Quantitative evaluation of spasticity

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2010

Contents

Preface

This PhD thesis is based on work carried out since 2007 at the Departments of Neuroscience and Pharmacology and of Exercise and Sport Sciences, University of Copenhagen and at the Department of Physiotherapy, Hvidovre Hospital and Department of Neurorehabilitation TBI UNIT, Copenhagen University Hospital, Glostrup.

It is based on four experimental studies, two of which have been published and two have been submitted to peer–reviewed journals. Throughout the thesis, the studies are referred to by the Roman numerals I-IV. The experimental work of Study I was carried out at the Department of Neuroscience and Pharmacology, University of Copenhagen, while parts of Studies II-IV were carried out at:

- University Hospital Hvidovre, Copenhagen
- Clinic for Spinal Cord Injury, University Hospital Rigshospitalet Copenhagen
- The Multiple Sclerosis Hospital in Haslev, Denmark
- Department of Biomedical Engineering, University of Alberta, Edmonton, Canada
- Service de Réadaptation Polyvalente, Pitié-Salpêtrière Hospital, Paris, France.

This thesis contains an introduction to the field of spasticity, including a description of spasticity and the neurophysiological mechanisms involved. It also discusses the importance of the quantification of spasticity and describes some means of quantification. The results and conclusions from the four studies are presented in a separate chapter. Details of methods and statistics can be found at the end of this thesis, which also includes the complete versions of the published and submitted papers.

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Acknowledgements

I wish to thank the participating patients and their relatives for their contributions to this work, but also for being the strongest motivators of all for me to continue in this research field.

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My thanks finally go to my family and friends for having patience with me and for listening to me when I needed it. The deepest thank to my beloved Sara for her patience and support of me in my strong need to spend a great part of my time on research and to Louisa, Adam and Julia - you have contributed to making this thesis my greatest challenge so far, but without you and your endless love I could not have done it, and I would have had no reason to do it – Thank you!

English Summary

Spasticity is a common manifestation of a lesion of the central motor pathways that in some cases interferes with motor function and affects quality of life. Different perceptions of spasticity among clinicians and researchers have led to confusion. Based on results from basic and clinical research, the aim of the work described in this thesis was to contribute to a clearer understanding of the rationale for distinguishing between different features of spasticity and to answer some of the questions related to its quantification.

The thesis summarizes the results of four studies which aimed to investigate and quantify 1) a single spinal mechanism with relation to spasticity Post Activation Depression (PAD) that is relevant for the development of hyperexcitable reflexes in spastic individuals 2) differences in reflex excitability measured clinically and by a combined electrophysiological and biomechanical method, 3) the reliability and sensitivity of a portable biomechanical method to measure spasticity 4) changes in spasticity due to physiotherapy treatment measured by clinical and biomechanical methods.

The first part of the thesis consists of a brief historical review of relevant mechanisms involved in spasticity. This section includes the results based on Study I that focuses on measurements of PAD and the biomechanical reaction to the identified electrophysiological phenomenon. The study shows that PAD is an important factor in the evaluation of stretch reflex excitability and muscle stiffness in spasticity that plays a role in its pathophysiology.

The second part of the thesis focuses on the distinction between increased muscle stiffness caused by increased reflex activity (active stiffness) and stiffness due to arthrogenic and myogenic changes (passive stiffness). The results from Study II based on measurement by an objective electrophysiological / biomechanical method show that the reflex-evoked torque was increased in spastic individuals. However, the clinical diagnosis of spasticity includes changes in both active and passive muscle properties, and the two can hardly be distinguished by a routine clinical examination. In Study III the results showed that a hand-held stiffness measurement device correlated well with measurements obtained by an objective electrophysiological / biomechanical device, had high intra- and inter-rater reliability, and could easily distinguish between spastic and control participants, but may have some practical problems that would not make it suitable as a clinical tool in the present form.

The third part of the thesis is based on the results of Study IV. Following treatments with Neurodynamics and Random Passive Movements (RPM) no significant reduction was found in stiffness measured with the hand-held device nor reduction in the clinical spasticity score. Significant increases in Range Of Motion (ROM) and a reduction in subjectively perceived muscle tone were found. For only one parameter (ROM) difference between the two treatments was found. The clinical measurements are highly dependent on the testers' awareness of the intervention.

The results contribute to a better understanding of the involvement of a spinal mechanism (PAD) in increased resistance to passive movements due to spasticity. The difficulties in clinical distinction between active and passive stiffness were also highlighted by the results of this study. In order to improve the clinical spasticity measurement methods there is need for further development of objective biomechanical clinically applicable methods. This is necessary for evaluation of the efficacy of anti-spastic treatments.

Dansk resumé

Spasticitet er et hyppigt symptom i forbindelse med læsion i centralnervesystemet som i visse tilfælde påvirker udførelse af motoriske funktioner samt livskvalitet. Forskellige opfattelser af spasticitet blandt klinikere og forskere har medført forvirring i forbindelse med begrebet. På baggrund af resultater fra basalforskning og klinisk forskning var formålet med arbejdet i denne afhandling at bidrage til en bedre forståelse af rationalet bag at skelne mellem forskellige elementer af spasticitet, samt at svare på nogle af spørgsmålene i forbindelse med kvantificering af spasticitet.

Afhandlingen opsummerer resultaterne fra fire studier, som havde til formål at kvantificere 1) en spinal mekanisme med relation til spasticitet Post Activation Depression (PAD) som er relevant for udviklingen af hyperrefleksi hos personer med spasticitet 2) forskelle i refleksaktivitet målt klinisk og med en kombineret biomekanisk og elektrofysiologisk metode 3) reliabiliteten og sensitiviteten for en håndholdt biomekanisk metode til at måle spasticitet 4) ændringer i spasticitet efter fysioterapeutiske behandlinger med neurodynamik målt klinisk og med en biomekanisk metode.

Den første del af afhandlingen består af en kort historisk gennemgang af begrebet spasticitet samt de involverede mekanismer. Denne sektion indeholder resultaterne baseret på Studie I, som fokuserer på måling af PAD og det biomekaniske respons på dette elektrofysiologiske fænomen. Studiet viser, at PAD spiller en rolle i patofysiologien bag spasticitet og er en vigtig faktor ved evaluering af refleksaktivitet og muskelstivhed i forbindelse med spasticitet.

Den anden del af afhandlingen fokuserer på adskillelsen af forøget muskelstivhed betinget af forøget refleksaktivitet (aktiv stivhed) og stivhed betinget af strukturelle ændringer i muskler og led (passiv stivhed). Resultaterne fra studie II, som baserer sig på måling med en objektiv elektrofysiologisk / biomekanisk metode, viser at den refleksbetingede stivhed var forøget hos personer med spasticitet. Imidlertid indeholder den kliniske diagnose spasticitet både forandringer i de aktive og passive komponenter af stivhed, og en adskillelse er meget vanskelig med en rutinemæssig klinisk undersøgelse. I studie III viste resultaterne, at målingerne med en håndholdt stivhedsmåler korrelerer godt med målingerne fra en objektiv elektrofysiologisk / biomekanisk målemetode, havde høj intra- og inter-rater reliabilitet og var i stand til at skelne mellem spastiske og raske forsøgsdeltagere, men har nogle praktiske problemer, som ikke gør den anvendelig som et klinisk redskab i den nuværende form.

Den tredje del er baseret på resultaterne fra studie IV. Efter behandling med neurodynamik og Random Passive Movements fandt vi ingen reduktion i stivhed målt med den håndholdte stivhedsmåler eller med et klinisk spasticitetsevalueringsredskab (MAS). Vi fandt signifikant forøgelse af Range Of Motion og reduktion af den subjektivt evaluerede tonus, men ingen parameter viste forskel mellem effekten af de to behandlinger. De kliniske målinger var i høj grad afhængige af, hvorvidt testeren var blindet i forhold til interventionen.

Resultaterne bidrager til en bedre forståelse af involveringen af den spinale mekanisme PAD I forhold til forøget modstand mod passive bevægelser på grund af spasticitet. Problemerne med at skelne aktiv og passiv stivhed blev understreget af resultaterne indeholdt i denne afhandling. Der er behov for yderligere udvikling af objektive klinisk anvendelige målemetoder til at forbedre klinisk spasticitetsmåling. Dette er nødvendigt til at kunne evaluere effekten af antispastiske behandlinger.

Thesis at a glance

Studies	Question	Methods	Answer
I	1) Are stretch reflexes reduced by post-activation depression to the same extent as H-reflexes? 2) Are stretch reflexes and the stretch-evoked torque less depressed by post-activation depression in people with spasticity than in healthy individuals?	The stretch and H-reflex responses of 30 spastic participants (with MS and spinal cord injury (SCI)) were compared with those of 15 healthy participants.	1) H-reflexes were depressed to a larger extent than the stretch reflexes in both healthy and spastic individuals. 2) The stretch and H-reflex were decreased as the interval between stimuli and perturbations decreased. In spastic patients the PAD of both reflexes and the stretch-evoked torque were significantly smaller than in healthy individuals.
II	To what extent are passive and active components of muscle stiffness distinguished clinically?	Combined biomechanical and electrophysiological measurements to distinguish passive and active contributions to ankle joint stiffness were compared with clinical measurements in 31 healthy, 10 stroke, 30 MS and 16 SCI individuals.	Poorly - the clinical diagnosis of spasticity includes changes in both active and passive muscle properties and it is very difficult to tell the two apart in a routine clinical examination.
III	Can a portable device (Prochazka, 1997), which provides an immediate value for stiffness be reliable and sensitive in measuring ankle and knee joint stiffness in control participants and in spastic SCI participants?	Ankle and knee stiffness measurements were made twice by two raters, at speeds above and below the stretch reflex threshold in 41 uninjured and 14 spastic SCI participants. Ankle torque was measured with the portable device and a stationary torque motor. Inter- and intra-rater reliability was assessed with the intra-class correlation coefficient.	The device correlated well with measurements obtained by a torque motor, had high intra- and inter-rater reliability, and could easily distinguish between spastic and control participants. However, it may not have provided an accurate measure of knee stiffness when the leg was moved rapidly; and the shape of the air-filled pads did not provide a good interface with the leg or foot.
IV	Are the muscle tone and range of motion (ROM) changed in TBI patients with spasticity after treatments with ND when measured clinically and with a	A randomized, controlled study with crossover design was used to evaluate differences in muscle tone before and after treatments with ND and RPM in 10 TBI patients with spasticity. Tone was measured with a hand-held device and with clinical	No significant reduction in stiffness at any movement velocities or amplitudes measured with the hand-held device. No reduction in the clinical spasticity score (MAS). A significant increase in ROM and a reduction in subjectively perceived muscle tone were found. For no

	hand held device?	assessments.	parameter difference was found between the two treatments. The clinical measurements are highly dependent on the testers' awareness of the intervention.

List of publications and studies

This thesis is based on the following four papers, which are referred to by their respective Roman numerals.

Paper I

Grey MJ, Klinge K, Crone C, Lorentzen J, Biering-Sørensen F, Ravnborg M, Nielsen JB. Post-activation depression of soleus stretch reflexes in healthy and spastic humans. Exp Brain Res. 2008 Feb;185(2):189-97. Epub 2007 Oct 12.

Paper II

Lorentzen J, Grey MJ, Crone C, Mazevet D, Biering-Sørensen F, and Nielsen JB. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. Clin Neurophysiol. 2010 May 8. [Epub ahead of print]

Paper III

Lorentzen J, Grey MJ, Geertsen SS, Biering-Sørensen F, Brunton K, Gorassini M and Nielsen JB. Assessment of a portable device for the quantitative measurement of spasticity in ankle and knee. Submitted to Clinical Neurophysiology.

Paper IV

Lorentzen J, Baagoe S, Nielsen D, Holm K, Grey MJ and Nielsen JB. Neurodynamics is no different from random passive movements in reducing spasticity. Submitted to Neurorehabil Neural Repair.

List of key terms and abbreviations

Active stiffness	The force required to lengthen a muscle which is active (i.e. the slope of the active force-displacement curve).
AS	Ashworth Score
CNS	Central Nervous System
DTR	Dorsal reticulospinal tract
EMG	Electromyography
GABA	Gamma-aminobutyric acid
H-reflex	H-reflex is the electrical analogue to the mechanically induced spinal stretch reflex.
Hyperreflexia	A greater than normal reflex response (e.g. the presence of reflex response when a relaxed muscle is stretched at the speed of normal movements).
Hypertonia	A greater than normal resistance felt when moving a limb passively
MAS	Modified Ashworth Score
MS	Multiple Sclerosis
ND	Neurodynamics
Passive stiffness	The force required to lengthen a muscle at rest (i.e. the slope of the force-displacement curve).
R1	The angle at which the first muscle reaction occurred during a passive movement.
R2	The angle where further resistance or pain was registered and compensatory movements in the body were observed.
ROM	Range of Motion
RPM	Repeated Passive Movements
SCI	Spinal Cord Injury
TBI	Traumatic Brain Injury
Tone	“the sensation of resistance felt as one manipulation of a joint through a range of motion, with the subject attempting to relax” by Lance and McLoud, 1981

Introduction and Background

In many clinical fields a lack of knowledge and understanding of the fundamental physiological mechanisms of a clinical symptom has led to misunderstanding and imprecise communication among clinicians and to treatments that are not beneficial for patients. This is indeed the case for spasticity where several ways to define the term exist in the current literature even though it has been a topic of interest for clinicians and researchers for centuries (Pandyan et al., 2005).

Previous research and observations of the symptoms have contributed to our understanding of the phenomenon; however, a common definition and understanding between clinicians and researchers are still missing. The aim of this thesis is to contribute to a clearer understanding of the rationale for distinguishing between different features of spasticity and to answer some of the questions related to its quantification.

Historical background of spasticity

The first mentions of the term are from 1753 where "gout" was defined as a "spastic and painful affection" (web page 1). In 1822 the term spasticity was used as a synonym for "want of pliancy in the muscular fibres" (web page 2). The first dictionary description was of the Latin word "Spasticus" defined as "pull toward itself" (web page 3).

Physiologists have tried to describe the mechanisms behind the clinical symptom since 1841 when Marshall Hall made the first description of muscle activity that was independent of control by higher levels of the nervous system in decapitated frogs (Hall, 1841). What he saw was what we would now call reflex activity, or perhaps even rhythmical activity from the spinal cord, also called Central Pattern Generator. He described "tonus" as a "certain degree of firmness" of the muscles lost when the spinal cord is damaged. Todd differentiated between different types of stiffness,

where the so-called “early rigidity” (later called decorticate rigidity) was stiffness due to non-reflex-produced muscle contractions, and “late rigidity” was a combination of spasticity due to increase in reflexes and contractures caused by changes in the passive structures (Todd, 1855). Both elements in the “late rigidity” (stiffness due to reflex activity and contractures) were, according to Todd’s findings, gradually developing but the distinction between the two components was not demonstrated until 1880, when Brissaud used a bandage to apply ischemia of the nerves in the limb (Brissaud, 1880). This allowed him to differentiate between the elements of “late rigidity” that depended on nervous function and those due to shortening of the muscles and other structures which is now recognized as contracture. Sechenov introduced the idea that increased reflex activity was a consequence of reduced cerebral inhibition (Sechenov, 1863). Haidenhain concluded that muscle “tone” was a consequence of reflex activity depending on tension (Bubnoff and Heidenhein, 1881). Gowers (1886) associated the increase of tendon reflexes with spasticity. In the late 19th and early 20th century Sherrington defined and elaborated the spinal reflexes and overactivity in the proprioceptive input as the underlying mechanisms for decerebrate rigidity based on animal experiments (Sherrington, 1906). He used the postural reflexes as an explanation for the term “muscle tone”, but emphasized that a specification of the meaning was required every time it was used (Sherrington, 1915). Eccles was a student of Sherrington and worked in the following period with the improvements of research techniques that gave insight in the synaptic mechanisms of the spinal motorneurons (Eccles and Hoff, 1932). Spinal inhibitory mechanisms that influences the reflexes were subsequently clarified (Eccles, 1956).

Based on research by neurophysiologists and on observations from clinicians, the term spasticity was defined by Denny-Brown (1966) as:

> “a soft yielding resistance that appeared only towards the end of a passive stretch and an increased amplitude stretch reflex”.

A couple of decades later, as the result of a discussion after a conference, the definition of spasticity by Lance appeared as:

> "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron lesion" (Lance, 1980).

In 2003, the North American Task Force for Childhood Motor Disorders made an attempt to improve the precision of the above definition, and suggested that spasticity should be redefined as:

> "a velocity dependent increase in hypertonia with a catch when a threshold is exceeded" (Sanger et al., 2003).

The most recent definition is by the SPASM consortium (a European Thematic Network to Develop Standardized Measures of Spasticity), putting forward the argument that the currently used definition, that by Lance (1980), was too narrow for clinical purposes. They suggested that the definition should be widened to:

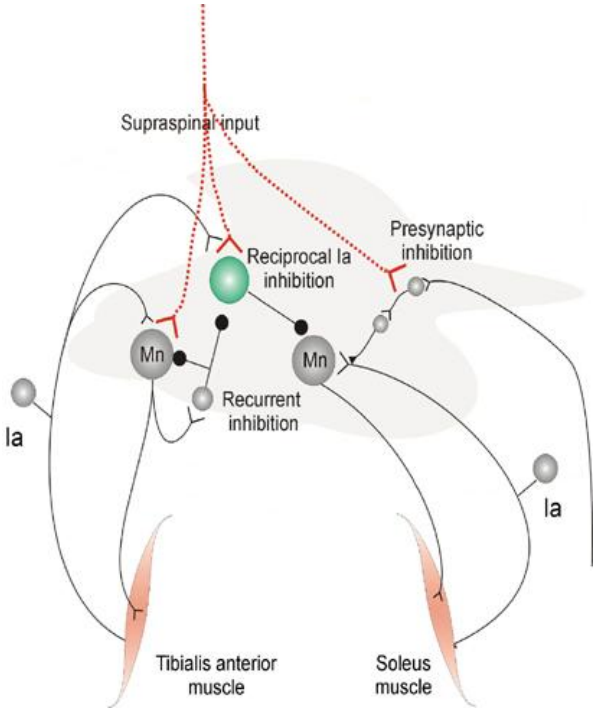
> "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles" (Pandyan et al., 2005).

There still seems to be no general agreement of a definition; a summary of the literature definitions of upper extremity spasticity showed that 31% of the references used the definition by Lance, 35% used "muscle tone", 3% used other definitions and 31% used no definition at all (Malhotra, 2009). One reason for these differences may be that there are two main approaches taken with respect to definition of spasticity. The narrow definition from Lance has not worked as well as it should since patients are being diagnosed as spastic without having increased reflexes. The definition by SPASM (Pandyan et al., 2005) takes the opposite approach, i.e. it attempts to provide a broad statement to catch all possible interpretations of the phenomenon even though different pathophysiology is behind the different symptoms. With this definition there is a risk of treating patients erroneously

because the different mechanisms involved in the pathophysiology are not taken into consideration. It is essential to distinguish between the different symptoms in the spasticity syndrome which require understanding of the pathophysiology. The only definition that makes that distinction is the one introduced by Lance.

The mechanisms behind spasticity

Our understanding of the mechanisms behind the increased reflexes (spasticity) after lesions in CNS was limited before the 1930s. However, technical improvements at that time made it possible to record EMG from individual motor units (Eccles and Hoff, 1932) and, with the introduction of monosynaptic test reflexes to assess motorneuronal excitability developed by Renshaw (1940), it became possible to measure the excitatory and inhibitory mechanisms influencing the activity in motorneurons (Renshaw, 1940, 1941). From this time until the 1960s important spinal mechanisms were identified. Two mechanisms appear to be of special interest when we discuss spasticity. Reciprocal inhibition, described by Sherrington at the end of the 19th century was, based on the new methods, more precisely described by Eccles et al. (1956) as a disynaptic inhibitory mechanism. He also described a depression of the monosynaptic reflex discharge due to presynaptic inhibition (Eccles et al., 1962). A schematic illustration of the mechanisms is shown in Fig. 1.



This figure illustrates some of the spinal mechanisms that are involved in controlling the size of the stretch reflex and which have been suggested to be involved in the pathophysiology of spasticity.

The mechanisms described were all based on experiments on animals. From the 1970s to the 1990s human studies were made to investigate the mechanisms that Eccles and others had found in cats. In healthy subjects reciprocal antagonist inhibition was found responsible for depression of activity in antagonistic muscles at the onset of and during movements (Kots and Zhukov, 1971; Tanaka, 1974; Crone, 1987, 1993; Crone and Nielsen, 1989, Crone et al.,1994; Panizza et al., 1995). Transmission in this pathway has been found to be decreased at rest in spastic patients with multiple sclerosis (Crone et al., 1994; Morita et al., 2001) and in hemiplegic patients (Artieda et al., 1991; Okuma and Lee 1996; Crone et al., 2000). Decreased reciprocal inhibition may thus be one of the pathophysiological mechanisms in spasticity, but none of these studies have been able to

demonstrate a correlation between the decrease of reciprocal inhibition and the severity of spasticity. This suggests that other mechanisms must be involved.

Other studies showed in the 1970s that vibration-induced inhibition of the monosynaptic stretch reflex was strongly reduced in spastic patients (Ashby and Verrier, 1975) and reduction in presynaptic inhibition is suggested as a mechanism that could result in increased tendon reflexes and possible spasticity (Delwaide and Pepin, 1993). Later, decreased presynaptic inhibition was demonstrated for the lower extremities in spastic MS patients (Nielsen et al., 1995) and spastic SCI patients (Faist et al., 1994) but not in spastic stroke patients (Faist et al., 1994) and in the upper extremities in spastic SCI patients (Aymard et al., 2000). Presynaptic inhibition is of special interest since knowledge of the influence of this specific mechanism on the stretch reflex activity leads to the idea that the reflex activity in spastic patients could be reduced by influencing the GABAergic transmission of the inhibitory interneuron. Diazepam was one of the first drugs used to influence the GABAergic transmission with the aim of increasing the presynaptic inhibition and thereby reducing spasticity. It was demonstrated as being effective in reducing spasticity as early as 1966 by Wilson & McKechine (1966), and later by Corbett et al. (1972). Later it was shown that, during muscle contractions in healthy people, different inhibitory mechanisms on reflexes such as reciprocal inhibition and presynaptic inhibition are removed (Nielsen et al., 2005). In spastic people a further decrease of presynaptic inhibition and reciprocal inhibition has not been found during contraction (Fig. 2) (Nielsen et al., 2005).

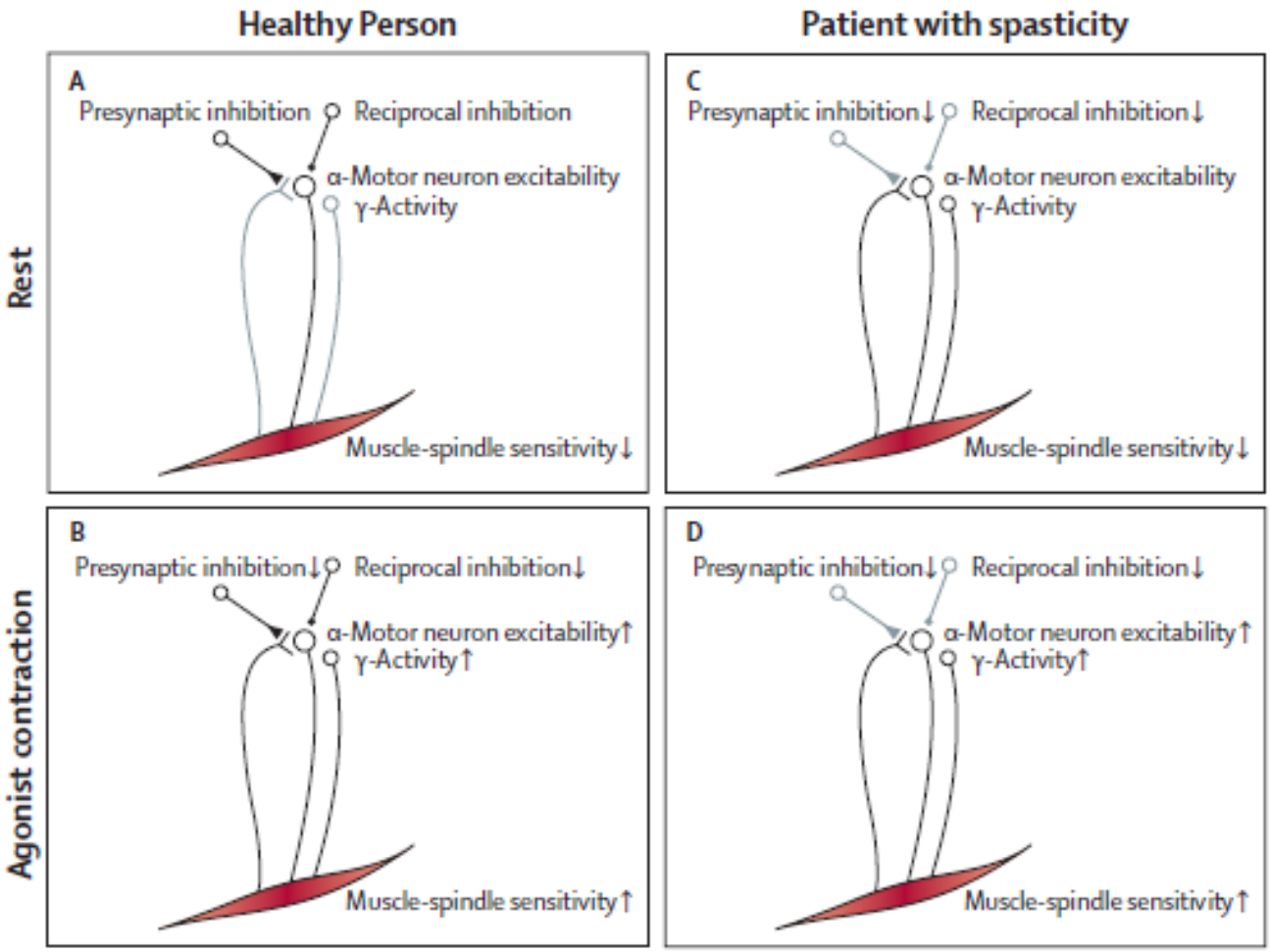


Fig. 2 Short-latency reflex behavior in passive and active muscle (from Dietz and Sinkjaer, 2007).

As mentioned above, it was widely believed in the 1970s and 1980s that spasticity was caused by increased transmitter release from the spindle afferents due to reduced presynaptic inhibition. This idea was supported by the demonstration of reduced inhibition of the soleus H-reflex by Achilles tendon vibration, believed to be caused by presynaptic inhibition of soleus Ia-afferents, in spastic humans (Ashby et al., 1974, 1975, 1976). However, later studies showed that vibratory inhibition is more likely caused by reduced spindle afferent transmitter release, probably due to their previous activation; this depression has subsequently been denoted as homosynaptic depression or post-activation depression (Nielsen et al., 1993, 1995; Aymard et al., 2000). Post-activation depression is therefore only seen when the Ia-afferents have been previously activated by a conditioning stimulus

(e.g. vibration, tendon tap, electrical nerve stimulation; Crone and Nielsen, 1989) and it is not widely distributed among all Ia-afferents in the leg as is the case for presynaptic inhibition (Hultborn et al., 1996). Usually, post-activation depression (and vibratory inhibition) is also observed for more than 10s following the conditioning stimulus, compared with only 300–400ms for presynaptic inhibition (Hultborn et al., 1996).

Post-activation depression was originally described by Curtis and Eccles (1960), who noticed that the size of Ia-excitatory postsynaptic potentials (EPSPs) in intracellular recordings from lumbar spinal motorneurons in cats was frequency-dependent, with a facilitation at short intervals (<50ms), and with a depression at longer intervals (>1s). The depression of the monosynaptic Ia-EPSP results primarily from mechanisms operating within the presynaptic terminals related to the probability of transmitter release, which depends on the history of activation of the synapse (Lev-Tov and Pinco 1993).

The reduction of post-activation depression observed in spastic humans (Nielsen et al., 1993, 1995) and the temporal changes in the depression in the months following spinal cord injury mimic the changes that are observed with vibratory inhibition (Ashby et al. 1974, 1975, 1976) and the development of spasticity (Schindler-Ivens and Shields 2000). Reduced post-activation depression has also been demonstrated in the upper limbs of spastic individuals and, in general, it is well-correlated with hyperreflexia and spasticity (Aymard et al. 2000).

In previous studies, post-activation depression has been induced with mechanical or electrical activation of the soleus Ia-afferents and evaluated by changes in the H-reflex. It is generally assumed that such observations would also apply to the stretch reflex, which is obviously of more direct relevance for spasticity, given the definition proposed by Lance (1980). However, recent experiments in both humans and cats have demonstrated that H-reflexes are more sensitive to

changes in the efficiency of the Ia-afferent synapses than are stretch reflexes (Morita et al. 2001; Enriquez-Denton et al. 2002). The significance of post-activation depression for the manifestation of spasticity (i.e. stretch reflex hyperexcitability and increased muscle resistance to stretch) could therefore be questioned.

If post-activation depression of stretch reflexes and the stretch-evoked torque is an important mechanism underlying spasticity, it should be impaired in people with signs of spasticity.

The objective of Study I was therefore to investigate the possibility that (1) stretch reflexes are reduced by post-activation depression to the same extent as H-reflexes and that (2) stretch reflexes and the stretch-evoked torque are less depressed by post-activation depression in people with spasticity than in healthy individuals.

We used the H-reflex as a traditional electrophysiological method in combination with a second laboratory method that combines biomechanics and electrophysiology. The latter method was presumed to be more related to clinical methods of measuring spasticity since it quantifies biomechanically and electrophysiologically the stretch reflex based on movements of the ankle (as done in the clinic) as opposed to the H-reflex that is an indirect measure of the stretch reflex. We therefore wanted to investigate whether the electrophysiological differences in PAD found in healthy and spastic individuals were reflected in the results when a biomechanical approach was applied.

The study demonstrated that the magnitude of the soleus stretch reflex and H-reflex decreased as the interval between the stimulus and perturbation was decreased. Similarly, the resistance evoked by the stretch reflex decreased with decrease in perturbation intervals. PAD measured by all three parameters (magnitude of H-reflex, stretch reflex and resistance evoked by the stretch reflex) was found to be significantly smaller in spastic participants than in healthy ones.

These results confirm previous findings about reduction in PAD in spastic individuals compared to healthy ones when measured electrophysiologically (Nielsen, 1993, 1995; Aymard, 2000; Schindler-Ivens and Shields, 2000). However, the measurements with the biomechanical/electrophysiological method also show that the decreased post-activation depression in spastic individuals influences the manifestation of spasticity in the form of increased stretch reflex activity and muscle stiffness. It may therefore influence the result of the clinical testing of spasticity with for example the AS. In the clinical evaluation of spasticity, the examiner is likely to induce passive movements in this frequency range rather than at intervals of more than 10s, which would be necessary to avoid post-activation depression. Based on our findings the clinician would therefore be more likely to diagnose spasticity when using rapid movements repeated at short intervals. In our study the stretch-evoked torque correlated significantly to the AS, but for PAD an insignificant trend to correlation to the AS was found. This could be due to lack of sensitivity of the clinical score to small changes in muscle stiffness, or other parameters not related to reflexes such as increased passive stiffness by arthrogenic and myogenic changes in the joint that are likely to contribute to the spastic participants' muscle stiffness and thereby complicate the clinical evaluation. As mentioned above, reduced PAD is unlikely to be the only pathophysiological mechanism in spasticity. Our results support this statement, since a significant difference between stretch reflexes (and muscle stiffness) in the spastic and in the healthy individuals were also seen at stimulus intervals of 15s, where PAD had no effect on the evoked responses.

Lesions leading to spasticity

Even though spasticity is a well-known clinical syndrome, most commonly arising after stroke, multiple sclerosis, spinal cord injury, some traumatic brain injuries, and other central nervous system (CNS) lesions, the specific areas in the brain responsible for the increased muscle tone observed in spastic patients have been discussed for many years. Based on experiments with

monkeys, Fulton and Kennard claimed in 1934 that a certain area in the pre-motor cortex was responsible for spasticity, and in 1940 Sarah Tower found absence of spasticity after section of the pyramids in the medulla (Tower, 1940). Electrical stimulation of the para-pyramidal fibres above the level of the medulla or the inhibitory DTR areas in cats has been demonstrated to reduce tone in rigid and spastic muscles (Magoun and Rhines, 1947) as well as to decrease reflex activity by inhibition of the afferents (Whitlock, 1990). However, the translation of the findings from the animal studies to humans was difficult. The decerebrate model used in cats, and developed by Sherrington, was for obvious reasons not usable in humans, therefore the only possibility was to investigate people with increase in muscle tone following change in the activity of the descending pathways due to diseases or lesions in the CNS. However in the 1990s, human studies were made with cordotomies for relief of the pain of cancer with observation of the following clinical symptoms. These studies showed that lesions in the pyramidal tract in combination with lesions in the reticulospinal fibres caused paralysis in the associated limb followed by severe spastic paresis (Nathan, 1994). In contrast, isolated lesions of the pyramidal tract in humans confirmed the results from cats where no spasticity was found (Nathan, 1994; Tower, 1940). The importance of the extrapyramidal tract in relation to the development of spasticity was further emphasized in the human study by the finding that the closer to the extrapyramidal tract the lesions were the more likely the patients were to show spasticity (Nathan, 1994). As a consequence, the term “pyramidal syndrome” should not be used in relation to spasticity, but, if used at all, it could be used as a description of the symptoms related to selective pyramidal lesions: mild hand and foot weakness, mild tendonreflexia, normal tone and an extensor plantar response (Bucy et al., 1964; van Gijn, 1978).

The para-pyramidal fibres from the pre-motor cortex have contact with the areas in the mid-brain that facilitate inhibitory areas in the medulla known as the ventromedial reticular formation (Brown,

1994). In this way, a lesion in the CNS can disturb the balance of supraspinal inhibitory and excitatory inputs and produce a state of net disinhibition of the spinal reflexes. The level of spasticity will therefore depend more on the extent to which the above mentioned structures are affected than the actual aetiology. However, the change in spinal reflex excitability cannot simply be due to an imbalance in supraspinal control. The delayed onset after the lesion and the frequent reduction in reflex excitability over time suggest plasticity in the CNS as described in the previous section.

The extra-pyramidal or para-pyramidal fibres are located close to the pyramidal fibres (Fig. 3). However, it is important to distinguish between these fibres and other extra-pyramidal fibres such as the ones from the basal ganglias that produce rigidity (or dystonia). In the clinical settings, however, almost no lesions are specifically located in areas that cause spasticity as the only symptom, and a consequence is that the clinical manifestation of a lesion includes several symptoms with different pathophysiology.

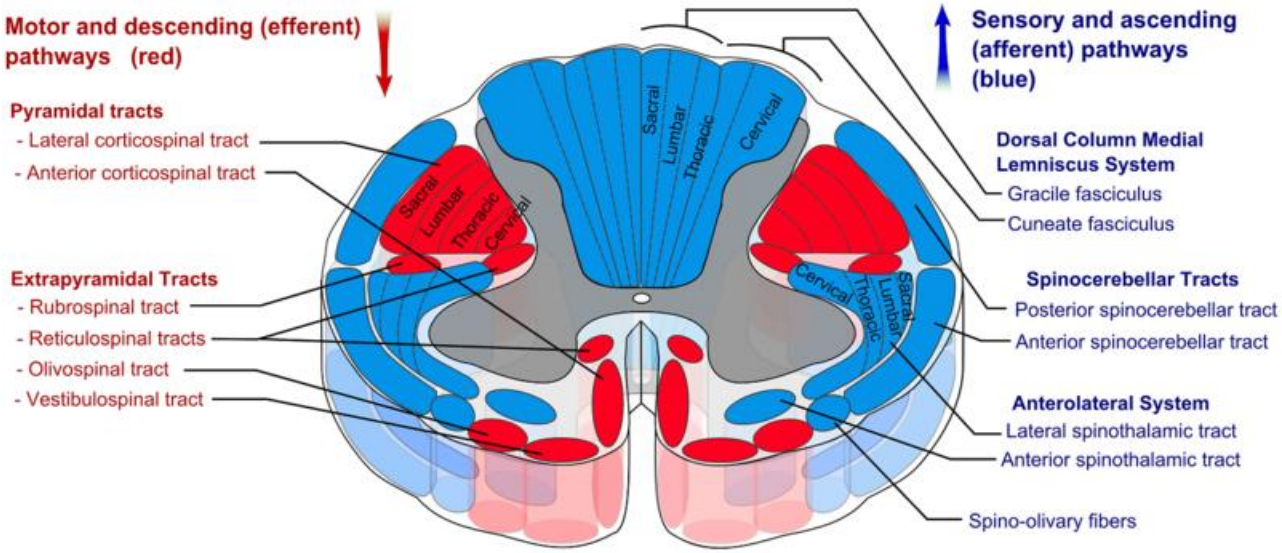


Fig. 3 Organization of the pyramidal and extra-pyramidal tracts in the spinal cord.

Measurements of muscle tone

New drug treatments such as botulinum toxin and baclofen provide incentives to evaluate the efficacy of the treatments by measuring changes in spasticity. Perhaps it is even more important to have valid methods to quantify spasticity as a prelude to clinical diagnosis when a drug treatment could follow.

The clinical decisions in relation to treatment should optimally be based on knowledge about which component is causing the hypertonicity. Is it muscle activity or is it the passive (mechanical) properties? If it is the active components then drug treatment could be considered whereas no effect will be found if the passive components are the reason for the hypertonicity (Table 1).

Factors causing hypertonicity				
Active stiffness			**Passive stiffness (Contracture)**	
Afferent (disinhibited spinal reflexes)		**Efferent (tonic supraspinal drive)**	**Arthrogenetic changes**	**Myogenetic changes**
Proprioceptive reflexes	*Cutaneous and nociceptive reflexes*	*(Spastic)* dystonia	Intra-articular adhesion formation	Loss of sacromers in series
Spasticity (tonic)	Flexor withdrawal reflexes	Associated reactions	Adaptive shortening of periarticular connective tissue	Increased intra-muscular collagen
Tendon hyperreflexia and Clonus (phasic)	Flexor spasms	Co-contraction	Reduced lubrication between collagen fibres	Disuse atrophy
Clasp knife syndrome	Clasp knife (with tonic stretch reflex)		Increased immature collagen	Muscle fibre transformation ST to FT
	Extensor reflexes			Degenerative changes in muscle-tendinous junction
	Extensor spasms			Increased actine-myosin cross-bridge linkage

Table 1. Summary of the elements that contribute to muscle tone. (Table modified from Sheean, 2002 and Singer et al., 2001).

The definition of spasticity by Lance (1980) focuses on the velocity-dependent nature of reflex excitability. This feature can assist the clinician in differentiating spasticity from stiffness caused by the passive structures (contracture) and spasticity from dystonia (Table 2) (Fig. 4).

	Spasticity	Dystonia	Rigidity	Contracture
Summary	Velocity-dependent resistance	Sustained or intermittent muscle contractions	Independent of both speed and posture	Independent of velocity
Effect of increasing speed of passive movement on resistance	Increases	No effect	No effect	No effect
Effect of rapid reversal of direction on resistance	Delayed	Immediate	Immediate	No effect
Presence of a fixed posture	Only in severe cases	Yes	No	Yes
Effect of voluntary activity on pattern of activated muscles	Minimal	Yes	Minimal	No effect
Effect of behavioural task and emotional state on pattern of activated muscles	Minimal	Yes	Minimal	No effect

Table 2 Comparison chart of principal differentiation diagnostic features (modified from Sanger, 2003)

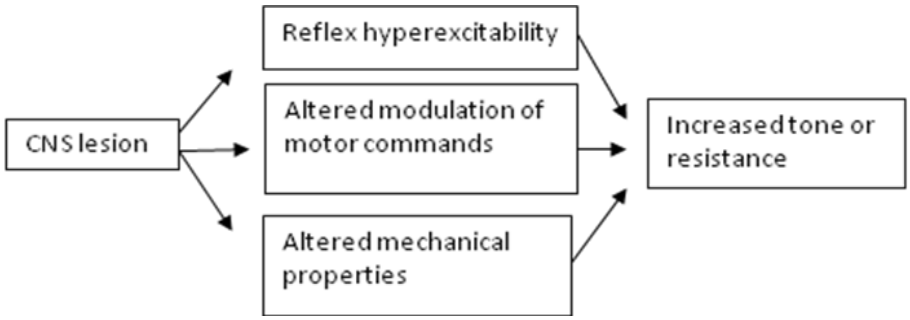


Fig. 4. The elements that contribute to increased resistance to passive movements in individuals with CNS lesions.

The stiffness arising from muscle activity is called active stiffness. Both reflex stiffness and stiffness caused by dystonia are manifested by muscle activity causing resistance to passive movements, but where reflex stiffness is sensitive to the afferent stimuli (velocity at which the movements are being made), dystonia manifests itself by continuous muscle contraction without limb movement, and is not mediated by the afferent input from the limb (Denny-Brown, 1966).

Passive stiffness is the resistance felt in a limb during a movement with no muscle activity. This is normally the situation when normal individuals are having their limbs moved manually when they are relaxed. However, in people with a CNS lesion, contractures are a well-known complication that reduces the range of motion of a joint. Over the last two decades, researchers have determined that non-reflex factors also contribute significantly to hypertonia (Dietz et al., 1981; Lorentzen et al., 2010) but they are clinically different and should be distinguished from each other. The passive stiffness reflects both the non-contractile (passive) and the contractile (intrinsic) properties of the musculo-tendinous unit (Singer et al., 2001). Changes in passive stiffness are thought to result from modifications in the rheological properties of the musculo-tendinous unit and surrounding connective tissues in addition to changes occurring within the joint itself (Singer et al., 2001). Intrinsic stiffness reflects the mechanical properties of the active motor units and is likely to be affected by the number of cross-bridge formations, even while the muscle is relaxed, and their rate of detachment during muscle stretch (Table 2) (Singer et al., 2001).

The clinical quantification of spasticity such as the AS (Ashworth, 1964) or MAS (Bohannon and Smith, 1987) are based on judgment of the resistance of the limb to manually imposed movements. One problem with these methods is that the evaluators must be able to distinguish between stiffness caused by neuronal activity and stiffness caused by passive elastic properties in the muscle, tendon and joints (passive and active stiffness). This has been demonstrated to be a very difficult task with

questionable reliability (Pandyan et al., 2003; O'Dwyer et al., 1996; Dietz and Sinkjær, 2007; Galiana et al., 2005; Malhotra et al., 2008; Biering-Sørensen et al., 2006; Lorentzen et al., 2010). The newly introduced Tardieu Scale emphasizes the use of different test velocities in accordance with Lance's definition, but this is problematic because of the difficulty in "judging" different velocities and joint angles in a clinical test situation (Biering-Sørensen et al., 2006; Malhotra et al., 2008).

The spasticity definition from Lance (1980) emphasizes the role of active reflex mechanisms in the generation of spasticity. Paradoxically, several studies have failed to find evidence of changes in active reflex mechanisms in individuals designated as spastic on clinical examination (Dietz, 1981, 1983; Lehmann et al., 1989; Dietz et al, 1991; Toft et al., 1993; Sinkjaer et al., 1993, 1994). These studies have instead raised the possibility that much of what is considered clinically as spasticity may in fact be caused by changes in passive muscle properties. If this is correct, there exists a risk that many patients will receive antispastic medication in vain, because the currently available antispastic medication acts to reduce reflex hyperactivity while having no effect on passive muscle properties. Different types of physical therapy would also be implemented if it were known that the increased muscle stiffness in a given individual was caused by passive muscle properties rather than by active reflex properties. Therefore there is a need to separate spasticity as defined by Lance (1980) from other related symptoms in order to avoid treating the spastic patient erroneously.

Biomechanical / electrophysiological approach

In contrast to current clinical scoring systems, biomechanical measures can provide an objective and easily quantifiable separation of passive and active contributions to muscle stiffness (Knuttson and Mårtensson, 1980; Sinkjaer et al., 1993, 1994; Mirbagheri et al. 2001; Galiana et al. 2005). Such techniques may lead towards a more objective *gold standard* against which clinical scoring

systems could be evaluated and possibly also help in the development of more efficient tools for clinical evaluation of muscle stiffness.

In Study II we therefore combined biomechanical and electrophysiological measures to distinguish between passive and active contributions to ankle joint stiffness. We then compared the results obtained with clinical estimates of ankle joint stiffness in order to identify the extent to which passive and active components of muscle stiffness are distinguished clinically.

We found significantly increased reflex stiffness in the overall spastic population of stroke, MS and SCI participants regardless of the origin of spasticity and length of time since injury or onset of disease. Similar results were also found in some studies (Jansen, 1962; Gottlieb et al., 1978; Broberg and Grimby, 1983; Mirbagheri et al., 2001, 2007) whereas others found no increase in reflex excitability in spastic individuals (Sinkjaer et al., 1993; Lehmann et al., 1989; Sinkjaer and Magnussen, 1994). At the same time, we found higher passive stiffness in spastic compared to non-spastic participants and, among the former, only in spastic stroke participants was the difference significant compared to healthy controls. Increased passive stiffness was also found in previous studies with similar biomechanical evaluation methods (Dietz et al., 1981; Dietz and Berger, 1983; Hufschmidt and Mauritz, 1985; Lehmann et al., 1989; Thilmann et al., 1991; Sinkjaer et al., 1993; Sinkjaer and Magnussen, 1994; Toft et al., 1993).

The objective biomechanical evaluation agreed in only 64% of cases with clinical evaluation on whether the reflex activity was increased or not. Despite a significant correlation between the stretch-evoked reflex torque and the AS a very large overlap was found, especially for AS 0-2. We conclude that passive and active components of ankle joint stiffness cannot be reliably distinguished

in the clinic with the present evaluation techniques. This potentially has the consequence that patients are being diagnosed incorrectly and thus treated erroneously.

Accordingly, there is a need for evaluation techniques which have the objective quantitative characteristics as the method used in this study, but also with practical characteristics such as ease of use, feasibility of use at the bed side and provision of immediate results.

Biomechanical / clinical approach

Elements such as velocity, measurement of reflex onset and resistance against a passive movement can be controlled very precisely in a laboratory setting as mentioned above where assessments of torque and muscle activity (EMG) can provide a reliable, objective and quantifiable separation of passive and active contributions to muscle stiffness (Knuttson and Mårtensson, 1980; Sinkjaer et al., 1993, 1994; Lorentzen et al., 2010). However, these methods are not easily applied in a clinical setting because they are time-consuming, expensive and require space, and are not always well-tolerated by patients. Therefore, there is a need for a portable device that can provide a quantification of muscle stiffness in a clinical setting with the qualities of stationary biomechanical devices.

Quantification of joint stiffness by portable hand-held devices has been reported for the ankle in children with cerebral palsy (CP) (Boiteau, 1995; Malouin, 1989) and in SCI participants (Lamontagne, 1998), in the knee in different neurological pathologies (Lebiedowska, 2009; Stein, 1996), in the elbow joint in individuals with stroke (Lee, 2002; 2004; Chen, 2005) and with Parkinson's Disease (Prochazka et al., 1997).

For the ankle, there appears to be no direct reliable correlation between the measured stiffness for the hand-held dynamometers and a quantitative stationary device (Malouin et al., 1989;

Lamontagne et al., 1998). Different resistive torques and a high degree of variability were found in the results obtained with the two methods (Malouin et al., 1989; Lamontagne et al., 1998).

Test-retest reproducibility of the resistive torque measured with hand-held devices has generally been demonstrated to be high (Boiteau et al, 1995; Malouin et al., 1989, Lamontagne et al., 1998), but inter-rater reliability has been investigated in only a few studies (Malouin et al., 1989; Dvir et al., 1991). Malouin et al. (1989) found a large variability between raters for stiffness measured during slow and fast ankle movements in 20 spastic individuals (ICC: 0.62; 0.59), whereas Dvir et al. (1991) found a high inter-rater reliability (ICC > 0.89) when measuring the resistive force of plantar flexors in CP children.

These variable results are one reason why portable devices that measure stiffness have not been adopted in the clinical setting. In addition, most of the hand-held devices consist of either a myometer or a hand-held strain gauge with electrogoniometry as two separate devices that require offline analysis in order to obtain a measure, which is not practical in a clinical setting.

In Study III we investigated the reproducibility and sensitivity in measuring ankle and knee joint stiffness in control participants and spastic, SCI participants using a portable device (Prochazka et al., 1997), which integrates these two components and provides an immediate value for stiffness. This device was originally developed to test rigidity of arm muscles in individuals with Parkinson's disease (Prochazka et al., 1997), but its design makes it also potentially suitable for evaluating leg stiffness in individuals with spasticity.

We found that stiffness measured with the portable and stationary devices were significantly correlated. The intra-rater reliability was 0.78-0.89 (SCI) and 0.63-0.67 (control) for the ankle, and 0.86-98 (SCI) and 0.81-0.91 (control) for the knee. Inter-rater reliability was 0.70-0.73 (SCI) and 0.61-0.77 (control) for the ankle, and 0.80-0.96 (SCI) and 0.53-0.78 (control) for the knee. Joint

stiffness measures for SCI participants were significantly higher than for control participants when stiffness was measured at movements with slow velocities ($p<0.05$) and at fast velocities. Stiffness measures for fast ankle movements were higher than for slow movements in SCI, but not for the controls.

The device's correlation with measures obtained by an objective biomechanical method, high intra- and inter-rater reliability, and ability to distinguish easily between spastic and control participants, demonstrates that a portable device may be a useful diagnostic tool for measurement of spasticity. However, problems in terms of practical use, and the fact that the inertial component of stiffness was not included in the calculations, may provide inaccurate stiffness measures of the knees especially when the leg is moved rapidly. Therefore, improvements in the device should be made before it can be used in the routine clinical testing of spasticity.

Treatment of spasticity

Increased muscle tone causes spastic muscles to resist stretch and to remain shortened for long durations. Prolonged muscle shortening leads to joint deformation and changes in the intrinsic properties of soft tissues and muscle fibres, which in turn restrict the range of motion (Barnes, 2008) and diminish the functional use of residual voluntary movements in individuals with CNS lesions. These changes contribute a biomechanical component, in addition to the neural components, to the disability resulting from spasticity. Whereas antispastic drugs act on the neural component of spasticity, physiotherapy can minimize the biomechanical side effects. Intensive, daily passive muscle stretching assists in reducing muscle tone and in maintaining joint mobility and range of motion. Orthoses are used to hold the limb in positions that resist contractures. Exercises are performed to strengthen the spastic and synergistic muscles (Barnes, 2008). New studies appear to have demonstrated an impact due to immobilization or training on the spinal mechanisms that are changed in spastic patients. Immobilization of healthy subjects has been demonstrated to increase

reflex activity (Lundby-Jensen and Nielsen, 2008) whereas strength training appears to increase the reciprocal inhibition (Geertsen et al., 2008).

Drug treatment to reduce muscle tone is used as a routine treatment in the clinic. However, the rationale for using drugs to reduce the reflex excitability seems to be questionable since active reflexes are essential when voluntary movements are being performed. It has been shown that an increase of reflex excitability is taking place in healthy individuals during activity (Nielsen et al., 2005), which makes hyperactive reflexes a problem that mainly exists when patients are being tested at rest.

Neurodynamics (ND) is a therapeutic concept based on the idea that the mechanoreceptors and their connectivity to the central nervous system can be clinically assessed and treated by mobilization of the nervous system (Butler, 2000; Shacklock, 1995). According to the ND theory, the assessment can be done by the so-called neural tension tests where passive mobilizations of the extremities are supposed to provoke (stretch) the peripheral nervous system. The response to the test is thought to give information about the mobility of the nerves in relation to the surrounding tissues and physiological abnormalities such as ischemia and inflammation in the nerves (Jaberzadeh et al., 2005; Shacklock, 1995). The lack of mobility of the nervous systems in relation to the surrounding structures (the so-called mechanical stresses) is suggested to be caused by variations in blood flow, axonal transport and impulse traffic (Shacklock, 1995).

The primary treatment objective for ND is thus to restore the natural movement of the neural tissue and surrounding mechanical tissue and thereby reduce the intrinsic pressure on the neural tissue and so to regain natural physiological function (Butler, 2000, Shacklock, 1995). The treatment consists of manually induced movements of the limbs with the purpose of performing the so-called “nerve gliding exercises”. These exercises are thought to induce “sliding of the nerves relative to the

surrounding structures by elongation of the structures that surrounds the nerves" (Coppienters and Butler, 2008).

The efficacy of ND in terms of pain reduction has been investigated in individuals with Carpal Tunnel Syndrome (Baysal et al., 2006; Pinard et al., 2005; Tal-Akabi and Rushton, 2000; Akalin et al., 2002), with low back pain (Cleland et al., 2005) and with cervicobrachial neurogenic pain (Coppieters and Butler, 2008). The efficacy illustrated in these studies is not conclusive; a recent systematic review of the therapeutic efficacy of neural mobilization found that there was a lack of quality studies on this topic and concluded that there is limited evidence to support treatment efficacy of ND (Ellis et al., 2008). To our knowledge only one small study, with five subjects and without any control group, has investigated the use of ND as an antispastic treatment in patients with damage to the CNS (Godio et al., 2010). The results suggest a small reduction in muscle activity after the ND treatment. Although the ND method thus appears not to have been validated scientifically for use in patients with damage to the CNS, it is nevertheless used extensively in neurological rehabilitation centres throughout Europe by physiotherapists with the aim of reducing muscle tone and increasing range of motion (ROM) in patients with brain injury.

In Study IV we investigated the effect of ND in relation to change in muscle tone and ROM by a hand-held device in TBI patients with spasticity defined as "velocity-dependent increase in tonic stretch reflexes to phasic stretch, in the absence of voluntary activity" (Lance 1980).

We found no significant change in stiffness measured with the portable stiffness measure device when measured with fast or slow movements. However, a trend to a reduction in stiffness was found when tested at slow velocities. Furthermore no change in the clinical spasticity score (MAS) was found. An increase in ROM was found for the R1 for both treatments whereas ROM for R2

was increased only after the ND treatment. Furthermore, no differences between the two treatments were found for any of the measured parameters.

Thus, ND seems not to be effective in reducing spasticity when evaluated objectively, but may increase ROM in the knee flexors to the same extent as random passive movements.

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Summary of the research questions

Research question in Study I:

The objective of Study I was to investigate the possibility that (1) stretch reflexes are reduced by post-activation depression to the same extent as H-reflexes and that (2) stretch reflexes and the stretch-evoked torque are less depressed by post-activation depression in people with spasticity than in healthy individuals.

Research question in Study II:

In Study II we combined biomechanical and electrophysiological measures to distinguish passive and active contributions to ankle joint stiffness. We then compared the results obtained to clinical estimates of ankle joint stiffness in order to identify the extent to which passive and active components of muscle stiffness are distinguished clinically.

Research question in Study III:

In Study III we investigated the reproducibility and sensitivity in measuring ankle and knee joint stiffness in control participants and spastic, SCI participants using a portable device (Prochazka et al., 1997), which integrates these two components and gives an immediate value for stiffness.

Research question in Study IV:

In Study IV we investigated the effect of ND in relation to change in muscle tone and range of motion (ROM) by a hand-held device in TBI patients with spasticity defined as “velocity-dependent increase in tonic stretch reflexes to phasic stretch, in the absence of voluntary activity” (Lance 1980).

Summary and conclusion of the four studies

Spasticity is a common disorder following lesions in CNS (Stroke: Simpson, 2008; SCI: Kirshblum, 1999; TBI: Sheean, 2002) and is defined as "a velocity-dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome (Lance 1980).

The four studies in this thesis have quantification of spasticity with clinical, electrophysiological and biomechanical methods as a main focus.

In the first study we investigated PAD as one of many mechanisms in the spinal nervous network (Crone & Nielsen, 1986; Hultborn, 1986). PAD is the depression of synaptic efficiency following previous synaptic activation of Ia afferents, and PAD was found reduced in spastic patients (Nielsen, 1993, 1995; Aymard, 2000; Schindler-Ivens and Shields, 2000). We used the H-reflex as a traditional electrophysiology method in combination with a second laboratory method that combines biomechanics and electrophysiology. The latter method was presumed to be more related to clinical ways of measuring spasticity since it quantified biomechanically and electrophysiologically the stretch reflex based on movements of the ankle (as done in the clinic) as opposed to the H-reflex that is an indirect measure of the stretch reflex. We therefore wanted to investigate if the electrophysiological differences in PAD found between healthy and spastic individuals were reflected in the results when a biomechanical approach was applied.

The study demonstrated that the magnitude of the soleus stretch reflex and the H-reflex decreased as the interval between the stimulus or perturbation was decreased. Similarly, the resistance evoked by the stretch reflex decreased with decrease in perturbation intervals. PAD measured by all three parameters (magnitude of H-reflex, stretch reflex and resistance evoked by the stretch reflex) were found to be significantly smaller in spastic participants than in healthy ones.

These results confirm previous findings about reduction in PAD in spastic individuals compared to healthy ones when measured electrophysiologically (Nielsen, 1993, 1995; Aymard, 2000; Schindler-Ivens and Shields, 2000). However, the measurements with the biomechanical / electrophysiological method also show that the decreased PAD in spastic individuals influences the manifestation of spasticity in the form of increased stretch reflex activity and muscle stiffness. It may therefore influence the result of the clinical testing of spasticity with for example the AS. In the clinical evaluation of spasticity, the examiner is likely to induce passive movements in frequency range of less than 10s rather than at intervals of more than 10s, which would be necessary to avoid post-activation depression. Based on our findings, the examiner would therefore be more likely to diagnose spasticity when using rapid movements repeated at short intervals. In our study the stretch evoked torque correlated significantly to the AS, but for PAD an insignificant trend to correlation to the AS was found. This could be due to lack of sensitivity of the clinical score to small changes in muscle stiffness or other parameters not related to reflexes such as increased passive stiffness by arthrogenic and myogenic changes in the joint. As mentioned above, reduced PAD is unlikely to be the only pathophysiological mechanism in spasticity. Our results support this statement, since a significant difference between stretch reflexes (and muscle stiffness) in the spastic and healthy individuals was also seen at stimulus intervals of 15s, whereas PAD has no effect on the evoked responses.

In the second study we wanted to separate and quantify the stretch reflex and the passive stiffness contribution to stiffness in the ankle joint with the combined biomechanical / electrophysiological method in healthy and spastic individuals. We then wanted to relate the results to the clinical evaluation of spasticity. This biomechanical method is based on ankle perturbations at different velocities above and below the reflex threshold. This type of methods has been demonstrated to be objective and reliable (Knutsson and Mårtensson, 1980; Sinkjaer et al., 1993, Sinkjaer and

Magnussen, 1994; Mirbagheri et al., 2001; Galiana et al., 2005) and could therefore work as a test of the size of the stretch reflex in healthy and spastic individuals, but also as a "gold standard" test against which the clinically applicable methods could be evaluated.

We found significantly increased reflex stiffness in the overall spastic population of stroke, MS and SCI participants regardless of the origin of spasticity and time since injury or onset of disease. Similar results were also found in the some studies (Jansen, 1962; Gottlieb et al., 1978; Broberg and Grimby, 1983; Thilmann and Fellows, 1991; Mirbagheri et al., 2001, 2007) whereas others found no increase in reflex excitability in spastic individuals (Sinkjaer et al., 1993; Lehmann et al., 1989; Sinkjaer and Magnussen, 1994). At the same time, we found higher passive stiffness in spastic compared to non-spastic participants and, among the former, only in spastic stroke participants was the difference significant compared to healthy controls. Increased passive stiffness was also found in previous studies with similar biomechanical evaluation methods (Dietz et al., 1981; Dietz and Berger, 1983; Hufschmidt and Mauritz, 1985; Lehmann et al., 1989; Thilmann et al., 1991; Sinkjaer et al., 1993; Sinkjaer and Magnussen, 1994; Toft et al., 1993).

The objective biomechanical evaluation agreed with clinical evaluation in only 64% of cases as to whether or not the reflex activity was increased. Despite a significant correlation between the stretch-evoked reflex torque and the AS a very large overlap was found, especially for AS 0-2. We conclude that the passive and active components of ankle joint stiffness cannot be reliably distinguished in the clinic with the present evaluation techniques. This has the clinical consequence that patients are potentially being diagnosed incorrectly and thus treated wrongly.

Accordingly, there is a need for evaluation techniques which have the same objective quantitative characteristics as the method used in this study, but also with practical characteristics such as ease of use, possibility of bringing to the bed side and capability of providing immediate results.

Therefore in the third study we investigated the reliability and sensitivity of a portable stiffness measurement device. This was done by 1) correlating the measured stiffness against the results measured with the biomechanical / electrophysiological method (as mentioned above) 2) calculation of the inter- and intra-rater variability of the portable stiffness measure device, and 3) investigating the ability of the portable device to distinguish between ankle and knee stiffness in healthy and spastic participants with SCI.

We found that stiffness results with the portable and stationary devices were significantly correlated. The Intra-rater reliability was 0.78-0.89 (SCI) and 0.63-0.67 (control) for the ankle, and 0.86-98 (SCI) and 0.81-0.91 (control) for the knee. Inter-rater reliability was 0.70-0.73 (SCI) and 0.61-0.77 (control) for the ankle, and 0.80-0.96 (SCI) and 0.53-0.78 (control) for the knee. Joint stiffness measures for SCI participants were significantly larger than control participants when stiffness was measured with movements at slow velocities ($p<0.05$) and at fast velocities. Stiffness measurements for fast ankle movements were greater than slow movements in SCI, but not for controls.

The device's correlation with measurements obtained by an objective biomechanical method, high intra- and inter-rater reliability, and ability to distinguish easily between spastic and control participants demonstrate that a portable device may be a useful diagnostic tool for measurement of spasticity. However, problems in terms of practical use, and the fact that the inertial component of stiffness was not included in the calculations, may provide inaccurate stiffness measurements of the knees, especially when the leg is moved rapidly.

Study IV was carried out while Study III was ongoing. Here we wanted to investigate if any change in spasticity could be detected as a consequence of a physiotherapy treatment (ND) on spastic patients with severe TBI. We used the portable stiffness measurement device as well as clinical

measure of spasticity and ROM to determine effects of the treatments and to investigate if greater effects were found with the ND treatment than with the RPM (control treatment).

We found no significant difference in stiffness measured with the portable stiffness measurement device when measured with fast or slow movements. However, a trend to a reduction in stiffness was found when the stiffness was tested at slow velocities. Also no change in the clinical spasticity score (MAS) was found. An increase in ROM was found for the R1 for both treatments whereas ROM for R2 was increased only after the ND treatment. Except for ROM, no differences were found for any of the measured parameters between the two treatments.

Thus, ND seems not to be effective in reducing spasticity when evaluated objectively, but may increase ROM in the knee flexors to the same extent as random passive movements.

Conclusion

Studies I and II illustrate clearly that the mechanisms behind spasticity, and spasticity itself (increased stretch reflexes), are poorly reflected by the existing clinical scoring systems. We therefore think that new objective spasticity evaluation techniques like the biomechanical / electrophysiological method used in these studies are needed to identify it in the clinic, but also to identify future subjects with spasticity when experiments are carried out to identify and quantify the spinal mechanisms involved.

Based on the good reliability of the portable stiffness measurement device and its good correlation to an objective, stationary stiffness measurement device we believe that with practical modifications and further development of the analysis of the stiffness a portable device could be used to measure stiffness.

No change in stiffness was found after treatment with ND when measured with clinical test methods and a hand –held dynamometer. Based on this, ND may not be useful to reduce spasticity. However, it may be beneficial in increasing ROM.