the fact that the participants did not receive the same treatment dose and different muscles in the forearm were injected. The study is exploratory and although there is some evidence that the NeuroFlexor is sufficiently sensitive to detect change on an individual level, further studies are needed. It is also important to evaluate whether a change greater than the measurement error is clinically significant. Important information could be derived from a randomised controlled study design with a standardised treatment with a active substance known to reduce spasticity. Optimally, both the NeuroFlexor and EMG would be used to evaluate spasticity. This would give the possibility to explore if the active group would have more participants with a change greater than the measurement error. It would also show whether a change in NC would correspond to a change in EMG. Determining if a change is clinically significant

is the most difficult to evaluate since there are no established limits by a gold standard and the experience of spasticity is highly subjective. This has to be established systematically on a long-term basis through a large number of studies including both objective measurements and subjective ratings of patients, caregivers and medical staff.

5.4 SPASTICITY AND FUNCTIONING

The association between spasticity and functioning has for a long time been a matter of debate (Ada et al., 2006; Kamper et al., 2006). In Study IV we tried to add some knowledge by exploring the impact on spasticity measured with the NeuroFlexor in persons with very poor motor function. In this sample the NC had stronger associations with measures of activity than with motor function. We chose to measure functions commonly reported in other studies, such as grip strength, passive range of movement, two point discrimination and the Box and Block Test. All of these assessments apart from the Box and Block Test proved appropriate in this study. The Box and Block Test was, however, too difficult for the majority of the participants and there was an obvious floor effect. We therefore had reduced the test to a dichotomous variable of the ability to grasp, that is: can/cannot.

In this study we also used a completely new instrument, the adult/ adolescent version of the Assisting Hand Assessment (AHA). It was used to assess the use of the affected hand in bimanual activity (see section 3.4.10 for detailed information on the instrument). The AHA was originally developed for children with unilateral disability such as hemiplegic cerebral palsy or obstetric brachial plexus palsy but has recently been adapted for adults with stroke (Ad-AHA Stroke) (Krumlinde-Sundholm & Hoare, 2013). Study IV was the first time that the Ad-AHA Stroke was used in a scientific study and we found that although the participants had very poor hand function there was no severe floor effect in the instrument. The correlation between Ad-AHA Stroke and NC was moderate, $r_s = .40 \, p < .05$. When we, in a multivariate analyis, we explored what factors affected the ability to perform activities spasticity did not contribute significantly. Instead, having sensation and being able to grasp was more important. These findings are in line with previous studies showing week associations between spasticity and functioning (Shaw et al., 2011).

The generalizability of our study is limited and cannot be directly applied to any other group than one similar to the participants of this study. Therefore, the aim is to continue data collection including a great number of participants with a wide range of functioning. This would then generate results that could be applied to a majority of the population of persons with stroke.

5.5 METHODOLOGICAL CONSIDERATIONS

A subject that has not been discussed above is the measurement error caused by the mechanical properties of the NeuroFlexor. The force sensor is placed on the moving arm of the NeuroFlexor and the hand platform is resting on top of the sensor. This means that the system is not rigid and oscillating movements occur. This may produce a systematic error and although the muscles in the forearm acts as a damper the frequency of the oscillations are dependent on the mechanical properties of the device.

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These oscillations may interfere with the recording of the force at P2. If the oscillations cause lowered amplitude of the P2, this becomes evident in the estimation of NC. In persons with low resistance to passive movement there is a risk that the NC becomes negative. This points at one weakness of the NeuroFlexor system, as negative NC cannot exist. There are at least three options how this problem could be dealt with. One is to optimise the mechanics of the device to reduce the oscillations; another is to mathematically compensate for the oscillations within the software. A third way is to add a constant P2 offset that would avoid negative NC values. This last option together with improving the mechanics appears the most attractive since it does not change the raw signal. Further exploration of these options is planned in close collaboration with experts in biomechanics and construction.

Sample size is often a problem in scientific studies. This is especially true for the Studies III and IV. A larger sample size in Study III would have increased the power of the results and, for example, have allowed analysis dependent on which muscles that were injected and the given dose. In Study IV a larger sample size with a wider spectrum of functioning would perhaps have allowed including more explanatory variables in the regression and perhaps also the use of parametric statistics such as linear regression. This could improve the sensitivity of the analysis by increasing power and also result in findings that are less complicated and that we might be able to interpret and to generalize.

With regards to data analaysis, alternative statistical methods could have been emplyed, In some cases we used less conventional statistical methods, for example in Study II, where the data were log transformed as we found it more suitable to the raw data; however, resulting data are more difficult to interpret than those resulting from applying more conventional statistical methods. In order to capture trends in the results, we did not correct for multiple comparisons in Study IV, being aware that the type II error would be increased.

5.6 DECLARATION OF CONFLICT OF INTEREST

The biomechanical model which is used in the NeuroFlexor is patented (WO/2008/121067) and the patent is owned by the manufacturer Aggero MedTech AB, www.aggeromedtech.com.
Johan Gäverth and co-authors Påvel Lindberg and Anders Fagergren own as shareholders parts of the commercial rights in Aggero Medtech AB.

6 CLINICAL IMPLICATIONS AND FUTURE RESEARCH PERSPECTIVES

The NeuroFlexor instrument was designed to be able to quantify the different components of the passive movement resistance with special emphasis on spasticity. The studies included in this thesis show that this aim has been accomplished to a large extent, and that the method can be used research. However, by no means is the development process finished. This concerns both technical improvements as well as adjustments in the biomechanical model. Also, as discussed above, regarding evidence of validity further studies are needed.

The method is designed for adults with spasticity after stroke or traumatic brain injury. Being able to use the method in children with small hands and in individuals with other diagnoses for example, cerebral palsy, multiple sclerosis, or spinal cord injury would be a desired development. Being able to measure in the lower extremity would also be a useful application of the NeuroFlexor.

The availability of the NeuroFlexor is limited. Currently, the method is only for research purposes and is not commercially available. The CE-marking process for approval to use the NeuoFlexor in a clinical setting is in progress.

The NeuroFlexor method has, in our opinion, the potential to compete with the Modified Ashworth Scale at least in a research setting. This, however, requires that the method is accepted and embraced by the scientific community, and there is some competition in the area with several groups working on similar research questions. Regardless of what the future brings, I believe that this work has added new knowledge about spasticity which is one of the pieces in the big puzzle that in the future will show the full picture.

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