Dynamics of upper limb spastic paresis post stroke

Mechanisms, measurement and treatment

Aukje Andringa

Dynamics of upper limb spastic paresis post stroke
Mechanisms, measurement and treatment
Thesis, VU University, Amsterdam, the Netherlands

The research described in this thesis was supported by the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013; grant no. 291339, 4D-EEG project), the Netherlands Organisation for Health Research and Development (ZonMw grant no. 104003008, PROFITS project), an unrestricted grant from IPSEN and a grant from the Spaarne Gasthuis Academy.

The research in this thesis was embedded in Amsterdam Movement Sciences and Neuroscience Research Institutes, at the department of rehabilitation medicine, Amsterdam UMC, location Vrije Universiteit Amsterdam, the Netherlands.

Layout Renate Siebes | Proefschrift.nu

VRIJE UNIVERSITEIT

Dynamics of upper limb spastic paresis post stroke

Mechanisms, measurement and treatment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus

in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde

in de aula van de universiteit,
De Boelelaan 1105

door

Aukje Andringa

geboren te Bemmel

promotor:	prof.dr. G. Kwakkel
copromotoren:	prof.dr. C.G.M. Meskers
	dr. I.G.L. van de Port

Contents

CHAPTER 1

Glossary of terms and general introduction

GLOSSARY OF TERMS

Activity: The execution of a task or action by an individual (see **ICF**).[1]

Associated reactions: Involuntary movements of the paretic arm following an effortful movement of other parts of the body or activities such as yawning, coughing, sneezing and laughing, as a component of the **positive features** of an upper motor neuron lesion.[2]

Body functions: Physiological functions of body systems, including psychological functions (see **ICF**).[1]

Body structures: Anatomical parts of the body such as organs, limbs and their components (see **ICF**).[1]

Botulinum toxin: A neurotoxin that causes a temporary reduction of muscle activity by blocking the release of acetylcholine at the neuromuscular junction which can be used in the treatment of disorders characterized by excessive or inappropriate muscle activity.[3]

Co-contraction: Involuntary antagonistic muscle activity during voluntary agonistic command and tonic stretch, as a component of the **positive features** of an upper motor neuron lesion.[4]

Construct validity: The degree to which the scores of a measurement instrument are consistent with hypotheses, e.g. with regard to internal relationships, relationships to scores of other instruments or differences between relevant groups, based on the assumption that the measurement instrument validly measures the construct to be measured.[5]

Content validity: The degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured.[5]

Criterion validity: The degree to which the scores of a measurement instrument are an adequate reflection of a gold standard.[5]

Elasticity: The ability of the muscle to restore its initial shape after elongation, which is caused by the parallel elastic components, including epi-, endo- and perimysium, the contractile components (sarcomeres) and the series elastic component (tendons). At lengths greater than their resting length, the muscle develops tension.[6]

Environmental factors: Factors that make up the physical, social and attitudinal environment in which people live and conduct their lives (see **ICF**).[1]

International Classification of Functioning, Disability and Health (ICF): A classification that provides a standardized framework to categorize health and health-related conditions.[1]

Involuntary background activation: Involuntary rise in resting muscle activity at rest, in absence of stretch or voluntary effort, as a component of the **positive features** of an upper motor neuron lesion.[7,8]

Joint hyper-resistance: Increased resistance perceived during passive movement of a joint which is caused by **neural** and **non-neural components**.[9] In this thesis, the term wrist hyper-resistance is used for the increased resistance to a passive wrist extension movement.
Motor function: The physiological **body function** to produce force, move a body part or maintain a posture under external disturbance.[1]
Muscle atrophy: Deterioration of muscle tissue due to extended periods of inactivity.[10]
Negative features: Decreased voluntary muscle activation, including paresis, loss of dexterity and fatigability, developing immediately after an upper motor neuron lesion.[11]
Neural components of joint hyper-resistance: Resistance perceived during passive movement of a joint caused by muscle overactivity, which consists of velocity- and muscle length-dependent increase of muscle activity (see **spasticity**) and non-velocity-dependent **involuntary background activation**.[9]
NeuroFlexor: A commercially available instrumented assessment method using a portable device and a simplified signal analysis model to automatically quantify **neural** and **non-neural (elastic and viscous) components** of wrist hyper-resistance.[12]
Non-neural components of joint hyper-resistance: Resistance perceived during passive movement of a joint caused by altered tissue properties of the muscles and soft tissues spanning the joint, including muscle atrophy, shortening and stiffness.[9]
Paresis: Weakness or partial loss of voluntary contraction force of a part of the body due to a lack of central facilitation of the agonistic muscles.[13]
Participation: Involvement in a life situation, see **ICF**.[1]
Phases in stroke recovery: Hyper-acute, 0–24 hours; acute, 1–7 days; early subacute, 7 days – 3 months; late subacute, 3–6 months; chronic, > 6 months.[14]
Positive features: Various forms of involuntary muscle overactivity, such as **spasticity**, **involuntary background activation**, **co-contraction** of antagonistic muscles and **associated reactions**, that develop gradually over days to months as a result of an upper motor neuron lesion.[11]
Reliability: The degree to which the measurement instrument is free from measurement error. The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: i.e. over time (test-retest), by different persons on the same occasion (interrater) or by the same person on different occasions (intrarater).[5]
Responsiveness: The ability of a measurement instrument to detect change over time in the construct to be measured.[5]

Spasticity: The velocity- and muscle length-dependent increase of muscle activity in response to an externally imposed stretch of a muscle at rest, as a component of the **positive features** of an upper motor neuron lesion.[15]

Spastic paresis: The dynamic combination of motor impairments post stroke, consisting of **negative** and **positive features** and altered tissue properties.[4,16]

Stroke: An episode of neurological dysfunction with symptoms lasting more than 24 hours or leading to death, caused by focal cerebral blood flow disruption, either by an arterial thrombotic blockage (*ischemic stroke*) or a rupture (*haemorrhagic stroke*) leading to oxygen deprivation in an area of the brain.[17]

Synergistic muscle activation: A pattern of muscle co-activation across multiple joints of the paretic limb. In the upper limb, the flexor synergy is most commonly seen.[18,19]

Validity: The degree to which a measurement instrument truly measures the construct(s) it purports to measure.[5]

Viscosity: Velocity-dependent resistance of soft tissue to elongation, i.e. highly viscous tissues causes higher resistance at higher elongation velocity compared to lower velocities.[6]

Wristalyzer: An experimental electromyography-based instrumented assessment method using a joint manipulator and a bidirectional antagonistic muscle model to quantify **neural** and **non-neural components** of wrist hyper-resistance.[20]

GENERAL INTRODUCTION

Washing, dressing, eating, hugging, waving … Just a small selection of the daily activities that we do with our arms and hands without even thinking about it. However, all these activities can suddenly become more challenging or even impossible after a stroke. One-sided loss of upper limb motor function is one of the most common impairments post stroke, occurring in up to 80% of all patients.[21] Upper limb impairments can have a major impact on a patient's daily activities and can limit social and vocational participation. As such, these impairments not only diminish patients' quality of life, but also lay a substantial burden on their caregivers and society.[22-25] It is, therefore, not surprising that treatments for upper limb impairments rank as item 4 in the top 10 research priorities related to life post stroke, based on consensus between patients with stroke, caregivers and health care professionals.[26]

Stroke

Stroke is defined as an episode of neurological dysfunction caused by focal cerebral blood flow disruption, either by a blood vessel blockage (ischaemic stroke) or a rupture (haemorrhagic stroke),[17] and is one of the major causes of death and disease burden worldwide. Annually, 15 million people suffer a stroke and more than 25 million stroke survivors live with the daily consequences.[27] Despite substantial improvement in primary prevention and acute stroke treatment, such as thrombolysis and thrombectomy, there is an increase in global stroke burden as the incidence of stroke increases mainly due to the ageing population and the absolute number of disability-adjusted life years in developing countries.[27-29] Depending on the size and location of the neurological damage, a stroke results in motor, somatosensory, cognitive, and/or speech impairments that further limit activities and restrict people's participation in society. The International Classification of Functioning, Disability and Health (ICF) model[1] is often used to classify the wide spectrum of impairments, limitations and restrictions post stroke. This classification provides an international standardized framework to distinguish impairments on the level of body functions and structures, affecting the levels of activity and participation, and the influence of contextual personal and environmental factors. Figure 1.1 shows an overview of the impairments and activity limitations in the upper limb post stroke, classified according to the ICF model.

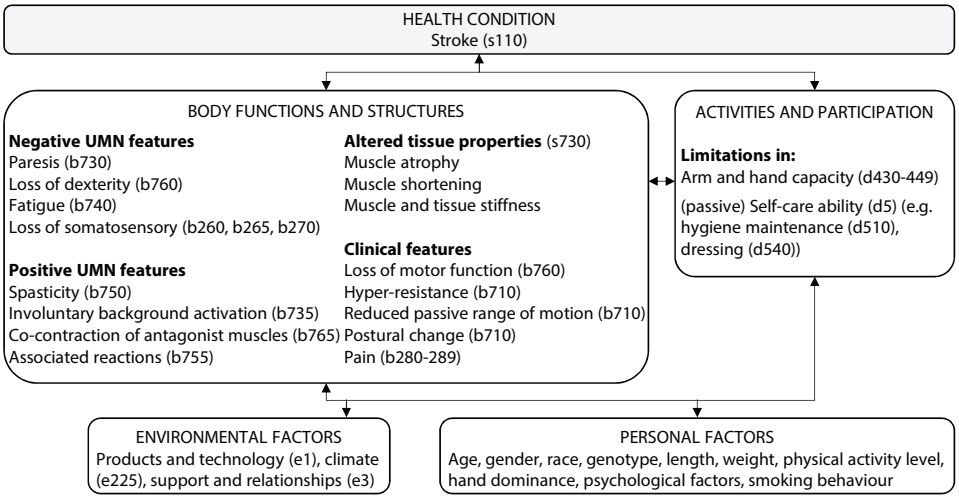


Figure 1.1. Overview of the impairments and activity limitations in the upper limb post stroke, categorized according to the International Classification of Functioning, Disability and Health.
The codes provided in parentheses represent ICF codes. Abbreviations: b, body function; d, activity and participation; e, environmental factors; s, body structure; UMN, upper motor neuron.

Upper limb spastic paresis post stroke

Upper limb spastic paresis is the commonly used term for the combination of upper limb motor impairments post stroke, which consists of the so-called negative and positive upper motor neuron (UMN) lesion features.[4,16] Clinically, spastic paresis is characterized by a loss of motor function, increased resistance to passive joint movement (i.e. joint hyper-resistance), reduced passive range of motion and postural change. The clinical presentation of upper limb spastic paresis shows a considerable, unexplained, variability between individual patients and changes over time post stroke. Although upper limb spastic paresis is easy to recognize in clinical practice, knowledge about the underlying pathophysiological mechanism that causes heterogeneity in the clinical presentation in patients with stroke is required.

Upper limb spastic paresis is assumed to result from a cascade of processes following the acute neurological damage, as shown in the model presented in Figure 1.2. Damage to the motor cortex and descending motor pathways due to stroke immediately causes loss of voluntary motor function, denoted as a negative UMN feature. This paresis, in turn, leads to a relative immobilization and reduced use of the paretic arm, which may alter tissue properties early after stroke.[13] Due to plastic neural rearrangements within the days to months following a stroke, various forms of involuntary muscle overactivity, such as involuntary background activation, co-contraction of antagonistic muscles, associated reactions and spasticity,

develop gradually post stroke.[30-32] These so-called positive UMN features lead to a preferred resting position of the elbow, wrist and fingers towards flexion and further reinforce the joint immobilization caused by paresis. The negative and positive features collectively lead to altered neural efferent commands to the muscles, which may further cause alterations in tissue properties such as muscle atrophy, muscle shortening and muscle and tendon stiffness, i.e. elasticity and viscosity.[10,13] Moreover, these three contributors may be interrelated, for example, altered tissue properties may influence stretch reflex thresholds[33] and may interfere with the initial loss of motor function, and are task-dependent. Additionally, both the altered neural efferent commands as well as the tissue alterations may be under influence of contextual personal and environmental factors. However, how these components develop to a certain magnitude in each individual, interact with each other and result in the dynamic presentation of the spastic paresis phenotype is still unknown.

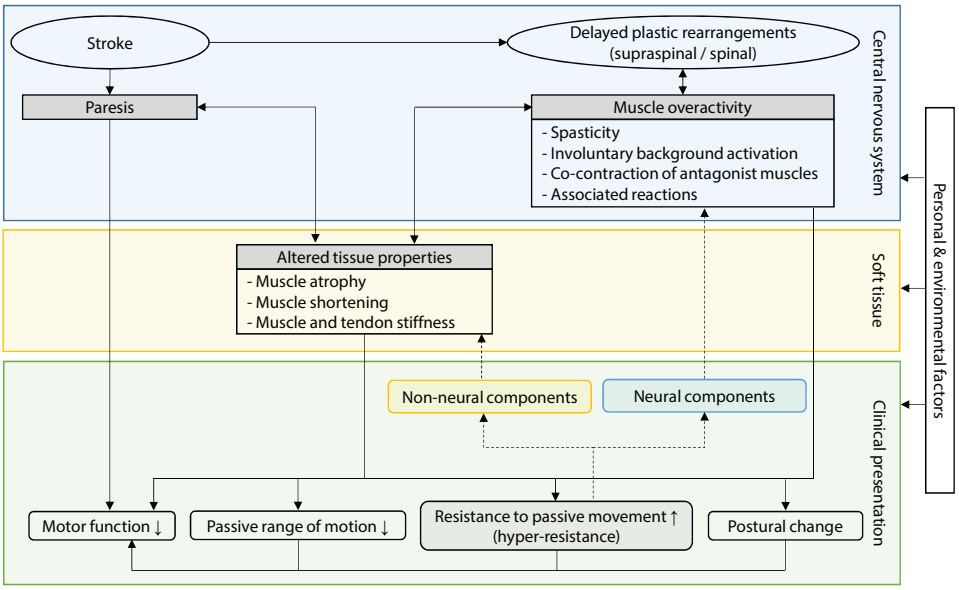


Figure 1.2. Upper limb spastic paresis post stroke.
Adapted from Sheean[32] and Gracies.[4] The dotted lines represent the objective of this thesis, that is, to distinguish between the neural and non-neural components of the clinically measured joint hyper-resistance.

Spasticity in 'sensu stricto'

Spasticity, as one of the forms of muscle overactivity post stroke, is most commonly detected and measured under passive conditions and is clinically manifested at rest by excessive muscle

responses to stretch. This phenomenon is always accompanied by negative UMN features causing deficit symptoms. Although considerable research has been devoted to spasticity, the term on itself is inconsistently defined in the literature and its pathophysiology is still poorly understood.[34,35] Moreover, agreement on construct-valid outcome measures and effective evidence-based interventions is still lacking in the literature.

Definition of spasticity

Establishing a uniform construct-valid definition of spasticity is ongoing for several decades. Spasticity is most often defined by the longstanding definition of Lance from the eighties 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 a component of the upper motor neuron syndrome*".[15] This definition includes the velocity-dependent muscle overactivity in patients who are at rest as a consequence of enhanced stretch reflex activity, resulting from abnormal spinal processing of proprioceptive input.[30,31] However, this definition contains some inadequacies. The term upper motor neuron syndrome suggests that the disruption of the descending pyramidal tract is responsible for the positive exaggerated features of spasticity, whereas it is known that isolated lesions of the corticospinal tract, primarily involved in voluntary movement, do not lead to spasticity.[36] Moreover, Lance's definition does not distinguish between different pathologies that result in an upper motor neuron syndrome, such as stroke, cerebral palsy and multiple sclerosis, while the neurological damage is of different origin.

In the clinical setting, the term spasticity is frequently used in a wider sense for the clinical presentation of all positive, and even negative, UMN features, as those components are difficult to distinguish by a lack of knowledge of the underlying pathophysiological mechanisms, construct-valid clinical outcome measures and uniform definitions. The SPASM (Support Programme for Assembly of database for Spasticity Measurement) consortium introduced a new, pragmatic definition for spasticity including all afferent-mediated positive features, as "*disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles*".[34] This definition may be more in agreement with the broad use of the word spasticity in clinical practice, however, the velocity-dependency of the muscle reaction to passive stretch, as a key feature of spasticity, is disregarded and the assumption of altered sensory input in the cause of spasticity is still unclear. Nevertheless, differentiating between the positive features may be important to better understand the underlying pathophysiological mechanisms of spastic

paresis as well as the unexplained variability in the clinical presentation of spastic paresis between patients.[31] Moreover, in accordance with the definition of Lance, this definition still contains the oversimplified term upper motor neuron lesion.

In this thesis, the term spasticity is used, in 'sensu stricto', for the velocity- and muscle length-dependent increase of muscle activity in response to an externally imposed stretch, as one of the separate positive UMN features post stroke, following the definition of Lance.[15]

Measurement of spasticity

Current clinical measurement of spasticity at the ICF body functions level is restricted to observer-perceived ordinal scaled outcome measures for resistance to passive movement of a joint under passive conditions, such as the modified Ashworth scale (MAS).[37] There are, however, multiple concerns about this scale as a measurement instrument for spasticity.[38,39] First, the MAS shows poor measurement properties with respect to reliability and responsiveness.[38-40] Due to the low responsiveness to change of this ordinal rating scale, it offers insufficient precision to measure the effectiveness of interventions and therefore to define the most effective treatment strategies. Second, the MAS lacks construct validity as a measure of spasticity which is characterized by its velocity-dependency.[15] The MAS consists of one manually applied fast movement of which the velocity is not controlled for, which will interfere with the perceived resistance.[41] Finally, and most importantly, the MAS assesses the total resistance to a manually applied passive movement of the joint and is unable to distinguish between the velocity-dependent spasticity and involuntary background activation, and altered tissue properties further influencing joint hyper-resistance at rest (Figure 1.2).[38,40,42] The magnitude and distribution of these so-called neural and non-neural components of joint hyper-resistance may vary between individual patients and can change in time post stroke. Importantly, these components will need different treatments. Patients with a dominant neural component of joint hyper-resistance are expected to benefit from treatment that focuses on reducing muscle overactivity and blocking the reflex loop, for example by botulinum toxin injections, while a suspected predominance of the non-neural components may need treatments as corrective casting or surgical lengthening. There is an overall agreement that the MAS should not be used as an outcome measure for spasticity.[39] However, despite the aforementioned problems and in the absence of an appropriate alternative clinical outcome measure, the MAS is still routinely used in clinical practice and often used in clinical trials as the primary measurement of outcome for evaluating interventions such as botulinum toxin.[43,44]

Instrumented assessment of neural and non-neural components of joint hyper-resistance

Disentangling joint hyper-resistance into its underlying neural and non-neural components leads to a better understanding of the pathophysiological mechanisms that are at the origin of spastic paresis post stroke and may help to explain the variability in the clinical presentation of spastic paresis between patients. Moreover, knowledge of the underlying components of joint hyper-resistance may gain better insight into their influence on motor recovery and may contribute to patient-specific treatment decision-making in rehabilitation. Additionally, quantification of the neural component, as a possible marker for spasticity, is important for trials evaluating high-cost interventions, such as botulinum toxin. Consequently, there is a need for an objective measurement tool, feasible for use in clinical practice, which is reliable and construct valid to quantify the separate neural and non-neural components of joint hyper-resistance in a standardized matter.

Recently, different instrumented assessment methods have been developed to address the drawbacks of the current manual assessment.[12,20,45-52] These instrumented methods allow for standardized assessment under passive conditions and can provide objective and quantitative information. Moreover, these instrumented methods allow for separating the components leading to joint hyper-resistance, i.e. neural or non-neural components. The NeuroFlexor,[12,53] for instance, is a portable and commercially available device that is potentially able to quantify the separate neural and non-neural elastic and viscous components of increased resistance to passive wrist extension using a simplified signal analysis model. This portable device can be easily transported between different locations allowing for longitudinal, repeated measurements in different settings. The experimental Wristalyzer, on the other hand, uses measured joint torque during an imposed perturbation of the wrist in combination with electromyography (EMG) of wrist flexor and extensor muscle activity to estimate neural and non-neural components using a neuromuscular model including wrist mechanics and muscle properties.[20]

Aims and outline of the thesis

The main aims of this thesis are to investigate instrumented assessment to clinically quantify the underlying neural and non-neural components of wrist hyper-resistance in patients in the subacute and chronic phase post stroke and to explore its potential value for timely and patient-specific management of upper limb spastic paresis post stroke. The first study, described in **chapter 2**, provides a comprehensive overview of the reported effects and

scientific robustness of botulinum toxin treatment regarding the main clinical goals related to post-stroke upper limb spastic paresis, using the ICF model. This study emphasizes the need for instrumented assessment methods that can assess the separate neural and non-neural components of resistance to passive movement and which can contribute to better indication and evaluation of treatments.

The studies presented in **chapters 3** and **4** focus on the measurement properties of instrumented assessment methods to assess the neural and non-neural components of wrist hyper-resistance in patients with chronic stroke. Test-retest reliability of the NeuroFlexor and its construct validity compared to recommended clinical scales are described in **chapter 3**. To further validate instrumented assessment methods to distinguish the neural and non-neural components of wrist hyper-resistance, the outcomes of two different methods, i.e. NeuroFlexor and Wristalyzer, are compared in **chapter 4**.

In **chapters 5** and **6**, the influence of time post stroke, upper limb motor recovery and an intervention on neural and non-neural components of wrist hyper-resistance are further investigated. First, we investigate the time course of neural and non-neural components of wrist hyper-resistance in relation to upper limb motor recovery in the first six months post stroke (**chapter 5**). Second, in **chapter 6**, we explore the effects of botulinum toxin-A therapy to modify the underlying neural and non-neural components of wrist hyper-resistance components. Finally, the main findings of this thesis with the recommendations for further research and clinical implications will be discussed in **chapter 7**.

REFERENCES

1. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization: 2001. Updated March, 2018. www.who.int/classifications/icf/en/
2. Mulley G. Associated reactions in the hemiplegic arm. *Scand J Rehabil Med.* 1982;14(3):117-120.
3. Wheeler A, Smith HS. Botulinum toxins: mechanisms of action, antinociception and clinical applications. *Toxicology.* 2013;306:124-146.
4. Gracies JM. Pathophysiology of spastic paresis. II: Emergence of muscle overactivity. *Muscle Nerve.* 2005;31(5):552-571.
5. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol.* 2010;63(7):737-745.

6. Özkaya N, Leger D, Goldsheyder D, Nordin M. *Fundamentals of biomechanics.* Fourth ed. New York, NY: Springer New York; 2018.
7. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry.* 2005;76(1):47-54.
8. Baude M, Nielsen JB, Gracies JM. The neurophysiology of deforming spastic paresis: A revised taxonomy. *Ann Phys Rehabil Med.* 2019;62(6):426-430.
9. Van den Noort JC, Bar-On L, Aertbelien E, et al. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. *Eur J Neurol.* 2017;24(7):981-989.
10. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. *Muscle Nerve.* 2004;29(5):615-627.
11. Mayer NH. Clinicophysiologic concepts of spasticity and motor dysfunction in adults with an upper motoneuron lesion. *Muscle Nerve Suppl.* 1997;6:S1-13.
12. Lindberg PG, Gaverth 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(7):617-625.
13. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve.* 2005;31(5):535-551.
14. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. *Neurorehabil Neural Repair.* 2017;31(9):793-799.
15. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koelle WP, eds. *Spasticity: disordered motor control.* Chicago: Year Book Medical Publishers; 1980:485-494.
16. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol.* 2007;6(8):725-733.
17. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013;44(7):2064-2089.
18. Brunnström S. *Movement therapy in hemiplegia: a neuropsychological approach.* New York: Harper and Row; 1970.
19. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain.* 1951; 74(4):443-480.

20. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech.* 2016;35:93-101.
21. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8(8):741-754.
22. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. *Neurology.* 2013;80(3 Suppl 2):S45-52.
23. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* 2013;35(4):291-299.
24. Doan QV, Brashear A, Gillard PJ, et al. Relationship between disability and health-related quality of life and caregiver burden in patients with upper limb poststroke spasticity. *PM R.* 2012;4(1):4-10.
25. Franceschini M, La Porta F, Agosti M, Massucci M, group ICR. Is health-related-quality of life of stroke patients influenced by neurological impairments at one year after stroke? *Eur J Phys Rehabil Med.* 2010;46(3):389-399.
26. Pollock A, St George B, Fenton M, Firkins L. Top ten research priorities relating to life after stroke. *Lancet Neurol.* 2012;11(3):209.
27. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology.* 2015;45(3):161-176.
28. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med.* 2015;372(14):1333-1341.
29. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-1623.
30. Brown P. Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry.* 1994;57(7):773-777.
31. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. *Neurology.* 2013;80(3 Suppl 2):S20-26.
32. Sheean G. The pathophysiology of spasticity. *Eur J Neurol.* 2002;9(Suppl 1):3-9.
33. Kamper DG, Schmit BD, Rymer WZ. Effect of muscle biomechanics on the quantification of spasticity. *Ann Biomed Eng.* 2001;29(12):1122-1134.
34. Pandyan AD, Gregoric M, Barnes MP, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disabil Rehabil.* 2005;27(1-2):2-6.
35. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil.* 2009;23(7):651-658.

36. Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain.* 1968;91(1):1-14.
37. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67(2):206-207.
38. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* 1999;13(5):373-383.
39. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry.* 2010;81(1):46-52.
40. Mehrholz J, Wagner K, Meissner D, et al. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. *Clin Rehabil.* 2005;19(7):751-759.
41. Sorinola IO, White CM, Rushton DN, Newham DJ. Electromyographic response to manual passive stretch of the hemiplegic wrist: accuracy, reliability, and correlation with clinical spasticity assessment and function. *Neurorehabil Neural Repair.* 2009;23(3):287-294.
42. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clin Rehabil.* 2006;20(2):173-182.
43. Gracies JM, Brashear A, Jech R, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. *Lancet Neurol.* 2015;14(10):992-1001.
44. Elovic EP, Munin MC, Kanovsky P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. *Muscle Nerve.* 2016;53(3):415-421.
45. Bar-On L, Aertbelien E, Molenaers G, Dan B, Desloovere K. Manually controlled instrumented spasticity assessments: a systematic review of psychometric properties. *Dev Med Child Neurol.* 2014;56(10):932-950.
46. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil.* 2010;7:35.
47. Lorentzen J, Grey MJ, Crone C, Mazevet D, Biering-Sorensen F, Nielsen JB. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. *Clin Neurophysiol.* 2010;121(11):1939-1951.
48. Mirbagheri MM, Barbeau H, Kearney RE. Intrinsic and reflex contributions to human ankle stiffness: variation with activation level and position. *Exp Brain Res.* 2000;135(4):423-436.

49. Bar-On L, Desloovere K, Molenaers G, Harlaar J, Kindt T, Aertbelien E. Identification of the neural component of torque during manually-applied spasticity assessments in children with cerebral palsy. *Gait Posture.* 2014;40(3):346-351.
50. Chung SG, van Rey E, Bai Z, Rymer WZ, Roth EJ, Zhang LQ. Separate quantification of reflex and nonreflex components of spastic hypertonia in chronic hemiparesis. *Arch Phys Med Rehabil.* 2008;89(4):700-710.
51. Zhang LQ, Rymer WZ. Simultaneous and nonlinear identification of mechanical and reflex properties of human elbow joint muscles. *IEEE Trans Biomed Eng.* 1997;44(12):1192-1209.
52. Pisano F, Miscio G, Del Conte C, Pianca D, Candeloro E, Colombo R. Quantitative measures of spasticity in post-stroke patients. *Clin Neurophysiol.* 2000;111(6):1015-1022.
53. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med.* 2013;45(7):630-636.

CHAPTER 2

Effectiveness of botulinum toxin treatment for upper limb spasticity post stroke over different ICF domains: a systematic review and meta-analysis

Aukje S. Andringa
Ingrid G.L. van de Port
Erwin E.H. van Wegen
Johannes C.F. Ket
Carel G.M. Meskers
Gert Kwakkel

Arch Phys Med Rehabil. 2019;100(9):1703–1725

ABSTRACT

Objective: To provide a comprehensive overview of reported effects and scientific robustness of botulinum toxin (BoNT) treatment regarding the main clinical goals related to post-stroke upper limb spasticity, using the International Classification of Functioning, Disability and Health.

Data sources: Embase, PubMed, Wiley/Cochrane Library and Ebsco/CINAHL were searched from inception up to 16 May 2018.

Study selection: We included randomized controlled trials comparing upper limb BoNT injections with a control intervention in patients with a history of stroke. A total of 1212 unique records were screened by two independent reviewers. Forty trials were identified, including 2718 patients with a history of stroke.

Data extraction: Outcome data were pooled according to assessment timing (i.e. 4–8wk and 12wk after injection) and categorized into 6 main clinical goals (i.e. spasticity-related pain, involuntary movements, passive joint motion, care ability, arm and hand use, and standing and walking performance). Sensitivity analyses were performed for the influence of study and intervention characteristics, involvement of pharmaceutical industry and publication bias.

Data synthesis: Robust evidence is shown for the effectiveness of BoNT in reducing resistance to passive movement, as measured with the (modified) Ashworth scale, and improving self-care ability for the affected hand and arm after intervention ($P < 0.005$) and at follow-up ($P < 0.005$). In addition, robust evidence is shown for the absence of effect on arm-hand capacity at follow-up. BoNT was found to significantly reduce involuntary movements, spasticity-related pain and caregiver burden, and improve passive range of motion, while no evidence was found for arm and hand use after intervention.

Conclusions: In view of the robustness of current evidence, no further trials are needed to investigate BoNT for its favourable effects on resistance to passive movement of the spastic wrist and fingers, and on self-care. No trials are needed to further confirm the lack of effects of BoNT on arm-hand capacity, whereas additional trials are needed to establish the suggested favourable effects of BoNT on other body functions, which may result in clinically meaningful outcomes at activity and participation levels.

INTRODUCTION

Botulinum toxin (BoNT) therapy aims to reduce upper limb spasticity, one of the positive features of the upper motor neuron syndrome. Although BoNT targets the International Classification of Functioning, Disability and Health (ICF) level[1] of body functions, it is unknown whether its effect can be extrapolated to the clinically important levels of activity and participation.[2] The most commonly used outcome measures at body functions level, the modified Ashworth scale (MAS) and the Ashworth scale (AS), have been criticized regarding their measurement properties[3,4] and the relation with other ICF domains is unknown. Problems associated with the use of MAS and AS may arise from a poor understanding of the pathophysiology of spasticity, which interferes with research to establish the effectiveness of BoNT therapy. Current BoNT research is further hampered by differences in dosing regimens, injection sites, concurrent treatments, outcomes selected, timing of assessments and difficulties with the methodological quality of trials with insufficient scientific rigour, in which the role of the industry is often unclear.[5,6]

In the past decade, several reviews[7-15] that have studied the effectiveness of BoNT injections most often focused on the reduction of spasticity on the body functions level in upper limb after stroke. Despite all aforementioned problems, the MAS is mainly used as a primary outcome measure of aforementioned reviews, showing that BoNT may decrease the resistance to passive movement. However, BoNT is used in clinical practice for various goals, and its effectiveness on the clinically important levels of activity and participation remains unclear. Assessing the effectiveness of BoNT on different levels of the ICF model would provide a comprehensive overview of the effectiveness of BoNT on the main clinical goals following upper limb post-stroke spasticity. Additionally, none of the systematic reviews[5,7-18] address the overall robustness of claimed effects of BoNT across the considerable amount of published and high-costs randomized controlled trials (RCT).

The purpose of the current systematic review and meta-analysis was therefore (1) to give an overview of outcome measures used for the evaluation of BoNT treatment in the upper limb; (2) to assess the methodological quality of included trials; and (3) to summarise the effects, and their scientific robustness, of BoNT treatment regarding the main clinical goals related to post-stroke upper limb spasticity, using the ICF classification. Finally, we investigated the influence of study type (publication year, methodological quality), intervention characteristics (BoNT dosage, timing of the intervention after the stroke, additional therapy) and the involvement of the pharmaceutical industry on the claimed effect of BoNT and the likelihood of publication bias.

METHODS

Search strategy and selection criteria

The clinical question was defined in PICOS format – Participants (ischemic, haemorrhagic or embolic stroke, without a restriction in time since stroke onset and baseline clinical characteristics); Intervention (intramuscular BoNT A or B injection in the upper limb, including shoulder muscles, possibly as a part of a more complex treatment); Comparison (placebo injection, control intervention or no intervention); Outcomes (at one of the levels of the ICF classification); Study design (randomized controlled trial). Criteria for study inclusion were (1) adult participants (aged 18 years or older) to avoid bias to effect sizes caused by normal development of children; (2) evaluation of effects of a single BoNT A or B treatment on any of the ICF domains of body functions and structures, activities, participation or environmental factors; (3) designed as an RCT; and (4) including more than 10 patients. Studies were excluded when: (1) different BoNT injection-guidance techniques (e.g. ultrasonography, electrical stimulation) were compared without a usual care arm or a no-treatment arm; or (2) different types or brands of BoNT were compared.

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA statement. The following sources were searched (by A.A. and J.K.) from inception: Embase.com, PubMed, Wiley/Cochrane Library and Ebsco/CINAHL (Cumulative Index to Nursing and Allied Health Literature) up to 16 May 2018. The following terms were used (including synonyms and closely related words) as index terms or free-text words: botulin toxin, upper extremity or upper extremity muscles, stroke or cerebrovascular accident or acquired brain injury or hemiplegia, and randomized controlled trial or systematic review or meta-analysis. The full search strategies for all the databases can be found in Supplement 2A. Duplicate articles were excluded. Publications in the English, French, German, Spanish and Dutch were accepted.

Titles and abstracts were screened by two independent raters (A.A., I.P.) to determine eligibility for further review of the full texts. Articles were retained for full review if their abstracts met the inclusion criteria or if more information was required from the full text to confirm that the study met all the eligibility criteria. A third rater (C.M.) was consulted when no agreement was reached. Next, the full texts of all eligible articles were screened by one rater (A.A.) to establish the definitive inclusion. Reference lists of included articles and relevant systematic reviews found were screened for additional eligible articles.

Taxonomy and definitions used

Stroke was defined according to the updated definition by the Stroke Council of the American Heart Association and the American Stroke Association as an acute episode of focal and neurological dysfunction caused by cerebral vascular injury as a result of ischemia or haemorrhage.[19] A study was regarded an RCT when it concerned a clinical trial involving at least one test treatment and one control treatment, concurrent enrolment and follow-up of the test- and control-treated groups, and with treatment allocation of included patients based on a random procedure.[20] All definitions of spasticity were accepted in this systematic review, acknowledging that several definitions are used in the current literature on BoNT treatment.[21]

The effect of BoNT injections was categorized into 6 main clinical goals related to post-stroke upper limb spasticity, using the ICF classification,[1] that is reduction of spasticity-related pain, reduction of involuntary movements, improvement of passive joint motion, improvement of ability to care for the affected hand and arm, improvement of arm and hand use, and improvement of standing and walking performance influenced by upper limb posture (see Supplement 2B).[2] In line with the trials, we defined data collected 4 to 8 weeks after injection as post-intervention effects of BoNT, and those collected 12 weeks after injection as follow-up effects.[22]

Data analysis

Data extraction

The following data were extracted: (1) authors and date of study; (2) sample size; (3) information on trial participants (including age, type of stroke, time after stroke); (4) inclusion criteria; (5) details of experimental and control interventions (including type of BoNT, injection sites, doses, injection technique); (6) outcome measures (including primary and secondary outcome measures clustered into the different ICF domains and follow-up period); (7) definition of spasticity used; and (8) influence of the pharmaceutical industry.

Methodological quality

The methodological quality of included trials was assessed by two independent raters (A.A., I.P.) using the Physiotherapy Evidence Database (PEDro) scale,[23-25] which consists of 11 items rating internal validity (10 items) and external validity (1 item). Disagreements were resolved by discussion between two authors (A.A., I.P.). If disagreement remained, a third reviewer (C.M.) was asked to help reach consensus. Consistent with PEDro, we

assessed the internal validity to assess the risk of bias, using the following cut-off points: 9 to 10, excellent; 6 to 8, good; 4 to 5, fair; and < 4, poor. We classified RCTs with a score of ≥ 4 as a low risk of bias.

Quantitative analysis

Numbers of patients, mean post-intervention scores and SD of the outcome in the experimental and control groups were collected for each study and entered into the Review Manager 5.3 statistical program. Outcome data were pooled in categories of outcome measures with comparable construct for the 6 main clinical goals related to post-stroke upper limb spasticity, the ICF classification, the timing of assessment (i.e. post-intervention 4–8wk after injection and at follow-up 12wk after injection) and the primary target joint (i.e. shoulder, elbow, wrist, or fingers). When post-intervention scores were unavailable, data were requested from the authors. If essential data remained unavailable, post-intervention scores were calculated, if possible, from published data (including median [range], SE, frequencies and mean baseline values combined with change scores). In trials that included participants with other diagnoses than stroke, such as traumatic brain injury, only the number of patients used for our meta-analysis was adjusted to the number of stroke patients involved. Studies with poor methodological quality (PEDro < 4) were excluded from the meta-analysis. Studies with a crossover design were regarded as RCTs until the moment of crossover. Measurements at the crossover point were used as post-intervention outcomes. In case studies included multiple intervention groups with different doses of BoNT, data of these groups were merged.

The effect size in each study was established by calculating the mean difference (MD) when combining studies that used the same scale for the outcome measure, or standardized mean difference (SMD) when combining study results of studies that measured the same outcome construct with different scales.[20] When scales with different outcome directions were used, mean values were multiplied by -1 to align all scales. The SMD for individual studies was established by calculating the difference between the post-intervention scores of the experimental and control groups, and dividing this by the pooled post-intervention SDs of both groups. Summary effect sizes (SESs) were obtained by averaging the effect sizes of the individual studies using a weighting factor for each study determined by the SD and sample size.[20] To obtain a comprehensive overview of the effects of BoNT on the main clinical goals, the SES for each clinical goal was calculated based on the SMDs of the individual studies. A positive SES indicates a favourable effect of BoNT, whereas a negative SES indicates

unfavourable effects of BoNT. SESs of at least 0.2 were considered to indicate a small effect size, those of 0.5–0.79 a moderate effect size and those of 0.8 or higher a large effect size.[26]

The heterogeneity among the studies was assessed by the I^2 statistic to determine whether studies shared a common effect size whose variance could be explained by sampling error alone.[27] If significant heterogeneity was found (I^2 values > 50%), a random-effects model was applied, while a fixed-effects model was applied in case of statistical homogeneity. A fixed-effects model (Hedges' *g*) or a random-effects model was used to decide whether the SES was statistically significant.

The statistical power of each meta-analysis was calculated post-hoc, using the number of included comparisons, mean within-study sample size of the experimental and control groups, SES and 2-tailed *P* value.[28] A statistical power ≥ 0.80 was classified as sufficient to draw conclusions about the statistical rigour of the effects of BoNT for that specific ICF domain.[29]

Sensitivity analyses

Sensitivity analyses using scatterplots and correlation coefficients were conducted for comparisons which showed a significant SES, to investigate the moderating effect of study characteristics (publication year and methodological quality) and intervention characteristics (BoNT dosage, timing of the intervention after the stroke, additional therapy), as well as the influence of involvement of the pharmaceutical industry in the study on the meta-analysis. To determine publication bias, funnel plots of the SE of the intervention effect estimate were plotted on a reverse scale to the effect size of each study for comparisons including data of at least ten studies.[20] The plots were then visually checked for asymmetry as a sign of bias.

RESULTS

Study selection

The literature search yielded a total of 1862 records, and 7 additional abstracts were found by screening reference lists of included full-text articles and relevant systematic reviews. A total of 1212 abstracts remained after adjusting for duplicates, and 1086 of these studies were discarded after reviewing title and abstract, as they obviously did not meet the inclusion criteria. The full texts of the remaining 126 abstracts were examined in more detail. Forty

articles fulfilled all criteria and were selected for review (Figure 2.1).[22,30-68] Four of the included articles[45,56,66,67] used data from previously published studies for secondary data analysis, and data of one research project had been published twice, once as a Health Technology Assessment[54] and once in the journal *Stroke*.[55]

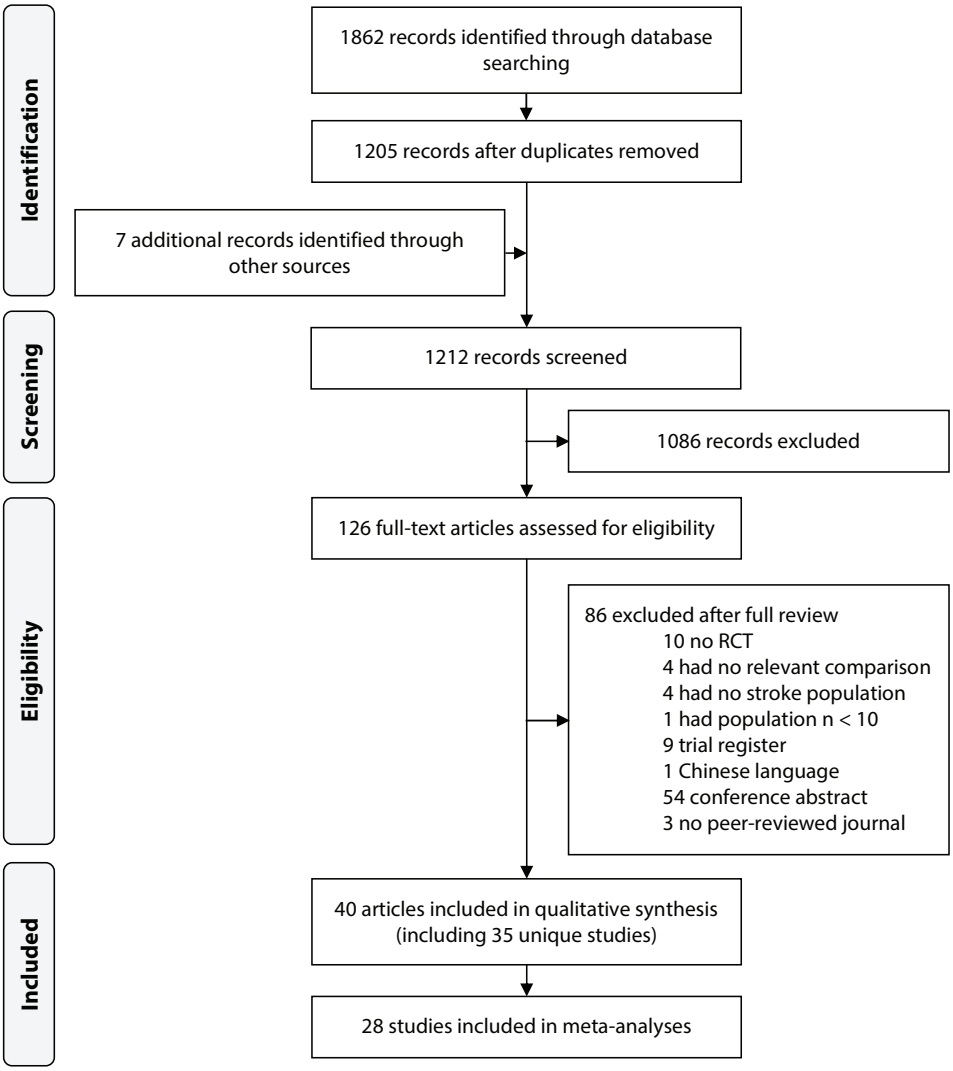


Figure 2.1. Study selection.

Description of studies

An overview of the included studies can be found in Table 2.1. All trials that were selected for this review were published in English between 1996 and April 2018. The 35 unique studies had included a total of 2718 patients with history of stroke indicated for BoNT treatment, with a sample size varying from 15 to 332 subjects; only four studies had included patients with history of stroke within three months after stroke.[40,52,57,59] The majority of the studies (n = 26) had included patients based on an increased resistance to passive movement, as measured by the MAS or AS. Interventions included BoNT injections using abobotulinum toxin-A (Dysport), onabotulinum toxin-A (Botox), incobotulinum toxin-A (Xeomin) or rimabotulinum toxin-B (NeuroBloc/Myobloc). This was administered without additional (usual) therapy in 16 studies, whereas in 19 studies patients received additional therapy, that is a rehabilitation program, electrical stimulation, robotic training or range of motion exercises. Control interventions encompassed placebo injections, using saline, except for three studies using intra-articular injections of triamcinolone acetonide[47] or oral tizanidine.[51,61] Methodological quality, as rated with the PEDro scale (Table 2.2), ranged from 4 to 10.

Table 2.1. Characteristics of included studies

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Bakheit et al.[32]	82 (63/19)	62.5±13.2 51/31	>3 mo 44 iCVA/ 15 hCVA/ 14 CE/ 9 NR	Severe or moderately severe spasticity (MAS ≥2 in wrist, elbow and finger flexors)
Bakheit et al.[35]	59 (27/32)	65.7±12.1 26/33	>3 mo 29 iCVA/ 11 hCVA/ 13 CE/ 6 not known	Spasticity (MAS≥2 in at least two out of the elbow, wrist and finger flexors and 1+ in the remaining area)
Bhakta et al.[33,45]	40 (20/20)	Age at stroke: 51.3±17.1 23/17	>6 mo 30 iCVA/10 hCVA	(1) finger flexor of elbow flexor spasticity (MAS>2) and (2) at least moderate difficulty with 2 out of 8 items defining patient disability
De Boer et al.[46]	21 (10/11)	57.4±8.8 12/9	exp 279 [512]; con 147 [158] d 18 iCVA/ 3 hCVA	(1) shoulder pain with a minimal score of 40mm on a pain VAS lasting for at least one wk, (2) restricted passive external rotation of the humerus >50% relative to the unaffected arm and (3) AS elbow ≥1
Brashear et al.[36]	126 (64/62)	61 (23–88) 63/63	>6 mo Stroke NS	(1) focal spasticity of the wrist and fingers (AS 3 or 4 for wrist flexor tone and AS≥2 for finger flexor tone) and (2) difficulty in maintaining hygiene or dressing, pain or malposition of the wrist or fingers
Brashear et al.[37]	15 (10/5)	55 (18–79) 8/7	>6 mo Stroke NS	AS≥2 for elbow, wrist and finger flexors

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- 500 U, 1000 U, or 1500 U Dysport - BB, FDP, FDS, FCU, FCR - MNP	Placebo	MAS,* aROM, PRoM, pain, RMA, BI, ORS	Baseline, 2, 4, 8, 12 and 16 wk	NR	Funding, study development, researcher recruitment and monitoring of data collection by IPSEN.
- 1000 U Dysport - BB, FDP, FDS, FCU, FCR - MNP	Placebo	MAS,* aROM, PRoM, pain, BI, GAS, ORS	Baseline, 4, 8, 12 and 16 wk	NR	Funding by IPSEN.
- 1000 U Dysport - BB, BR, FDS, FDP, FCU - MNP	Placebo Concurrent treatments remained unchanged	DS,* CBS,* MRC, MVG, MAS, PRoM, aROM, pain, AR*	Baseline, -1, 2, 6 and 12 wk	NR	Funding by IPSEN.
- 100 U Botox + some form of (physical) therapy - SS - MNP	Placebo + some form of (physical) therapy	Pain,* PRoM*	Baseline, 6 and 12 wk	NR	No competing interests.
- 200–240 U Botox - FCR, FCU, FDP, FDS, FPL - technique NR	Placebo	DAS,* AS, GA	Baseline, 1, 4, 6, 8 and 12 wk	NR	Funding, study development, data management and statistical analysis by Allergan. Two authors are former Allergan employees (with stock options).
- 10,000 U Myobloc - BB, FCU, FCR, FDS, FDP - ES	Placebo Concurrent treatments remained unchanged	AS,* GAC, aROM, PRoM, NHPT, JT	Baseline, 2, 4, 8, 12 and 16 wk	NR	Funding by Elan Pharmaceuticals.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Childers et al.[38]	91 (65/26)	60.0 (30.4–79.4) 61/30	25.8 (0.9–226.9) mo 51 iCVA/ 19 hCVA/ 16 EC/ 5 not known	Focal spasticity of upper limb (excessive wrist flexor muscle tone score of 3 or higher and elbow flexor tone score of 2 or more on MAS)
Cousins et al.[52]	30 (19/11)	69±11.8 13/17	23±9 d 17 TACS/ 9 PACS/ 4 LS	Unable to score maximal on the easiest test of the Grasp subsection of the ARAT
Elovic et al.[65]	259 (171/88)	56.0 ± 11.4 147/112	28 (3–412) mo Stroke NS	Flexed elbow, flexed wrist and clenched fist clinical pattern of spasticity with muscle tone ≥2 on the AS at each site
Gracies et al.[62]	24 (16/8)	55±15 14/10	108±121 mo 15 iCVA/4 hCVA/5 TBI	(1) Overactivity in upper limb muscles causing impaired active function, discomfort, disfigurement or pain, and in particular (2) elbow flexor overactivity causing impaired function or disfigurement
Gracies et al.[22]/ Marciniak et al.[66]/O'Dell et al.[67]	238 (159/79)	52.8±13.5 153/85	5.6±5.1 y 215 CVA/23 TBI	(1) MAS score in the primary target muscle group (PTMG) at least 2 for patients who had no previous btxA injection or at least 3 for patients with previous injections of btxA, (2) Disability Assessment Scale score of at least 2 on the principal target of treatment, (3) spasticity angle of at least 10 degrees in the PTMG and (4) mean Modified Frenchay Scale score of 1–8 (max 10)

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- 90 U, 180 U, or 360 U Botox - BB, FCU, FCR, FDP, FDS - EMG	Placebo Concurrent treatments remained unchanged	MAS,* GAC, DS, pain, FIM, SF-36	Baseline, 1, 2, 3, 4, 5, 6, 9, 12, 18 and 24 wk	Lance, 1980	Funding and one authorship by Allergan.
- 155 U or 77.5 U Botox + regular therapy - BB, B, BR, FDS, FDP - technique NR	Placebo + regular therapy	ARAT,* EMG, MVG, aROM, PRoM	Baseline, 4, 8, 12 and 20 wk	Pandyan, 2005	Funding by Allergan.
- 400 U Xeomin - One primary target clinical pattern (flexed elbow, flexed wrist or clenched fist) - EMG and/or ES, US as a supplement	Placebo	AS,* GAC, DAS	Baseline, 4, 8 and 12 wk	NR	Funding by Merz Pharmaceuticals.
- 10,000 U or 15,000 U Myobloc/ Neurobloc - BB, B, BR and additional upper limb muscles - ES and endplate targeting technique	Placebo Concurrent treatments remained unchanged	aROM,* PRoM, TS, MFS, pain, AS	Baseline, 1, 2 and 3 mo	NR	Funding by Solstice Neurosciences.
- 500 U or 1000 U Dysport - most hypertonic muscle group among elbow, wrist and finger flexors as the PTMG. At least two additional upper limb muscles among elbow, wrist, or finger flexors or shoulder extensors - ES	Placebo Concurrent treatments remained unchanged	MAS,* GAC, DAS, TS, aROM, SF-36, EQ-5D	Baseline, 1, 4 and 12 wk	NR	Funding and three authorships by IPSEN.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Guo et al.[40]	60 (30/30)	43±13 39/21	Time NR 22 iCVA/21 hCVA/17 TBI	Obvious increase of spastic muscle strength in upper limbs (AS ≥2)
Hesse et al.[31]	24 (12/12)	52.3 (32–73) 19/5	7.45 (6–11) mo 18 iCVA/6 hCVA	(1) demonstrate severe upper limb flexor spasticity of at least MAS 3 and (2) affected extremity is non-functional, with no possibility of any selective movement except protracting the shoulder girdle
Hesse et al.[57]	18 (9/9)	62±12 6/12	5.7±1.2 wk 13 iCVA/5 hCVA	(1) at least wheelchair-mobilized and partly independent in the basis activities of living (BI>25 (0–100)), (2) non-functional upper extremity with a FM-UE score <20, no (MRC 0) volitional wrist of finger extensor activity and (3) beginning finger and/or wrist flexor stiffness MAS 1 or 2
Jahangir et al.[41]	52 (27/25)	60.8±11.2 33/19	45.2±40.0 mo 49 iCVA/3 hCVA	Focal spasticity of wrist and fingers at least 3 months before enrolment (MAS≥2)
Kaji et al.[53]	109 (72/37)	63.3±10.5 74/35	82.9±72.3 mo Stroke NS	(1) focal spasticity of both wrist and fingers (3 or 4 for wrist flexors and 2 or higher for finger flexors on the MAS) and (2) 2 or 3 on the DAS for at least one of 4 areas of functional disability

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- 400 U botulinum toxin-A + rehabilitative training - BB, BR, B, FCR, FCU, PL, FDS, FDP, FPL - EMG	Rehabilitative training	MAS,* FM-UE, BI	Baseline, 1 and 2 wk, and 1 and 3 mo	NR	NS
- 1000 U Dysport with or without electrical stimulation + regular physiotherapy (30min/wk) - BB, B, FCU, FCR, FDP, FDS - EMG	Placebo with or without electrical stimulation + regular physiotherapy (30min/wk)	MAS,* limb position at rest, ORS	Baseline, 2, 6 and 12 wk	NR	Funding by Speywood Pharmaceuticals.
- 150 U Xeomin + inpatient rehabilitation program - FDP, FDS, FCR, FCU - US	Inpatient rehabilitation program	MAS,* REPAS, FM-UE, DS	Baseline, 1 and 6 mo	Pandyan, 2005	NS
- 80 U Botox + regular physiotherapy (2 hrs/wk) - FCU, FCR, FDS, FDP - Technique NR	Placebo + regular physiotherapy (2 h/wk)	MAS, BI, EQ-5D	Baseline, 1 and 3 mo	NR	NS
- 120–150 U or 200–240 U Botox - FCR, FCU, FDS, FDP, FPL, AP - EMG or ES	Placebo	MAS,* DAS, GAC	Baseline, 1, 4, 6, 8 and 12 wk	Lance, 1980	Funding and 5 authorships by GlaxoSmithKline K.K.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Kanovsky et al.[48]	148 (73/75)	55.7±13.3 95/53	55.0±48.7 mo Stroke NS	Focal spasticity of wrist and finger flexors (as demonstrated by the clinical patterns and a score of ≥ 2 on the AS)
Kong et al.[42]	16 (7/9)	51.8±13.6 11/5	9.3±6.5 mo 10 iCVA/6 hCVA	(1) hemiplegic shoulder pain of 2 wk duration or more, with pain severity score of 4 or higher when assessed on a visual analogue scale and (2) shoulder adductor and elbow flexor spasticity of at least 2 or higher on the AS
Lim et al.[47]	29 (16/13)	61.4±11.2 15/14	261±237 d 20 iCVA/9 hCVA	(1) hemiplegia in an arm, (2) pain level in the hemiplegic shoulder of ≥6 (on NRS 0–10) as rated by the patient during passive ROM (duration of pain ≤ 12 months) and (3) limitation of passive external rotation of the hemiplegic shoulder of at least 20 degrees compared with the unaffected side
Marciniak et al.[58]	21 (10/11)	60.0±9.0 13/8	Time NR Stroke NS	(1) hemiplegia/ hemiparesis, (2) received physical therapy or occupational therapy for shoulder pain for at least 2 wk with no change in pain or function and (3) shoulder pain of at least 4 on the VAS, an AS of 3 or greater for shoulder tone for adductors and internal rotators
Marco et al.[43]	29 (14/15)	65.6±9.1 21/8	141 [107–241] d 29 iCVA	(1) spastic hemiparesis, (2) moderate-severe spastic shoulder pain, (3) VAS pain ≥40m and (4) spasticity MAS ≥3

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- Max 400 U Xeomin - FCR, FCU, FDS, FDP, BR, BB, B, PQ, PT, FPL, AP, FPB - ES or EMG	Placebo Concurrent treatments remained unchanged	AS,* DAS, CBS, GAC	Baseline, 2, 4, 8 and 12 wk	Lance, 1980	Funding and three authorships by Merz Pharmaceuticals.
- 500 U Dysport + range of motion exercises (twice/d) - PM, BB - MNP	Placebo + range of motion exercises (twice/d)	Pain,* AS, PRoM	Baseline, 4, 8 and 12 wk	NR	Funding by IPSEN.
- 100 U Botox + intraarticular placebo injection + physiotherapy (twice/wk) + range of motion exercises - IS, PM, SS - EMG	Intraarticular injection of triamcinolone acetonide + intramuscular placebo injection + physiotherapy (twice/wk) + range of motion exercises	Pain,* GAC, PRoM, FM-UE, MAS	Baseline, 2, 6 and 12 wk	NR	Funding by Allergan Korea.
- 140–200 U Botox - PM, TM - EMG	Placebo	Pain,* MAS, PRoM, McGill pain score, BDI, FM-UE, FIM-upper body dressing/hygiene, DAS	Baseline, 2, 4 and 12 wk	NR	Funding by Allergan.
- 500 U Dysport + TENS + rehabilitation program - PM - EMG	Placebo + TENS + rehabilitation program	Pain,* MAS, PRoM	Baseline, 1 wk and 1, 3 and 6 mo	NR	No competing interests.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
McCrory et al.[49]/ Turner-Stokes et al.[56]	96 (54/42)	59.1±13.2 58/38	5.9±10.5 y iCVA/hCVA (NS)	Moderate to severe spasticity (minimal score of 2 on MAS in at least 2 out of 3 of wrist, elbow and finger flexor muscles and a minimum of 1+ for the third area)
Meythaler et al.[50]	21 (11/10)	53.34±14.40 15/6	>6 mo iCVA/hCVA (NS)	Spasticity (AS elbow or wrist >3 or Penn Spasm frequency scale ≥2)
Pennati et al.[64]	15 (7/8)	53.66 (38–69) 9/6	10 mo to 20 y 10 iCVA/5 hCVA	Unilateral upper limb paresis or plegia with spasticity
Rosales et al.[59]	163 (80/83)	55.1 (17–79)† 109/54	7.4±3.0 wk 118 iCVA/45 hCVA	(1) MAS score of 1+ or higher in elbow or wrist joint and (2) weakness of at least MRC 2 in the relevant joints
Shaw et al.[54,55]	332 (170/162)	exp 67 [58.8–74]; con 66 [59.8–72.3] 225/107	exp 324 [128.5–1387.5] d; con 280 [148.8–1145.8] d 143 TACS/118 PACS/59 LS/5 PCS/7 not known	(1) spasticity at the elbow (MAS >2) and/or spasticity at shoulder, wrist or hand, and (2) reduced upper limb function (ARAT 0–56)
Simpson et al.[30]	37 (27/10)	59±12 16/21	37 (9–133) mo 22 iCVA/8 hCVA/5 EC/2 not known	Average elbow and wrist flexor tone of AS grade 2.5 or higher, with a minimum flexor score of 2 at both joints

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- 750–1000 U Dysport - BB, BR, B, TB, FDP, FDS, FCR, FCU, FPL, FPB - EMG or ES	Placebo Concomitant therapies according to routine practice	AQoL,* GAS, pain, HADS, GAC, MAS, DS, CBS, MMAS	Baseline, 8, 12, 20 and 24 wk (reinjection after 12 wk)	NR	Funding by IPSEN. One author is member of advisory board IPSEN.
- 300–400 Botox + therapy program (2 h/wk occupational therapy) - FCR, FCU, BB, BR - EMG	Placebo + therapy program (2 h/wk occupational therapy)	MAL,* AS, KB-ADL, BI, MOS-36, aROM, PRoM, MRC, MVG, pain	Baseline, 12 and 24 wk (cross-over after 12 wk)	NR	Funding by Allergan. Allergan was allowed to see a prior draft and make comments, but authors made all decisions regarding the final content.
- individual dose, dependent on muscles affected, of Dysport + robotic training (10 sessions, 2 or 3/wk) - PM, BB, TB, FCU, FCR, FDS, FDP, FPL - ES	Robotic training (10 sessions, 2 or 3/wk)	FM-UE, B&B test, MAS, FIM, Euro QoL	Baseline and at the end of training	Lance, 1980	No competing interests.
- 500 U Dysport + rehabilitation program - BB, BR, FCU, FCR, FDS, FDP, FPL - technique NR	Placebo + rehabilitation program	MAS,* BI, mRS, FMAS, pain, aROM, PRoM	Baseline, 2, 4, 8, 12 and 24 wk	NR	Funding, logistical support and data analysis by IPSEN.
- 100 U Dysport + 4-wk upper limb therapy program - injected muscle NR - technique NR	4-wk upper limb therapy program	ARAT,* MAS, MI, MVG, NHPT, ORS, BI, pain	Baseline, 1, 3 and 12 mo	NR	Funding by IPSEN.
- 75 U, 150U, or 300U Botox - BB, FCR, FCU - EMG	Placebo Concurrent treatments remained unchanged	AS, CDS, pain, MVG, GAC, FIM, RAND-36, FM-UE	Baseline, 2, 4, 6, 10 and 16 wk	Lance, 1980	Funding and 5 authorships by Allergan.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Simpson et al.[51]	60 (20/40)	55.9±12.8 33/27	>3 mo 49 Stroke/11 TBI	(1) spasticity of the wrist (MAS≥3 for wrist flexor) and (2) difficulty with hygiene or dressing, pain or malposition of the wrist (DAS score ≥2)
Smith et al.[34]	25 (19/6)	52±18 10/15	1064±810 d 14 iCVA/5 hCVA/3 TBI/ 3 not known	(1) troublesome spasticity in the upper hemiparetic limb (interfering with hand grasp or release, dexterity, reaching and/or dressing) and (2) flexor deformity at elbow, wrist or fingers in a non-functioning or partially functioning arm
Suputtitada et al.[39]	50 (35/15)	52.4±13.0 26/24	8.3±0.8 mo 28 iCVA/20 hCVA/2 EC	(1) upper limb spasticity and (2) the subjects having received at least 6 months of rehabilitation therapy
Umar et al.[68]	41 (21/20)	46.2±11.0 24/17	>6 mo 29 iCVA/12 hCVA	Post-stroke focal dystonia or spastic dystonia of upper limb causing limitations in daily activities

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- Max 500 U Botox + oral placebo - FCR, FCU - ES	Placebo injection + oral tizanidine, or placebo injection + oral placebo	MAS,* DAS, MFS, 10m walking speed, contralateral MVG, finger tap test, Epworth Sleepiness Scale, cognitive evaluation	Baseline, 3, 6, 12 and 18 wk	NR	Funding by Allergan.
- 500 U, 1000 U, or 1500 U Dysport - injected muscle NR - technique NR	Placebo Concurrent physiotherapy remained unchanged	PRoM,* aROM,* MAS,* postural alignment, time to dress upper half body, FAT	Baseline, 2, 6 and 12 wk	NR	Funding by IPSEN.
- 350 U, 500 U, or 1000 U Dysport + daily stretching exercises + rehabilitation program (3 d/wk) - BB, FCU, FCR, FDP, FDS - EMG	Placebo + daily stretching exercises + rehabilitation program (3 d/wk)	MAS, ARAT, BI, pain	Baseline, 2, 4, 8, 16 and 24 wk	NR	Funding by IPSEN.
- 100 U Botox + task-specific training (3 d/wk) - B, BB, TB, FDS, FDP, FCU, FCR, EPL, FPL - MNP	Task-specific training (3 d/wk)	MoAS, FM-UE	Baseline, 4 and 8 wk	NR	No competing interests.

Table 2.1 continues on next page

Table 2.1. *Continued*

Study name	No. of patients N (exp/ con)	Participants - Mean age ± SD/ (range) or median age [IQR] (y) - Sex (male/ female)	Stroke - Mean time ± SD/ (range) or median time [IQR] (d, mo, or y) post stroke - Stroke type	Inclusion criteria - Indication for BoNT
Ward et al.[63]	274 (139/135)	58.1±14.6 161/113	94.2±87.4 mo 204 iCVA/69 hCVA/1 not known	(1) hemiplegia/ hemiparesis and (2) the potential for functional gains following treatment with BoNT for upper or lower limb spasticity
Wolf et al.[60]	25 (12/13)	49.3±14.3 15/10	3 to 24 mo iCVA/hCVA (NS)	(1) spasticity in wrist/finger muscles but with ability to initiate wrist extension of at least 10 degrees, (2) active shoulder flexion and abduction to 45 degrees and no less than -30 of elbow extension, (3) ability to repeat these movements 3 times within 1 minute and (4) EMG evidence of volitional activation of wrist and finger extensor and flexor muscles
Yazdchi et al.[61]	68 (34/34)	66.1 (35–70) 39/29	>3 mo iCVA/hCVA (NS)	Minimum score of MAS 2 in the upper limb
Yelnik et al.[44]	20 (10/10)	54.1±6.6 15/5	509±790 d 11 iCVA/9 hCVA	Upper limb spasticity (at least MAS 1+ for the medial rotators and elbow flexors), with limited range of passive motion of the shoulder (external rotation 10 degrees or <30 degrees related to the opposite side)

Experimental intervention - Dosage/BoNT type - Injection sites - Injection technique	Control intervention	Outcome measures*	Assessment moments (d, wk, mo, or y)	Used definition of spasticity	Influence of pharmaceutical industry
- Max 800 U Botox + standard care - injected muscle NR - technique NR	Placebo + standard care	GAS,* REPAS	Baseline, 12 and 22–24 wk	NR	Funding, study development, data collection, statistical analysis and data interpretation by Allergan. The authors had sole control over the preparation, review and approval of the manuscript.
- < 300U Botox + exercise program - wrist and finger muscles (NS) - technique NR	Placebo + exercise program	WMFT,* MAS, aROM, SIS	Baseline, 1, 2 and 3 mo	NR	Funding by Allergan.
- 500 U Dysport + physiotherapy program (3 h/wk) - BB, FCR, FCU, FDP - technique NR	Oral tizanidine + physiotherapy program (3 h/wk)	MAS, ARAT	Baseline, 12 and 24 wk	Daroff, 2012	No competing interests.
- 500 U Dysport + physiotherapy (5d/wk) - SS - ES	Placebo + physiotherapy (5d/wk)	Pain,* PRoM, MAS	Baseline, 1, 2 and 4 wk	NR	Two authors have been reimbursed by IPSEN for attending conferences.

Table 2.1 continues on next page

Table 2.1. *Continued*

* Primary study outcome measures.
† Unless Rosales study inclusion criteria, one 17-year old person included.
Abbreviations: AP, m. adductor pollicis; AQoL, health status to disability and handicap; AR, associated reaction in the paretic arm muscles; ARAT, Action Research Arm Test; aROM, active range of motion; AS, Ashworth Scale; B, m. brachialis; B&B test, Box & Block Test; BB, m. biceps brachii; BDI, Beck Depression Inventory; BI, Barthel Index; BR, m. brachioradialis; CBS, Carer Burden Scale; CDS, Caregiver Dependency Scale; CE, cerebral embolism / embolic stroke; d, days; DAS, Disability Assessment Scale; DS, disability scale; EMG, electromyogram; EPL, m. extensor pollicis longus; EQ-5D, EuroQol; ES, electrical stimulation; FCR, m. flexor carpi radialis; FCU, m. flexor carpi ulnaris; FDP, m. flexor digitorum profundus; FDS, m. flexor digitorum superficialis; FIM, Functional Independence Measure; FMAS, Functional Motor Assessment Scale; FM-UE, Fugl-Meyer motor Assessment of the upper limb; FPB, m. flexor pollicis breves/opponens; FPL, m. flexor pollicis longus; GA, Global Assessment scale; GAC, Global Assessment of Change / benefit; GAS, Goal Attainment Scale; h, hours; HADS, Hospital Anxiety and Depression scale; hCVA, haemorrhagic stroke; iCVA, ischemic stroke/thrombotic; IS, m. infraspinatus; JT, Jebsen Test of hand function; KB-ADL, Klein-Bell Activity of Daily Living Scale; LS, Lacunar syndrome/stroke; MAL, Motor Activity Log; MAS, Modified Ashworth Scale; MFS, Modified Frenchay Scale; MI, Motricity Index; MMAS, Modified Motor Assessment Scale; MNP, manual needle placement/anatomic landmarks; mo, months; MoAS, Motor Assessment Scale; MRC, Medical Research Council muscle power grading; mRS, modified Rankin Scale; MVG, maximum voluntary grip strength; NHPT, Nine Hole Peg Test; NR, not reported; NRS, numeric rating scale for pain; NS, not specified; ORS, ordinal rating scale performing three passive functional activities; PACS, Partial anterior circulation syndrome/stroke; PCS, Posterior circulation stroke; PL, m. palmaris longus; PM, m. pectoralis major; PQ, m. pronator quadratus; PRoM, passive range of motion; PT, m. pronator teres; REPAS, Resistance to Passive movement scale; RMA, Rivermead Motor Assessment; SF-36/MOS-36/RAND-36, Short Form Health Survey; SIS, Stroke impact scale; SS, m. subscapularis; TACS, Total anterior circulation syndrome/stroke; TB, m. triceps brachii; TBI, traumatic brain injury; TM, m. teres major; TS, Tardieu Scale; US, ultrasonography; VAS, visual analogue scale for pain; wk, weeks; WMFT, Wolf Motor Function Test; y, years.

Table 2.2. Methodological quality of included studies (PEDro scale)

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Bakheit et al.[32]	1	1	0	1	1	0	1	1	1	1	1	8
Bakheit et al.[35]	1	1	1	1	1	0	1	1	1	1	1	9
Bhakta et al.[33]	1	1	1	1	1	1	1	1	1	1	1	10
Bhakta et al.[45]	1	1	1	1	1	1	1	1	1	1	1	10
De Boer et al.[46]	1	1	0	1	1	0	0	1	0	1	1	6
Brashear et al.[36]	1	1	0	1	1	1	1	1	0	1	1	8
Brashear et al.[37]	1	1	1	1	1	1	1	1	0	1	1	9
Childers et al.[38]	1	1	1	1	1	1	0	0	0	1	1	7
Cousins et al.[52]	1	1	1	0	1	0	1	0	0	1	1	6
Elovic et al.[65]	1	1	1	1	1	0	0	1	0	1	1	7
Gracies et al.[62]	1	1	1	1	1	1	1	1	0	1	1	9
Gracies et al.[22]	1	1	1	1	1	1	1	1	1	1	1	10
Guo et al.[40]	1	1	0	1	0	0	0	1	0	1	1	5
Hesse et al.[31]	1	1	0	1	1	0	1	0	0	1	1	6
Hesse et al.[57]	1	1	1	1	0	0	1	1	0	1	1	7
Jahangir et al.[41]	1	1	0	1	0	0	0	0	0	1	1	4
Kaji et al.[53]	1	1	1	1	0	0	0	1	1	1	1	7
Kanovsky et al.[48]	1	1	1	0	0	0	0	1	1	1	1	6
Kong et al.[42]	1	1	1	1	1	1	1	1	0	1	1	9
Lim et al.[47]	1	1	1	1	1	0	1	0	1	1	1	8
Marciniak et al.[58]	1	1	1	1	1	1	1	1	1	1	1	10
Marciniak et al.[66]	1	1	1	1	1	1	1	1	0	0	1	8
Marco et al.[43]	1	1	1	1	1	1	1	1	0	1	1	9
McCrory et al.[49]	1	1	1	1	1	1	1	1	1	1	1	10
Meythaler et al.[50]	1	1	1	1	1	1	0	1	0	1	1	8
O'Dell et al.[67]	1	1	1	1	1	1	0	0	0	0	1	6
Pennati et al.[64]	1	1	1	0	0	0	1	1	0	0	1	5
Rosales et al.[59]	1	1	1	1	1	1	1	1	1	1	1	10
Shaw et al.[54,56]	1	1	1	1	0	0	1	1	1	1	1	8
Simpson et al.[30]	1	1	0	1	1	1	0	1	0	1	1	7
Simpson et al.[51]	1	1	0	1	1	1	1	1	1	1	1	9
Smith et al.[34]	1	1	0	0	1	0	1	0	0	1	1	5
Suputtitada et al.[39]	1	1	0	1	1	0	1	0	0	1	1	6
Turner-Stokes et al.[56]	1	1	1	1	1	1	1	1	0	1	1	9
Umar et al.[68]	1	1	1	1	1	0	0	1	1	1	1	8
Ward et al.[63]	1	1	0	1	1	0	0	1	1	1	1	7
Wolf et al.[60]	1	1	0	1	1	1	0	1	1	1	1	8
Yazdchi et al.[61]	1	1	0	0	0	0	1	1	0	0	1	4
Yelnik et al.[44]	1	1	1	1	0	0	0	1	0	1	1	6

Note. 0 indicates no; 1 indicates yes; and total score is the sum score item 2–11 (internal validity).

Outcome measures

Figure 2.2 provides an overview of the primary and secondary outcome measures used to evaluate the effect of BoNT therapy on the six main clinical goals. In total, 35 different outcome measures were identified from the 40 included trials. As shown in Figure 2.2, multiple outcome measures were used for effect evaluation of the same clinical goal. Overall, the MAS and AS were used as the primary measurement of outcome in 15 (37.5%) of the 40 trials.

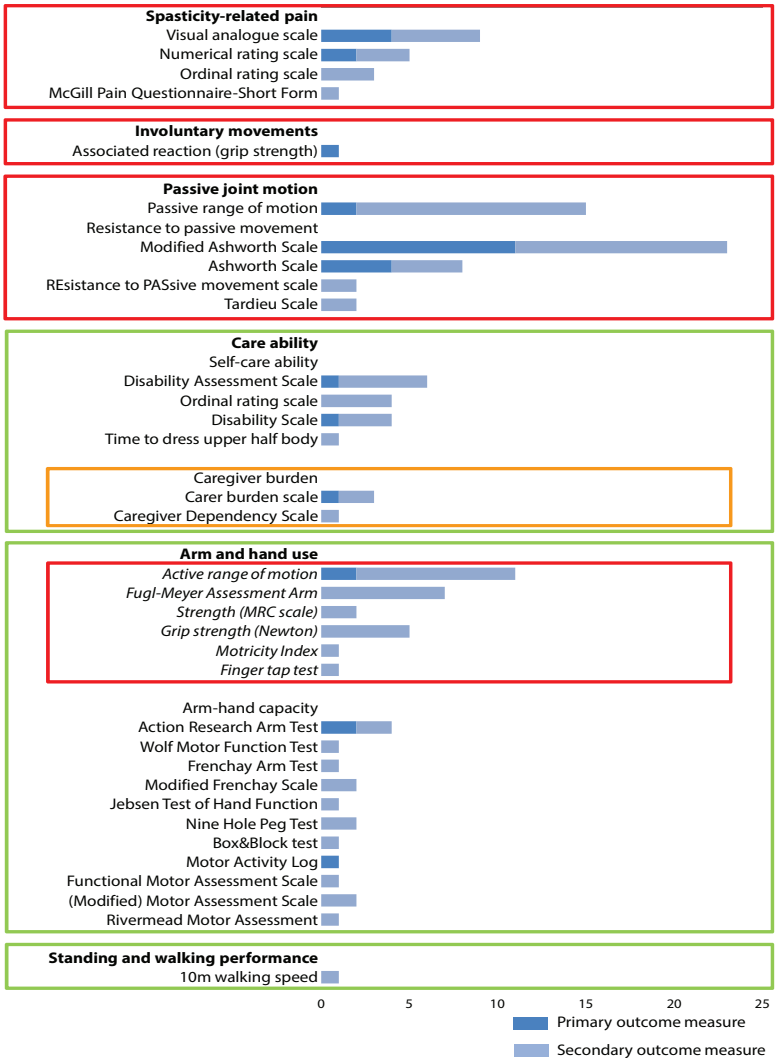


Figure 2.2. Overview of primary and secondary outcome measures used for effect evaluation of BoNT treatment for each clinical goal (number of times used in the included studies).
Coloured frames represent ICF-domains; 'body functions' (red), 'activity' (green) and 'environmental' (orange).

Quantitative analysis

Fifteen of the 40 included articles reported post-intervention means and SDs, or the authors provided data after our e-mail request. Thirteen studies reported data from which post-intervention means and SDs could be calculated. Several study authors refused to share raw data of post-intervention means and SDs, and did not reply to repeated data requests, so these studies had to be excluded from the meta-analysis. A comprehensive overview of the meta-analysis of data post-intervention (4–8wk after injection) and at follow-up (12wk after injection) is shown in Figures 2.3 and 2.4. Separate meta-analyses regarding all clinical goals, including different subgroups at both time points, are provided in Supplement 2C.

Effect of BoNT on the reduction of spasticity-related pain

Spasticity-related pain was investigated in eleven RCTs.[33,42-44,46,47,49,50,55,58,62] Pooling resulted in a non-significant SES for the reduction of spasticity-related pain post-intervention and a significant homogeneous positive SES at follow-up (SES, 0.25; 95% confidence interval [CI], 0.06–0.44; $P = 0.01$). All six RCTs[42-44,46,47,58] with the shoulder joint as the primary target joint recorded spasticity-related pain as a primary outcome measure. Subgroup analyses of these studies yielded non-significant SESs for spasticity-related shoulder pain post-intervention (SES, 0.29; 95% CI, -0.06 to 0.64; $P = 0.11$), as well as at follow-up (SES, 0.34; 95% CI, -0.04 to 0.72; $P = 0.08$). The remaining RCTs,[33,49,50,55,62] reporting data about overall spasticity-related pain in the arm showed a significant homogeneous positive SES for the reduction of spasticity-related pain at follow-up (SES, 0.22; 95% CI, 0.00–0.44; $P = 0.05$). All SESs had insufficient statistical power (range 0.11–0.45).

Effect of BoNT on the reduction of involuntary movements

One study[45] examined the effect of BoNT on the reduction of associated reactions in the affected upper limb during maximum voluntary grip in the unaffected arm. A significant positive SES was found post-intervention (SES, 0.70; 95% CI, 0.04–1.35; $P = 0.04$) while a non-significant SES was found at follow-up, both with insufficient statistical power.

Effect of BoNT on the improvement of passive joint motion

Improvement of passive joint motion, using passive range of motion (PRoM) as an outcome measure, was investigated by 15 RCTs, only two of which defined PRoM as the primary outcome. Pooling resulted in a significant homogeneous SES for the increase in PRoM post-intervention (SES, 0.28; 95% CI, 0.02–0.55; $P = 0.04$) and a non-significant SES at

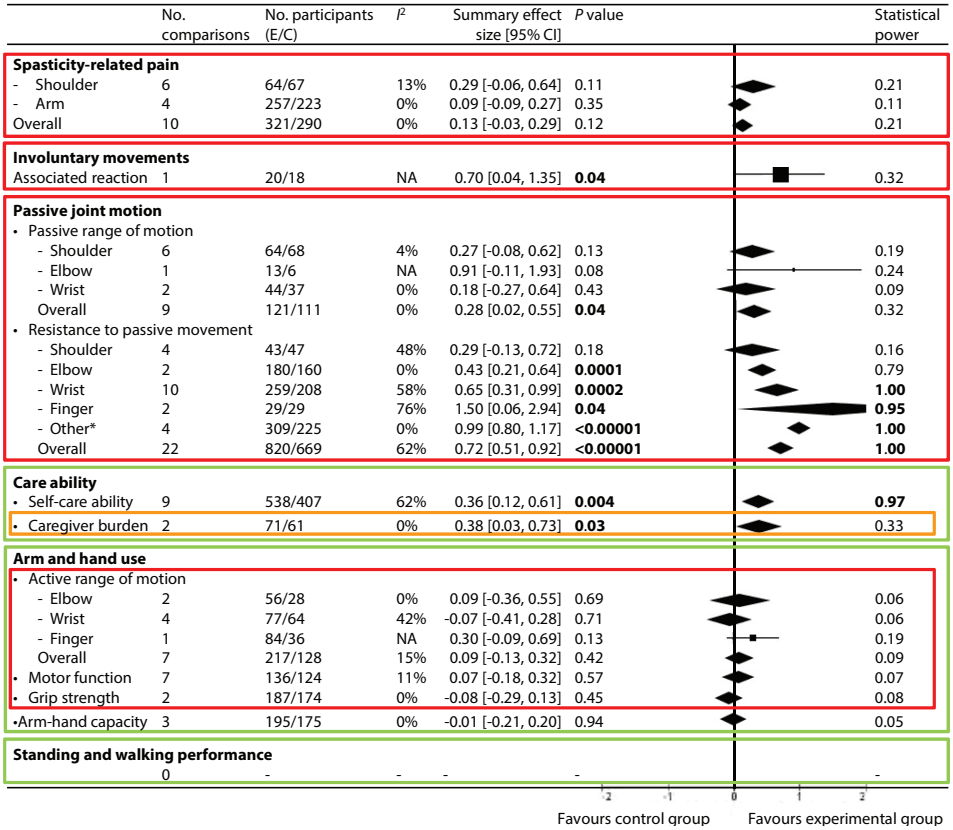


Figure 2.3. Forest plot of post-intervention SES of BoNT treatment for each clinical goal (4–8wk after injection). Coloured frames represent the clinical goals on ICF domains body functions and structures (red), activities (green) and environmental factors (orange). Please consult Supplement 2C for detailed meta-analyses. Note. I^2 represents heterogeneity (%). Abbreviations: C, control group; E, experimental group; NA, not applicable. * Measured upper limb joint not specified or multiple upper limb joint scores combined.

follow-up. However, subgroup analyses of the individual joints yielded non-significant SESs post-intervention and only the shoulder joint showed a significant homogeneous SES for the increase in PRoM at follow-up (SES, 0.44; 95% CI, 0.05–0.82; $P = 0.03$). All analyses lacked statistical power (range 0.09–0.36).

A total of 35 studies used resistance to passive movement (AS, MAS, Tardieu Scale, or REsistance to PAssive movement Scale) as an outcome measure; data of only 22 of these studies were available. Overall, significant heterogeneous positive SESs were found for the reduction of resistance to passive movement post-intervention (SES, 0.72; 95% CI, 0.51–0.92; $P < 0.00001$) and at follow-up (SES, 0.49; 95% CI, 0.28–0.70; $P < 0.00001$), both having sufficient power (1.00). Subgroup analyses of the individual joints yielded significant

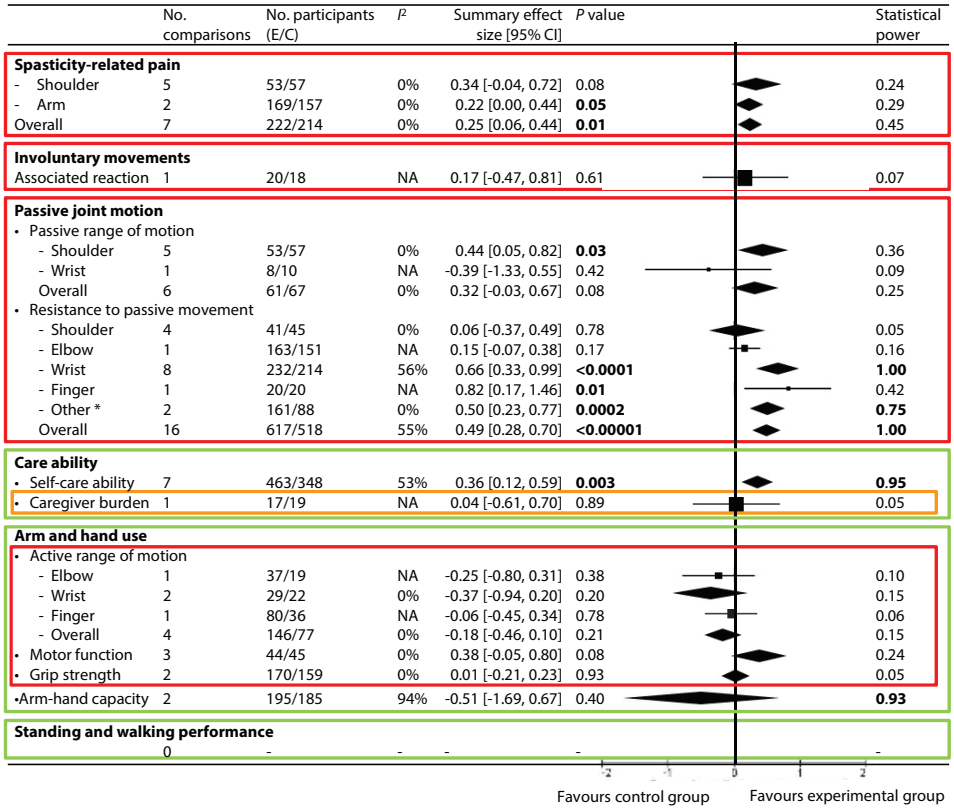


Figure 2.4. Forest plot of follow-up SES of BoNT treatment for each clinical goal (12wk after injection). Coloured frames represent the clinical goals on ICF-domains body functions and structures (red), activities (green) and environmental factors (orange). Please consult Supplement 2C for detailed meta-analyses. Note. I^2 represents heterogeneity (%). Abbreviations: C, control group; E, experimental group; NA, not applicable. * Measured upper limb joint not specified or multiple upper limb joint scores combined.

positive SESs for the elbow, wrist and finger joints, whereas non-significant SESs were found for the shoulder joint.

Effect of BoNT on the improvement of ability to care for the hand and arm

Nine studies[22,31,33,48,49,53,55,57,58] provided data concerning self-care ability, as measured with the Disability Assessment Scale or other subjective disability rating scales for self-care ability. Significant heterogeneous positive SESs were found for the improvement of self-care ability post-intervention and at follow-up (SES, 0.36; 95% CI, 0.12–0.61; $P = 0.004$ and SES, 0.36; 95% CI, 0.12–0.59; $P = 0.003$, respectively). Both pooled comparisons had sufficient power (0.97 and 0.95, respectively). Caregiver burden, which was assessed by two

studies,[33,49] demonstrated a significant homogeneous SES post-intervention (SES, 0.38; 95% CI, 0.03–0.73; $P = 0.03$) and a non-significant SES at follow-up, both with insufficient power (0.33 and 0.05, respectively).

Effect of BoNT on the improvement of arm and hand use

Twenty-seven studies measured determinants of improving arm use (at the body functions level), in terms of active range of motion, motor function and grip strength. Meta-analysis yielded non-significant SESs for these determinants post-intervention and at follow-up. Non-significant SESs were found for the activity level of arm-hand capacity post-intervention and at follow-up. Except for arm-hand capacity at follow-up (statistical power 0.93), all SESs regarding arm and hand use had insufficient statistical power to allow conclusions on the effect of BoNT (range 0.05–0.24).

Effect of BoNT on the improvement of standing and walking performance influenced by upper limb posture

One study used a gait parameter (10-meter walking speed) as an outcome measure for the effect of BoNT injections in the upper limb.[51] Due to lack of data, no meta-analysis could be performed for the clinical goal of standing and walking performance.

Sensitivity analyses

Sensitivity analyses yielded no higher or lower inference moderator variables associated with study and intervention characteristics, that is publication year and methodological quality, BoNT dosage and the use of additional therapy, on SESs (Supplement 2D). A significant positive correlation was found between the timing of intervention after the stroke and the spasticity-related pain score at follow-up, showing a significantly larger effect size at follow-up for those who received BoNT earlier after stroke. Greater influence of the pharmaceutical industry was significantly associated with a lower effect of BoNT on pain scores at follow-up.

Publication bias was assessed only for resistance to passive movement post-intervention and at follow-up, and for spasticity-related pain post-intervention, as insufficient trials were available for other comparisons. Visual examination of the funnel plots of standard error vs effect size (Supplement 2E) showed symmetrical distributions around the summary effect size for studies on the effect of BoNT on spasticity-related pain post-intervention and resistance to passive movement at follow-up, assuming the absence of publication bias as both smaller and larger studies are published, with effect sizes equally distributed around the summary

effect size. Asymmetry was present in the funnel plot for resistance to passive movement post-intervention, where on the right bottom of the plot studies, with higher SE, assumed to be smaller RCT, and small negative or positive MD values are missing.

DISCUSSION

The present systematic review and meta-analysis yielded robust evidence in favour of BoNT treatment in the upper limb after stroke in reducing resistance to passive movement mainly at the wrist, at the ICF body functions level, as measured with the AS or MAS, and improving self-care ability of the affected upper limb, at the activity level, assessed after the intervention and at follow-up. In particular, the SES provide robust evidence for the reduction of resistance to passive movement in the wrist and fingers. Given the robustness of the current evidence, the use of BoNT for the clinical goals of improving passive joint motion and improvement of ability to care for the affected hand and arm has been validated. In addition, the present meta-analysis yielded robust evidence that BoNT has no effect on arm-hand capacity measured at follow-up. There is insufficient evidence for any effects of BoNT on other components at the body functions level. The significant SESs suggest a favourable effect of BoNT in reducing spasticity-related pain and involuntary movements, and improving the passive range of motion, at the body functions level, and in reducing caregiver burden, an environmental factor. However, the SESs of significant findings lacked sufficient statistical power due to the lack of trials in this field. Finally, the present comprehensive meta-analysis showed no influence of the study and intervention characteristics, nor of the involvement of the pharmaceutical industry, or of publication bias for most of the domains investigated, with the exception of small-sample neutral trials on resistance to passive movement. This latter finding suggests a current overestimation of the SES of BoNT for reducing resistance to passive movement.

Our findings suggest there is no need for further trials investigating the effectiveness of BoNT injections in the upper limb after stroke on the AS or MAS in the wrist. Compared to controls, BoNT treatment leads to a mean post-intervention reduction on the ordinal AS or MAS scale of 0.6 points (12%), with sustained beneficial effects of 0.4 points (8%) at follow-up. The sufficiently powered results are in line with the findings of various published reviews and meta-analyses, which have yielded evidence for a favourable effect of BoNT on the MAS in the elbow, wrist and fingers (MD range 0.87–0.95).[7-15] The lack of effect on the shoulder joint may be explained by difficulties of injection and measurement in this complex joint structure, and interference with frequently reported shoulder pain.[69]

Despite the demonstrated robust positive effect of BoNT on the MAS or AS, it is arguable whether this measure is an adequate primary outcome measure for BoNT trials in terms of construct validity and sensitivity. First of all, the underlying construct of this subjective ordinal rating scale is unknown, as a result of which the underlying mechanism of how BoNT affects the resistance to passive movement remains unclear. Second, and more importantly, the MAS only provides subjective data on the total perceived resistance during passive movement of a joint, whereas this resistance is thought to be the result of the interaction between improper muscle activation, including spasticity and baseline activation (neural component), and tendomuscular changes (non-neural component).[70-72] The distribution of these neural and non-neural components might vary between individual patients and can change with the time after stroke.[71,73] Differentiation and objective quantification of neural and non-neural components can contribute to patient-specific treatment-decision making in rehabilitation by means of phenotyping and selection of patients based on the quantification of the neuromechanical parameters. If the neural component is suspected to be dominant, treatment should focus on reducing the muscle activation and blocking the reflex loop, for example by BoNT injections, whereas in the case of suspected predominance of the non-neural component, impairments can be treated by methods like corrective casting or surgical lengthening.[74,75] In recent years, new techniques with standardized measurement conditions have become available which differentiate between neural and non-neural components of resistance to passive movement.[76-78] These devices with modelling techniques can yield more information about the underlying mechanism of the influence of BoNT on the neural component of resistance to passive movement and its interaction with post-stroke non-neural changes longitudinally. Additionally, the MAS suffers from methodological problems.[3,4] Due to the low responsiveness to change of this ordinal rating scale, it offers insufficient precision to measure the effectiveness of BoNT and therefore to define most effective injection protocols. In addition to the imprecision of the MAS, there is a substantial variation in treatment effects between studies, as reflected in the heterogeneity in MAS values found in our meta-analysis. A potential source of this between-study variance is the lack of documented assessment techniques for the MAS, in addition to the heterogeneity of inclusion criteria regarding post-stroke timing. Most included trials selected patients in the chronic phase of stroke, whereas it is known that spasticity develops in the subacute phase.[79] Although our sensitivity analysis showed no influence of post-stroke timing on the effect sizes, this was only based on four trials performed within three months after stroke.[40,52,57,59] Early intervention might decrease early-onset problems related to spasticity

and achieve better long-term results.[80] Lastly, the relationship between the positive effects found on the MAS at the body functions level and effects at the clinically important activity and participation levels remains unclear.

The effects found on the MAS are in line with the positive findings on the clinical goal of increasing care ability, where robust evidence is shown for the improvement of self-care ability of the affected arm and hand at the activity level, as measured with subjective rating scales such as the Disability Assessment Scale. These findings agree with the effects found in other systematic reviews.[5,15,17] Additionally, these effects might relate to the decrease in caregiver burden at the environmental level found after the intervention.

As the MAS measures resistance in the joint in a passive condition, the effects cannot be extrapolated to an active muscle situation, as can be observed from the lack of effects regarding the clinical goal of improvement of arm and hand use. Our review shows a lack of robustness of existing evidence for a favourable effect of BoNT injections regarding the improvement of arm and hand use, at both the body functions and activity levels, with the exception of the robust evidence for the absence of an effect in improving arm-hand capacity at follow-up. Results from previous systematic reviews concerning the effect of BoNT on arm and hand use have been ambiguous. Dong et al.[15] reported no favourable effects of the BoNT on arm-hand capacity, while Foley[5] and Baker[18] and colleagues did find positive effects of BoNT on arm and hand use. However, the significant MDs found by Baker et al.[18] for the improvement of the active range of motion (MD, 4.53; 95% CI, 2.43–6.64; $P < 0.0001$) and the score on the Action Research Arm Test (ARAT) (MD, 1.86; 95% CI, 0.52–3.19; $P = 0.006$) are of questionable clinical relevance in view of the minimal clinically important difference (MCID) of 6 points on ARAT. In our opinion, ambiguous results and lack of robustness regarding the improvement of arm and hand use might be due to the diversity of clinical measures being used. In addition, BoNT causes a temporary and local paresis to the injected muscles, without influencing the actual voluntary control. Adjunctive therapies after BoNT injections within a multidisciplinary rehabilitation program might help to optimise voluntary control during the period of paralysis in overactive injected muscles. However, the additional value of adjunctive therapy after BoNT injections has not yet been properly addressed.[81]

Besides the robust findings on the MAS scores at the body functions level, our review suggests insufficient evidence for other outcome measures at this ICF level. BoNT injections might decrease involuntary movements and increase the overall passive range of motion, while there appears to be a decrease in spasticity-related pain in the arm at follow-up.

However, the current lack of standardized and widely accepted measurement protocols leads to insufficient precision to establish changes on the body functions level by BoNT.

Future research

In view of the robustness of current evidence, no further trials are needed to investigate BoNT as regards its favourable effects on resistance to passive movement of the spastic wrist and fingers, and self-care ability for the affected upper limb. No trials are needed to further confirm the lack of effects of BoNT on arm-hand capacity at follow-up. Improving and extending the evidence for BoNT injections in the upper limbs of patients with history of stroke requires high-quality phase III trials investigating the extrapolation of BoNT (with or without additional exercise programs), which may result in clinically meaningful outcomes at the activity and participation levels. First of all, this requires an understanding of the working mechanism responsible for the effects of BoNT, together with construct-valid outcome measures consistent with these definitions and classified according to the ICF. In addition, attention must be paid to improving measurement methods and standardized protocols, in order to distinguish between neural and non-neural components of resistance to passive movement. More fundamental studies are needed to investigate the longitudinal interaction between the different components of resistance to passive movement after a stroke and the actual working mechanism of BoNT on these components in the upper limb after stroke. New haptic robots[76,78] and mechanical devices[77] can contribute to the phenotyping and selection of patients for treatment indication, and can provide more accurate data for the optimisation of the BoNT injection protocols. It is remarkable that none of the included trials examined the influence of BoNT on the quality of movement. Despite the lack of effect found in ARAT scores, quality of movement in terms of smoothness and grasp aperture could have improved. Future trials using kinematic measurements could assess the effect of BoNT on the quality of movement. A challenging next step would be to prevent the development of spasticity and the attendant complications after stroke. Early intervention with BoNT in a selection of patients might be beneficial.[80] A final step towards higher-powered and more accurate trials on the effectiveness of BoNT would be to use appropriate trial designs, including stratified patient selection and adjunctive therapies, as a part of a broader multifaceted spasticity management treatment.[82]

Study limitations

The present systematic review had some limitations. First, we had to exclude 10 of the 40 included studies from the meta-analysis, due to missing raw post-intervention scores and SDs. Although we performed a broad search, we might have missed studies due to the restriction in languages and electronic databases. Next, we included studies using BoNT types A and B, and studies using a variety of injection protocols. In trials with multiple experimental groups using different doses of BoNT, data of all experimental groups were combined to obtain one overall post-intervention score. Therefore, the results of the meta-analysis in this review need to be read while keeping in mind that relevant data may have been missed, and no conclusions can be drawn about the most efficient BoNT intervention protocol.

CONCLUSION

This systematic review provides robust evidence for the effectiveness of BoNT treatment in the upper limb after stroke in reducing resistance to passive movement of the wrist and fingers, and improving self-care ability of the affected arm and hand. In addition, robust evidence is shown for the absence of effect on arm-hand capacity at follow-up. In view of the robustness of current evidence, no further trials are needed to investigate the effects of BoNT on resistance to passive movement and self-care ability. No additional trials are needed to further confirm the lack of effects of BoNT on arm-hand capacity. The suggested favourable effects of BoNT on other body functions, and whether these effects can be extrapolated to the clinically important levels of activity and participation, require further investigation.

FUNDING

The present study was supported by the European Research Council (grant no. 291339, 4D-EEG project) and the Netherlands Organisation for Health Research and Development (ZonMw grant no. 104003008, PROFITS program). The funders had no role in study design, data collection, data analysis, data interpretation or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization: 2001. Updated March, 2018. www.who.int/classifications/icf/en/
2. Ashford S, Fheodoroff K, Jacinto J, Turner-Stokes L. Common goal areas in the treatment of upper limb spasticity: a multicentre analysis. *Clin Rehabil.* 2016;30(6):617-622.
3. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil* 1999;13(5):373-383.
4. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry* 2010;81(1):46-52.
5. Foley N, Pereira S, Salter K, et al. Treatment with botulinum toxin improves upper-extremity function post stroke: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 2013;94(5):977-989.
6. Kwakkel G, Meskers CG. Botulinum toxin A for upper limb spasticity. *Lancet Neurol* 2015;14(10):969-971.
7. Cardoso E, Rodrigues B, Lucena R, Reis De Oliveira L, Pedreira G, Melo A. Botulinum toxin type a for the treatment of the upper limb spasticity after stroke: A meta-analysis. *Arq Neuropsiquiatr* 2005;63(1):30-33.
8. Francisco GE. Botulinum toxin for post-stroke spastic hypertonia: a review of its efficacy and application in clinical practice. *Ann Acad Med Singapore* 2007;36(1):22-30.
9. Rosales RL, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J Neural Transm* 2008;115(4):617-623.
10. Elia AE, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post-stroke spasticity in adults: A systematic review. *Mov Disord* 2009;24(6):801-812.
11. Olvey EL, Armstrong EP, Grizzle AJ. Contemporary pharmacologic treatments for spasticity of the upper limb after stroke: a systematic review. *Clin Ther* 2010;32(14):2282-2303.
12. Baker JA, Pereira G. The efficacy of Botulinum Toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. *Clin Rehabil* 2013;27(12):1084-1096.
13. Esquenazi A, Albanese A, Chancellor MB, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. *Toxicon* 2013;67:115-128.

14. Dashtipour K, Chen JJ, Walker HW, Lee MY. Systematic literature review of abobotulinumtoxinA in clinical trials for adult upper limb spasticity. *Am J Phys Med Rehabil* 2015;94(3):229-238.
15. Dong Y, Wu T, Hu X, Wang T. Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. *Eur J Phys Rehabil Med* 2017;53(2):256-267.
16. Singh JA, Fitzgerald PM. Botulinum toxin for shoulder pain. *Cochrane Database Syst Rev* 2010; 9:CD008271.
17. Baker JA, Pereira G. The efficacy of Botulinum Toxin A on improving ease of care in the upper and lower limbs: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. *Clin Rehabil* 2015;29(8):731-740.
18. Baker JA, Pereira G. The efficacy of Botulinum Toxin A for limb spasticity on improving activity restriction and quality of life: a systematic review and meta-analysis using the GRADE approach. *Clin Rehabil* 2016;30(6):549-558.
19. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(7):2064-2089.
20. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1. The Cochrane Collaboration: 2011. Updated March, 2011. www.cochrane-handbook.org
21. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil* 2009;23(7):651-658.
22. Gracies JM, Brashear A, Jech R, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: A double-blind randomised controlled trial. *Lancet Neurol* 2015;14(10):992-1001.
23. Sherrington C, Herbert RD, Maher CG, Moseley AM. PEDro. A database of randomized trials and systematic reviews in physiotherapy. *Man Ther* 2000;5(4):223-226.
24. Maher CG, Sherrington C, Herbert RD, Moseley AM , Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83(8):713-721.
25. De Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009;55(2):129-133.
26. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-560.

28. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods* 2001; 6(3):203-217.
29. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis.* 1st ed. New Jersey: John Wiley & Sons, Ltd.; 2009.
30. Simpson DM, Alexander DN, O'Brien CF, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: A randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46(5):1306-1310.
31. Hesse S, Reiter F, Konrad M, Jahnke MT. Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: A randomized, double-blind, placebo-controlled trial. *Clin Rehabil* 1998;12(5):381-388.
32. Bakheit AMO, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. *Stroke* 2000;31(10):2402-2406.
33. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: A randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatry* 2000;69(2):217-221.
34. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14(1):5-13.
35. Bakheit AMO, Pittock S, Moore AP, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. *Eur J Neurol* 2001;8(6):559-565.
36. Brashear A, Gordon MF, Elovic E, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;347(6):395-400.
37. Brashear A, McAfee AL, Kuhn ER, Fyffe J. Botulinum toxin type B in upper-limb poststroke spasticity: A double-blind, placebo-controlled trial. *Arch Phys Med Rehabil* 2004;85(5):705-709.
38. Childers MK, Brashear A, Jozefczyk P, et al. Dose-dependent response to intramuscular botulinum toxin type a for upper-limb spasticity in patients after a stroke. *Arch PhysMed Rehabil* 2004;85(7):1063-1069.
39. Suputtitada A, Suwanwela NC. The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity. *Disabil Rehabil* 2005;27(4):176-184.
40. Guo F, Yue W, Ren L, Zhang YM, Yang J. Botulinum toxin type A plus rehabilitative training for improving the motor function of the upper limbs and activities of daily life in patients with stroke and brain injury. *Neural Regen Res* 2006;1(9):859-561.

41. Jahangir AW, Tan HJ, Norlinah MI, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke. *Med J Malaysia* 2007;62(4):319-322.
42. Kong KH, Neo JJ, Chua KSG. A randomized controlled study of botulinum toxin A in the treatment of hemiplegic shoulder pain associated with spasticity. *Clin Rehabil* 2007;21(1):28-35.
43. Marco E, Duarte E, Villa J, et al. Is botulinum toxin type A effective in the treatment of spastic shoulder pain in patients after stroke? A double-blind randomized clinical trial. *J Rehabil Med* 2007;39(6):440-447.
44. Yelnik AP, Colle FM, Bonan IV, Vicaut E. Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: A randomised, double blind, placebo controlled study of botulinum toxin A. *J Neurol Neurosurg Psychiatry* 2007;78(8):845-848.
45. Bhakta BB, O'Connor RJ, Cozens JA. Associated reactions after stroke: A randomized controlled trial of the effect of botulinum toxin type A. *J Rehabil Med* 2008;40(1):36-41.
46. De Boer KS, Arwert HJ, De Groot JH, Meskers CGM, Rambaran Mishre AD, Arendzen JH. Shoulder pain and external rotation in spastic hemiplegia do not improve by injection of botulinum toxin A into the subscapular muscle. *J Neurol Neurosurg Psychiatry* 2008;79(5):581-583.
47. Lim JY, Koh JH, Paik NJ. Intramuscular botulinum toxin-A reduces hemiplegic shoulder pain: A randomized, double-blind, comparative study versus intraarticular triamcinolone acetonide. *Stroke* 2008;39(1):126-131.
48. Kanovsky P, Slawek J, Denes Z, et al. Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. *Clin Neuropharmacol* 2009;32(5):259-265.
49. McCrory P, Turner-Stokes L, Baguley IJ, et al. Botulinum toxin a for treatment of upper limb spasticity following stroke: A multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J Rehabil Med* 2009;41(7):536-544.
50. Meythaler JM, Vogtle L, Brunner RC. A Preliminary Assessment of the Benefits of the Addition of Botulinum Toxin A to a Conventional Therapy Program on the Function of People With Longstanding Stroke. *Arch Phys Med Rehabil* 2009;90(9):1453-1461.
51. Simpson DM, Gracies JM, Yablon SA, Barbano R, Brashear A. Botulinum neurotoxin versus tizanidine in upper limb spasticity: A placebo-controlled study. *J Neurol Neurosurg Psychiatry* 2009;80(4):380-385.
52. Cousins E, Ward A, Roffe C, Rimington L, Pandyan A. Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size. *Clin Rehabil* 2010;24(6):501-513.

53. Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M. Botulinum toxin type A in post-stroke upper limb spasticity. *Curr Med Res Opin* 2010;26(8):1983-1992.
54. Shaw L, Rodgers H, Price C, et al. BoTULS: A multicentre randomized controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol Assess* 2010;14(26):1-113, iii-iv.
55. Shaw LC, Price CIM, Van Wijck FMJ, et al. Botulinum toxin for the upper limb after stroke (BoTULS) trial: Effect on impairment, activity limitation, and pain. *Stroke* 2011;42(5):1371-1379.
56. Turner-Stokes L, Baguley IJ, De Graaff S, et al. Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double-blind placebo-controlled randomized clinical trial. *J Rehabil Med* 2010;42(1):81-89.
57. Hesse S, Mach H, Fröhlich S, Behrend S, Werner C, Melzer I. An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. *Clin Rehabil* 2012;26(3):237-245.
58. Marciniak CM, Harvey RL, Gagnon CM, et al. Does botulinum toxin type A decrease pain and lessen disability in hemiplegic survivors of stroke with shoulder pain and spasticity?: a randomized, double-blind, placebo-controlled trial. *Am J Phys Med Rehabil* 2012;91(12):1007-1019.
59. Rosales RL, Kong KH, Goh KJ, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: A randomized controlled trial. *Neurorehabil Neural Repair* 2012;26(7):812-821.
60. Wolf SL, Milton SB, Reiss A, Easley KA, Shenvi NV, Clark PC. Further assessment to determine the additive effect of botulinum toxin type A on an upper extremity exercise program to enhance function among individuals with chronic stroke but extensor capability. *Arch Phys Med Rehabil* 2012;93(4):578-587.
61. Yazdchi M, Ghasemi Z, Moshayedi H, et al. Comparing the efficacy of botulinum toxin with tizanidine in upper limb post stroke spasticity. *Iran J Neurol* 2013;12(2):47-50.
62. Gracies JM, Bayle N, Goldberg S, Simpson DM. Botulinum toxin type B in the spastic arm: A randomized, double-blind, placebo-controlled, preliminary study. *Arch Phys Med Rehabil* 2014;95(7):1303-1311.
63. Ward AB, Wissel J, Borg J, et al. Functional goal achievement in post-stroke spasticity patients: the BOTOX® Economic Spasticity Trial (BEST). *J Rehabil Med* 2014;46(6):504-513.

64. Pennati GV, Da Re C, Messineo I, Bonaiuti D. How could robotic training and botolinum toxin be combined in chronic post stroke upper limb spasticity? A pilot study. *Eur J Phys Rehabil Med* 2015;51(4):381-387.
65. Elovic EP, Munin MC, Kanovsky P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. *Muscle Nerve* 2016;53(3):415-421.
66. Marciniak C, McAllister P, Walker H, et al. Efficacy and Safety of AbobotulinumtoxinA (Dysport) for the Treatment of Hemiparesis in Adults With Upper Limb Spasticity Previously Treated With Botulinum Toxin: Subanalysis From a Phase 3 Randomized Controlled Trial. *PM R* 2017;9(12):1181-1190.
67. O'Dell MW, Brashear A, Jech R, et al. Dose-Dependent Effects of AbobotulinumtoxinA (Dysport) on Spasticity and Active Movements in Adults With Upper Limb Spasticity: Secondary Analysis of a Phase 3 Study. *PM R* 2018;10(1):1-10.
68. Umar M, Masood T, Badshah M. Effect of botulinum toxin A & task-specific training on upper limb function in post-stroke focal dystonia. *JPMA* 2018;68(4):526-531.
69. Ansari NN, Naghdi S, Arab TK, Jalaie S. The interrater and intrarater reliability of the Modified Ashworth Scale in the assessment of muscle spasticity: limb and muscle group effect. *NeuroRehabilitation* 2008;23(3):231-237.
70. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve* 2005;31(5):535-551.
71. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol* 2007;6(8):725-733.
72. Meskers CG, Schouten AC, de Groot JH, et al. Muscle weakness and lack of reflex gain adaptation predominate during post-stroke posture control of the wrist. *J Neuroeng Rehabil* 2009;6:29.
73. Van der Krogt HJ, Meskers CG, de Groot JH, Klomp A, Arendzen JH. The gap between clinical gaze and systematic assessment of movement disorders after stroke. *J Neuroeng Rehabil* 2012;9:61.
74. Lannin NA, Novak I, Cusick A. A systematic review of upper extremity casting for children and adults with central nervous system motor disorders. *Clin Rehabil* 2007;21(11):963-976.
75. Renzenbrink GJ, Buurke JH, Nene AV, Geurts AC, Kwakkel G, Rietman JS. Improving walking capacity by surgical correction of equinovarus foot deformity in adult patients with stroke or traumatic brain injury: a systematic review. *J Rehabil Med* 2012;44(8):614-623.
76. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, Van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil* 2010;7:35. doi:10.1186/1743-0003-7-35.

77. Lindberg PG, Gaverth 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(7):617-625.
78. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech* 2016;35:93-101.
79. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, Von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 2004;35(1):134-139.
80. Rosales RL, Efendy F, Teleg ES, et al. Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: A meta-analysis. *J Neurol Sci* 2016;371:6-14.
81. Demetrios M, Khan F, Turner-Stokes L, Brand C, McSweeney S. Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. *Cochrane Database Syst Rev* 2013;6:CD009689.
82. Lannin NA, Ada L, English C, Ratcliffe J, Crotty M. Effect of adding upper limb rehabilitation to botulinum toxin-A on upper limb activity after stroke: Protocol for the InTENSE trial. *Int J Stroke* 2018;13(6):648-653.

SUPPLEMENTARY MATERIAL

Supplement 2A. Search strategies

Search strategy for Embase.com (16 May 2018)

/exp = EMtree keyword with explosion
/de = EMtree keyword without explosion
:ab,ti,kw = words in title, abstract or author keywords
NEAR/x = words near to each other, x places apart
NEXT/x = words next to each other, x places apart

Search	Query	Items found
#9	#1 AND #2 AND #6 AND #8	529
#8	#3 OR #7	749,589
#7	'muscle hypertonia'/exp OR 'muscle spasm'/de OR 'flexion contracture'/exp OR 'muscle contracture'/de OR 'joint contracture'/exp OR hyperton*:ab,ti,kw OR contractur*:ab,ti,kw OR spastic*:ab,ti,kw OR spasm:ab,ti,kw OR spasms:ab,ti,kw OR ((muscle* NEAR/3 rigidit*):ab,ti,kw)	134,142
#6	#4 OR #5	3,091,712
#5	random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat*OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp	2,229,673
#4	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes*NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database*OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial*OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti)) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp)	1,075,164

Search	Query	Items found
#3	'cerebrovascular accident'/exp OR 'acquired brain injury'/exp OR cva:ab,ti,kw OR cvas:ab,ti,kw OR stroke:ab,ti,kw OR apoplex*:ab,ti,kw OR poststroke*:ab,ti,kw OR ((brain*:ab,ti,kw OR cerebr*:ab,ti,kw OR cerebell*:ab,ti,kw OR intracran*:ab,ti,kw OR intracerebral*:ab,ti,kw OR vertebrobasilar*:ab,ti,kw) AND vascular*:ab,ti,kw AND (disease:ab,ti,kw OR diseases:ab,ti,kw OR accident*:ab,ti,kw OR disorder*:ab,ti,kw)) OR (cerebrovascular*:ab,ti,kw AND (disease:ab,ti,kw OR diseases:ab,ti,kw OR accident*:ab,ti,kw OR disorder*:ab,ti,kw)) OR ((brain*:ab,ti,kw OR cerebr*:ab,ti,kw OR cerebell*:ab,ti,kw OR intracran*:ab,ti,kw OR intracerebral*:ab,ti,kw OR vertebrobasilar*:ab,ti,kw) AND (haemorrhag*:ab,ti,kw OR hemorrhag*:ab,ti,kw OR ischemi*:ab,ti,kw OR ischaemi*:ab,ti,kw OR infarct*:ab,ti,kw OR haematoma*:ab,ti,kw OR hematoma*:ab,ti,kw OR bleed*:ab,ti,kw)) OR (('acquired brain' NEAR/3 injur*):ab,ti,kw) OR abi:ab,ti,kw	624,508
#2	'arm'/exp OR 'shoulder'/exp OR 'rotator cuff'/exp OR 'arm muscle'/exp OR 'biceps brachii muscle'/exp OR 'deltoid muscle'/exp OR 'extensor digitorum longus muscle'/exp OR 'extensor muscle'/exp OR 'flexor digitorum brevis muscle'/exp OR 'flexor muscle'/exp OR 'hand muscle'/exp OR 'pectoralis major muscle'/exp OR 'pectoral muscle'/exp OR 'triceps brachii muscle'/exp OR ((upper NEAR/3 limb*):ab,ti,kw) OR arm:ab,ti,kw OR arms:ab,ti,kw OR forearm*:ab,ti,kw OR ((fore NEXT/1 arm*):ab,ti,kw) OR metacarp*:ab,ti,kw OR forelimb*:ab,ti,kw OR ((fore NEXT/1 limb*):ab,ti,kw) OR ((upper NEAR/3 extremit*):ab,ti,kw) OR hand:ab,ti,kw OR hands:ab,ti,kw OR finger*:ab,ti,kw OR wrist*:ab,ti,kw OR elbow*:ab,ti,kw OR shoulder*:ab,ti,kw OR 'rotator cuff':ab,ti,kw OR digits:ab,ti,kw OR digit:ab,ti,kw OR bicep:ab,ti,kw OR biceps:ab,ti,kw OR ((deltoid* NEAR/3 musc*):ab,ti,kw) OR ((scapulohumer* NEAR/3 muscle*):ab,ti,kw) OR digitorum:ab,ti,kw OR ((extensor NEAR/3 musc*):ab,ti,kw) OR ((flexor NEAR/3 musc*):ab,ti,kw) OR ((pectoral* NEAR/3 musc*):ab,ti,kw) OR triceps:ab,ti,kw OR tricep:ab,ti,kw OR brachial*:ab,ti,kw OR coracobrachial*:ab,ti,kw OR infraspinatus*:ab,ti,kw OR 'latissimus dorsi':ab,ti,kw OR subscapular*:ab,ti,kw OR supraspinat*:ab,ti,kw OR 'teres major':ab,ti,kw OR 'teres minor':ab,ti,kw OR 'serratus anterior':ab,ti,kw OR subclavius:ab,ti,kw OR ((levator* NEAR/3 scapula*):ab,ti,kw) OR trapezius:ab,ti,kw OR brachioradial*:ab,ti,kw OR (('extensor carpi' NEAR/3 radial*):ab,ti,kw) OR digiti:ab,ti,kw OR digitis:ab,ti,kw OR 'extensor carpi ulnaris':ab,ti,kw OR 'flexor carpi':ab,ti,kw OR 'palmaris longus':ab,ti,kw OR 'pronator teres':ab,ti,kw OR anconeus:ab,ti,kw OR supinator*:ab,ti,kw OR 'abductor pollicis':ab,ti,kw OR 'extensor pollicis':ab,ti,kw	1,171,663
#1	'botulinum toxin'/exp OR 'botulinum toxin a'/exp OR 'botulinum toxin b'/exp OR 'botulinum toxin e'/exp OR 'botulinum toxin f'/exp OR ((botulin*NEAR/3 toxin*):ab,ti,kw) OR ((botulin* NEAR/3 neurotoxin*):ab,ti,kw) OR ((botulism* NEAR/3 toxin*):ab,ti,kw) OR ((botulin* NEAR/3 exotoxin*):ab,ti,kw) OR abobotulinumtoxin*:ab,ti,kw OR azzalure*:ab,ti,kw OR bocouture*:ab,ti,kw OR bont:ab,ti,kw OR botox:ab,ti,kw OR 'botulin a':ab,ti,kw OR btxa:ab,ti,kw OR btx:ab,ti,kw OR ((botulin* NEAR/3 endotoxin*):ab,ti,kw) OR dyslor*:ab,ti,kw OR dysport*:ab,ti,kw OR ((evabotulin*NEAR/3 toxin*):ab,ti,kw) OR evabotulinumtoxin*:ab,ti,kw OR ((incobotulin* NEAR/3 toxin*):ab,ti,kw) OR incobotulinumtoxin*:ab,ti,kw OR meditoxin*:ab,ti,kw OR 'nt 201':ab,ti,kw OR nt201:ab,ti,kw OR oculinum*:ab,ti,kw OR ((onabotulin* NEAR/3 toxin*):ab,ti,kw) OR onabotulinumtoxin*:ab,ti,kw OR onaclostox*:ab,ti,kw OR prosigne*:ab,ti,kw OR purtox*:ab,ti,kw OR reloxin*:ab,ti,kw OR vistabel*:ab,ti,kw OR vistabex*:ab,ti,kw OR xeomin*:ab,ti,kw OR myobloc*:ab,ti,kw OR myoblock*:ab,ti,kw OR neurobloc*:ab,ti,kw OR ((rimabotulin* NEAR/3 toxin*):ab,ti,kw) OR rimabotulinumtoxin*:ab,ti,kw OR bontf:ab,ti,kw	35,478

Search strategy for PubMed (16 May 2018)

[Mesh] = Medical subject headings (MeSH)
[Mesh:NoExp] = Medical subject headings (MeSH) without explosion
[pt] = publication type from MeSH
[tiab] = words in title or abstract
[ti] = words in title
[ta] = title abbreviation of journal

Search	Query	Items found
#5	(#1 AND #2 AND #3 AND #4)	599
#4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR ((review*[tiab] OR search*[tiab] OR survey*[tiab] OR handsearch*[tiab] OR hand-search*[tiab]) AND (databa*[tiab] OR databa*[tiab] OR bibliograph*[tiab] OR electronic*[tiab] OR medline*[tiab] OR pubmed*[tiab] OR embase*[tiab] OR Cochrane[tiab] OR cinahl[tiab] OR psycinfo[tiab] OR psychinfo[tiab] OR cinhal[tiab] OR "web of science"[tiab] OR "web of knowledge"[tiab] OR ebsco[tiab] OR ovid[tiab] OR mrct[tiab] OR metaregist*[tiab] OR meta-regist*[tiab] OR ((predetermined[tiab] OR predetermined[tiab]) AND criteri*[tiab]) OR apprais*[tiab] OR inclusion criteri*[tiab] OR exclusion criteri*[tiab])) OR (review[pt] AND systemat*[tiab]) OR "systematic review"[tiab] OR "systematic literature"[tiab] OR "integrative review"[tiab] OR "integrative literature"[tiab] OR "evidence-based review"[tiab] OR "evidence-based overview"[tiab] OR "evidence-based literature"[tiab] OR "evidence-based survey"[tiab] OR "literature search"[tiab] OR ((systemat*[ti] OR evidence-based[ti]) AND (review*[ti] OR literature[ti] OR overview[ti] OR survey[ti])) OR "data synthesis"[tiab] OR "evidence synthesis"[tiab] OR "data extraction"[tiab] OR "data source"[tiab] OR "data sources"[tiab] OR "study selection"[tiab] OR "methodological quality"[tiab] OR "methodologic quality"[tiab] OR cochrane database syst rev[ta] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-analysis[pt] OR meta-synthesis[tiab] OR metasynthesis[tiab] OR meta-study[tiab] OR metastudy[tiab] OR metaethnograph*[tiab] OR meta-ethnograph*[tiab] OR Technology Assessment, Biomedical[mh] OR hta[tiab] OR health technol assess [ta] OR evid rep technol assess summ[ta] OR health technology assessment[tiab])	4,575,154
#3	(acquired brain injur*[tiab] OR abi[tiab] OR ("Stroke"[Mesh] OR cva[tiab] OR cvas[tiab] OR poststroke*[tiab] OR stroke*[tiab] OR apoplex*[tiab]) OR ((brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab]) AND vascular*[tiab] AND (disease[tiab] OR diseases[tiab] OR accident*[tiab] OR disorder*[tiab])) OR (cerebrovascular*[tiab] AND (disease[tiab] OR diseases[tiab] OR accident*[tiab] OR disorder*[tiab])) OR ((brain*[tiab] OR cerebr*[tiab] OR cerebell*[tiab] OR intracran*[tiab] OR intracerebral*[tiab] OR vertebrobasilar*[tiab]) AND (haemorrhag*[tiab] OR hemorrhag*[tiab] OR ischemi*[tiab] OR ischaemi*[tiab] OR infarct*[tiab] OR haematoma*[tiab] OR hematoma*[tiab] OR bleed*[tiab])) OR ("Hemiplegia"[Mesh] OR "Paresis"[Mesh] OR hemipleg*[tiab] OR hemipar*[tiab] OR paresis[tiab] OR paretic[tiab]) OR "Muscle Hypertonia"[Mesh] OR "Spasm"[Mesh:NoExp] OR "Contracture"[Mesh:NoExp] OR hyperton*[tiab] OR contractur*[tiab] OR spastic*[tiab] OR spasm[tiab] OR spasms[tiab] OR (muscle*[tiab] AND rigidit*[tiab]))	503,365

Search	Query	Items found
#2	("Upper Extremity"[Mesh] OR "Rotator Cuff"[Mesh] OR "Deltoid Muscle"[Mesh] OR "Pectoralis Muscles"[Mesh] OR (upper[tiab] AND limb*[tiab]) OR arm[tiab] OR arms[tiab] OR forearm*[tiab] OR fore arm*[tiab] OR metacarp*[tiab] OR forelimb*[tiab] OR fore limb*[tiab] OR (upper[tiab] AND extremit*[tiab]) OR hand[tiab] OR hands[tiab] OR finger*[tiab] OR wrist*[tiab] OR elbow*[tiab] OR shoulder*[tiab] OR "rotator cuff"[tiab] OR digits[tiab] OR digit[tiab] OR bicep[tiab] OR biceps[tiab] OR (deltoid*[tiab] AND muscle*[tiab]) OR (scapulohumer*[tiab] AND muscle*[tiab]) OR digitorum[tiab] OR (extensor[tiab] AND muscle*[tiab]) OR (flexor[tiab] AND muscle*[tiab]) OR (pectoral*[tiab] AND muscle*[tiab]) OR triceps[tiab] OR tricep[tiab] OR brachial*[tiab] OR coracobrachial*[tiab] OR infraspinatus*[tiab] OR "latissimus dorsi"[tiab] OR subscapular*[tiab] OR supraspinat*[tiab] OR "teres major"[tiab] OR "teres minor"[tiab] OR "serratus anterior"[tiab] OR subclavius[tiab] OR (levator*[tiab] AND scapula*[tiab]) OR trapezius[tiab] OR brachioradial*[tiab] OR ("extensor carpi"[tiab] AND radial*[tiab]) OR digiti[tiab] OR digitis[tiab] OR "extensor carpi ulnaris"[tiab] OR "flexor carpi"[tiab] OR "palmaris longus"[tiab] OR "pronator teres"[tiab] OR anconeus[tiab] OR supinator*[tiab] OR "abductor pollicis"[tiab] OR "extensor pollicis"[tiab])	895,204
#1	("Botulinum Toxins"[Mesh] OR (botulin*[tiab] AND toxin*[tiab]) OR (botulin*[tiab] AND neurotoxin*[tiab]) OR (botulism*[tiab] AND toxin*[tiab]) OR (botulin*[tiab] AND exotoxin*[tiab]) OR abobotulinumtoxin*[tiab] OR azzalure*[tiab] OR bocouture*[tiab] OR bont[tiab] OR botox[tiab] OR "botulin a"[tiab] OR btxa[tiab] OR btx[tiab] OR (botulin*[tiab] AND endotoxin*[tiab]) OR dyslor*[tiab] OR dysport*[tiab] OR (evabotulin*[tiab] AND toxin*[tiab]) OR evabotulinumtoxin*[tiab] OR (incobotulin*[tiab] AND toxin*[tiab]) OR incobotulinumtoxin*[tiab] OR meditoxin*[tiab] OR "nt 201"[tiab] OR nt201[tiab] OR oculinum*[tiab] OR (onabotulin*[tiab] AND toxin*[tiab]) OR onabotulinumtoxin*[tiab] OR onaclostox*[tiab] OR prosigne*[tiab] OR purtox*[tiab] OR reloxin*[tiab] OR vistabel*[tiab] OR vistabex*[tiab] OR xeomin*[tiab] OR myobloc*[tiab] OR myoblock*[tiab] OR neurobloc*[tiab] OR (rimabotulin*[tiab] AND toxin*[tiab]) OR rimabotulinumtoxin*[tiab] OR bontf[tiab])	20,814

Search strategy for Wiley/Cochrane Library (16 May 2018)

ti,ab,kw = words in title, abstract or author keywords

Search	Query	Items found
#1	((botulin* and toxin*) or (botulin* and neurotoxin*) or (botulism* and toxin*) or (botulin* and exotoxin*) or abobotulinumtoxin* or azzalure* or bocouture* or bont or botox or "botulin a" or btxa or btx or (botulin* and endotoxin*) or dyslor* or dysport* or (evabotulin* and toxin*) or evabotulinumtoxin* or (incobotulin* and toxin*) or incobotulinumtoxin* or meditoxin* or "nt 201" or nt201 or oculinum* or (onabotulin* and toxin*) or onabotulinumtoxin* or onaclostox* or prosigne* or purtox* or reloxin* or vistabel* or vistabex* or xeomin* or myobloc* or myoblock* or neurobloc* or (rimabotulin* and toxin*) or rimabotulinumtoxin* or bontf):ti,ab,kw	2,732
#2	((upper and limb*) or arm or arms or forearm* or fore arm* or metacarp* or forelimb* or fore limb* or (upper and extremit*) or hand or hands or finger* or wrist* or elbow* or shoulder* or "rotator cuff" or digits or digit or bicep or biceps or (deltoid* and muscle*) or (scapulohumer* and muscle*) or digitorum or (extensor and muscle*) or (flexor and muscle*) or (pectoral* and muscle*) or triceps or tricep or brachial* or coracobrachial* or infraspinatus* or "latissimus dorsi" or subscapular* or supraspinat* or "teres major" or "teres minor" or "serratus anterior" or subclavius or (levator* and scapula*) or trapezius or brachioradial* or ("extensor carpi" and radial*) or digiti or digitis or "extensor carpi ulnaris" or "flexor carpi" or "palmaris longus" or "pronator teres" or anconeus or supinator* or "abductor pollicis" or "extensor pollicis"):ti,ab,kw	101,458
#3	("acquired brain injur*" or abi or (cva or cvas or poststroke* or stroke* or apoplex*) or ((brain* or cerebr* or cerebell* or intracran* or intracerebral* or vertebrobasilar*) and vascular* and (disease or diseases or accident* or disorder*)) or (cerebrovascular* and (disease or diseases or accident* or disorder*)) or ((brain* or cerebr* or cerebell* or intracran* or intracerebral* or vertebrobasilar*) and (haemorrhag* or hemorrhag* or ischemi* or ischaemi* or infarct* or haematoma* or hematoma* or bleed*)) or (hemipleg* or hemipar* or paresis or paretic) or hyperton* or contractur* or spastic* or spasm or spasms or (muscle* and rigidit*)):ti,ab,kw	60,493
#4	#1 and #2 and #3	410

Distribution of references per database: CDSR: 6; DARE: 9; CENTRAL: 387; HTA: 5; EED: 3.

Search strategy for Ebsco/CINAHL (16 May 2018)

MH = keywords
+ = keywords with explosion
DE = keywords without explosion
TI = words in title
AB = words in abstract

Search	Query	Items found
S4	S1 AND S2 AND S3	**324**
S3	((MH "Stroke") OR (MH "Stroke Patients")) OR (TI(cva OR cvas OR poststroke* OR stroke* OR apoplex*) OR AB(cva OR cvas OR poststroke* OR stroke* OR apoplex*)) OR ((TI(brain* OR cerebr* OR cerebell* OR intracran* OR intracerebral* OR vertebrobasilar*) OR AB(brain* OR cerebr* OR cerebell* OR intracran* OR intracerebral* OR vertebrobasilar*)) N3 (TI(vascular*) OR AB(vascular*)) N3 (TI(disease OR diseases OR accident* OR disorder*) OR AB(disease OR diseases OR accident* OR disorder*))) OR (TI(cerebrovascular*) OR AB(cerebrovascular*) N3 (TI(disease OR diseases OR accident* OR disorder*) OR AB(disease OR diseases OR accident* OR disorder*))) OR ((TI(brain* OR cerebr* OR cerebell* OR intracran* OR intracerebral* OR vertebrobasilar*) OR AB(brain* OR cerebr* OR cerebell* OR intracran* OR intracerebral* OR vertebrobasilar*)) N3 (TI(haemorrhag* OR hemorrhag* OR ischemi* OR ischaemi* OR infarct* OR haematoma* OR hematoma* OR bleed*) OR AB(haemorrhag* OR hemorrhag* OR ischemi* OR ischaemi* OR infarct* OR haematoma* OR hematoma* OR bleed*))) OR (DE "Hemiplegia" OR DE "General Paresis" OR TI(hemipleg* OR hemipar* OR paresis OR paretic) OR AB(hemipleg* OR hemipar* OR paresis OR paretic))) OR (MH "Muscle Hypertonia+") OR (MH "Contracture") OR (MH "Muscle Spasticity") OR (MH "Spasm") OR TI ("acquired brain injur*" OR abi OR hyperton* OR contractur* OR spastic* OR spasm OR spasms OR (muscle* AND rigidit*)) OR AB ("acquired brain injur*" OR abi OR hyperton* OR contractur* OR spastic* OR spasm OR spasms OR (muscle* AND rigidit*))	**84,991**
S2	(MH "Upper Extremity+") OR (MH "Hand+") OR (MH "Fingers+") OR (MH "Deltoid Muscles") OR (MH "Rotator Cuff+") OR (MH "Flexor Pollicis Longus Muscle") OR (MH "Biceps Brachii Muscles") OR (MH "Abductor Pollicis Longus Muscle") OR (MH "Latissimus Dorsi Muscles") OR (MH "Triceps Brachii") OR (MH "Trapezius Muscles") OR (MH "Coracobrachialis") OR (MH "Pectoralis Muscles") OR (MH "Stapedius") OR (MH "Teres Major Muscle") OR TI ((upper AND limb*) OR arm OR arms OR forearm* OR fore arm* OR metacarp* OR forelimb* OR fore limb* OR (upper AND extremit*) OR hand OR hands OR finger* OR wrist* OR elbow* OR shoulder* OR "rotator cuff" OR digits OR digit OR bicep OR biceps OR (deltoid* AND muscle*) OR (scapulohumer* AND muscle*) OR digitorum OR (extensor AND muscle*) OR (flexor AND muscle*) OR (pectoral* AND muscle*) OR triceps OR tricep OR brachial* OR coracobrachial* OR infraspinatus* OR "latissimus dorsi" OR subscapular* OR supraspinat* OR "teres major" OR "teres minor" OR "serratus anterior" OR subclavius OR (levator* AND scapula*) OR trapezius OR brachioradial* OR ("extensor carpi" AND radial*) OR digiti OR digitis OR "extensor carpi ulnaris" OR "flexor carpi" OR "palmaris longus" OR "pronator teres" OR anconeus OR supinator* OR "abductor pollicis" OR "extensor pollicis") OR AB ((upper AND limb*) OR arm OR arms OR forearm* OR fore arm* OR metacarp* OR forelimb* OR fore limb* OR (upper AND extremit*) OR hand OR hands OR finger* OR wrist* OR elbow* OR shoulder* OR "rotator cuff" OR digits OR digit OR bicep OR biceps OR (deltoid* AND muscle*) OR (scapulohumer* AND muscle*) OR digitorum OR (extensor	**102,879**

Search	Query	Items found
	AND muscle*) OR (flexor AND muscle*) OR (pectoral* AND muscle*) OR triceps OR tricep OR brachial* OR coracobrachial* OR infraspinatus* OR "latissimus dorsi" OR subscapular* OR supraspinat* OR "teres major" OR "teres minor" OR "serratus anterior" OR subclavius OR (levator* AND scapula*) OR trapezius OR brachioradial* OR ("extensor carpi" AND radial*) OR digiti OR digitis OR "extensor carpi ulnaris" OR "flexor carpi" OR "palmaris longus" OR "pronator teres" OR anconeus OR supinator* OR "abductor pollicis" OR "extensor pollicis")	
S1	(MH "Botulinum Toxins") OR TI ((botulin* AND toxin*) OR (botulin* AND neurotoxin*) OR (botulism* AND toxin*) OR (botulin* AND exotoxin*) OR abobotulinumtoxin* OR azzalure* OR bocouture* OR bont OR botox OR "botulin a" OR btxa OR btx OR (botulin* AND endotoxin*) OR dyslor* OR dysport* OR (evabotulin* AND toxin*) OR evabotulinumtoxin* OR (incobotulin* AND toxin*) OR incobotulinumtoxin* OR meditoxin* OR "nt 201" OR nt201 OR oculinum* OR (onabotulin* AND toxin*) OR onabotulinumtoxin* OR onaclostox* OR prosigne* OR purtox* OR reloxin* OR vistabel* OR vistabex* OR xeomin* OR myobloc* OR myoblock* OR neurobloc* OR (rimabotulin* AND toxin*) OR rimabotulinumtoxin* OR bontf) OR AB ((botulin* AND toxin*) OR (botulin* AND neurotoxin*) OR (botulism* AND toxin*) OR (botulin* AND exotoxin*) OR abobotulinumtoxin* OR azzalure* OR bocouture* OR bont OR botox OR "botulin a" OR btxa OR btx OR (botulin* AND endotoxin*) OR dyslor* OR dysport* OR (evabotulin* AND toxin*) OR evabotulinumtoxin* OR (incobotulin* AND toxin*) OR incobotulinumtoxin* OR meditoxin* OR "nt 201" OR nt201 OR oculinum* OR (onabotulin* AND toxin*) OR onabotulinumtoxin* OR onaclostox* OR prosigne* OR purtox* OR reloxin* OR vistabel* OR vistabex* OR xeomin* OR myobloc* OR myoblock* OR neurobloc* OR (rimabotulin* AND toxin*) OR rimabotulinumtoxin* OR bontf)	**3,478**

Supplement 2B. Classification of the main clinical goals following ICF

Spasticity-related pain. 'Sensation of unpleasant feeling indicating potential or actual damage to some body structure', experienced in the affected upper limb and related to spasticity (ICF–b280).

Involuntary movements. Unwanted movements of the affected upper limb whilst performing activities with the non-affected body side or legs, or during activities such as yawning, sneezing and coughing (ICF–b755/b760/b765).

Passive joint motion. The combination of passive range of motion of the joint (ICF–b7100) and its resistance during this passive movement (ICF–b7100/7350).

Ability to care for the hand and arm. The ability of either the patient or the caregiver to take care of the affected arm and hand, including washing the palm of the hand or the axilla, cutting the fingernails and dressing the upper limb (ICF–d510/d520/d540/e3).

Arm and hand use. The capability to perform daily activities with the arm (ICF–d430/d440/d445/d500/510/d540/d550/d560/d630/d640/d850/d920).

Standing and walking performance. The capacity to maintain standing balance (ICF–d415), to make transfers (ICF–d420) and to walk (ICF–d450) without falling or tripping.

Supplement 2C. Meta-analyses

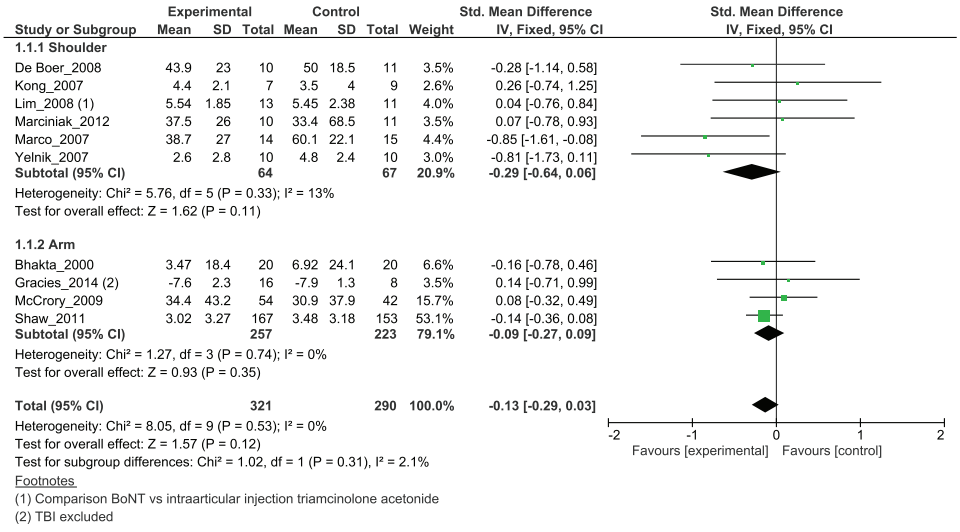


Figure S2.1a. Forest plot of post-intervention effect sizes (SMDs) of BoNT treatment on spasticity-related pain; 4–8wk after injection (higher = worse pain).

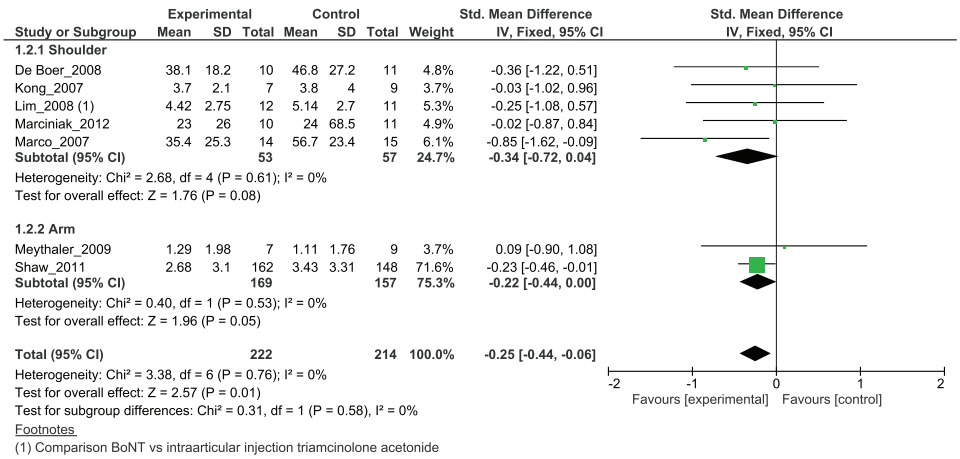


Figure S2.1b. Forest plot of follow-up effect sizes (SMDs) of BoNT treatment on spasticity-related pain; 12wk after injection (higher = worse pain).

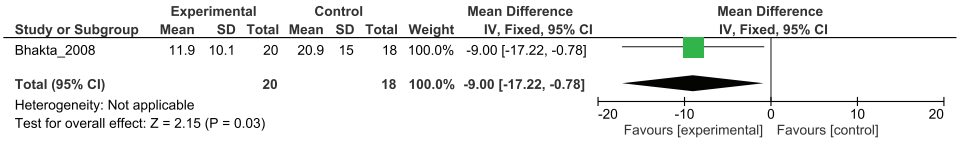


Figure S2.2a. Forest plot of post-intervention effect sizes (MDs) of BoNT treatment on involuntary movements; 4–8wk after injection (higher = more involuntary movements).

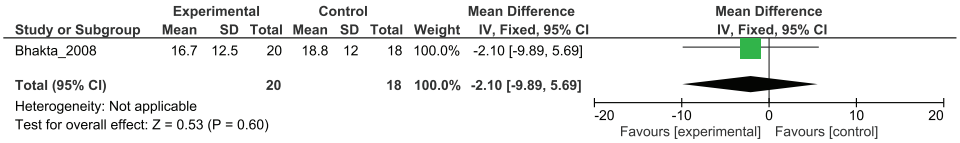


Figure S2.2b. Forest plot of follow-up effect sizes (MDs) of BoNT treatment on involuntary movements; 12wk after injection (higher = more involuntary movements).

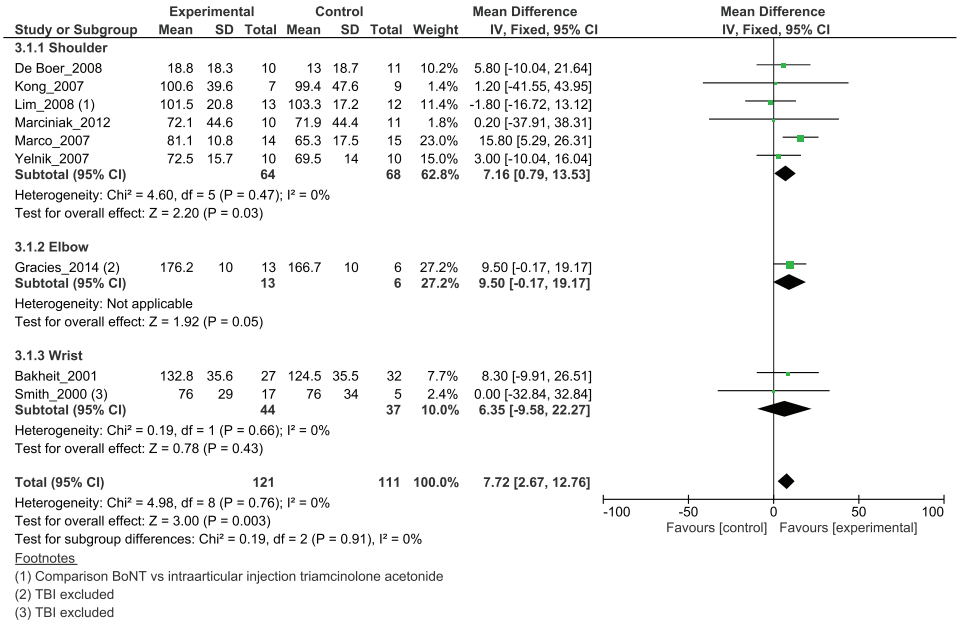


Figure S2.3a. Forest plot of post-intervention effect sizes (MDs) of BoNT treatment on passive range of motion; 4–8wk after injection (higher = better range).

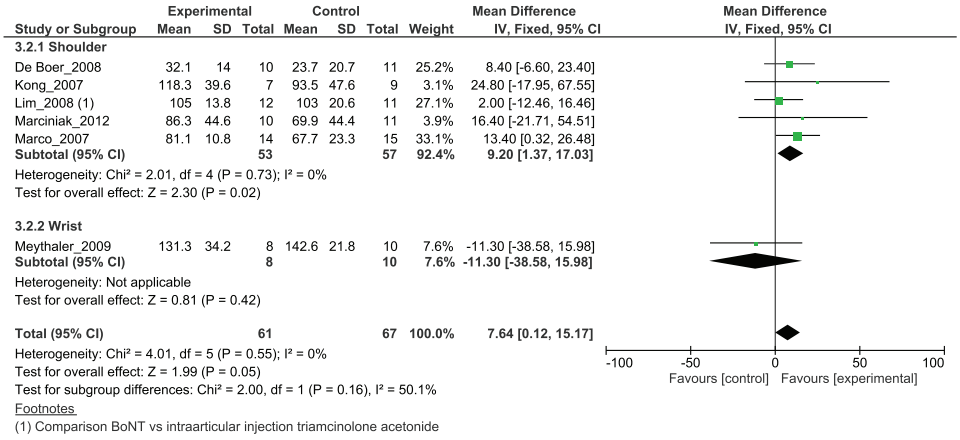


Figure S2.3b. Forest plot of follow-up effect sizes (MDs) of BoNT treatment on passive range of motion; 12wk after injection (higher = better range).

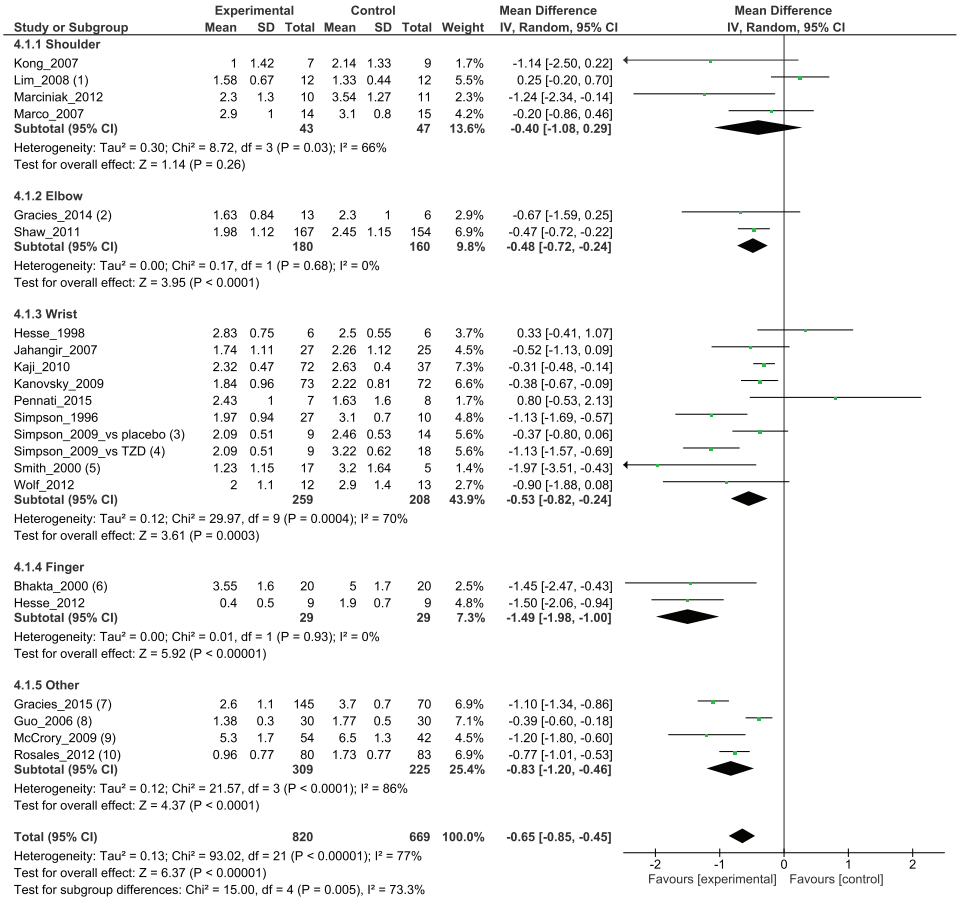


Figure S2.3c. Forest plot of post-intervention effect sizes (MDs) of BoNT treatment on resistance to passive movement; 4–8wk after injection (higher = worse resistance to passive movement).

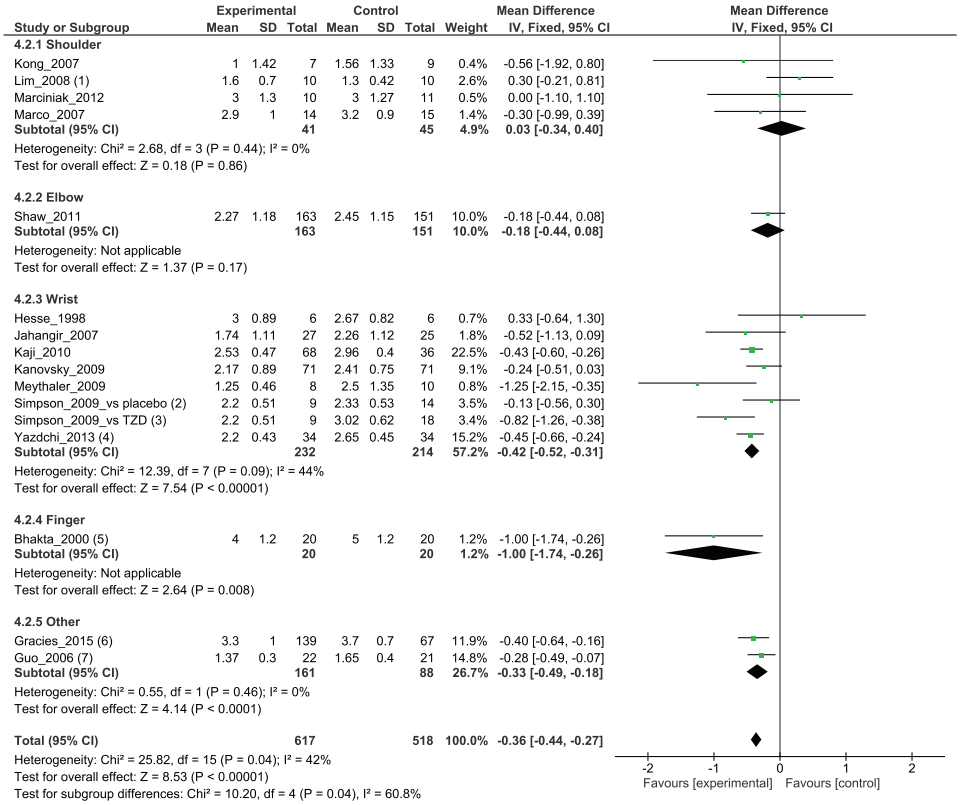


Figure S2.3d. Forest plot of follow-up effect sizes (MDs) of BoNT treatment on resistance to passive movement; 12wk after injection (higher = worse resistance to passive movement).

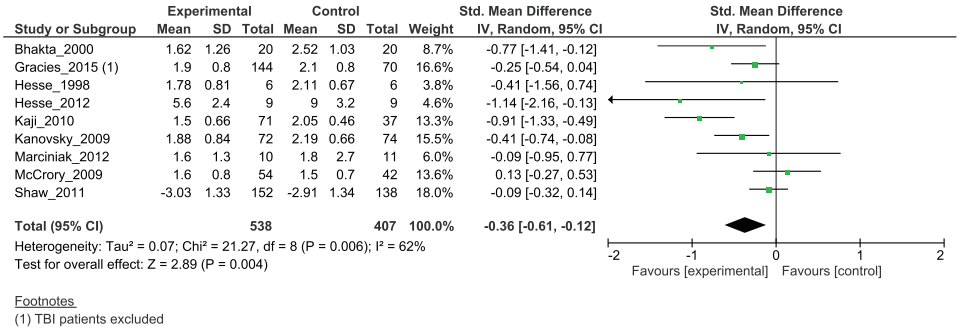


Figure S2.4a. Forest plot of post-intervention effect sizes (SMDs) of BoNT treatment on self-care ability; 4–8wk after injection (higher = more restrictions in self-care).

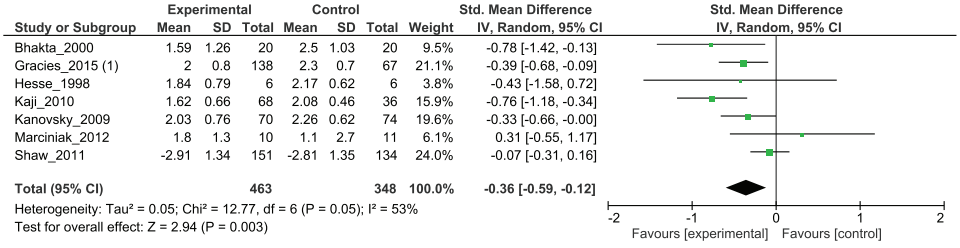


Figure S2.4b. Forest plot of follow-up effect sizes (SMDs) of BoNT treatment on self-care ability; 12wk after injection (higher = more restrictions in self-care).

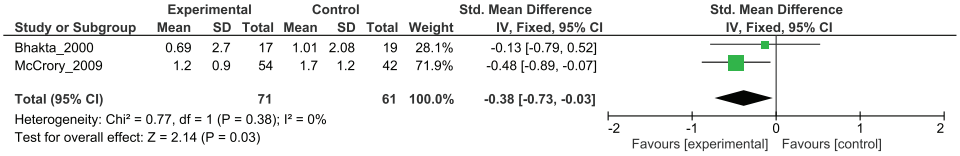


Figure S2.4c. Forest plot of post-intervention effect sizes (SMDs) of BoNT treatment on caregiver burden; 4–8wk after injection (higher = worse burden).

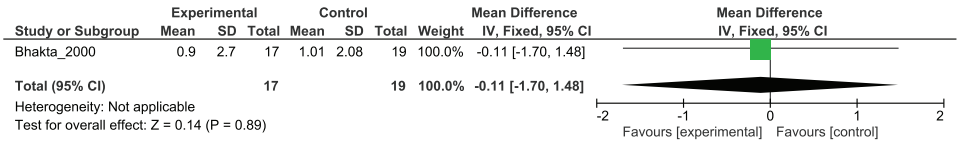


Figure S2.4d. Forest plot of follow-up effect sizes (SMDs) of BoNT treatment on caregiver burden; 12wk after injection (higher = worse burden).

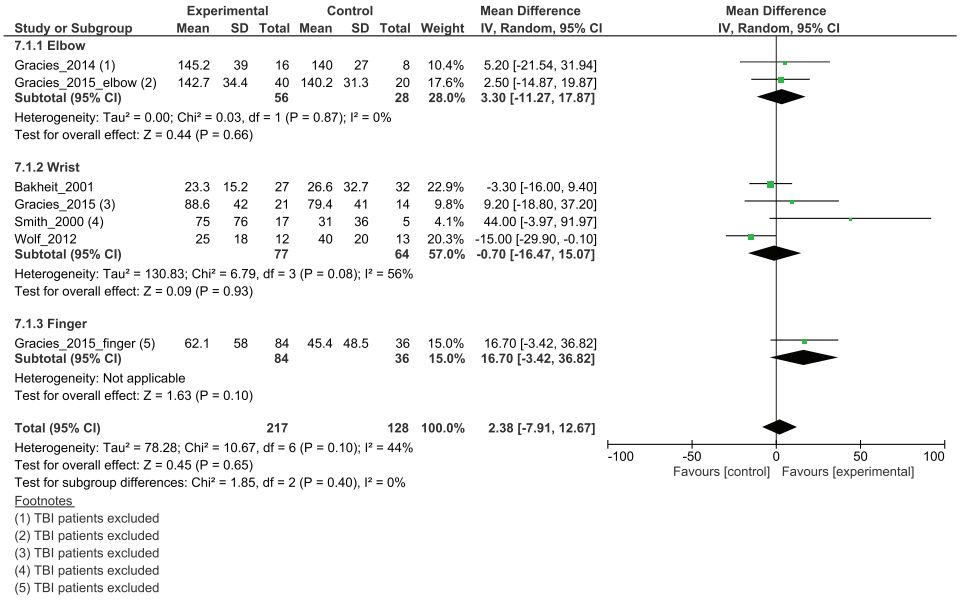


Figure S2.5a. Forest plot of post-intervention effect sizes (MDs) of BoNT treatment on active range of motion; 4–8wk after injection (higher = better function).

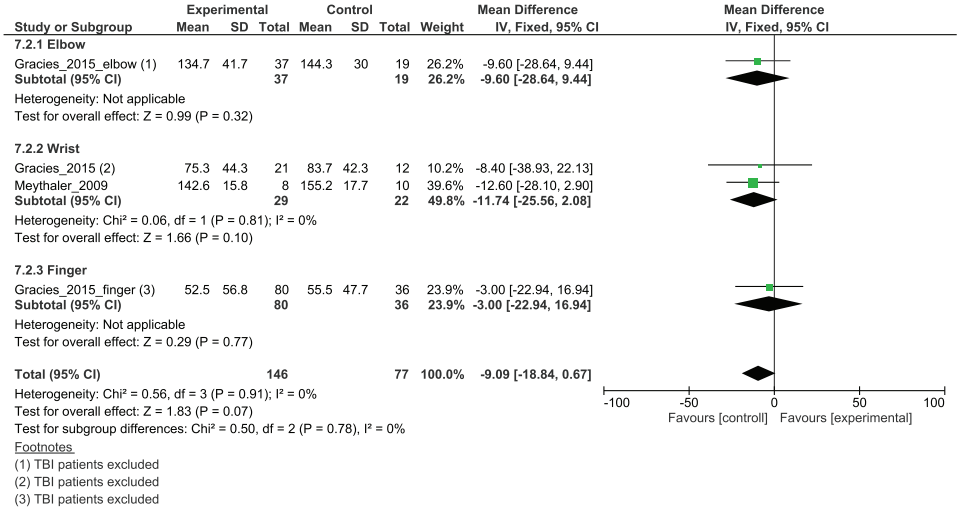


Figure S2.5b. Forest plot of follow-up effect sizes (MDs) of BoNT treatment on active range of motion; 12wk after injection (higher = better function).

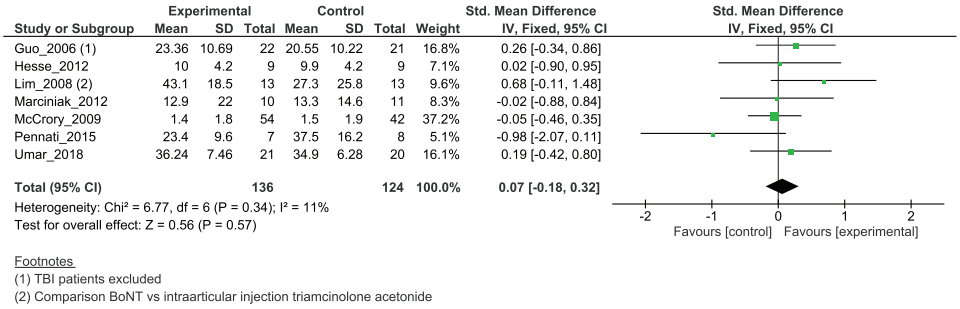


Figure S2.5c. Forest plot of post-intervention effect sizes (SMDs) of BoNT treatment on motor function; 4–8wk after injection (higher = better function).

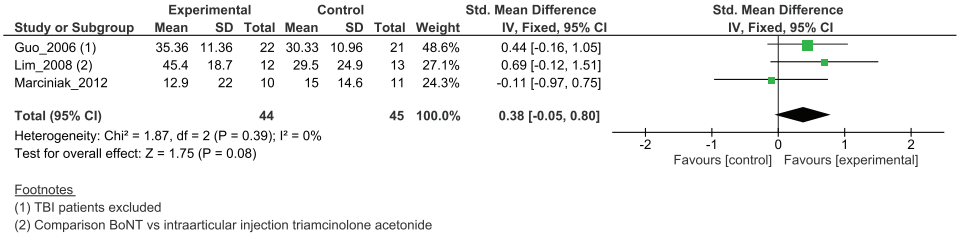


Figure S2.5d. Forest plot of follow-up effect sizes (SMDs) of BoNT treatment on motor function; 12wk after injection (higher = better function).

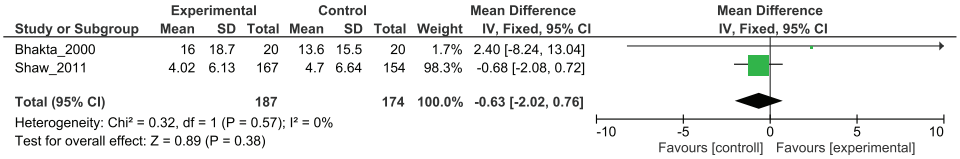


Figure S2.5e. Forest plot of post-intervention effect sizes (MDs) of BoNT treatment on grip strength; 4–8wk after injection (higher = better function).

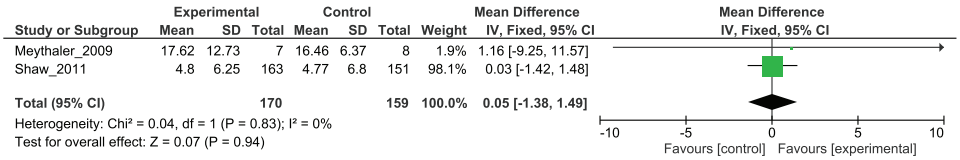
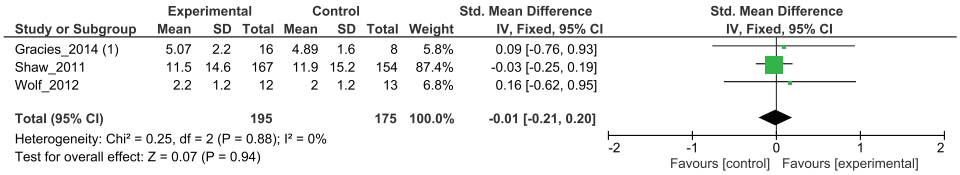
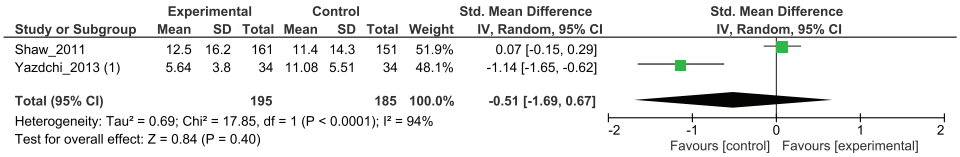


Figure S2.5f. Forest plot of follow-up effect sizes (MDs) of BoNT treatment on grip strength; 12wk after injection (higher = better function).



Footnotes
(1) TBI patients excluded

Figure S2.5g. Forest plot of post-intervention effect sizes (SMDs) of BoNT treatment on arm-hand capacity; 4–8wk after injection (higher = better capacity).



Footnotes
(1) Comparison BoNT vs oral tizanidine

Figure S2.5h. Forest plot of follow-up effect sizes (SMDs) of BoNT treatment on arm-hand capacity; 12wk after injection (higher = better capacity).

Supplement 2D. Sensitivity analyses

Table S2.1. Overview of correlation coefficients; moderator effects of study and intervention characteristics, and influence of study involvement of the pharmaceutical industry on the meta-analyses

	Publication year*	PEDro score*	Doses BoNT*	Timing post-stroke (months)*	Additional therapy†	Influence pharmaceutical industry†
Spasticity-related pain, wk12	0.476 *P* = 0.28 *n* = 7	0.115 *P* = 0.81 *n* = 7	0.293 *P* = 0.52 *n* = 7	**0.913** ***P* = 0.03** ***n* = 5**	-0.408 *P* = 0.36 *n* = 7	**0.791** ***P* = 0.03** ***n* = 7**
Passive range of motion, wk4–8	0.083 *P* = 0.83 *n* = 9	0.277 *P* = 0.47 *n* = 9	0.118 *P* = 0.78 *n* = 8	0.202 *P* = 0.66 *n* = 7	0.000 *P* = 1.00 *n* = 9	-0.518 *P* = 0.15 *n* = 9
Passive range of motion, wk12	-0.092 *P* = 0.86 *n* = 6	0.424 *P* = 0.40 *n* = 6	-0.436 *P* = 0.39 *n* = 6	0.145 *P* = 0.86 *n* = 4	-0.393 *P* = 0.44 *n* = 6	0.000 *P* = 1.00 *n* = 6
Resistance to passive movement, wk4–8	0.171 *P* = 0.45 *n* = 22	-0.328 *P* = 0.14 *n* = 22	-0.214 *P* = 0.37 *n* = 20	-0.121 *P* = 0.67 *n* = 15	0.291 *P* = 0.19 *n* = 22	-0.173 *P* = 0.48 *n* = 19
Resistance to passive movement, wk12	-0.063 *P* = 0.82 *n* = 16	-0.144 *P* = 0.60 *n* = 16	-0.309 *P* = 0.24 *n* = 16	-0.475 *P* = 0.20 *n* = 9	-0.005 *P* = 0.99 *n* = 16	0.041 *P* = 0.89 *n* = 14
Self-care ability, wk4–8	0.138 *P* = 0.72 *n* = 9	0.431 *P* = 0.25 *n* = 9	0.181 *P* = 0.64 *n* = 9	0.201 *P* = 0.67 *n* = 7	-0.099 *P* = 0.80 *n* = 9	-0.456 *P* = 0.26 *n* = 8
Self-care ability, wk12	0.441 *P* = 0.32 *n* = 7	0.213 *P* = 0.65 *n* = 7	-0.523 *P* = 0.23 *n* = 7	-0.685 *P* = 0.20 *n* = 5	0.000 *P* = 1.00 *n* = 7	-0.144 *P* = 0.76 *n* = 7
Carer burden, wk4–8	NA	NA	NA	NA	NA	NA

* Pearson correlation coefficient; † Spearman correlation coefficient; *P* value; n, number of studies included; NA, not applicable.

Presence of additional therapy classified as: 0) no additional therapy; 1) continuation of regular therapy after injection; 2) additional specified therapy combined with BoNT treatment. Influence of pharmaceutical industry classified as: 0) no competing interests reported; 1) funding from the pharmaceutical industry; 2) funding and involvement in study design/protocol development from the pharmaceutical industry; 3) funding and authorship from pharmaceutical industry; 4) funding, authorship and statistical analysis by the pharmaceutical industry.

Supplement 2E. Funnel plots

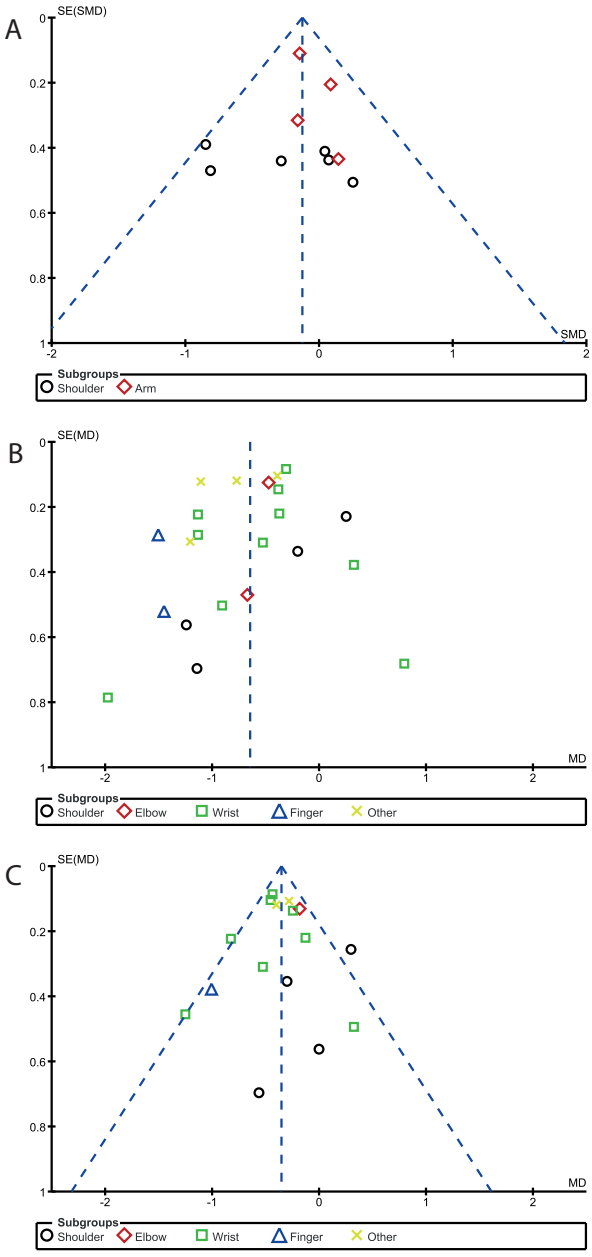


Figure S2.6. Analysis of publication bias for study size.
Funnel plots of the standard error of the intervention effect estimate plotted on a reverse scale to the effect size of each study for comparisons including data of at least ten studies. (A) Spasticity-related pain, 4–8wk after injection. (B) Resistance to passive movement, 4–8wk after injection. (C) Resistance to passive movement, 12wk after injection.

CHAPTER 3

Measurement properties of the NeuroFlexor device for quantifying neural and non-neural components of wrist hyper-resistance in chronic stroke

Aukje S. Andringa
Erwin E.H. van Wegen
Ingrid G.L. van de Port
Gert Kwakkel
Carel G.M. Meskers

Front Neurol. 2019;10:730

ABSTRACT

Introduction: Differentiating between the components of wrist hyper-resistance post stroke, i.e. pathological neuromuscular activation ("spasticity") and non-neural biomechanical changes, is important for treatment decisions. This study aimed to assess the reliability and construct validity of an innovative measurement device that quantifies these neural and non-neural components by biomechanical modelling.

Methods: Forty-six patients with chronic stroke and 30 healthy age-matched subjects were assessed with the NeuroFlexor, a motor-driven device that imposes isokinetic wrist extensions at two controlled velocities (5 and 236°/second). Test-retest reliability was evaluated using intraclass correlation coefficients (ICC) and smallest detectable changes (SDC), and construct validity by testing the difference between patients and healthy subjects and between subgroups of patients stratified by modified Ashworth scale (MAS), and the association with clinical scales.

Results: Test-retest reliability was excellent for the neural (NC) and non-neural elastic (EC) components (ICC 0.93 and 0.95, respectively), and good for the viscous component (VC) (ICC 0.84), with SDCs of 10.3, 3.1 and 0.5 N, respectively. NC and EC were significantly higher in patients compared to healthy subjects ($P < 0.001$). Components gradually increased with MAS category. NC and EC were positively associated with the MAS (r_s 0.60 and 0.52, respectively; $P < 0.01$) and NC with the Tardieu scale (r_s 0.36, $P < 0.05$). NC and EC were negatively associated with the Fugl-Meyer Assessment of the upper extremity and action research arm test ($r_s \leq -0.38$, $P < 0.05$).

Conclusions: The NeuroFlexor reliably quantifies neural and non-neural components of wrist hyper-resistance in chronic stroke, but is less suitable for clinical evaluation at individual level due to high SDC values. Although construct validity has been demonstrated, further investigation at component level is needed.

INTRODUCTION

Hyper-resistance in the wrist joint after stroke is a result of pathological neuromuscular activation ("spasticity") and biomechanical changes in muscles and soft tissues overlying the joint.[1-3] Distribution and level of these neural and non-neural components may diverge between individual patients, and may change during the time course post stroke.[4,5] Distinguishing between components will impact on the choice of tailored interventions for the prevention and treatment of joint hyper-resistance.

The modified Ashworth scale (MAS) is routinely used as a clinical measurement scale for spasticity, as it is easily applicable, time-efficient and cost-free. However, this ordinal rating scale has poor measurement properties regarding reliability[6-8] and validity,[6,8-10] and is unable to discriminate between spasticity and other factors influencing joint hyper-resistance. There is a need for an objective, quantitative measurement tool, with a standardized assessment protocol, feasible for clinical practice, which is reliable and valid. In recent years, various instrumented measurement setups using different modelling techniques were developed.[11-14] However, these are generally time-consuming and require extensive training. The NeuroFlexor (Aggero MedTech AB, Älta, Sweden) is a recently developed, portable, easily applicable and commercially available alternative. The underlying biomechanical model for the quantification of the neural component ("spasticity") was previously validated.[4] Good inter- and intrarater reliability for both neural and non-neural components has been demonstrated for patients with chronic stroke.[15] However, all studies of the measurement properties of the NeuroFlexor so far have been published by authors who potentially have commercial interest in the device. Furthermore, information regarding the validity of the different components compared to commonly used clinical scales is lacking.

Therefore, the aim of this study is to perform an independent investigation of the reliability and construct validity of the NeuroFlexor for the quantification of neural and non-neural components of wrist hyper-resistance in patients with chronic stroke.

MATERIALS AND METHODS

Participants

We recruited patients with chronic stroke from Revant rehabilitation centre Breda, Klimmendaal Rehabilitation centre Apeldoorn, Bravis hospital Bergen op Zoom and Roosendaal, and from physiotherapists of the stroke network Amsterdam and FysioNet

Breda. The inclusion criteria for this study were: (1) an ischemic or haemorrhagic stroke at least six months prior to inclusion; (2) an initial upper limb deficit as defined by the National Institutes of Health Stroke Scale (NIHSS) item 5 a/b score > 0 (i.e. not able to hold the affected arm at a 90° angle for at least 10 seconds); (3) age ≥ 18 years; and (4) the ability to follow test instructions (mini mental state examination (MMSE) > 19). Exclusion criteria were: (1) limitations of arm-hand function of the affected side other than due to stroke; (2) limitation of the wrist passive range of motion (PRoM) with extended fingers that limits the extension to < 40°; and (3) botulinum toxin injections in the affected arm in the previous 3 months. A group of right-handed healthy age-matched adults without wrist function restrictions volunteered as a reference group. Ethical approval was obtained from the Medical Ethics Committee of the VU University medical centre, Amsterdam, The Netherlands. In accordance with the Declaration of Helsinki (2013), all participants gave written informed consent.

Outcome measures

NeuroFlexor

The NeuroFlexor (Aggero MedTech AB, Älta, Sweden) is a motor-driven device that imposes isokinetic displacements on the wrist with extended fingers in the direction of extension, at two controlled velocities (5 and 236°/second) as pictured in Figure 3.1. Resistance during the passive movement is measured in Newton (N) using a force sensor, which is placed underneath the moveable hand platform. The resulting resistance trace during the displacement is subsequently analysed by a biomechanical model, which results in quantification of the different components of joint resistance, i.e. the neural component (NC), elastic component (EC) and viscous component (VC).[4] The NC represents the velocity-dependent force due to muscle contractions induced by the stretch reflexes. The non-neural component consists of an elastic and a viscous component. The EC is the length-dependent force, assessed 1 second after the end of the slow movement. The VC is velocity-dependent and is most prominent during initial acceleration. During wrist extension movement with extended fingers, both the wrist flexor muscles, as well as the finger flexor muscles were lengthened. The neural and non-neural values of the NeuroFlexor, therefore, represent a combination of wrist and finger flexor muscle groups.

During the measurement, the participant was seated comfortably parallel to the device with the shoulder in 45° abduction and 0° flexion, the elbow in 90° flexion, the forearm in pronation and the fingers extended. The arm rested in a support and was fastened to the device using two straps for the forearm and two straps for the hand and fingers, to minimize

displacements during measurement. The wrist joint was visually aligned to the rotation axis, and the hand was placed on the hand platform in a standardized way according to anatomical landmarks. The participant was instructed to relax the arm during the movements of the device. The device imposed wrist joint displacements from 30° wrist flexion to 20° wrist extension. A test session consisted of five slow movements followed by ten fast movements with a pause of at least one second in between the movements. In order to avoid bias from startle reflexes and mechanical hysteresis, the first slow and first fast movements were excluded from the analysis. The NeuroFlexor Scientific v0.06 software program automatically calculated the different components of joint resistance using the biomechanical model described by Lindberg et al.[4] (Supplement 3A).

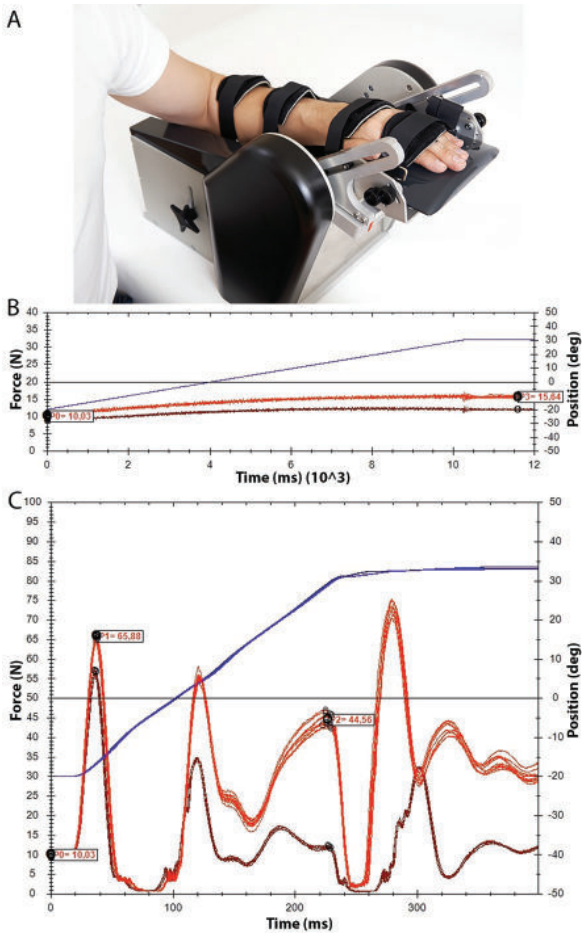


Figure 3.1. NeuroFlexor method.
(A) Measurement set-up. (B) An example of data obtained during slow movements (5°/second). (C) An example of data obtained during fast movements (236°/second).

Clinical assessment

Total resistance to passive movement in the wrist was measured manually using the ordinal modified Ashworth scale (MAS),[16] which ranges from 0, indicating no increased tone, to 4, indicating that the joint is rigid. The Tardieu scale (TS),[17] which has been suggested to be more appropriate for the measurement of velocity-dependent spasticity, was used to assess the PRoM at slow velocity (R2) without the effect of stretch reflex hyperactivity, the joint angle of muscle reaction at fast velocity stretch when the overactive stretch reflex produces a first catch (R1), and the quality of the muscle response at fast speed (Q). The quality of the muscle response at fast speed is described on an ordinal five-point scale, where 0 means no resistance to passive motion and 4 means a clonus that does not cease within 10 seconds. The MAS and TS were performed for the wrist and finger flexor muscles separately. The wrist extension movement with extended fingers was used as a representation of the resistance mostly caused by the finger flexors muscles, while the wrist extension movement with flexed fingers represented the resistance mostly caused by the wrist flexor muscles. PRoM of the wrist was determined using a goniometer. The mean of three PRoM assessments was used for the validation analysis. The Fugl-Meyer assessment of the upper extremity (FM-UE)[18] was used to assess motor performance of the affected arm and hand, and the action research arm test (ARAT)[19] was used to assess arm and hand capacity. Both the FM-UE and ARAT have been shown to be reliable and valid tests.[20-22]

Procedure

We used a test-retest design within a cross-sectional cohort with a single experimental session. First, demographic data, medical history, type of stroke, time post stroke, neurological status (NIHSS), cognitive function (MMSE), affected body side and hand dominance were recorded. All measurements were done by a trained researcher, and were performed on the patients' impaired arm and on the dominant right arm of the healthy subjects. To determine test-retest reliability, NeuroFlexor measurements were performed twice within the single experimental session. To achieve stable levels of hyper-resistance, the environment was quiet and no great physical effort was required from the patient in between the tests. The two NeuroFlexor measurements and the clinical assessments were performed in a random order to avoid systematic influence of the clinical assessments on the test-retest values, with at least 15 minutes between the two NeuroFlexor measurements, during which interval the participants' arm was removed from the device and then replaced anew.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical characteristics. We used the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines regarding definitions of reliability and validity.[23]

Test-retest reliability of the NeuroFlexor was defined as the extent to which scores for patients with unchanged impairments were the same in two repeated measurements.[23,24] First, scatterplots were used to obtain a visual overview of the distribution of test-retest data and to check for potential outliers. Test-retest reliability was evaluated using intraclass correlation coefficients (ICC), which were calculated with a single-measures, two-way random-effects model for absolute agreement with 95% confident intervals. Following Portney and Watkins' recommendations, ICC values < 0.50 were considered to indicate poor, 0.50 to 0.75 moderate, 0.75 to 0.90 good and values > 0.90 excellent reliability.[25]

To evaluate measurement error we obtained Bland-Altman plots (mean of measurements 1 and 2 [x-axis] compared with the difference between the two measurements [y-axis]) with limits of agreement, standard errors of measurement (SEM) and smallest detectable changes (SDC). Limits of agreement were calculated based on the standard deviation of the mean difference between measurements 1 and 2 ($d \pm 1.96 * SD\ \Delta$). SEM was calculated from the square root of the within-subject variance (i.e. the sum of the between-measurements variance and the residual variance), and SDC was calculated using the formula: $SDC = 1.96 * \sqrt{2} * SEM$.[24] SDC was defined as the smallest change in score that can be detected by the device and can be interpreted as a real change, which is important for use in clinical practice.

Due to the lack of an appropriate gold standard, validity was assessed in terms of construct validity. Prior hypotheses were formulated stating the expected relation between the NeuroFlexor and clinical scales. We expected (1) significantly higher neural and non-neural components in patients compared to healthy subjects; (2) positive associations between the total resistance to passive movement and the MAS scores of the wrist and fingers flexor muscles and (3) between the neural component and the scores on the Tardieu Scale; and (4) negative associations between the non-neural elastic component and wrist PRoM and (5) between both the neural and non-neural components and the motor performance of the arm.

Statistical analysis of the difference in neural and non-neural components between patients and healthy subjects used the Mann-Whitney U test. Stratification by MAS score of patients was based on the highest MAS value for the wrist or the finger flexor muscles. Differences between patients, stratified by MAS, and healthy subjects were assessed by

Kruskal-Wallis analysis, with Mann-Whitney U *post-hoc* analyses. The correlation between neural and non-neural components and clinical scales was calculated using Spearman's rank correlation coefficient (r_s). $P < 0.05$ were considered significant. Correlation coefficients < 0.25 were considered as little to no, 0.25 to 0.50 as fair, 0.50 to 0.75 as moderate to good and > 0.75 as good to excellent association.[25]

RESULTS

Population characteristics

A total of 46 patients with chronic stroke and 30 healthy age-matched participants were included. One of the patients was not able to perform the NeuroFlexor measurements due to pain during wrist extension. Furthermore, data of three patients were excluded from the reliability analysis as their second measurement was missing due to technical problems. The main population characteristics are shown in Table 3.1.

The majority of data was non-normally distributed, except for the VC in patients, the neural and non-neural components in healthy subjects, and the PRoM of the wrist in both groups. The differences between NeuroFlexor measurements 1 and 2 were normally distributed for all three components.

Table 3.1. Demographic and clinical characteristics of the study population

	Stroke patients	Healthy subjects
Participants (n)	46	30
Age, years (mean ± SD)	59.9 ± 10.0	59.0 ± 11.5
Gender, male/female (n)	31/15	14/16
Stroke type, iCVA/hCVA (n)	39/7	
Time post stroke, months (mean ± SD)	61.5 ± 76.5	
NIHSS score (mean ± SD)	4.8 ± 3.2	
Affected side, left/right (n)	26/20	
Dominant hand, left/right/ambidextrous (n)	3/42/1	0/30/0
MAS wrist flexor muscles (median [IQR])	1 [0–1.5]	
MAS finger flexor muscles (median [IQR])	1.5 [1–2]	
PRoM affected/dominant wrist, ° (mean ± SD)	172.3 ± 20.1	167.9 ± 17.6
FM-UE (mean ± SD)	32.5 ± 18.7	
ARAT (mean ± SD)	21.0 ± 20.8	

Abbreviations: ARAT, action research arm test [range: 0–57]; FM-UE, Fugl-Meyer assessment of the upper extremity [range: 0–66]; hCVA, haemorrhagic stroke; iCVA, ischemic stroke; IQR, interquartile range; MAS, modified Ashworth scale [range 0–4], (score 1+ is reported as 1.5); NIHSS, National Institutes of Health Stroke Scale [range: 0–42]; PRoM: passive range of motion.

Test-retest reliability

An overview of the reliability parameters can be found in Table 3.2. The test-retest reliability (ICC) in the group of patients was excellent for the NC and EC (respectively 0.93 and 0.95), and good for the VC (0.84). The SDC for the NC was 10.31 N, that for the EC 3.14 N and that for the VC 0.53 N. Scatterplots of patients' test-retest data are presented in Supplement 3B and show a linear relationship between measurements 1 and 2 for all components. The plot for the EC shows three outliers with higher values (> mean value + 2 SD). Excluding these patients from analysis decreased the ICC to 0.75 (95% CI, 0.58–0.86) and changed the SDC from 3.14 N to 3.02 N. Supplement 3C presents Bland-Altman plots, showing a distribution scattered around the mean difference of 0 for all components, which means there was no systematic difference between measurements 1 and 2.

Table 3.2. Reliability parameters of neural and non-neural components in patients with chronic stroke (n = 42)

	ICC (95% CI)	Mean diff (SD)	SEM	SDC
NC	0.93 (0.88–0.96)	0.27 (5.31)	3.72	10.31
EC	0.95 (0.92–0.98)	0.27 (1.60)	1.13	3.14
VC	0.84 (0.73–0.91)	-0.06 (0.27)	0.19	0.53

Abbreviations: EC, elastic component; ICC, intraclass correlation coefficient, two-way random-effects model for absolute agreement; Mean diff, mean difference between measurements 1 and 2 (N); NC, neural component; SDC, smallest detectable change (N); SEM, standard error of measurement (N); VC, viscous component.

Construct validity

The NeuroFlexor values of measurement 1 were used for the validation part of this study. Table 3.3 shows an overview of the median component values in healthy subjects and patients, stratified by MAS. Mann-Whitney U tests revealed significantly higher NC, EC and total resistance for patients compared to healthy subjects ($P < 0.001$) with significant differences between patients stratified by MAS score and healthy subjects (NC, $P < 0.001$; EC, $P < 0.001$; VC, $P < 0.05$; total resistance, $P < 0.001$). *Post-hoc* analyses revealed significantly higher NC and EC values and a lower VC value for patients with MAS = 0 compared to healthy subjects for all components ($P < 0.03$). Overall, the NC, EC and VC gradually increased with MAS category, except for the VC for MAS categories 2 and 3.

A moderate to good significant positive correlation ($r_s > 0.50$, $P > 0.01$) was found between the NC, EC and the total of components, and the MAS of both the wrist and finger flexor muscles (Table 3.4, Supplement 3D). The NC and the total of components revealed a fair significant positive correlation with the Tardieu scale ($r_s \geq 0.30$, $P < 0.05$). The NC, EC

Table 3.3. Neural and non-neural components of wrist hyper-resistance in healthy subjects and patients with chronic stroke

			Stroke, stratified by MAS				
	Healthy n = 30	Stroke n = 45	MAS 0 n = 9	MAS 1 n = 12	MAS 1+ n = 11	MAS 2 n = 7	MAS 3 n = 6
NC (N)	0.36 [-0.07 to 1.66]	11.54* [4.84 to 20.99]	2.35‡ [0.86 to 10.88]	6.49 [3.58 to 15.75]	11.54 [8.96 to 20.29]	12.09 [8.93 to 26.64]	35.77 [21.97 to 47.21]
EC (N)	1.92 [1.41 to 2.72]	4.51* [3.31 to 7.87]	3.15† [2.32 to 3.99]	4.37 [2.88 to 6.99]	5.92 [4.43 to 8.12]	6.15 [4.38 to 8.10]	8.38 [3.92 to 22.11]
VC (N)	0.36 [0.15 to 0.63]	0.38 [0.04 to 0.67]	0.12‡ [-0.20 to 0.34]	0.22 [-0.20 to 0.57]	0.64 [0.38 to 1.04]	0.57 [0.11 to 0.75]	0.52 [-0.12 to 1.18]
Total (N)	2.61 [2.28 to 3.56]	17.43* [8.53 to 28.96]	4.62† [4.27 to 14.47]	12.71 [6.61 to 21.32]	18.74 [12.84 to 29.48]	18.64 [14.98 to 31.82]	43.28 [28.39 to 69.96]

Values are median [interquartile range]. * $P < 0.001$; † $P < 0.01$; ‡ $P < 0.05$.
Abbreviations: EC, elastic component; MAS, modified Ashworth scale; NC, neural component; total, sum of three components; VC, viscous component. Level of significance of difference compared to healthy subjects (Mann-Whitney U test).

and total of components showed fair significant negative correlation coefficients with the FM-UE and ARAT ($r_s \leq -0.38$, $P < 0.05$).

Table 3.4. Spearman's rank correlation coefficients (r_s) between neural and non-neural components of wrist hyper-resistance and clinical scales

	NC	EC	VC	Total
Wrist flexor muscles				
MAS	0.56**	0.49**	0.42**	0.57**
TS Q	0.34*	0.21	0.26	0.30*
TS R2–R1	0.36*	0.20	0.20	0.33*
Finger flexor muscles				
MAS	0.60**	0.52**	0.37*	0.62**
TS Q	0.24	0.23	0.30	0.26
TS R2–R1	0.36*	0.26	0.19	0.37*
PRoM wrist	0.12	-0.11	0.03	0.06
FM-UE	-0.41**	-0.47**	-0.29	-0.47**
ARAT	-0.38*	-0.42**	-0.24	-0.44**

* $P < 0.05$; ** $P < 0.01$.
Abbreviations: ARAT, action research arm test; EC, elastic component; FM-UE, Fugl-Meyer assessment of the upper extremity; MAS, modified Ashworth scale; NC, neural component; PRoM, passive range of motion; total, sum of three components; TS Q, Tardieu scale, quality score; TS R2–R1, Tardieu scale, range R2–R1; VC, viscous component.

DISCUSSION

We have investigated the test-retest reliability and construct validity of the easily applicable and commercially available NeuroFlexor for the quantification of neural and non-neural components of hyper-resistance in the wrist joint in a group of 46 patients with chronic stroke with initial upper limb impairments, using a test-retest design with a single experimental session. The reliability for the neural and elastic components was excellent, and good reliability was found for the viscous component. Despite the promising reliability results, the SDC for all components was large compared to the median values (70–140% of the median). The significantly greater NC and EC in patients compared to healthy subjects, as well as the positive association of NC and EC with the MAS scores of both the wrist and fingers flexor muscles, the positive association of NC with the Tardieu scale, and the negative association with the motor performance of the arm, suggest that the NeuroFlexor method has good construct validity.

Reliability

In the previous study by Gäverth et al.,[15] equivalent ICC values were found for test-retest reliability (NC, 0.93; EC, 0.84; VC, 0.89) in a comparable group of patients with chronic stroke. Comparison of measurement error is difficult, however, as Gäverth et al.[15] used a logarithmic transformation to cope with the heteroscedasticity of their data, whereas there was no need for log transformation in our data. The calculated SDC scores allow for an easier interpretation in clinical practice. Moreover, reliability may have been exaggerated in the study by Gäverth et al.,[15] because a constant value was added to the raw data to compensate for negative values of the measured components to allow logarithmic transformation, which influences the variances.[26]

The relatively high SDC values we found, with good to excellent ICC values, can be explained by the heterogeneity of the study population we included, as ICC is strongly influenced by the variability between patients, whereas this variability is not included in the calculation of the SDC. A real change that could be measured (SDC value) is only a little smaller than the median values for the NC and EC, and even higher than the median value for the VC. This suggests that the NeuroFlexor is a reliable method for research purposes at group level and to differentiate between patients, but is less capable of detecting changes within individual patients over time. When monitoring a treatment effect in a single patient, a decrease of at least the SDC has to be achieved by the intervention to be interpreted as a real treatment effect. To use the NeuroFlexor for individual treatment decisions and evaluation, the method needs further improvement in terms of standardization.

To our knowledge, the NeuroFlexor is the first instrument available for the quantification of the neural and non-neural components of hyper-resistance without the assessment of electromyography (EMG) of the muscles involved. This means that this device is more feasible for use in clinical practice. Other measurement setups which use EMG for the quantification of components of hyper-resistance, have shown comparable or even poorer reliability values in terms of ICC and SDC.[13,27-29] Adding EMG to the NeuroFlexor measurement would presumably not improve the reliability. However, previous research showed that torque-related biomechanical parameters alone are less valid to describe the construct of spasticity than EMG-related parameters.[30,31] Moreover, the quantification of the neural component will always remain challenging, as spasticity is known to be variable in time and dependent on multiple factors such as posture, temperature and emotional status.[32] To account for natural fluctuations and to decrease SDC, repeated measurements within one session might be a solution.[33] However, this will also reduce the clinical applicability.

Construct validity

The NeuroFlexor is able to discriminate between healthy subjects and patients, even when classified as MAS = 0 for the wrist and finger flexor muscles. According to the pathology of stroke, patients show increased neural and non-neural hyper-resistance in the wrist.[1,2] The difference in the neural component we found between healthy subjects and patients in the MAS = 0 category emphasizes the presence of hyper-excitability of the stretch reflex in all patients, even without clinical hyper-resistance.[34] Additionally, the variances in neural and non-neural components of hyper-resistance were larger in patients compared to healthy subjects, reflecting the heterogeneity and therefore emphasizing the importance of individualized assessments for treatment decisions.

As expected, the total resistance to passive movement, as measured with the NeuroFlexor, was higher for patients in higher MAS categories. Both the NC and EC showed a good association with the MAS score, which emphasizes the criticism that has been made about the MAS, that it is not able to differentiate between these components and is influenced by both. A fair positive association was found between the NC and TS, which is supposed to be a more valid measure of the velocity-dependent spasticity.[9] The expected association between the EC and the PRoM of the wrist was not found, probably because we used PRoM restriction as an exclusion criterion for study participants. Performing the NeuroFlexor measurements requires a wrist extension with extended fingers of at least 40°. However, there was a significant difference in EC between healthy subjects and patients. If the NeuroFlexor is to be used in the future as a treatment evaluation method following, for example, botulinum toxin injections, the device and model need to be adapted for patients with PRoM restrictions, as these are most often treated.

Our findings suggest that the NeuroFlexor shows concurrent validity against the MAS and the Tardieu scale. However, future research is necessary to further validate its ability to distinguish the neural and non-neural components of hyper-resistance. This could be achieved by comparing the NeuroFlexor method with other instrumented assessment techniques, and more fundamental studies are needed to validate the different components of hyper-resistance. Furthermore, the responsiveness of the NeuroFlexor measurements to different treatments should be evaluated in relation to the SDC and minimal important change. The neural component can be influenced by treatments such as botulinum toxin and baclofen, whereas the non-neural component could be influenced by casts, splints, or orthopaedic surgery.

Interestingly, both the NC and EC have a fair negative association with the FM-UE and ARAT scores. Increased neural and non-neural hyper-resistance in the wrist is associated with poorer motor performance and arm-hand capacity. Further longitudinal studies are needed to investigate the development of hyper-resistance post stroke and its interaction with synergy-dependent motor recovery as measured with FM-UE, as well as the recovery of quality of movement. Knowledge of the time course of development of post-stroke hyper-resistance and its interaction with motor recovery is very important to better understand the neurophysiological changes that occur when patients recover.

Study limitations

This study did not address interrater reliability. However, adding another source of variance by a second observer would likely increase the measurement error, and would therefore not change our conclusion about the limited suitability of the NeuroFlexor for individual treatment evaluation. The ICC of the EC might have been inflated by three outliers observed in the scatterplot, which emphasizes the impact of heterogeneity of the study population on the ICC value. Due to a lack of an appropriate gold standard, it is not possible to study the criterion validity of the NeuroFlexor, and construct validity is to date the only possibility. Additionally, assessment of construct validity was difficult due to the fact that the constructs of the commonly used clinical scales MAS and TS are ambiguous. It is important to note that the correlation between the neural and non-neural components and the MAS confirms the inadequacy of this manual test, rather than highlighting the construct validity of the NeuroFlexor. Although we tried to limit influences on hyper-resistance, we were not able to estimate the variance in wrist hyper-resistance between the two measurement sessions in lack of a gold standard. As the NeuroFlexor provokes a wrist movement with extended fingers in a small range around the neutral position, both the wrist flexor muscles as well as the finger flexor muscles lengthen and contribute to the neural and non-neural components. To address test-retest reliability, we strictly adhered to a fixed position of the hand and fingers in the device. Future studies, however, may use different finger positions with respect to wrist and finger flexor muscle lengths, depending on the research or clinical question and the mechanical constraints of the device. Furthermore, the wrist was extended at two arbitrarily selected velocities (5 and 236°/second, respectively), which are assumed to be well below and well above expected reflex threshold velocity.[35] It should be acknowledged that the current linear approach does not address non-linear features as length and velocity dependent threshold of the stretch reflex.[36] Lastly, due to restrictions in the measurement

setup of the NeuroFlexor, we had to exclude patients with passive wrist extension limited to < 40°, which will have affected the association between the EC and the PRoM, and limits the generalization of our results.

CONCLUSIONS

The NeuroFlexor is a reliable instrument for the quantification of neural and non-neural components of hyper-resistance in the wrist joint at group level in patients with chronic stroke who exhibit initial upper limb impairments. The instrument showed good to excellent reliability for both neural and non-neural components. However, high SDC values make it difficult to use this technique for individual treatment decisions. The NeuroFlexor method appears to be construct valid against clinical scales, although the validity of the different components needs further investigation.

Overall, the NeuroFlexor can replace current clinical scales to evaluate wrist hyper-resistance for research purposes at group level and to differentiate between patients. For individual use in clinical practice, however, the NeuroFlexor needs further improvement in terms of measurement error and applicability in patients with decreased wrist range of motion.

ACKNOWLEDGMENTS

We would like to thank Mique Saes, Dirk Hoevenaars, Amy Otto and Robert Croese for their contributions to the data collection. We are grateful to Prof. H.C.W. de Vet for her advice about the statistical analysis.

FUNDING

The present study was supported by the European Research Council (grant no. 291339, 4D-EEG project), the Netherlands Organisation for Health Research and Development (ZonMw grant no. 104003008, PROFITS program) and an unrestricted support from IPSEN.

REFERENCES

1. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol.* 2007;6:725-733.
2. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve.* 2005;31:535-551.
3. Van den Noort JC, Bar-On L, Aertbelien E, et al. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. *Eur J Neurol.* 2017;24:981-991.
4. Lindberg PG, Gaverth 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.
5. Van der Krogt HJ, Meskers CG, de Groot JH, Klomp A, Arendzen JH. The gap between clinical gaze and systematic assessment of movement disorders after stroke. *J Neuroeng Rehabil.* 2012; 9:61.
6. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry.* 2010;81:46-52.
7. Mehrholz J, Wagner K, Meissner D, et al. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. *Clin Rehabil.* 2005;19:751-759.
8. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* 1999;13:373-383.
9. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clin Rehabil.* 2006;20:173-182.
10. Sorinola IO, White CM, Rushton DN, Newham DJ. Electromyographic response to manual passive stretch of the hemiplegic wrist: accuracy, reliability, and correlation with clinical spasticity assessment and function. *Neurorehabil Neural Repair.* 2009;23:287-294.
11. Klomp A, van der Krogt JM, Meskers CGM, et al. Design of a concise and comprehensive protocol for post stroke neuromechanical assessment. *J Bioeng Biomed Sci.* 2012;S1:008.
12. De Gooijer-van de Groep KL, de Vlugt E, de Groot JH, et al. Differentiation between non-neural and neural contributors to ankle joint stiffness in cerebral palsy. *J Neuroeng Rehabil.* 2013;10:81.
13. Bar-On L, Aertbelien E, Wambacq H, et al. A clinical measurement to quantify spasticity in children with cerebral palsy by integration of multidimensional signals. *Gait Posture.* 2013; 38:141-147.

14. Koo TK, Mak AF. A neuromusculoskeletal model to simulate the constant angular velocity elbow extension test of spasticity. *Med Eng Phys* 2006;28:60-69.
15. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med*. 2013;45:630-636.
16. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67:206-207.
17. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. *Disabil Rehabil.* 2006;28:899-907.
18. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med.* 1975;7:13-31.
19. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair.* 2008;22:78-90.
20. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther.* 1983;63:1606-1610.
21. Sullivan KJ, Tilson JK, Cen SY, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke*. 2011;42:427-432.
22. Nijland R, van Wegen E, Verbunt J, van Wijk R, van Kordelaar J, Kwakkel G. A comparison of two validated tests for upper limb function after stroke: The Wolf Motor Function Test and the Action Research Arm Test. *J Rehabil Med* 2010;42:694-696.
23. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol.* 2010;63:737-745.
24. De Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in medicine: a practical guide.* 3rd ed. Cambridge: Cambridge University Press; 2014.
25. Portney LG, Watkins MP. *Foundations of clinical research: applications to practice.* New Jersey: Prentice Hall; 2000.
26. Nakagawa S, Schielzeth H. Repeatability for Gaussian and non-Gaussian data: a practical guide for biologists. *Biol Rev Camb Philos Soc.* 2010;85:935-956.
27. Sloot LH, van der Krogt MM, de Gooijer-van de Groep KL, et al. The validity and reliability of modelled neural and tissue properties of the ankle muscles in children with cerebral palsy. *Gait Posture.* 2015;42:7-15.
28. Van der Krogt H, Klomp A, de Groot JH, et al. Comprehensive neuromechanical assessment in stroke patients: reliability and responsiveness of a protocol to measure neural and non-neural wrist properties. *J Neuroeng Rehabil.* 2015;12:28.

29. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech.* 2016;35:93-101.
30. Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assessment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. *Disabil Rehabil.* 2005;27:33-68.
31. Pandyan AD, Van Wijck FM, Stark S, Vuadens P, Johnson GR, Barnes MP. The construct validity of a spasticity measurement device for clinical practice: an alternative to the Ashworth scales. *Disabil Rehabil* 2006;28:579-585.
32. Phadke CP, Balasubramanian CK, Ismail F, Boulias C. Revisiting physiologic and psychologic triggers that increase spasticity. *Am J Phys Med Rehabil.* 2013;92:357-369.
33. Starsky AJ, Sangani SG, McGuire JR, Logan B, Schmit BD. Reliability of biomechanical spasticity measurements at the elbow of people poststroke. *Arch Phys Med Rehabil.* 2005;86:1648-1654.
34. Thilmann AF, Fellows SJ, Garms E. Pathological stretch reflexes on the "good" side of hemiparetic patients. *J Neurol Neurosurg Psychiatry.* 1990;53:208-214.
35. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil.* 2010;7:35.
36. Levin MF, Feldman AG. The role of stretch reflex threshold regulation in normal and impaired motor control. *Brain Res.* 1994;657:23-30.

SUPPLEMENTARY MATERIAL

Supplement 3A. Biomechanical model NeuroFlexor

In the biomechanical model of the NeuroFlexor, previously described by Lindberg et al.,[1] the total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r) and inertial forces of the limb and the moving parts of the device (F_{in}), described as:

$$F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta), \quad (1)$$

where θ denotes a specific angle.

In the model, three force points in the resistance trace of the slow and fast displacements are used to estimate the different components of the total measured passive force. Two force points are defined within the fast passive wrist extension movement (236°/second): P1, the initial peak in resistance, and P2, the late peak in resistance (Figure S3.1A). One force point (P3) is defined at the end position of the slow wrist extension movement (5°/second) (Figure S3.1B).

The **inertia component (IC)** corresponds to the force resisting the acceleration of the hand and is calculated in the model as:

$$\mathrm{IC} = m \times \alpha, \quad (2)$$

where *m* is the mass of the hand and the movable platform, and *a* is the angular acceleration (21 m/s^2). The mass of the hand is estimated to be 0.6% of the total body weight.

The **elastic component (EC)** is a length-dependent resisting force which increases when the muscles are stretched, with an exponential increase when the muscle is stretched close to its end range. The EC is recorded 1 second after the end of the slow movement. The EC corresponds to P3, i.e. the fully stretched position during the slow movement (Figure S3.1B).

The **viscous component (VC)** is velocity-dependent. Lindberg et al.[1] assumed that the viscous resistance is highest during the initial acceleration and continues at a lower level during further extension movement. To calculate the viscous component, first, the early viscous component (VC_{P1}) is calculated.

$$VC_{P1} = Total\ force_{P1} - \mathrm{IC}, \tag{3}$$

where Total force$_{P1}$ is the measured force at P1 (Figure S3.1A), and IC the inertial component calculated as above. Since there is a comparatively stable relationship between the early and late viscosity, Lindberg et al.[1] assumed that the late viscosity is approximately 20% of the early viscosity.

$$\mathrm{VC} = VC_{P1} \times 0.2. \tag{4}$$

Finally, P2 is defined as the late force peak during the fast wrist extension movement (Figure S3.1A) and consists of the neural, viscous and elastic component together. The **neural component (NC)** is estimated by:

$$\mathrm{NC} = Total\ force_{P2} - (\mathrm{EC} + \mathrm{VC}). \tag{5}$$

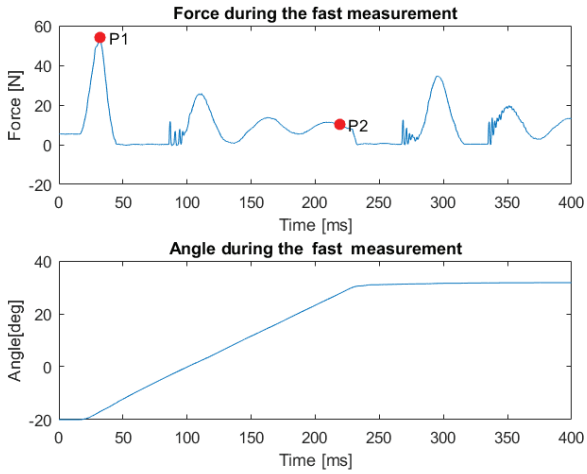


Figure S3.1A. Measured force and wrist angle during fast movement of the NeuroFlexor.

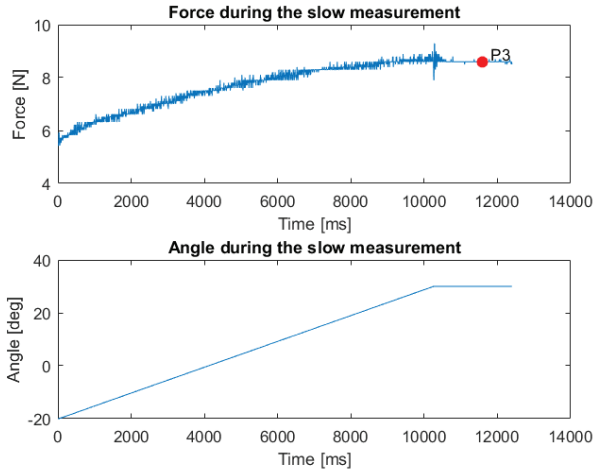


Figure S3.1B. Measured force and wrist angle during slow movement of the NeuroFlexor.

REFERENCES SUPPLEMENTARY MATERIAL

1. Lindberg PG, Gaverth 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(7):617-625.

Supplement 3B. Scatterplots

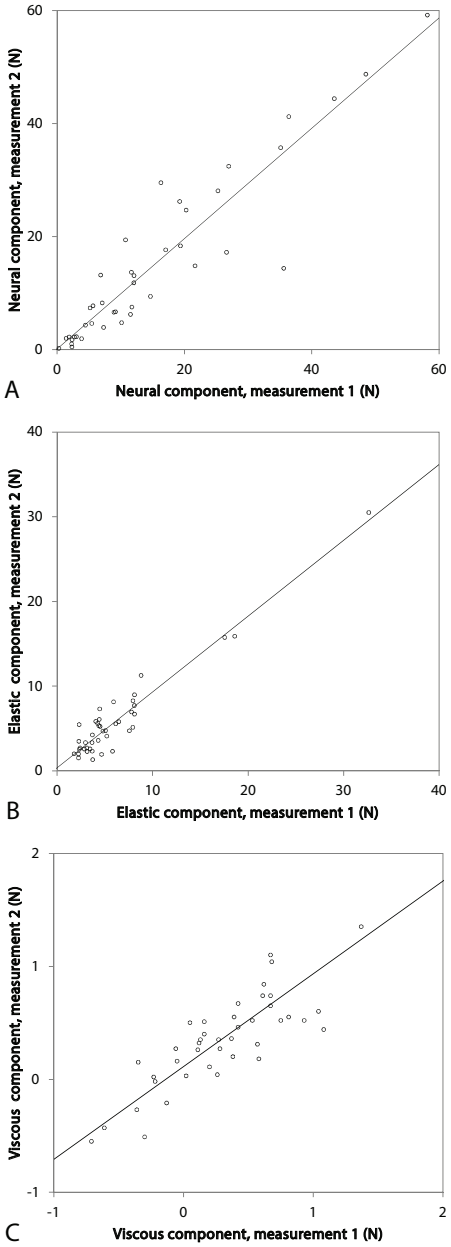


Figure S3.2. Scatterplots, measurement 1 against measurement 2 in patients with chronic stroke.
(A) Neural component. (B) Elastic component. (C) Viscous component.

Supplement 3C. Bland-Altman plots

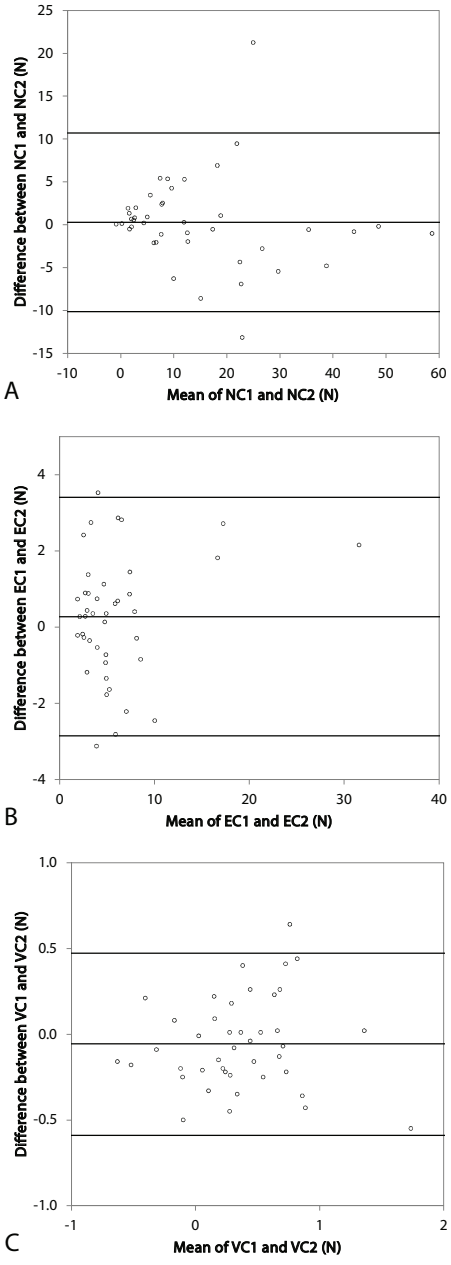
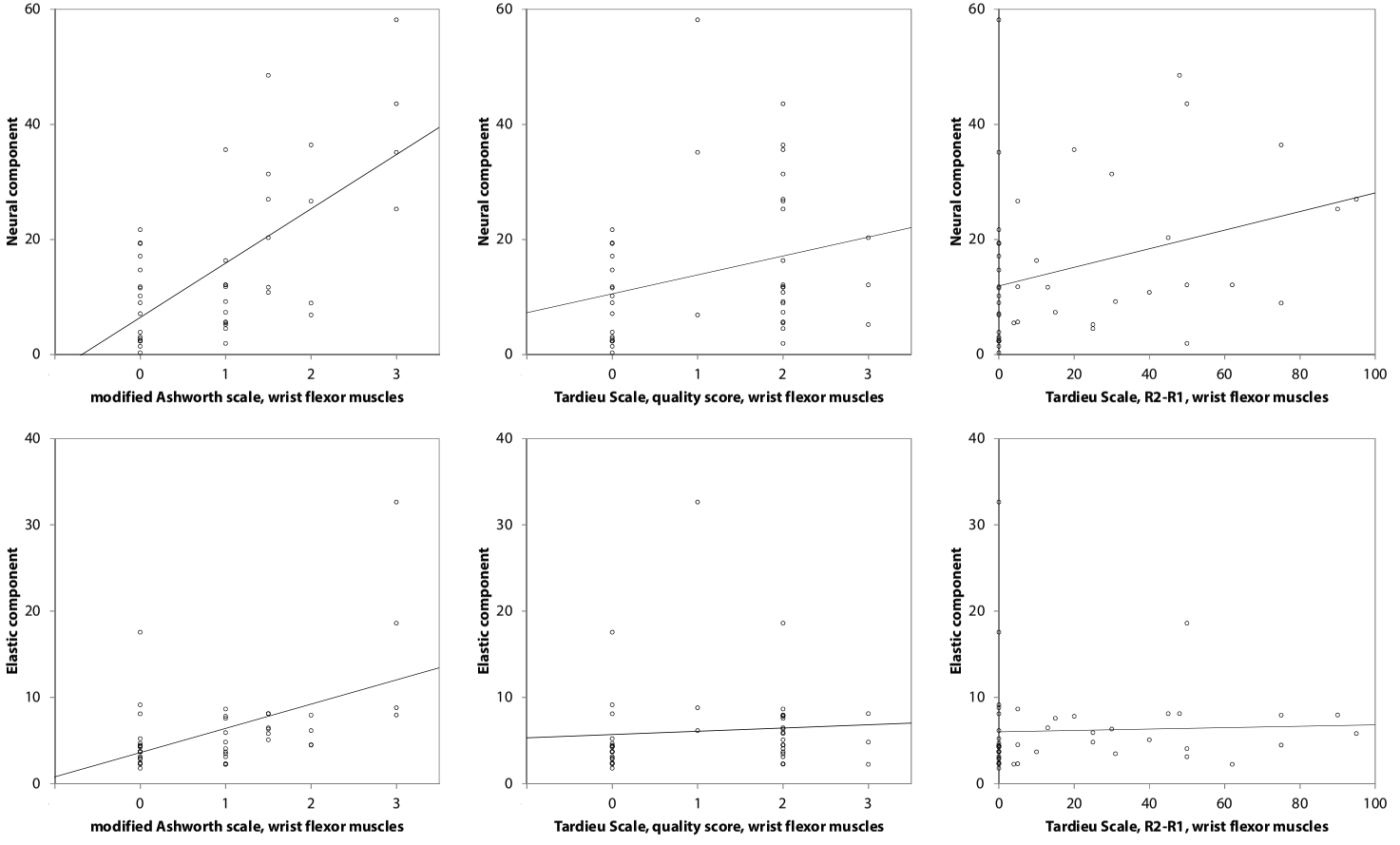


Figure S3.3. Bland-Altman plots for neural, elastic and viscous component in patients with chronic stroke. (A) Neural component (NC). (B) Elastic component (EC). (C) Viscous component (VC) .

Supplement 3D. Scatterplots of correlation between neural and non-neural components of wrist hyper-resistance and clinical assessments



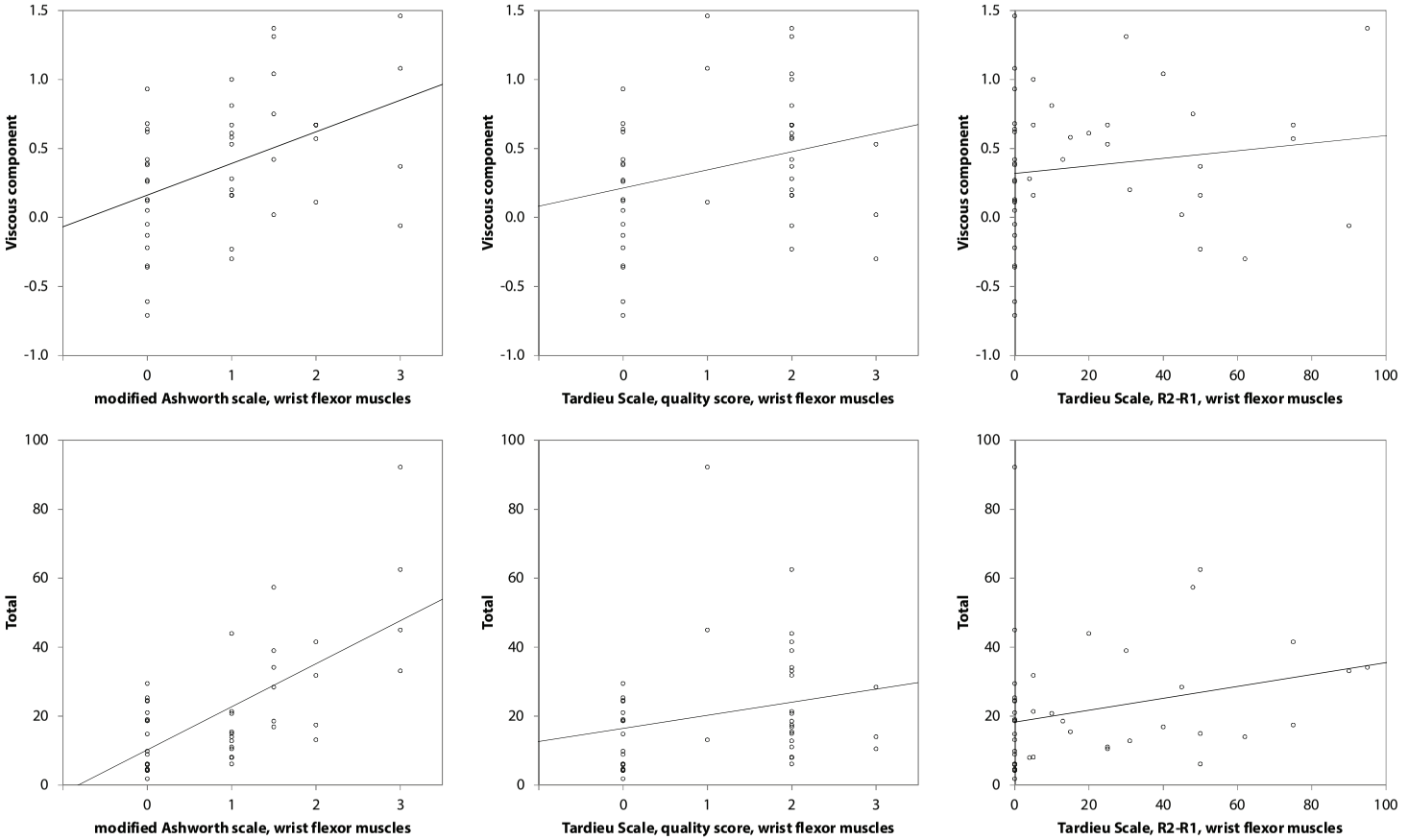
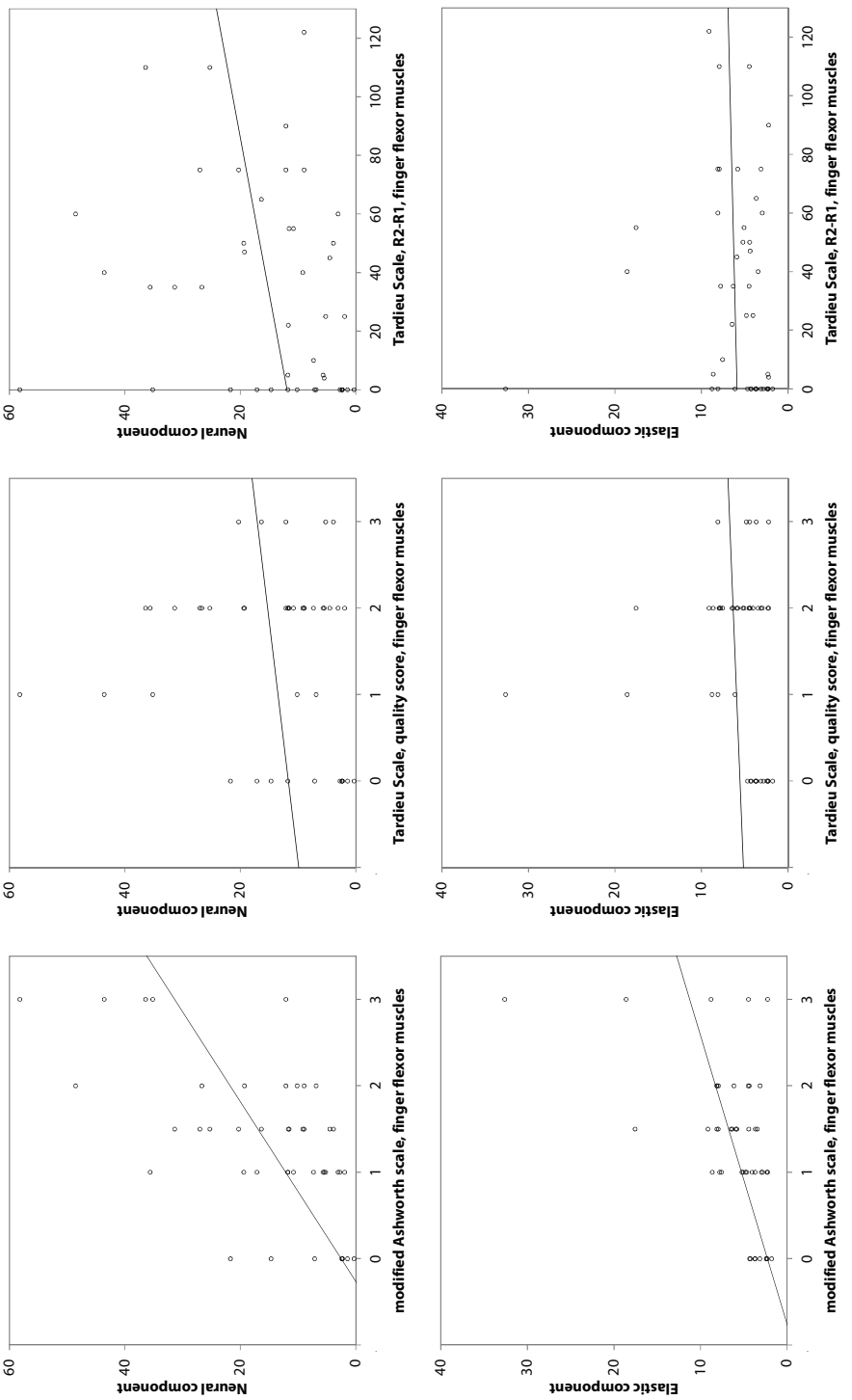


Figure S3.4. Correlation between modified Ashworth scale, Tardieu scale quality score and Tardieu scale R2–R1 of wrist flexor muscles, and neural and non-neural components.


Neural component
Elastic component
modified Ashworth scale, finger flexor muscles
Tardieu Scale, quality score, finger flexor muscles
Tardieu Scale, R2-R1, finger flexor muscles
0
20
40
60
80
100
120
1
2
3
10
30

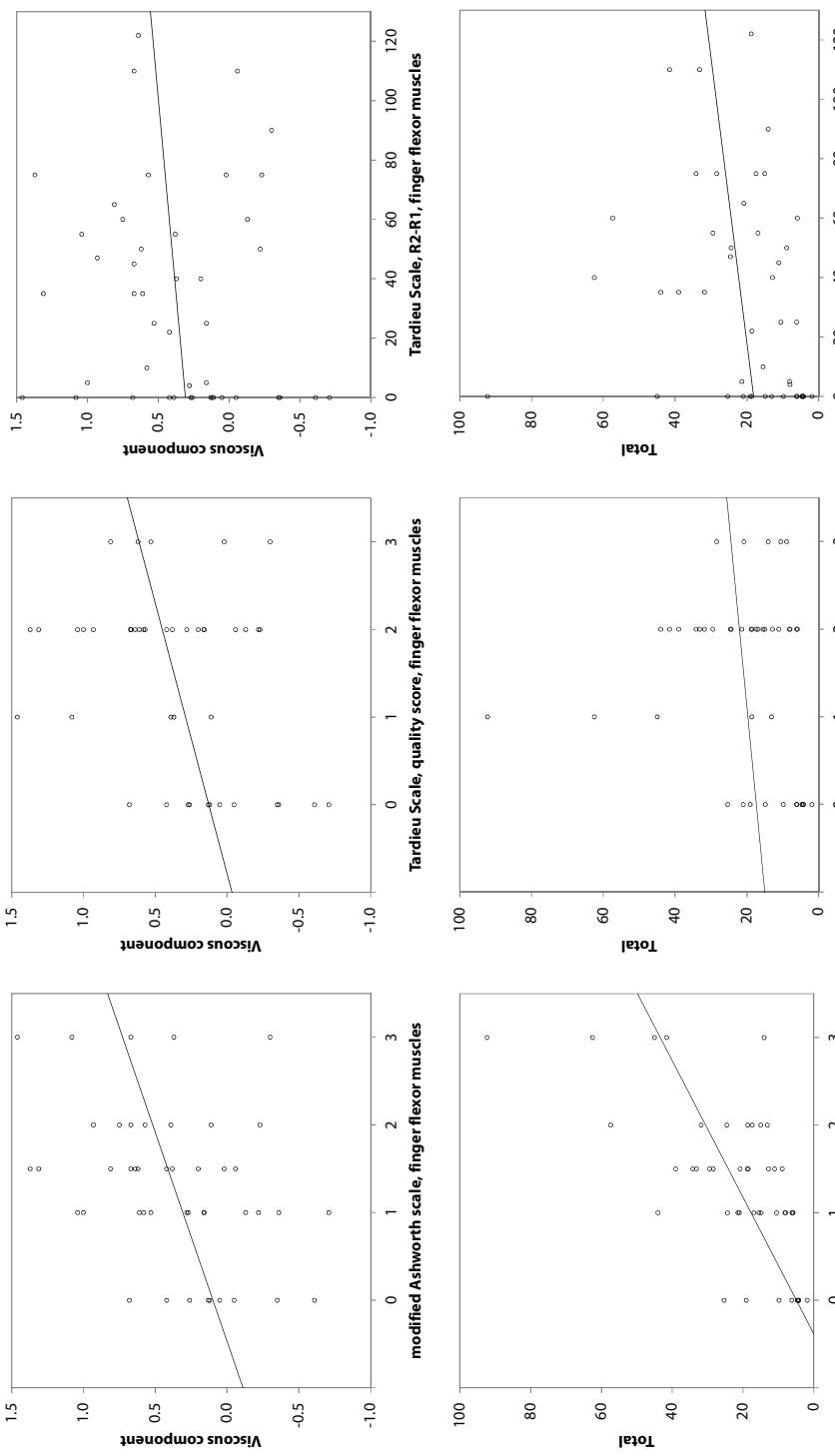
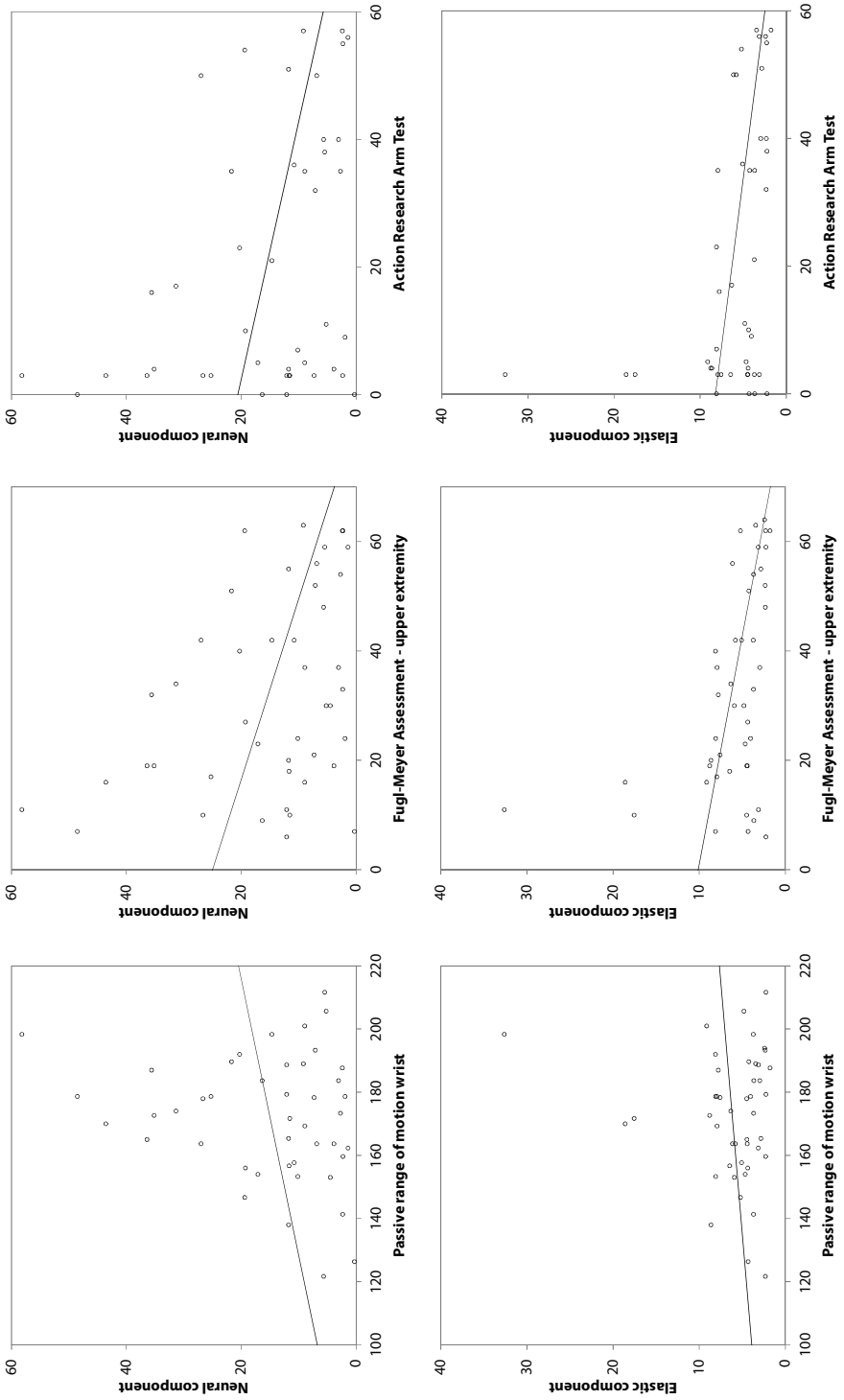


Figure S3.5. Correlation between modified Ashworth scale, Tardieu Scale quality score and Tardieu Scale R2-R1 of finger flexor muscles, and neural and non-neural components.


Neural component
Elastic component
Action Research Arm Test
Fugl-Meyer Assessment - upper extremity
Passive range of motion wrist
0
20
40
60
10
30
100
120
140
160
180
200
220

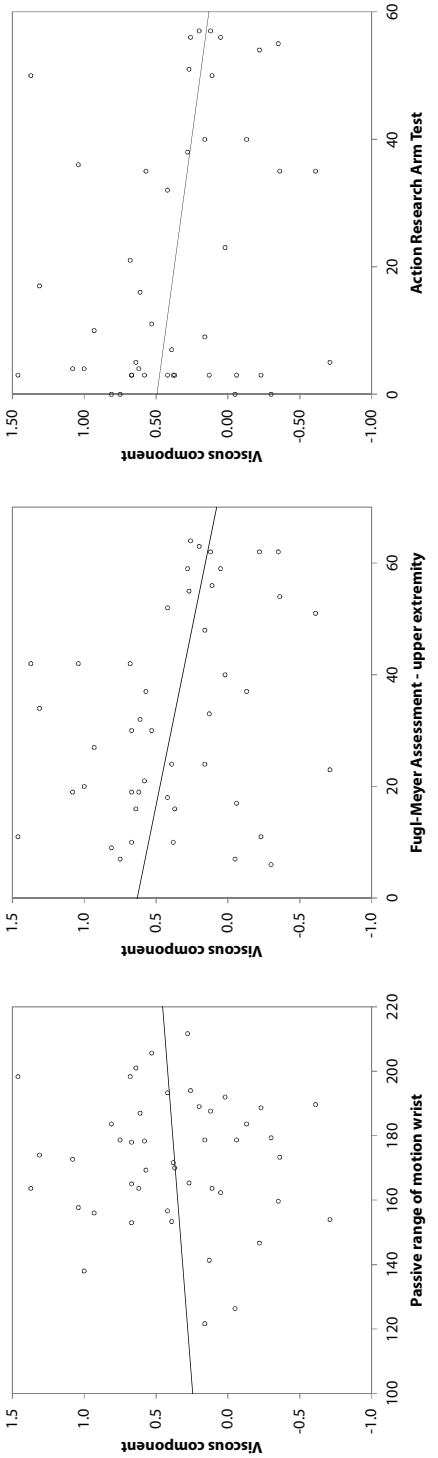


Figure S3.6. Correlation between passive range of motion of the wrist, Fugl-Meyer assessment of the upper extremity and action research arm test, and neural and non-neural components.

CHAPTER 4

Quantifying neural and non-neural components of wrist hyper-resistance after stroke: comparing two instrumented assessment methods

Aukje S. Andringa
Carel G.M. Meskers
Ingrid G.L. van de Port
Sarah B. Zandvliet
Larissa Scholte
Jurriaan H. de Groot
Gert Kwakkel
Erwin E.H. van Wegen

Med Eng Phys. 2021;98:57-64

ABSTRACT

Patients with poor upper limb motor recovery after stroke are likely to develop increased resistance to passive wrist extension, i.e. wrist hyper-resistance. Quantification of the underlying neural and non-neural elastic components is of clinical interest. This cross-sectional study compared two methods: a commercially available device (NeuroFlexor) with an experimental EMG-based device (Wristalyzer) in 43 patients with chronic stroke. Spearman's rank correlation coefficients (r) between components, modified Ashworth scale (MAS) and range of passive wrist extension (PRoM) were calculated with 95% confidence intervals. Neural as well as elastic components assessed by both devices were associated (r = 0.61, 95% CI: 0.38–0.77 and r = 0.53, 95% CI: 0.28–0.72, respectively). The neural component assessed by the NeuroFlexor associated significantly with the elastic components of NeuroFlexor (r = 0.46, 95% CI: 0.18–0.67) and Wristalyzer (r = 0.36, 95% CI: 0.06–0.59). The neural component assessed by the Wristalyzer was not associated with the elastic components of both devices. Neural and elastic components of both devices associated similarly with the MAS (r = 0.58, 95% CI: 0.34–0.75 vs. 0.49, 95% CI: 0.22–0.69 and r = 0.51, 95% CI: 0.25–0.70 vs. 0.30, 95% CI: 0.00–0.55); elastic components associated with PRoM (r = -0.44, 95% CI: -0.65– -0.16 vs. -0.74, 95% CI: -0.85– -0.57 for NeuroFlexor and Wristalyzer respectively). Results demonstrate that both methods perform similarly regarding the quantification of neural and elastic wrist hyper-resistance components and have an added value when compared to clinical assessment with the MAS alone. The added value of EMG in the discrimination between neural and non-neural components requires further investigation.

INTRODUCTION

Worldwide, 15 million people suffer a stroke each year,[1] of which about 80% initially experience upper limb motor deficits.[2] More than half of these patients show poor to moderate upper limb motor recovery in the first six months post stroke[3] and experience long-term upper limb impairments that severely affect their daily activities and quality of life.[4,5] Patients showing limited upper limb motor recovery are likely to develop increased resistance to passive wrist extension, i.e. wrist hyper-resistance, in weeks to months post stroke.[6,7] This hyper-resistance of the wrist joint is hypothesized to originate from a complex interaction between impaired neuromuscular activation and altered tissue properties of the muscles spanning the joint.[8,9] Impaired neuromuscular activation includes spasticity, defined as velocity-dependent stretch hyperreflexia,[10] and involuntary background activation.[11] Altered tissue properties comprise changes in elasticity, viscosity and muscle shortening.[12] The distribution and level of aforementioned neural and non-neural tissue property-related components may change over time post stroke[13-15] and may differ between individual patients.[16] Accurate discrimination between the components is important to understand their influence on post-stroke motor recovery and may help to optimize individual treatment decisions.[17] However, this is not possible by manual assessment of joint resistance, which is the current clinical standard.[18,19] There is a need for a valid and reliable non-invasive assessment method that is easy to apply in clinical practice.[19,20]

Various instrumented assessment methods have been developed that differ in setup and neuromuscular modelling.[16,21-23] The commercially available medical device NeuroFlexor (Aggero MedTech AB, Älta, Sweden)[21] derives the neural and non-neural elastic components from resistance to a passive wrist extension movement. Construct validity,[21,24,25] good to excellent test-retest reliability[25,26] and good responsiveness[27] of this device were shown. The experimental Wristalyzer[16] uses measured joint torque during an imposed perturbation of the wrist in combination with electromyography (EMG) of wrist flexor and extensor muscle activity to estimate neural and elastic components using a neuromuscular model including wrist mechanics and muscle properties. Similar instrumented assessment methods for the wrist and ankle joint have shown to be valid in patients with acute[13] and chronic[16,28] stroke and have shown moderate to good test-retest reliability.[29,30] However, as far as we know, a head-to-head comparison of methods within the same patient sample has not been done.

The aim of the present study was to compare the NeuroFlexor with the EMG-based Wristalyzer for the quantification of neural and non-neural elastic components of wrist hyper-resistance in patients with chronic stroke. Additionally, we compared the outcomes of

both devices with the modified Ashworth scale (MAS) and range of passive wrist extension, obtained by goniometry and the Wristalyzer. We hypothesized similarity between both devices in the quantification of the neural as well as elastic components. Additionally, we expected similar discriminative validity of both devices compared to the clinical MAS[16,25] and similar association strength between the elastic components of both devices and range of passive wrist extension.

METHODS

Participants

For this study, patients with chronic stroke and initial upper limb paresis were recruited. Inclusion criteria were: (1) ischemic or haemorrhagic stroke at least six months prior to inclusion; (2) initial upper limb paresis as defined by the National Institutes of Health Stroke Scale (NIHSS) item 5 a/b-score > 0 (i.e. not able to hold the affected arm at a 90° angle for at least 10 seconds); (3) age 18 years or older; and (4) sufficient cognitive ability to follow test instructions (mini-mental state examination > 17).[31] Exclusion criteria were: (1) limitations of the arm-hand function of the affected side other than due to stroke; (2) less than 40° of passive wrist extension with extended fingers in order to comply with the NeuroFlexor protocol; and (3) botulinum toxin injections in the affected arm in the previous three months which may have affected wrist hyper-resistance components. Ethical approval was obtained from the Medical Ethics Committee of the VU University medical centre, Amsterdam, The Netherlands (NL47079.029.14). In accordance with the Declaration of Helsinki[32] all participants gave written informed consent.

Experimental design

In this cross-sectional study, demographic data, stroke characteristics, neurological status (NIHSS and Fugl-Meyer motor assessment of the upper extremity) and medical history were collected. NeuroFlexor (NF), Wristalyzer (WA) and clinical assessments were performed in an arbitrary sequence on the same day, with at least 10 minutes in between, or, for practical reasons, on two separate days with a maximum of one day in between. When performed on two separate days, the MAS was performed on the same day as the NF assessment. All assessments were performed on the patients' impaired arm by a team of five trained researchers according to a standardized protocol.

Table 4.1. Comparison of characteristics of the NeuroFlexor versus Wristalyzer

	NeuroFlexor	Wristalyzer
		
Device:	NeuroFlexor	Wristalyzer
Range wrist perturbation:	20° flexion to 30° extension	Max flexion to max extension and back
Movement in:	Vertical plane (rotation axis horizontal)	Horizontal plane (rotation axis vertical)
Position forearm:	Pronation	Neutral position in between pronation and supination
Modelling:	Unidirectional biomechanical model based on signal analysis	Bi-directional EMG-based optimization model
Input parameters:	Wrist angle Force	Wrist angle Torque EMG FCR and ECR
Outcome parameters:	Neural force [N]* Elastic force [N]* Viscous force [N]	Neural torque of FCR&ECR [Nm] Elastic stiffness of FCR&ECR [Nm/rad]*

Abbreviations: ECR, extensor carpi radialis muscle; EMG, electromyography; FCR, flexor carpi radialis muscle.
* Determined at 30° wrist extension. Detailed information about the models and the model parameters is described in Supplement 4A and 4B.

NeuroFlexor

Instrumentation and measurement protocol

The NeuroFlexor[21] is a motor-driven device which applies isokinetic positional perturbations to the wrist with extended fingers from 20° flexion towards 30° extension at two controlled velocities (5 and 236°/second), see Table 4.1 for characteristics. Resistance during passive wrist extension is measured in Newton [N] using a force sensor mounted underneath the moveable hand platform. The patient was seated comfortably beside the device with the shoulder in 45° of abduction, 0° of flexion, the elbow in 90° of flexion, with the forearm fastened to the device in pronation and the hand pronated (facing down) with extended fingers fastened to the movable platform. The axis of the wrist joint was visually aligned with the rotation axis of the device. One measurement consisted of five slow movements,

followed by ten fast movements. The first movement at both velocities was excluded from the analysis to avoid bias from startle reflexes and mechanical hysteresis. Two NeuroFlexor measurements were performed at least 15 minutes apart and mean values were used for further analysis.

Model description and component calculation

Wrist hyper-resistance components were derived from a unidirectional biomechanical model[21,33] based on the force-time traces during passive wrist extension (software program NeuroFlexor Scientific v0.06, Supplement 4A). The neural component (NF-NC, in Newton) is defined as the immediate resisting force at the end of the fast passive wrist extension movement (i.e. 30° wrist extension) minus the non-neural elastic and viscous components. The elastic component (NF-EC, in Newton) is the length-dependent resisting force recorded 1 s after stopping the slow movement (i.e. 30° wrist extension). The viscous component is the velocity-dependent resisting force of soft tissues to stretch.

Wristalyzer

Instrumentation and measurement protocol

The Wristalyzer is a one degree-of-freedom haptic manipulator (MOOG, Nieuw Vennep, The Netherlands)[34] rotating a custom-made handle (Meester Techniek, Leiden, The Netherlands) by a vertically positioned servo motor (Parker SMH100 series, Parker Hannifin, Charlotte, NC, USA), see Table 4.1 for characteristics. Patients were seated comfortably with the shoulder slightly abducted and elbow in 90° flexion. The forearm was strapped in a lower arm cuff in a neutral position between pronation and supination with the hand in the neutral (parasagittal) plane with extended fingers fixated to the handle. The axis of the wrist joint was visually aligned with the vertical rotation axis of the haptic manipulator. Muscle activity of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles was measured by EMG using pairs of unipolar electrodes (Blue Sensor N, Ambu, Ballerup, Denmark) placed on the muscle belly.[16] Maximal passive range of wrist extension and flexion was determined by applying a slow increasing torque with a duration of 15 s up to a maximal torque of 2 Nm in both flexion and extension direction. Subsequently, the wrist was passively extended and flexed over the full recorded passive range of motion (PRoM) minus one degree in both the maximal flexion and extension direction (sweep), including two slow sweep trials at 5°/second, two sweeps at PRoM/second and two fast sweep trials at 236°/second. Each sweep trial contained a preparatory movement from neutral wrist angle position towards maximal

flexion, followed by a sweep towards maximal extension, returning to maximal flexion and ending towards neutral position respectively.

Wrist angle, torque and EMG signals of the FCR and ECR were recorded simultaneously at 2048 Hz using a Refa amplifier (TMSi, Oldenzaal, The Netherlands). Matlab R2017b (The Mathworks, Inc., Natick, MA, USA) was subsequently used for offline data analysis. Wrist angle and torque signals were low-pass filtered at 20 Hz (3rd-order Butterworth). EMG signals were band-pass filtered at 20–450 Hz (3rd-order Butterworth), full-wave rectified and subsequently low-pass filtered at 20 Hz (3rd-order Butterworth), to obtain the EMG envelope. Finally, the minimal EMG value, determined with steps of 8 ms during the total time window, was subtracted from the total EMG to reduce the influence of noise and offset muscle activation.

Model description and component calculation

An EMG-based antagonistic optimization wrist model was used based on a bidirectional wrist model[16] which is derived from an ankle model.[28] Wrist angle, torque and EMG of the FCR and ECR were used to estimate 12 parameters by a nonlinear least squares optimization algorithm and minimizing the error function, i.e. the difference between the measured torque and predicted torque. The model optimized the parameters over the full duration of the sweep protocol with different joint velocities in both extension and flexion direction. Detailed information about the optimization model is described in Supplement 4B. After parameter optimization, the neural component induced by the velocity-dependent stretch reflex of the FCR during passive wrist extension (WA-NC, in Newton · meter [Nm]) was calculated based on root mean square values of the modelled variant active torque within the time window of the fast (236°/second) extension sweeps and the elastic tissue component of the FCR during passive wrist extension (WA-EC, in Nm/rad) was taken at 30° wrist extension at a velocity of 5°/second.

Clinical assessment

Resistance to manually applied passive wrist extension movement with extended fingers was measured using the modified Ashworth scale,[35] an ordinal scale with scores ranging from 0 (no increased tone) to 4 (the joint is rigid). The maximal range of passive wrist extension with extended fingers was determined using a goniometer. Mean values of three extension movements were used for further analysis.

Statistical analysis

In the absence of a gold standard, a priori assumptions for the similarity between outcomes of the NeuroFlexor and Wristalyzer were formulated.[36] Correlation coefficients above 0.50 were considered as similar constructs, between 0.30–0.50 as related, but distinct constructs, and below 0.30 as unrelated constructs.[37] We expected 1_{a-b}) correlation coefficients above 0.50 between the corresponding components of both devices (convergent validity); 2_{a-b}) correlation coefficients below 0.30 between the different components of both devices (discriminant validity); 3_{a-b}) both devices to separate wrist hyper-resistance in two different components ($r < 0.30$) (discriminant validity); 4) similar individual ranking of the wrist hyper-resistance components of both devices; 5_{a-b}) neural and elastic components of both devices to relate in the same way to the clinical MAS ($0.30 < r < 0.50$); 6) higher neural and elastic components in patients with higher MAS scores for both devices (discriminative validity); and 7_{a-b}) the elastic component of both devices to relate in the same way to the range of passive wrist extension, obtained by goniometry and the Wristalyzer respectively ($0.30 < r < 0.50$).

Study data were analysed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical characteristics. Correlation coefficients between components, and with the MAS and range of passive wrist extension, were calculated using Spearman's rank correlation coefficients to address assumptions 1, 2, 3, 5 and 7, respectively. A Fisher's z transformation was used to calculate 95% confidence intervals of the correlation coefficients.[38] To test whether components relate in the same way to the MAS and the range of passive wrist extension, 95% confidence intervals were compared (assumption 5 and 7). Overlapping confidence intervals were considered similar. Percentage explained variance was calculated by r^2*100%.

To deal with the differences in metric units used by both devices, outcomes of each component were ranked in order from the lowest to the highest value (rank 1 to 43 respectively). Wilcoxon signed-ranks tests were used to test the differences between the individual ranks of the neural and elastic components of both devices (assumption 4). In addition, for both components of both devices, patients' scores were classified into quartiles. The quartile classifications of the two devices were compared at individual level for both the neural and elastic components. A difference of more than one quartile between the two devices for the same component within one patient was classified as divergent.

Patients were classified according to their MAS score. Patients with a MAS score of 1 and 1+ were both classified as MAS_1. The between MAS group differences in neural and

elastic components for both devices were assessed by the Kruskal-Wallis analysis, with Mann-Whitney U *post-hoc* analyses (assumption 6). The level of significance was set two-tailed at 0.05. To correct for multiple testing in the *post-hoc* analyses, a Bonferroni correction was applied.

RESULTS

Of the 46 patients in the study, data of 43 patients were included in the analysis. Two patients could not perform the measurements due to pain during passive wrist extension movement and data of one patient was excluded from analysis due to a technical problem of the NF during wrist extension. For three patients, the second NF measurement was missing and data of one measurement was used for analysis. The main demographic and clinical characteristics of the patient population are summarized in Table 4.2.

Table 4.3 shows an overview of the pre-determined assumptions and the results of the similarity between the outcomes of the NF and WA, and their relation with the MAS and range of passive wrist extension. Corresponding scatterplots of the correlations are presented in Supplement 4C. NF-NC showed a significant correlation coefficient with WA-NC (0.61, 95% CI: 0.38 to 0.77) and NF-EC showed a significant correlation coefficient with WA-EC (0.53, 95% CI: 0.28 to 0.72). NF-NC showed significant correlation coefficients with WA-EC (0.36, 95% CI: 0.06 to 0.59) and with NF-EC (0.46, 95% CI: 0.18 to 0.67). WA-NC showed non-significant correlation coefficients with NF-EC (0.15, 95% CI: -0.16 to 0.43) and with WA-EC (0.16, 95% CI: -0.15 to 0.44).

Figure 4.1 presents an overview of the rank numbers for each component of both devices per patient, ordered by NF-NC. Wilcoxon signed-ranks tests did not show a difference in individual ranks on the NC and EC between the two devices ($P = 0.57$ and $P = 0.87$, respectively). As illustrated in Figure 4.2, for the neural component, 20 of the 43 patients (47%) were categorized into equal quartiles by both devices. Nineteen patients (44%) were categorized into different, but adjacent, quartiles, while four patients (9%) were categorized into divergent quartiles. For the elastic component, 17 of the 43 patients (40%) were categorized into equal quartiles. Nineteen patients (44%) were categorized into adjacent quartiles, while seven patients (16%) were categorized into divergent quartiles.

The neural components of both devices, i.e. NF-NC and WA-NC, showed significant correlation coefficients with overlapping confidence intervals with the MAS (0.58, 95% CI: 0.34 to 0.75 and 0.49, 95% CI: 0.22 to 0.69, respectively) (Table 4.3). The elastic

Table 4.2. Demographic and clinical characteristics of the study population, stratified by modified Ashworth scale

	Overall	MAS_0	MAS_1	MAS_2	MAS_3
	n = 43	n = 8	n = 24	n = 7	n = 4
Age, years (mean ± SD)	60.1 ± 10.0	65.5 ± 7.2	59.3 ± 10.4	56.9 ± 11.8	60.3 ± 8.5
Gender, male/female (n)	29/14	4/4	18/6	5/2	2/2
Stroke type, iCVA/hCVA (n)	37/6	7/1	22//2	5/2	3/1
Time post stroke, months (mean ± SD)	61.1 ± 78.4	33.9 ± 48.0	68.5 ± 93.2	78.3 ± 65.3	41.0 ± 44.7
Affected side, left/right (n)	23/20	3/5	14/10	3/4	3/1
NIHSS score (mean ± SD)	4.7 ± 3.2	4.3 ± 3.9	3.9 ± 2.3	6.6 ± 4.0	6.8 ± 4.3
FM-UE (mean ± SD (min; max))	34.0 ± 18.4 (6; 64)	53.1 ± 11.0 (33; 64)	33.5 ± 16.6 (9; 63)	24.6 ± 17.6 (7; 56)	15.0 ± 6.2 (6; 19)
Passive wrist extension$_{,gonio,}$ ° (mean ± SD)	73.2 ± 14.3	82.9 ± 13.8	71.7 ± 14.0	68.6 ± 14.1	71.0 ± 13.8
Passive wrist extension$_{,wa,}$ ° (mean ± SD)	56.4 ± 18.1	65.0 ± 13.5	57.4 ± 16.7	51.2 ± 23.9	42.5 ± 18.9
MAS (median [25th–75th percentile])	1.5 [1 to 2]				

Abbreviations: FM-UE, Fugl-Meyer motor assessment of the upper extremity [range: 0–66]; hCVA, haemorrhagic stroke; iCVA, ischemic stroke; MAS, modified Ashworth scale [range 0–4]; NIHSS, National Institutes of Health Stroke Scale [range: 0–42]; passive wrist extension$_{,gonio,}$ obtained by goniometry; passive wrist extension$_{,wa,}$ obtained by the Wristalyzer using 2 Nm.

Table 4.3. Overview of pre-determined assumptions and their results for similarity between the outcomes of the NeuroFlexor and Wristalyzer

Pre-determined assumptions for similarity			Expected correlation	Results		
				Correlation coefficients (95% CI)	Explained variance	Assumption confirmed?
1	a	NF-NC vs. WA-NC	$r > 0.50$	0.61 (0.38 to 0.77)	37%	√
	b	NF-EC vs. WA-EC	$r > 0.50$	0.53 (0.28 to 0.72)	28%	√
2	a	NF-NC vs. WA-EC	$r < 0.30$	0.36 (0.06 to 0.59)	13%	x
	b	WA-NC vs. NF-EC	$r < 0.30$	0.15 (-0.16 to 0.43)	2%	√
3	a	NF-NC vs. NF-EC	$r < 0.30$	0.46 (0.18 to 0.67)	21%	x
	b	WA-NC vs. WA-EC	$r < 0.30$	0.16 (-0.15 to 0.44)	3%	√
4		Ranking of components per individual is similar in both devices				√
5	a	NF-NC vs. MAS (r_1) is equal to WA-NC vs. MAS (r_2)	$r_1 = r_2$	r_1 = 0.58 (0.34 to 0.75) r_2 = 0.49 (0.22 to 0.69)		√
	b	NF-EC vs. MAS (r_3) is equal to WA-EC vs. MAS (r_4)	$r_3 = r_4$	r_3 = 0.51 (0.25 to 0.70) r_4 = 0.30 (0.00 to 0.55)		√
6		NC's and EC's measured by devices are higher in patients with higher MAS scores				√
7	a	NF-EC vs. passive wrist extension,$_{gonio}$ (r_1) is equal to WA-EC vs. passive wrist extension,$_{gonio}$ (r_2)	$r_1 = r_2$	r_1 = -0.44 (-0.65 to -0.16) r_2 = -0.74 (-0.85 to -0.57)		√
	b	NF-EC vs. passive wrist extension,$_{wa}$ (r_3) is equal to WA-EC vs. passive wrist extension,$_{wa}$ (r_4)	$r_3 = r_4$	r_3 = -0.54 (-0.72 to -0.28) r_4 = -0.87 (-0.93 to -0.78)		x

Values are Spearman's rank correlation coefficients (*r*) with 95% confidence intervals. √, assumption confirmed; x, assumption not confirmed.
Abbreviations: MAS, modified Ashworth scale [-]; NF-EC, NeuroFlexor, elastic component [N]; NF-NC, NeuroFlexor, neural component [N]; passive wrist extension,$_{gonio}$, obtained by goniometry [°]; passive wrist extension,$_{wa}$, obtained by the Wristalyzer using 2 Nm [°]; WA-NC, Wristalyzer, neural component [Nm]; WA-EC, Wristalyzer, elastic component [Nm/rad].

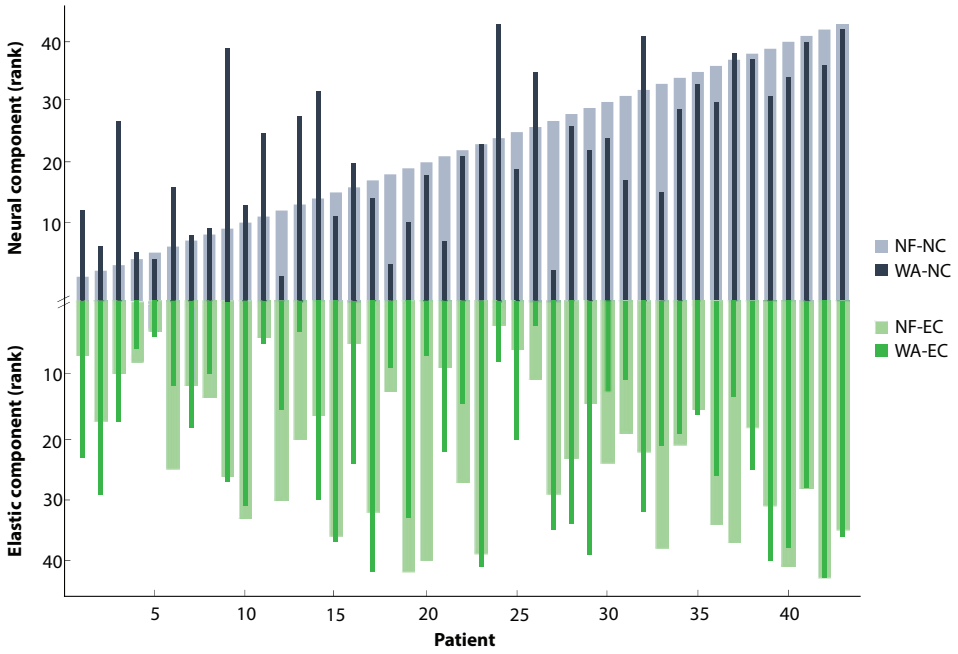


Figure 4.1. Overview of the ranking of neural and elastic components of both devices per patient, with patients ordered according to the ranking of the neural component assessed by the NeuroFlexor.
The outcomes of each component were ranked in order from the lowest to the highest value (rank 1 to 43 respectively). NF-NC, NeuroFlexor, neural component; WA-NC, Wristalyzer, neural component; NF-EC, NeuroFlexor, elastic component; WA-EC, Wristalyzer, elastic component.

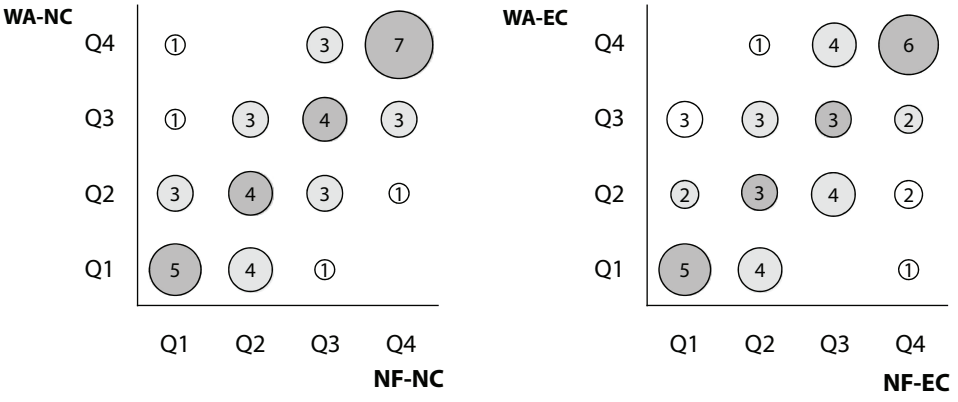


Figure 4.2. Comparison of the NeuroFlexor (NF) and Wristalyzer (WA) for the classification into quartiles at the individual level for the neural component (NC) and the elastic component (EC).
The numbers in the circles represent the number of patients categorized according to the quartile classification of the two devices. Q, quartile.

Table 4.4. Neural and elastic components of wrist hyper-resistance as obtained by the NeuroFlexor and Wristalyzer, stratified by modified Ashworth scale

	Overall	MAS_0	MAS_1	MAS_2	MAS_3	*P* Kruskal-Wallis
	n = 43	n = 8	n = 24	n = 7	n = 4	
NeuroFlexor						
NF-NC [N]	10.01 [5.02 to 22.47]	1.87 [1.45 to 10.93]	9.29 [5.16 to 21.57]	12.57 [7.75 to 22.73]	37.11 [17.81 to 42.68]	0.005
NF-EC [N]	4.88 [3.01 to 7.03]	2.63 [2.46 to 3.70]	4.93[a] [3.35 to 7.29]	5.85[a] [4.85 to 7.40]	7.96 [2.89 to 15.44]	0.014
Wristalyzer						
WA-NC [Nm]	0.42 [0.08 to 0.95]	0.20 [0.02 to 0.43]	0.32 [0.08 to 0.85]	0.68 [0.17 to 2.07]	1.53[a,b] [1.04 to 2.27]	0.010
WA-EC [Nm/rad]	1.26 [0.62 to 2.30]	1.01 [0.40 to 1.38]	1.23 [0.61 to 2.22]	2.26 [0.82 to 3.39]	2.54 [0.79 to 7.11]	0.333

Values are median [25th and 75th percentile]. Mann-Whitney U *post-hoc* analysis: [a] significantly different from MAS_0 ($P \leq 0.008$); [b] significantly different from MAS_1 ($P \leq 0.008$). Abbreviations: MAS, modified Ashworth scale; NF-EC, NeuroFlexor, elastic component; NF-NC, NeuroFlexor, neural component; WA-EC, Wristalyzer, elastic component; WA-NC Wristalyzer, neural component.

components NF-EC and WA-EC also showed correlation coefficients with overlapping confidence intervals with the MAS (0.51, 95% CI: 0.25 to 0.70 and 0.30, 95% CI: 0.00 to 0.55, respectively). All components showed a gradual increment with MAS category (Table 4.4). Kruskal-Wallis analysis revealed a significant difference between the MAS categories for NF-NC ($P = 0.005$), NF-EC ($P = 0.014$) and WA-NC ($P = 0.010$). *Post-hoc* Mann-Whitney U analyses showed a significantly higher NF-EC for patients with MAS_1 and MAS_2 compared to MAS_0 ($P \leq 0.008$). WA-NC for patients with MAS_3 was significantly higher compared to MAS_0 and MAS_1 ($P \leq 0.008$).

The elastic components of both devices, i.e. NF-EC and WA-EC, showed significant negative correlation coefficients with overlapping confidence intervals with the range of passive wrist extension, as obtained by goniometry (-0.44, 95% CI: -0.65 to -0.16 and -0.74, 95% CI: -0.85 to -0.57, respectively). Significant negative correlation coefficients with non-overlapping confidence intervals were found with the range of passive wrist extension, as obtained by the WA at 2 Nm (-0.54, 95% CI: -0.72 to -0.28 and -0.87, 95% CI: -0.93 to -0.78, respectively) (Table 4.3).

DISCUSSION

We performed a head-to-head comparison of the NeuroFlexor (NF) with the EMG-based Wristalyzer (WA) for the quantification of neural and non-neural elastic components of resistance to passive wrist extension in 43 patients with chronic ischemic or haemorrhagic stroke with initial upper limb paresis. The majority (9/12) of our pre-determined assumptions were confirmed by this study, which supports the similarity between the two instrumented assessment methods.

Significant associations above 0.50 between the neural components as well as between the elastic components obtained by the two devices were as expected, suggesting that the components measured by both devices represent similar constructs. The remaining unexplained variance (i.e. 63% for the neural components and 72% for the elastic components) is substantial and may evolve from differences in measurement setup and protocol, including the presence or absence of direct determination of muscle activity, the different modelling methods in deriving the components and/or the different states at which both components are determined. In comparison, the NF uses a fixed position of 30° wrist extension after a fast wrist extension movement over a fixed 50° perturbation range to obtain the neural component, regardless of the patients' passive range of motion, whereas

the WA estimates the neural component over the patients' full passive range of motion at a velocity of 236°/second, using EMG, which will affect the estimate of the reflexive response of muscle activity. Furthermore, the position of the forearm in which the wrist is moved differs per device. In the wrist extension movement in the vertical plane, which is imposed by the NF, the gravitational component of the mass of the hand may influence the exerted force from which the neural and elastic components are obtained. Additionally, the NF, unlike the WA, uses a unidirectional (i.e. extension) biomechanical modelling method based on the force-time traces only, without taking muscle activity and tissue properties of the extensor muscle into account. Despite the possible limitations of the NF, this portable device, which determines the components immediately after the measurement, may be more practical for clinical use. The WA, on the other hand, uses a more extensive EMG-based optimization model, including all contributing factors, supported by literature. However, the clinical applicability of this experimental method is currently still limited as the offline signal analysis is yet complex and computationally intensive.

NF-NC showed unexpectedly high associations with the elastic components of both devices, while WA-NC showed no association with both elastic components, which may be explained in two ways. First, the discrimination between the neural and elastic component in the NF is less adequate in absence of a direct measurement of muscle activity. Second, NF-NC may have been influenced by other factors that are not included in the unidirectional biomechanical model. This can be due to either a non-neural component, such as viscosity, or other neural factors, such as involuntary background activation. Our findings suggest that the WA, using input from EMG, provides better discrimination between the neural and elastic component of wrist hyper-resistance. Our findings are consistent with previous studies that suggest that assessments using biomechanical parameters, such as joint angle and resistance, alone may be less valid to describe neural components than measurements using EMG-related parameters.[39,40] In contrast, EMG-based instrumented assessment of the neural component previously showed poorer reliability in terms of intraclass correlation coefficients and smallest detectable change[16,29,30,41] compared to the NF.[25] Further investigations are required to assess whether muscle activity measurements by EMG are needed to gain a valid, reliable and accurate discrimination between the neural and non-neural tissue property-related components.

The overall results of our study indicate comparable outcomes for the NF and WA at group level, however, there is misclassification at the individual level given the values seen in Figure 4.2. This may lead to different treatment decisions in clinical practice at the

individual level. The responsiveness of the neural and non-neural components to different treatments, such as botulinum toxin and orthotics, should be evaluated in future studies to gain insight into treatment options for patients with increased neural and/or non-neural components of wrist hyper-resistance and the associated cut-off values that can be used for patient selection.

As expected, components of both devices were moderately associated with the MAS, and the elastic components of both devices showed negative associations with the range of passive wrist extension, suggesting construct validity of both devices for quantification of neural and elastic components of wrist hyper-resistance in patients with chronic stroke. However, these assessment methods that are able to discriminate between components of wrist hyper-resistance have an added value compared to clinical assessment with the MAS alone.

Study limitations

Differences in metric units prevented the assessment of absolute agreement. Patients with passive wrist extension of less than 40° had to be excluded due to the NF protocol, which may have affected the variance in the passive tissue properties of the wrist flexor muscle in the included group of patients. Due to pragmatic reasons, the NF and WA assessments were performed in a semi-randomized order and, in thirteen patients, on different days. As the neural drive can vary from day-to-day and even within a day, these fluctuations could have influenced the variance in the neural component between the devices.

CONCLUSIONS

The current study shows similarity between two instrumented assessment methods, i.e. NeuroFlexor and the EMG-based Wristalyzer, for the quantification of neural and non-neural elastic components of wrist hyper-resistance in patients with chronic stroke. The NeuroFlexor is easier for clinical use, while the EMG-based Wristalyzer may provide a better distinction between the independent components of wrist hyper-resistance. The possible added value of EMG in the discrimination between the neural and non-neural components, as well as the improvement of the classification of wrist hyper-resistance components at the individual level, requires further investigation.

ACKNOWLEDGEMENTS

We are grateful to all patients for their participation in the study. We would like to thank Mique Saes, Dirk Hoevenaars and Robert Croese for their contribution to the data collection and Caroline Terwee for her contribution to the interpretation of the data.

FUNDING

This work was supported by the European Research Council (grant no. 291339, 4D-EEG project), the Netherlands Organisation for Health Research and Development (ZonMw grant no. 104003008, PROFITS project) and an unrestricted grant from IPSEN.

REFERENCES

1. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology.* 2015;45(3):161-176.
2. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8(8):741-754.
3. Van der Vliet R, Selles RW, Andrinopoulou ER, et al. Predicting Upper Limb Motor Impairment Recovery after Stroke: A Mixture Model. *Ann Neurol.* 2020;87(3):383-393.
4. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. *Disabil Rehabil.* 2013;35(4):291-299.
5. Doan QV, Brashear A, Gillard PJ, et al. Relationship between disability and health-related quality of life and caregiver burden in patients with upper limb poststroke spasticity. *PM R.* 2012;4(1):4-10.
6. Sommerfeld DK, Gripenstedt U, Welmer AK. Spasticity after stroke: an overview of prevalence, test instruments, and treatments. *Am J Phys Med Rehabil.* 2012;91(9):814-820.
7. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Early prediction of long-term upper limb spasticity after stroke: part of the SALGOT study. *Neurology.* 2015;85(10):873-880.
8. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil.* 1989;70(2):144-155.
9. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol.* 2007;6(8):725-733.

10. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koelle WP, eds. *Spasticity: disordered motor control.* Chicago: Year Book Medical Publishers; 1980:485-494.
11. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry.* 2005;76(1):47-54.
12. Van den Noort JC, Bar-On L, Aertbelien E, et al. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. *Eur J Neurol.* 2017;24(7):981-989.
13. De Gooijer-van de Groep KL, de Groot JH, van der Krogt H, de Vlugt E, Arendzen JH, Meskers CGM. Early Shortening of Wrist Flexor Muscles Coincides With Poor Recovery After Stroke. *Neurorehabil Neural Repair.* 2018;32(6-7):645-654.
14. Mirbagheri MM, Tsao C, Rymer WZ. Natural history of neuromuscular properties after stroke: a longitudinal study. *J Neurol Neurosurg Psychiatry.* 2009;80(11):1212-1217.
15. Andringa A, Meskers C, van de Port I, van Wegen E, Kwakkel G. Time Course of Wrist Hyper-Resistance in Relation to Upper Limb Motor Recovery Early Post stroke. *Neurorehabil Neural Repair.* 2020;34(8):690-701.
16. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech.* 2016;35:93-101.
17. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of Botulinum Toxin Treatment for Upper Limb Spasticity Poststroke Over Different ICF Domains: A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil.* 2019;100(9):1703-1725.
18. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil.* 1999;13(5):373-383.
19. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry.* 2010;81(1):46-52.
20. Van der Krogt HJ, Meskers CG, de Groot JH, Klomp A, Arendzen JH. The gap between clinical gaze and systematic assessment of movement disorders after stroke. *J Neuroeng Rehabil.* 2012; 9:61.
21. Lindberg PG, Gaverth 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(7):617-625.
22. Pisano F, Miscio G, Del Conte C, Pianca D, Candeloro E, Colombo R. Quantitative measures of spasticity in post-stroke patients. *Clin Neurophysiol.* 2000;111(6):1015-1022.

23. Wang R, Herman P, Ekeberg O, Gaverth J, Fagergren A, Forssberg H. Neural and non-neural related properties in the spastic wrist flexors: An optimization study. *Med Eng Phys.* 2017;47:198-209.
24. Leng Y, Wang Z, Bian R, et al. Alterations of Elastic Property of Spastic Muscle With Its Joint Resistance Evaluated From Shear Wave Elastography and Biomechanical Model. *Front Neurol.* 2019;10:736.
25. Andringa A, van Wegen E, van de Port I, Kwakkel G, Meskers C. Measurement Properties of the NeuroFlexor Device for Quantifying Neural and Non-neural Components of Wrist Hyper-Resistance in Chronic Stroke. *Front Neurol.* 2019;10:730.
26. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med.* 2013;45(7):630-636.
27. Gaverth J, Eliasson AC, 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. *J Rehabil Med.* 2014;46(7):629-634.
28. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil.* 2010;7:35.
29. Van der Krogt H, Klomp A, de Groot JH, et al. Comprehensive neuromechanical assessment in stroke patients: reliability and responsiveness of a protocol to measure neural and non-neural wrist properties. *J Neuroeng Rehabil.* 2015;12:28.
30. Sloot LH, van der Krogt MM, de Gooijer-van de Groep KL, et al. The validity and reliability of modelled neural and tissue properties of the ankle muscles in children with cerebral palsy. *Gait Posture.* 2015;42(1):7-15.
31. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* 1992;40(9):922-935.
32. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191-2194.
33. Koo TK, Mak AF. A neuromusculoskeletal model to simulate the constant angular velocity elbow extension test of spasticity. *Med Eng Phys.* 2006;28(1):60-69.
34. Manto M, Van Den Braber N, Grimaldi G, Lammertse P. A new myohaptic instrument to assess wrist motion dynamically. *Sensors.* 2010;10(4):3180-3194.
35. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67(2):206-207.

36. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol.* 2010;63(7):737-745.
37. De Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in medicine: a practical guide.* 3rd ed. Cambridge: Cambridge University Press; 2014.
38. Lane DM. Online Statistics Education: A Multimedia Course of Study. Rice University. Accessed August 30, 2019. www.onlinestatbook.com
39. Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assessment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. *Disabil Rehabil.* 2005; 27(1-2):33-68.
40. Pandyan AD, Van Wijck FM, Stark S, Vuadens P, Johnson GR, Barnes MP. The construct validity of a spasticity measurement device for clinical practice: an alternative to the Ashworth scales. *Disabil Rehabil.* 2006;28(9):579-585.
41. Bar-On L, Aertbelien E, Wambacq H, et al. A clinical measurement to quantify spasticity in children with cerebral palsy by integration of multidimensional signals. *Gait Posture.* 2013; 38(1):141-147.

SUPPLEMENTARY MATERIAL

Supplement 4A. Biomechanical model of the NeuroFlexor

In the biomechanical model of the NeuroFlexor, described by Lindberg et al.[1] and based on previous work by Koo and Mak,[2] the total measured resisting force (F_m) expressed in Newton during passive wrist extension is assumed to be a summation of passive elastic force (F_p), viscous force (F_v), reflexive forces (F_r) and inertial forces of the limb and the moving parts of the device (F_{in}), described as:

$$F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta), \quad (1)$$

where θ denotes a specific angle.

In the model, four force magnitudes, identified in the force-time traces of the slow and fast movements, are used to estimate the different components of the total measured passive force. F0 is the resting force of the hand before onset of stretch, with wrist angle equals 20° flexion. Two force magnitudes are defined within the fast passive wrist extension movement (236°/second): F1, the initial force peak (occurring at about 15ms after movement onset), and F2, the force at the end of the passive movement in 30° extension (Figure S4.1A). One force magnitude (F3) is defined at the end position of the slow wrist extension movement (5°/second) (Figure S4.1B). Resting force (F0) is subtracted from F1, F2 and F3 prior to further calculations. Two slow and two fast movements without the hand and forearm fastened to the device are run as a reference for the mechanical resistance by the hand platform on the force sensor.

The force traces include an angle-dependent variation of the gravitational force exerted to the hand and hand platform (i.e. largest in the horizontal plane at 0°). To compensate for this angle-dependent gravitational variation, the total force is corrected according to the following formula:

$$F_{\text{corrected}} = F_{\text{total}} + m_{\text{hand}} \times g\left(1 - \cos\left[\text{angle}_{\text{hand}} \times \frac{3.14}{180}\right]\right) + m_{\text{platform}} \times g\left(1 - \cos\left[\text{angle}_{\text{platform}} \times \frac{3.14}{180}\right]\right), \quad (2)$$

where g = 9.81 m/s^2. The zero angle of the platform ($\text{angle}_{\text{platform}} = 0$) is defined as the angle of maximum F_{total} without hand. The zero angle of the hand ($\text{angle}_{\text{hand}} = 0$) is defined as the horizontal plane.

The **inertia component (IC)** corresponds to the force resisting the acceleration of the hand and movable platform and is calculated in the model as:

$$\mathrm{IC} = m \times \alpha\,, \tag{3}$$

where m is the mass of the hand and the movable platform, and α is the acceleration of the movement (21 m/s^2). The mass of the hand is estimated to be 0.6% of the total body weight.[3]

The **elastic component (EC)** is a length-dependent resisting force which increases when the flexor muscles are stretched (and the extensor muscles are shortened). There is also an exponential increase when the muscle is stretched close to its end range. EC corresponds to F3, the force recorded 1 second after the end of the slow movement, minus resting force (F0) (Figure S4.1B). EC includes both the linear elasticity and the nonlinear end range stiffness.

The **viscous component (VC)** is a velocity-dependent resisting force of soft tissues to stretch, produced by, for example, sliding muscle fibres. Lindberg et al.[1] assumed that the viscous resistance is highest during the initial acceleration and continues at a lower level during further extension movement. To calculate the viscous component, first, the early viscous component (VC_{F1}) is calculated.

$$VC_{F1} = Total\ force_{F1} - \mathrm{IC}\,, \tag{4}$$

where Total force$_{F1}$ is the measured force at F1 (Figure S4.1A), and IC the inertial component calculated as above. Since Halaki et al.[4] described a comparatively stable relationship between the early and late viscosity, Lindberg et al.[1] assumed that the late viscosity is approximately 20% of the early viscosity.

$$\mathrm{VC} = VC_{F1} \times 0.2\,. \tag{5}$$

Finally, F2 is defined as the force peak at the end of the fast passive wrist extension movement, i.e. 30° wrist extension, (Figure S4.1A) and consists of the neural, viscous and elastic components together. The **neural component (NC)** is estimated by:

$$\mathrm{NC} = Total\ force_{F2} - (\mathrm{EC} + \mathrm{VC})\,. \tag{6}$$

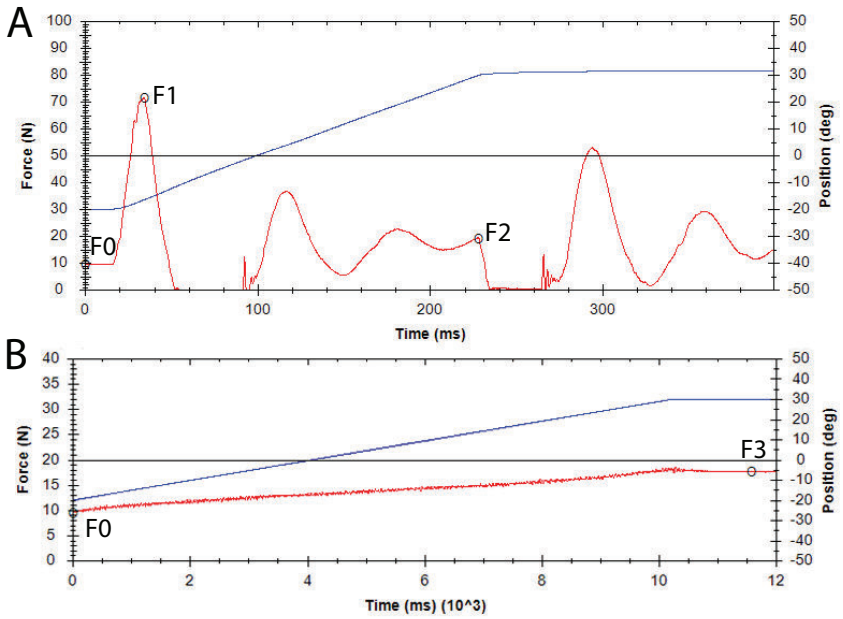


Figure S4.1. Examples of force-time traces (red line), measured in Newton (N), from a patient with stroke obtained during (A) a fast movement (236°/second) and (B) a slow movement (5°/second).
The blue line represents the angle of the wrist joint.

Supplement 4B. EMG-based optimization model of Wristalyzer

The model used in this study is based on the bidirectional wrist model of De Gooijer et al.,[5] which arises from an ankle model of De Vlugt et al.[6] The input signals of measured angle, torque and electromyography (EMG) of the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles are used to estimate a total of 12 parameters by a nonlinear least squares optimization algorithm and minimizing the error function, i.e. the difference between the measured torque and predicted torque. After parameter optimization, neural reflex torque of both the FCR and ECR, and non-neural elastic stiffness of the soft tissue of both the FCR and ECR are calculated.

The torque generated during passive ramp-and-hold (RaH) movements of the wrist is modelled by:

$$\hat{T}(t) = I\ddot{\theta}(t) + T_{ecr}(t) - T_{fcr}(t) \tag{7}$$

with t the time in seconds $[s]$, $\hat{T}$ the modelled wrist torque $[Nm]$, I the inertia of the hand and handle $[kg.m^2]$, $\ddot{\theta}$ the angular acceleration $[rad/s^2]$, T_{ecr} the torque generated by the extensor carpi radialis (ECR) muscle $[Nm]$ and T_{fcr} the torque generated by the flexor carpi radialis (FCR) muscle $[Nm]$.

Muscle torque (T_m) of the muscles is divided in torques generated by the elastic force of the parallel connective tissues ($F_{e,m}$) and the active or reflexive muscle forces according to the Hill-type model (F_{act}), and is described by:

$$T_m(\theta, t) = \left(F_{e,m}(l_m) + F_{act,m}(v_m, l_m, \alpha_m)\right) \cdot r_m(\theta) \tag{8}$$

with l_m the muscle length $[m]$, v_m the lengthening velocity $[m/s]$, α_m the active state [-] and $r_m(\theta)$ the angle dependent moment arm of the tendon $[m]$.

Passive properties

The elastic force ($F_{e0,m}$) of the muscles is modelled as:

$$F_{e0,m}(t) = e^{k_m(l_m(\theta) - l_{slack,m})} \tag{9}$$

where k_m is the estimated stiffness coefficient of the muscle $[1/m]$, $l_{slack,m}$ the slack length of the connective tissue $[m]$.

The relaxation dynamics are modelled by a first order filter, resulting in elastic forces modelled by:

$$F_{e,m}(t) = \frac{\tau_{rel}s + 1}{\tau_{rel} + 1 + k_{rel}} \cdot F_{e0,m}(s) \tag{10}$$

with τ_{rel} the tissue relaxation time $[s]$, s the Laplace operator and k_{rel} the estimated relaxation factor [-] of the tissue. Elastic forces in negative direction are set to zero, as the tissue can only exert pulling forces.

The moment arms of the ECR (r_{ecr}) and the FCR (r_{fcr}) are assumed to scale linearly with joint angle, and defined using the equations of Ramsay et al.[7]

$$r_{ecr,brevis}(\theta) = (13.4337 - 2.1411\theta) \cdot 10^{-3} \quad \text{for } \theta < 10° \tag{11}$$

$$r_{ecr,longus}(\theta) = (11.7166 - 2.2850\theta) \cdot 10^{-3} \quad \text{for } \theta > 10° \tag{12}$$

$$r_{ecr}(\theta) = (r_{ecr,brevis}(\theta) + r_{ecr,longus}(\theta))/2 \tag{13}$$

$$r_{fcr}(\theta) = (13.2040 + 1.5995\theta) \cdot 10^{-3} \quad \text{for } \theta > -10° \tag{14}$$

The muscle length (l_m) of the ECR and FCR muscles is determined by:

$$l_{ecr} = l_{ecr,0} + r_{ecr}(\theta)\theta \tag{15}$$

$$l_{fcr} = l_{fcr,0} - r_{fcr}(\theta)\theta \tag{16}$$

with $l_{ecr,0}$ and $l_{fcr,0}$ the muscle lengths of the ECR and FCR, at zero degrees wrist angle position (hand(le) in line with the forearm). The zero muscle lengths are 6.3 cm for the FCR and 7.0 cm for the ECR (average of ECR longus and brevis, optimal fibre lengths from Murray et al.[8] and Lieber et al.[9] Positive values for θ $[rad]$ denote flexion direction, and thus positive values for θ denote lengthening of the ECR and shortening of the FCR, and vice versa for extension direction.

Active properties

To compute the active force ($F_{act,m}$) generated by the ECR and FCR, a Hill-type muscle model is used:

$$F_{act,m} = f_{v,m}(v_m) f_{l,m}(l_m, l_{o,m}) \alpha_m \tag{17}$$

where $f_{v,m}$ is the force-velocity relationship, $f_{l,m}$ the force-length relationship, $l_{o,m}$ the estimated optimal muscle lengths $[m]$ and α_m the active state of the muscle [-]. The force-velocity relationship is dependent on whether the muscle lengthened $v > 0$ or shortened $v < 0$[10]:

$$f_{v,m}(v_m) = \begin{cases} 1 - \dfrac{(1 + m_{vsh} \cdot m_{vshl}) \cdot (f_{ecc} - 1) \cdot v_m}{m_{vsh} \cdot m_{vshl} \cdot v_{max,m} + v_m} & \text{if } v_m \geq 0 \\ \dfrac{v_m + v_{max,m}}{\dfrac{v_m}{m_{vsh}} - v_{max,m}} & \text{if } v_m < 0 \end{cases} \tag{18}$$

with $v_{max,m}$ the maximum shortening velocity, which was 8 times the optimal muscle length,[5,10] the maximum eccentric force f_{ecc} was 1.5 times the isometric force and the isometric force is normalized to 1 because the force had been scaled by the EMG weighing factors G_m. Furthermore, m_{vsh} and m_{vshl} are shaping factors with values 0.25 and 0.5 respectively.

The optimal muscle lengths are used to estimate the force-length relationship.

$$f_{l,m}(l_m, l_{o,m}) = e^{-(l_m - l_{o,m})^2 / w_m} \tag{19}$$

with w_m the shape factors, defined as:

$$w_m = cf \cdot {l_{o,m}}^2 \tag{20}$$

with *cf* the shape parameter of the force-length relationship with value 0.1 to resemble the force-generating range of the FCR and ECR. The active state of the muscle is obtained by filtering the weighted EMG signals by a linear second order filter:

$$\alpha_m(s) = \frac{\omega_0^2}{s^2 + 2\beta\omega_0 s + \omega_0^2} G_m EMG_m(s) \tag{21}$$

where $\omega_0 = 2\pi f_0$, with f_0 the estimated cut off frequency of the activation filter, s the Laplace operator denoting the first time derivative, β the relative damping, G_m the estimated EMG weights of the ECR and FCR muscles and EMG_m the filtered EMG signals of the ECR and FCR muscles [v].

The inertial component (I) is modelled as:

$$I = ml_a^2 \tag{22}$$

with m the estimated mass of the hand and the handle [kg] and l_a the distance from the rotation axis [m], fixed at 0.1 m.

The final parameters, i.e. neural component and elastic component of resistance to passive wrist extension, are calculated for both the FCR and ECR after parameter optimization. The neural component induced by the velocity-dependent stretch reflex of the FCR during fast passive wrist extension (WA-NF) is calculated based on root mean square (RMS) values of the modelled variant active torque within the time window of the fast (236°/second) extension sweeps:

$$WA\text{-}NC_{reflex,fcr} = \sqrt{\frac{1}{N}\int (F_{act,fcr} r_{fcr})^2} \tag{23}$$

where N are the number of data points.

The elastic component is taken for the FCR at an angle that is the same for all patients (θ^*), i.e. at 30° wrist extension.

$$WA\text{-}EC = k_{fcr} e^{k_{fcr}(l_{fcr}(\theta^*) - l_{slack,fcr})} r_{mfcr}^2(\theta^*) \tag{24}$$

Table S4.1. Parameters optimized by the EMG-based optimization model

Parameter	Description [unit]	Initial value	Lower bound	Upper bound
Intrinsic parameters				
m	Mass of the hand + handle [kg]	0.6	0.5	5
k_{ecr}	Stiffness coefficient ECR [1/m]	240	10	800
k_{fcr}	Stiffness coefficient FCR [1/m]	230	10	800
τ_{rel}	Relaxation time constant [s]	0.9	0	10
k_{rel}	Relaxation factor [-]	1	0	50
$l_{slack,ecr}$	Connective tissue ECR slack length [m]	0.06	-0.1	0.1
$l_{slack,fcr}$	Connective tissue FCR slack length [m]	0.04	-0.1	0.1
Neural parameters				
G_{ecr}	EMG weighing factor ECR [1/V]	1×10^4	1	1×10^{11}
G_{fcr}	EMG weighing factor FCR [1/V]	1×10^4	1	1×10^{11}
$l_{o,ecr}$	Optimal muscle length ECR [m]	0.070	0.04	0.11
$l_{o,fcr}$	Optimal muscle length FCR [m]	0.063	0.04	0.11
f_0	Activation cut-off frequency [Hz]	3	1	10

The validity of the model is assessed with the root mean square error (RMSE) is calculated by

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}(T(i) - \hat{T}(\hat{\theta}, i))^2}{N}} \tag{25}$$

with $\hat{\theta}$ the optimized parameter vector, N the total number of time samples, i the index of the time sample, T the measured torque, $\hat{T}$ the estimated torque. A lower RMSE shows a better performance of the model.

Reliability of the parameters is assessed with the normalized standard error of the mean (nSEM), which is based in the sensitivity of each parameter to the error function. A parameter with a low nSEM value has a substantial contribution to the error function. SEM values were calculated using the covariance matrix P:

$$P = \sqrt{\frac{1}{N}\,(J^T \cdot J)^{-1}\epsilon \cdot \epsilon^T} \tag{26}$$

with N the number of parameters, J the Jacobian matrix (partial derivatives of the prediction error for each parameter) and ϵ the error function. SEM values are calculated by taking the square root of the diagonal terms of P. Thereafter, SEM values are normalized to their corresponding parameter value.

Supplement 4C. Scatterplots

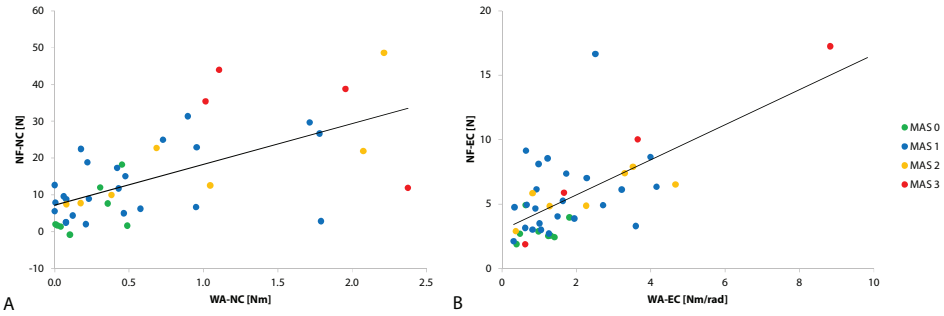


Figure S4.2. Outcomes of the Wristalyzer (WA) versus NeuroFlexor (NF) for (A) neural component (NC) and (B) elastic component (EC).

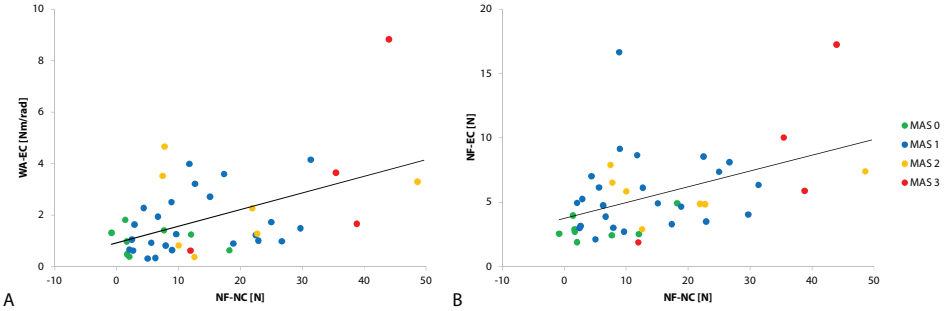


Figure S4.3. Neural component of the NeuroFlexor (NF-NC) versus (A) elastic component of the Wristalyzer (WA-EC) and (B) elastic component of the NeuroFlexor (NF-EC).

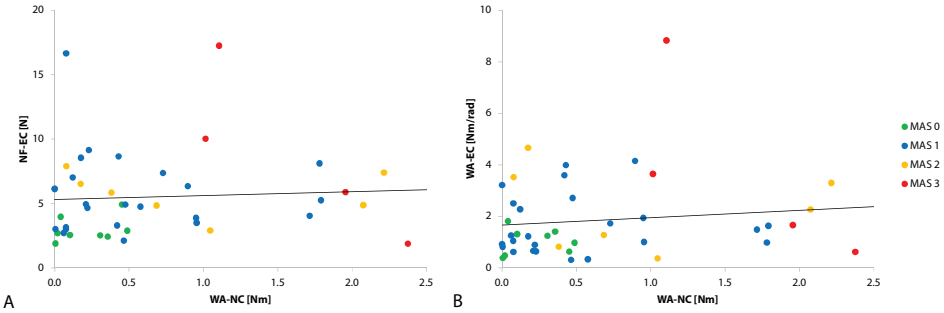


Figure S4.4. Neural component of the Wristalyzer (WA-NC) versus (A) elastic component of the NeuroFlexor (NF-EC) and (B) elastic component of the Wristalyzer.

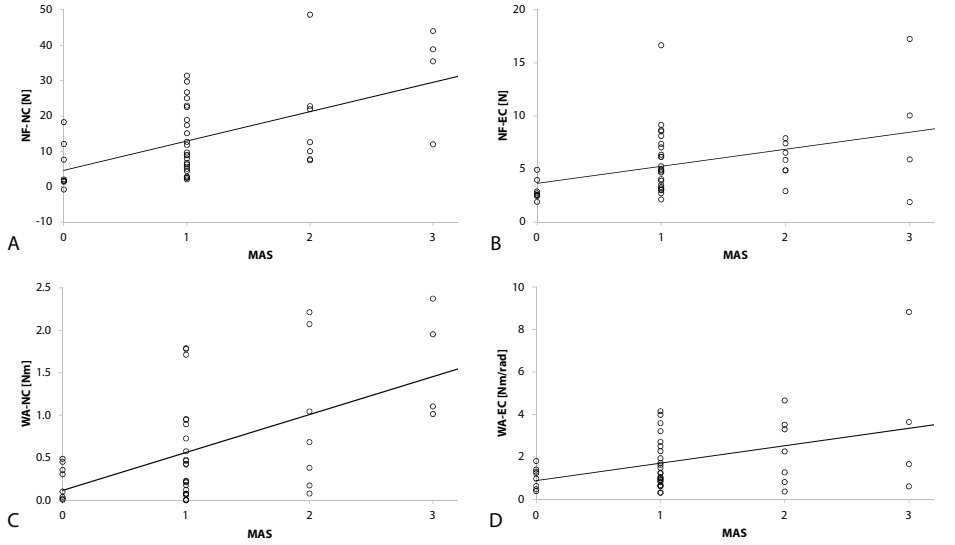


Figure S4.5. Neural (NC) and elastic (EC) components of the NeuroFlexor (NF) and Wristalyzer (WA) versus the modified Ashworth scale (MAS). (A) NF-NC, (B) NF-EC, (C) WA-NC and (D) WA-EC.

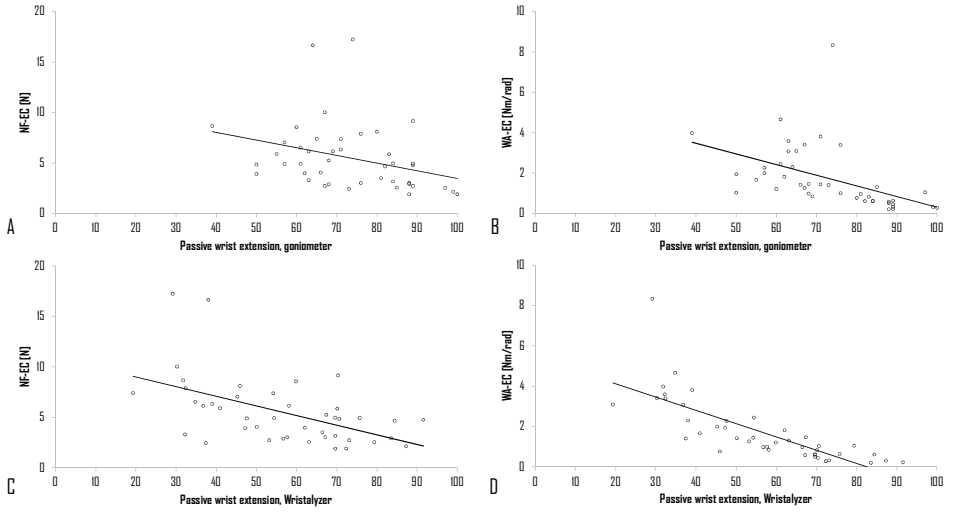


Figure S4.6. Elastic component of the NeuroFlexor (NF-EC) and Wristalyzer (WA-EC) versus passive wrist extension as determined with goniometry and Wristalyzer.

REFERENCES SUPPLEMENTARY MATERIAL

1. Lindberg PG, Gaverth 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.
2. Koo TK, Mak AF. A neuromusculoskeletal model to simulate the constant angular velocity elbow extension test of spasticity. *Med Eng Phys*. 2006;28:60-69.
3. Winters JM, Stark L. Analysis of fundamental human movement patterns through the use of in-depth antagonistic muscle models. *IEEE Trans Biomed Eng*. 1985;32:826-839.
4. Halaki M, O'Dwyer N, Cathers I. Systematic nonlinear relations between displacement amplitude and joint mechanics at the human wrist. *J Biomech*. 2006;39:2171-2182.
5. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech*. 2016;35:93-101.
6. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil*. 2010;7:35.
7. Ramsay JW, Hunter BV, Gonzalez RV. Muscle moment arm and normalized moment contributions as reference data for musculoskeletal elbow and wrist joint models. *J Biomech*. 2009;42:463-73.
8. Murray WM, Buchanan TS, Delp SL. The isometric functional capacity of muscles that cross the elbow. *J Biomech*. 2000;33:943-952.
9. Lieber RL, Fazeli BM, Botte MJ. Architecture of selected wrist flexor and extensor muscles. *J Hand Surg Am*. 1990;15:244-50.
10. Thelen DG. Adjustment of muscle mechanics model parameters to simulate dynamic contractions in older adults. *J Biomech Eng*. 2003;125:70-77.

CHAPTER 5

Time course of wrist hyper-resistance in relation to upper limb motor recovery early post stroke

Aukje S. Andringa
Carel G.M. Meskers
Ingrid G.L. van de Port
Erwin E.H. van Wegen
Gert Kwakkel

Neurorehabil Neural Repair. 2020;34(8):690-701

ABSTRACT

Background: Patients with an upper limb motor impairment are likely to develop wrist hyper-resistance during the first months post stroke. The time course of wrist hyper-resistance in terms of neural and non-neural components, and their interaction with motor recovery, is poorly understood.

Objective: To investigate the time course of neural and non-neural components of wrist hyper-resistance in relation to upper limb motor recovery in the first 6 months post stroke.

Methods: Neural (NC), non-neural elastic (EC) and viscous (VC) components of wrist hyper-resistance (NeuroFlexor device), and upper limb motor recovery (Fugl-Meyer upper extremity scale (FM-UE)), were assessed in 17 patients within 3 and at 5, 12 and 26 weeks post stroke. Patients were stratified according to the presence of voluntary finger extension (VFE) at baseline. Time course of wrist hyper-resistance components and assumed interaction effects were analysed using linear mixed models.

Results: On average, patients without VFE at baseline (n = 8) showed a significant increase in NC, EC and VC, and an increase in FM-UE from 13 to 26 points within the first 6 months post stroke. A significant increase in NC within 5 weeks preceded a significant increase in EC between weeks 12 and 26. Patients with VFE at baseline (n = 9) showed, on average, no significant increase in components from baseline to 6 months whereas FM-UE scores improved from 38 to 60.

Conclusion: Our findings suggest that the development of neural and non-neural wrist hyper-resistance components in patients with severe baseline motor deficits is determined by lack of spontaneous neurobiological recovery early post stroke.

INTRODUCTION

Recovery of post stroke upper limb motor impairment is heterogeneous. Recent studies suggest that most patients follow a predictable pattern of spontaneous neurobiological recovery within the first 3 months after stroke, while 20% to 30% of the patients fail to show any motor recovery.[1-3] Previous observational studies have shown that early control of voluntary finger extension (VFE) is an important determinant of upper limb motor recovery at 6 months post stroke.[4,5] In addition, several studies suggested that patients with poor motor recovery are likely to show increased resistance to passive muscle stretch,[6-8] that is hyper-resistance. This hyper-resistance is hypothesized to be caused by a poorly understood and complex interaction between pathological neuromuscular activation due to damage to descending pathways as well as non-neural changes in the muscles and soft tissues spanning the joint post stroke.[9-11] The neural components of hyper-resistance may be divided into velocity-dependent stretch hyperreflexia (altered set point and/or gain of the stretch reflex, i.e. spasticity following the definition of Lance)[9,12] and non-velocity-dependent involuntary activation (i.e. increased background levels of contraction).[11,13] Non-neural components of joint hyper-resistance include altered tissue properties, for example, elasticity, viscosity and muscle shortening.[11,14]

In particular, there is a lack of knowledge about the time course of wrist hyper-resistance in terms of its neural and non-neural components, and its interaction with motor recovery early post stroke,[15] yet this is important for understanding observed improvements in motor control of the upper paretic limb in terms of behavioural restitution and compensation strategies.[16,17] Development of the velocity and non-velocity-dependent neural components, among which spasticity, as a reflection of reorganization of spared descending pathways, might reflect neural repair processes during upper limb recovery, further influencing behavioural restitution.[16,18] Moreover, information about the time course of different components of wrist hyper-resistance may help to optimize individualized treatment decisions, for example when and to whom to apply botulinum toxin treatment[19-21] during the early post stroke phase. Considering the target mechanism of botulinum toxin, blocking neural signal transmission to the muscle, it is expected that patients with an increased neural component of wrist hyper-resistance will benefit most from this treatment. Recently, a new measurement technique, called NeuroFlexor (Aggero MedTech, AB), has been developed for the quantification of neural and non-neural elastic and viscous components of wrist hyper-resistance, which has proved to be valid[22,23] and reliable[23,24] in patients with chronic stroke.

The first aim of the present study was to investigate the time course of wrist hyper-resistance in the first 6 months post stroke, separated into its neural and non-neural elastic

and viscous components. This was done in patients with and without VFE within 3 weeks post stroke, in relation to the critical time-window of spontaneous neurobiological recovery as reflected by improvements observed using the Fugl-Meyer upper extremity scale (FM-UE). Findings were compared with healthy reference data. The second aim was to investigate the association between neural and non-neural elastic and viscous components of wrist hyper-resistance in the first 6 months post stroke.

We hypothesized that in patients without VFE within 3 weeks post stroke, in the absence of spontaneous neurobiological recovery, both the neural and non-neural components of wrist hyper-resistance would gradually increase over time.[15] In addition, we hypothesized that the neural component would increase within the time-window of spontaneous neurobiological recovery, while an increase of the non-neural components would not be restricted to this specific time-window. In a similar vein, we hypothesized that an increase in the neural component would be accompanied by an increase in non-neural components, in reaction to a pathological neuromuscular activation. In patients with VFE within 3 weeks post stroke, that is those showing spontaneous neurobiological recovery, components of wrist hyper-resistance were hypothesized to normalize to values seen in age- and gender-matched healthy subjects.

METHODS

Participants

All patients with stroke who were admitted to Revant Rehabilitation Centre Breda, The Netherlands, for inpatient rehabilitation were screened for eligibility between July 2015 and July 2016. The inclusion criteria for this study were (1) a first-ever ischemic stroke within the past 3 weeks, with an initial upper limb deficit as defined by the National Institutes of Health Stroke Scale item 5 a/b score > 0 (i.e. not able to hold the affected arm at a 90° angle for at least 10 seconds); (2) ≥ 18 years of age; (3) able to sit in a chair for at least 1 hour; and (4) sufficient cognitive ability to follow test instructions as indicated by a score higher than 17 on the Mini Mental State Examination.[25] Exclusion criteria were (1) a history of other neurological impairments and (2) limitations of arm-hand function of the affected side prior to the stroke. A group of healthy, right-handed, age- and gender-matched adults without wrist function restrictions served as a reference group. Ethical approval was obtained from the Medical Ethics Reviewing Committee of the VU University medical centre, Amsterdam,

The Netherlands (NL47079.029.14). In accordance with the Declaration of Helsinki (2013), all participants gave written informed consent.

Study design and procedures

In this prospective cohort study, repeated measurements were performed at fixed times post stroke, that is within 3 weeks and at 5, 12 and 26 weeks. The first measurement was performed as soon as possible after stroke onset, with more intensive repeated measurements within the window of nonlinear spontaneous neurobiological recovery within the first 12 weeks post stroke[3] and a follow-up measurement at the start of the chronic phase after stroke.[26] Demographics and stroke characteristics were collected at baseline. All measurements were performed by a trained assessor. In the healthy controls, neural and non-neural components of wrist hyper-resistance were determined for the dominant arm. All patients received usual care. The use of botulinum toxin injections was recorded throughout the study period.

At baseline, patients were stratified into two groups, based on the presence or absence of VFE within 3 weeks post stroke[4,5]: (1) a group of patients showing any VFE, according to the FM-UE item of finger extension > 0, within 3 weeks and (2) a group of patients showing no VFE (FM-UE item finger extension = 0) within 3 weeks.

Outcome measures

Neural and non-neural elastic and viscous components of resistance to passive wrist extension were assessed with a validated and commercially available measurement technique, the NeuroFlexor, feasible for use in clinical practice (Figure 5.1).[22] This motor-driven device imposes isokinetic wrist displacements with extended fingers from 20° palmar flexion to 30° dorsal flexion at two controlled velocities (5 and 236°/second), for which a minimal passive wrist extension of 40° is needed. A force sensor, placed underneath the moveable hand platform, measures the resistance trace during the passive wrist movement. The participant was seated comfortably parallel to the device with the shoulder in 45° of abduction, 0° of flexion, the elbow in 90° of flexion, with the forearm fastened to the device in pronation and the hand with extended fingers fastened to the hand platform. Participants were instructed to relax their arm and to look ahead of them during the measurements. The experimental session consisted of five slow movements (5°/second) followed by ten fast movements (236°/second). The first movement at both velocities was excluded from analysis to avoid bias from startle reflexes and mechanical hysteresis. The resting torque of the hand before onset of stretch was subtracted from the resistance traces prior to further calculations. Using the

biomechanical model described by Lindberg et al.,[22] the different components of wrist hyper-resistance, that is the velocity-dependent part of the neural component (NC), the non-neural elastic component (EC) and viscous component (VC), were derived from the resistance traces (using the NeuroFlexor Scientific v0.06 software program, Supplement 5A). The NC was determined as a derivative of the velocity-dependent resistance to passive wrist extension, which is to reflect the neural, velocity-dependent part of wrist hyper-resistance, that is assumed proxy of spasticity as defined by Lance,[12] not including the non-velocity-dependent part of neural activity, that is involuntary background activation. The length-dependent EC was determined as the resistance at the end of the slow movement. It was assumed that the velocity-dependent VC was highest during the initial acceleration and continued at a lower level, that is 20%, during further extension movement. The developers of the NeuroFlexor have previously underpinned the validity of the NC based on three arguments: (1) the NC as measured by the device was reduced after an ischemic nerve block, (2) the NC correlated with the integrated electromyography (EMG) across subjects and in the same subject during the ischemic nerve block and (3) the NC was found to be velocity-dependent.[22] In a recent study,[23] the NeuroFlexor method was suggested to be construct-valid against clinical assessments using the modified Ashworth and Tardieu scales. In addition, good to excellent reliability was shown for the quantification of the different components.[23,24] As a result of the positioning of the fingers, the measured resistance was a combination of resistance caused by wrist and finger flexor muscle groups. Measurements were performed twice at the same occasion and mean values were used for further analysis.

Synergy-dependent motor recovery of the upper limb, as a reflection of spontaneous neurobiological recovery, was assessed by the FM-UE[27] with a scoring range from 0 to 66 points. To test voluntary finger extension, patients were instructed to open the hand as much as possible starting from the resting position of the wrist and fingers, and the forearm in a neutral position between pronation and supination (0 = no voluntary extension movement in the metacarpophalangeal (MCP) or interphalangeal (IP) joints occurs, 1 = any degree of extension movement in the MCP or IP in any finger and/or thumb, 2 = full extension movement of all fingers that is equal to or greater than the unaffected side). Good measurement properties of the FM-UE have been established in studies of patients with stroke.[28,29]

Total resistance to passive wrist extension with extended fingers was measured manually using the modified Ashworth scale (MAS),[30] an ordinal scale with scores ranging from 0, no increased tone, to 4, the joint is rigid.

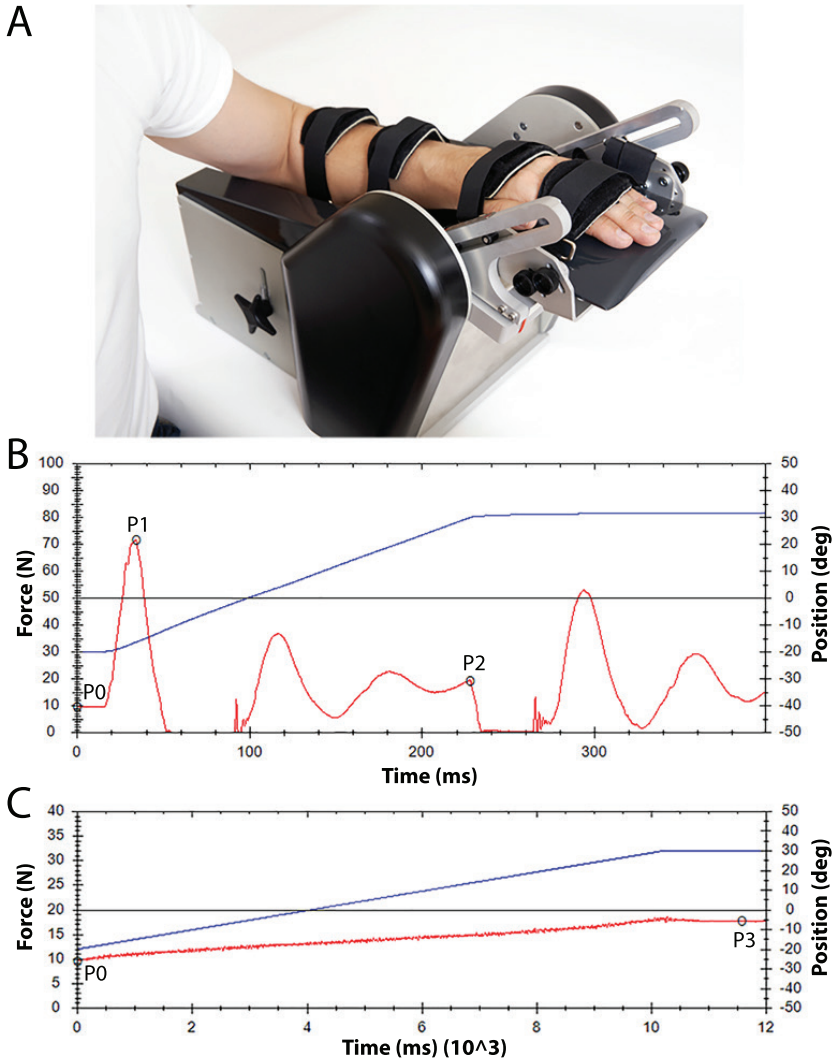


Figure 5.1. NeuroFlexor method.
(A) Measurement set-up. (B) An example of the force trace (red line) obtained during a fast movement (236°/second). (C) An example of the force trace obtained during a slow movement (5°/second). The blue line represents the angle of the wrist joint. The recorded force traces, measured in Newton (N), are analysed by a biomechanical model, which results in the quantification of the velocity-dependent part of the neural component (NC), elastic component (EC) and viscous component (VC) of wrist hyper-resistance. The total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r) and inertial forces of the limb and the moving parts of the device (F_{in}), described as: $F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta)$, where θ denotes a specific angle. In the model, four force points in the resistance trace of the slow and fast movements are used to estimate the different components of the total measured passive force. P0 is the resting torque of the hand before onset of stretch. Two force points are defined within the fast passive wrist extension movement (236°/second): P1, the initial peak in resistance, and P2, the late peak in resistance. One force point (P3) is defined at the end position of the slow wrist extension movement (5°/second). Resting torque (P0) is subtracted from P1, P2 and P3 prior to further calculations. Detailed information about the biomechanical model can be found in Supplement 5A.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical characteristics.

Linear mixed model analyses were used to investigate the time course of neural and non-neural components of wrist hyper-resistance during the first 6 months post stroke, and the interaction between this time course and the prognosis of upper limb motor recovery as defined by presence or absence of VFE within 3 weeks post stroke. Fixed effects were modelled for the time and group factors, and for the interaction between time and group. To correct for dependencies between the measurements, a random intercept per participant was used. For all three components, assumptions of normally distributed residuals were confirmed by inspecting histograms and Q-Q plots. Statistical level of significance was set at 0.050.

Statistical analysis of the difference in neural and non-neural components between patients and healthy controls was performed using the Mann-Whitney U test. The associations between FM-UE and NC and EC at week 26, as well as between neural and non-neural components over time, were calculated using Pearson correlation coefficients. Correlation coefficients below 0.25 were classified as no to little, 0.25 to 0.50 as fair, 0.50 to 0.75 as moderate to good and greater than 0.75 as good to excellent association.[31]

RESULTS

Figure 5.2 shows the participant flowchart. A total of 153 patients were screened for eligibility and 17 were included within 3 weeks post stroke. The demographic and clinical characteristics of the patients at baseline are summarized in Table 5.1. The baseline measurement was performed on average 15 ± 4 days post stroke (range 8–19 days). At baseline, 9 patients showed any VFE while 8 patients showed no VFE. Seventeen age- and gender-matched healthy controls (11 males and 6 females, mean age 60 ± 8 years, all right-handed) were included in the study.

Figure 5.3 shows the averaged time course of the neural and non-neural elastic and viscous components of wrist hyper-resistance, as well as the FM-UE and MAS scores. In patients with VFE at baseline, mean FM-UE scores improved from 38 points at baseline to 60 points (range 48–64) at week 26. In patients without VFE at baseline, mean FM-UE scores improved from 13 points at baseline to 26 points (range 13–42) at week 26. The mean

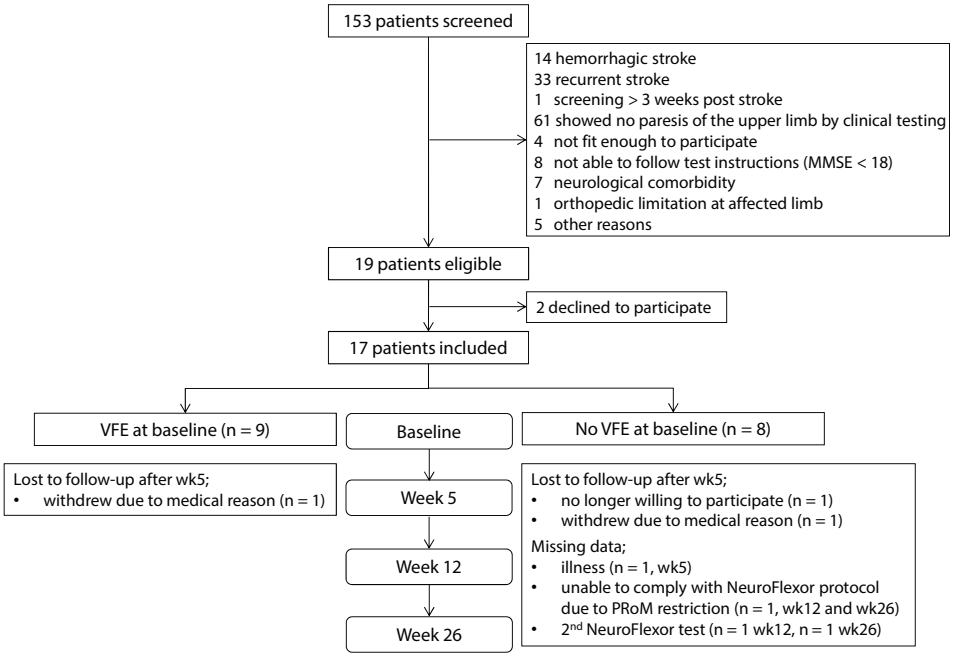


Figure 5.2. Flowchart.

Table 5.1. Demographic and clinical characteristics of the study population at baseline

	Overall	VFE at baseline	No VFE at baseline
Participants (n)	17	9	8
Age, years (mean ± SD)	62 ± 8	61 ± 6	62 ± 10
Gender, male/female (n)	11/6	6/3	5/3
Bamford classification, LACI/PACI/TACI (n)	6/8/3	4/4/1	2/4/2
Affected side, left/right (n)	11/6	6/3	5/3
Dominant hand, left/right (n)	2/15	2/7	0/8
Time between stroke and baseline measurement, days (mean ± SD)	15 ± 4	13 ± 4	16 ± 3
Clinical characteristics at baseline (median [IQR])			
NIHSS	7 [4.5 – 8]	5 [4.5 – 7.5]	7.5 [3.5 – 8.75]
FM-UE	21 [7.5 – 42.5]	42 [25.5 – 51]	7.5 [6.25 – 19]
FM-wrist	0 [0 – 3.5]	3 [1 – 6]	0 [0 – 0]
FM-hand	2 [0 – 6.5]	6 [2.5 – 10.5]	0 [0 – 1]
NC	1.95 [1.02 – 5.99]	1.95 [0.87 – 3.66]	2.89 [0.87 – 10.18]
EC	3.93 [3.36 – 4.77]	4.00 [2.94 – 4.91]	3.77 [3.30 – 4.80]
VC	0.20 [0.00 – 0.30]	0.15 [-0.10 – 0.27]	0.26 [0.18 – 0.42]

Abbreviations: EC: elastic component (N); FM-hand: Fugl-Meyer upper extremity scale, hand subsection [range 0–14]; FM-UE: Fugl-Meyer upper extremity scale [range: 0–66]; FM-wrist: Fugl-Meyer upper extremity scale, wrist subsection [range 0–10]; LACI: lacunar infarct; NC: velocity-dependent part of the neural component (N); NIHSS: National Institutes of Health Stroke Scale [range: 0–42]; PACI: partial anterior circulation infarct; TACI: total anterior circulation infarct; VC: viscous component (N); VFE: voluntary finger extension.

total resistance to passive wrist extension, as manually measured with the MAS, increased in patients with VFE at baseline from 0.3 at baseline to 0.7 at week 26 and in patients without VFE at baseline from 0.8 at baseline to 1.4 at week 26. None of the patients received botulinum toxin injections during the study period.

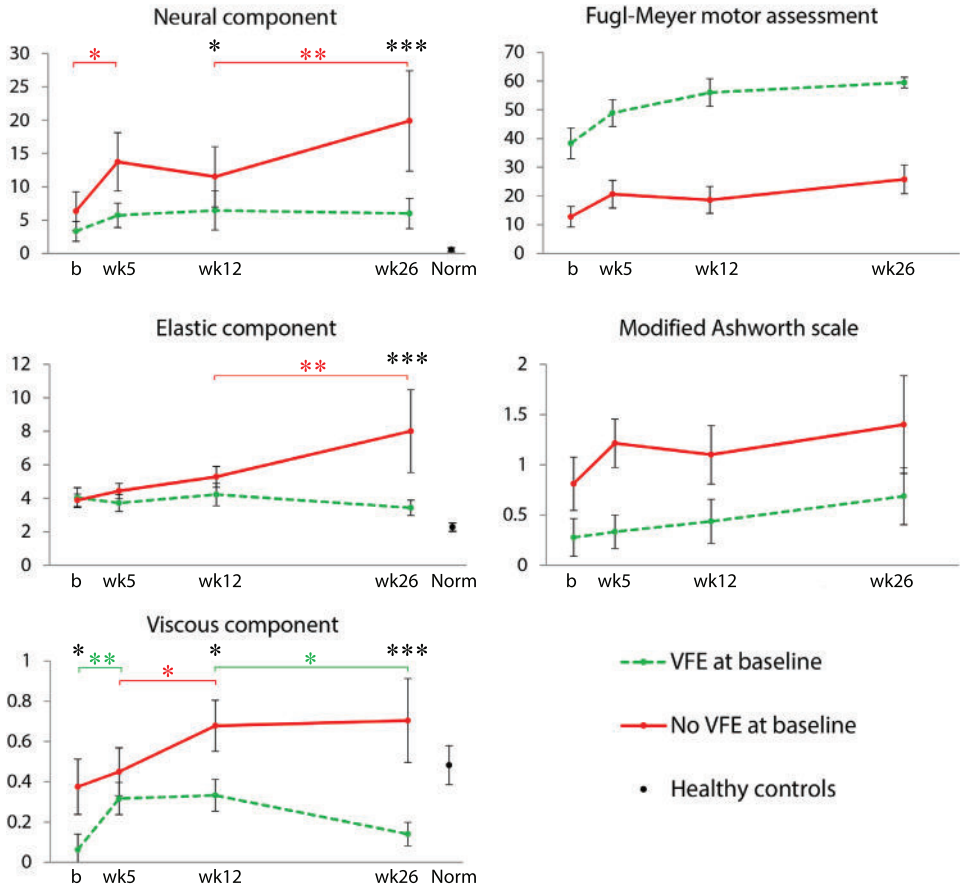


Figure 5.3. Time course of neural and non-neural elastic and viscous components of wrist hyper-resistance, motor recovery and total resistance to passive wrist extension post stroke.
Values are mean (SE). Baseline, n = 17 (VFE 9/no-VFE 8); week 5, n = 16 (VFE 9/no-VFE 7); week 12, n = 13 (VFE 8/no-VFE 5); week 26, n = 13 (VFE 8/no-VFE 5). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; black *, sign. difference between groups; green*/red*, sign. change over time within the groups of patients with and without voluntary finger extension.
Abbreviations: b, baseline measurement within 3 weeks post stroke; VFE, voluntary finger extension; wk, measurement week post stroke.

Time course of neural and non-neural elastic and viscous components of wrist hyper-resistance

Table 5.2 shows the results of the linear mixed model analyses for the total group, and for patients with and without VFE at baseline. For the total group, a significant increase in NC was found between baseline and week 5 (β = +4.04, *P* = 0.049). A significant increase in EC over time was found between baseline and week 26 (β = +1.37, *P* = 0.047), and a significant increase in VC was found between baseline and week 5 (β = +0.16, *P* = 0.028). The time course of the neural and non-neural elastic and viscous components of wrist hyper-resistance between baseline and week 26 differed between the 2 stratified groups (Figure 5.3). In patients with VFE at baseline, no significant changes over time in components of wrist hyper-resistance were found, except for a significant increase in VC between baseline and week 5 (β = +0.25, *P* = 0.004), and a significant decrease of VC between weeks 12 and 26 (β = -0.19, *P* = 0.034). In patients without VFE at baseline, the NC showed a significant

Table 5.2. Time course of neural and non-neural elastic and viscous components of wrist hyper-resistance in the first 6 months post stroke

	Baseline – week 5	Week 5 – 12	Week 12 – 26	Baseline – week 26
Total group				
NC	+4.04 (0.02 – 8.05) *P* = 0.049	+1.15 (-3.28 – 5.58) *P* = 0.603	+2.94 (-1.57 – 7.44) *P* = 0.178	+8.12 (3.78 – 12.47) *P* < 0.001
EC	+0.02 (-1.24 – 1.28) *P* = 0.976	+0.79 (-0.59 – 2.16) *P* = 0.253	+0.56 (-0.85 – 1.97) *P* = 0.429	+1.37 (0.02 – 2.72) *P* = 0.047
VC	+0.16 (0.02 – 0.31) *P* = 0.028	+0.08 (-0.08 – 0.24) *P* = 0.304	-0.11 (-0.27 – 0.05) *P* = 0.173	+0.13 (-0.02 – 0.29) *P* = 0.091
VFE at baseline				
NC	+2.39 (-1.76 – 6.53) *P* = 0.252	+0.35 (-3.97 – 4.68) *P* = 0.869	-0.46 (-4.86 – 3.94) *P* = 0.833	+2.28 (-2.05 – 6.61) *P* = 0.294
EC	-0.31 (-1.69 – 1.07) *P* = 0.648	+0.74 (-0.70 – 2.17) *P* = 0.307	-0.79 (-2.26 – 0.67) *P* = 0.280	-0.37 (-1.81 – 1.06) *P* = 0.603
VC	+0.25 (0.09 – 0.42) *P* = 0.004	0.00 (-0.17 – 0.18) *P* = 0.996	-0.19 (-0.37 – -0.02) *P* = 0.034	+0.06 (-0.12 – 0.23) *P* = 0.496
No VFE at baseline				
NC	+5.55 (0.95 – 10.15) *P* = 0.019	+3.68 (-1.84 – 9.20) *P* = 0.186	+8.38 (2.82 – 13.94) *P* = 0.004	+17.61 (12.34 – 22.87) *P* < 0.001
EC	+0.32 (-1.21 – 1.85) *P* = 0.673	+1.09 (-0.71 – 2.89) *P* = 0.231	+2.72 (0.87 – 4.57) *P* = 0.005	+4.13 (2.40 – 5.86) *P* < 0.001
VC	+0.04 (-0.14 – 0.23) *P* = 0.642	+0.22 (0.00 – 0.44) *P* = 0.046	0.02 (-0.20 – 0.25) *P* = 0.838	+0.29 (0.08 – 0.50) *P* = 0.008

Values are estimated regression coefficients (β), 95% confidence interval and probability estimates (*P*). Abbreviations: EC, elastic component (N); NC, velocity-dependent part of the neural component (N); VC, viscous component (N); VFE, voluntary finger extension.

increase over time (β = +17.61, $P < 0.001$), with significant increases between baseline and week 5 (β = +5.55, $P = 0.019$), and between weeks 12 and 26 (β = +8.38, $P = 0.004$). EC showed a significant increase over time (β = +4.13, $P < 0.001$), with a significant increase between weeks 12 and 26 (β = +2.72, $P = 0.005$). VC significantly increased between weeks 5 and 12, and between baseline and week 26 (β = +0.22, $P = 0.046$, and β = +0.29, $P = 0.008$, respectively). The individual data of wrist hyper-resistance components over time are shown in Supplement 5B.

As shown in Table 5.3, the NC and VC were significantly higher at week 12 in patients without VFE at baseline, compared to patients with VFE at baseline (NC β = +9.52, $P = 0.046$ and VC β = +0.33, $P = 0.029$, respectively). The neural as well as both non-neural components in patients without VFE at baseline were significantly higher at 26 weeks post stroke compared to those in patients with VFE at baseline (NC β = +18.36, $P < 0.001$, EC β = +4.35, $P < 0.001$ and VC β = +0.54, $P < 0.001$, respectively).

At 26 weeks post stroke, a negative correlation coefficient was found between the FM-UE score and the NC ($r = -0.54$, $P = 0.055$) and between the FM-UE score and the EC ($r = -0.73$, $P = 0.004$) (Supplement 5C).

Table 5.3. Differences in neural and non-neural elastic and viscous components of wrist hyper-resistance between patients with and without voluntary finger extension at baseline in the first 6 months post stroke

	Baseline no-VFE vs. VFE	Week 5 no-VFE vs. VFE	Week 12 no-VFE vs. VFE	Week 26 no-VFE vs. VFE
NC	+3.03 (-5.85 – 11.92) *P* = 0.487	+6.20 (-2.78 – 15.17) *P* = 0.167	+9.52 (0.16 – 18.88) *P* = 0.046	+18.36 (9.00 – 27.72) *P* < 0.001
EC	-0.16 (-2.09 – 1.77) *P* = 0.869	+0.48 (-1.50 – 2.46) *P* = 0.628	+0.83 (-1.34 – 2.99) *P* = 0.445	+4.35 (2.18 – 6.51) *P* < 0.001
VC	+0.31 (0.05 – 0.57) *P* = 0.022	+0.10 (-0.17 – 0.37) *P* = 0.449	+0.33 (0.04 – 0.61) *P* = 0.029	+0.54 (0.25 – 0.83) *P* < 0.001

Values are estimated regression coefficients (β), 95% confidence interval and probability estimates (*P*). Abbreviations: EC, elastic component (N); NC, velocity-dependent part of the neural component (N); no-VFE, group of patients without voluntary finger extension at baseline; VC, viscous component (N); VFE, group of patients with voluntary finger extension at baseline.

Healthy reference values

Healthy controls had a mean (SD) NC of 0.55 N (1.21), an EC of 2.27 N (1.01) and a VC of 0.48 N (0.40). Patients had significantly higher neural and elastic components, and a significantly lower viscous component at baseline compared with healthy controls (NC: $P = 0.001$; EC: $P < 0.001$; VC: $P = 0.016$). At 26 weeks post stroke, the NC in patients with

VFE at baseline was still significantly higher than that in healthy controls ($P = 0.010$), while the EC in these patients was not significantly different from the reference value of healthy controls ($P = 0.055$). Patients with VFE at baseline had significantly lower VC values at 26 weeks post stroke ($P = 0.027$) compared with healthy controls, while the VC of the patients without VFE at baseline did not differ from the reference value of healthy controls ($P = 0.649$).

Interaction between neural and non-neural elastic and viscous components of wrist hyper-resistance

As shown in Figure 5.3 for patients without VFE at baseline, the first significant increase in NC appeared in the time-window between baseline and week 5, preceding the first significant increase in EC between weeks 12 and 26. Correlation coefficients over time between the neural and non-neural elastic and viscous components are shown in Supplement 5D. At baseline and week 5 post stroke, no significant association was found between the NC and the EC. From week 12 onward, the NC and the EC showed significant correlation coefficients, from 0.78 at week 12 to 0.80 at week 26.

DISCUSSION

The current prospective cohort study investigated the time course of wrist hyper-resistance in the first 6 months post stroke, separated into its neural and non-neural elastic and viscous components using a commercially available measurement technique. First, as hypothesized, patients showing no VFE at baseline showed a gradual, significant increment in NC and subsequently also in the non-neural EC and VC components of wrist hyper-resistance within the first 6 months post stroke, whereas no significant change in either of the components of wrist hyper-resistance over time was seen in patients showing VFE at baseline. Second, the main increase in NC in patients without VFE at baseline occurred within the first 5 weeks post stroke, paralleling the time-window of spontaneous motor recovery as reflected by FM-UE improvements.[32-34] Last, our findings suggest that the increase in NC within the first 5 weeks post stroke in the group of patients without VFE preceded the increase in EC after 12 weeks post stroke.

The group of patients showing no VFE at baseline showed poor upper limb motor recovery in the first 6 months post stroke, as reflected by a FM-UE ≤ 42.[35] As shown in previous studies, the absence of VFE at baseline is highly associated with absence of spontaneous neurobiological recovery and damage of the corticospinal tract (CST) early

after stroke.[4,33] The development of the neural component of wrist hyper-resistance early after stroke in patients with severe baseline motor deficits, as seen in our study, might be driven by enhanced multisynaptic descending pathways, when CST integrity is compromised,[36-40] however, this hypothesis requires further investigation. Moreover, the negative association between the FM-UE score and NC at week 26 suggests that the degree of spontaneous neurobiological recovery is associated with a decrease in the severity of wrist hyper-resistance.

In this study with a relatively small sample size, we used the presence of VFE at baseline as a proxy for CST intactness allowing to dichotomize the study population into a group of patients with poor and with good upper limb motor recovery post stroke.[1,41] In addition, other markers of CST integrity such as transcranial magnetic stimulation (TMS)-induced motor-evoked potentials (MEPs) of the extensor carpi radialis[33] or the adductor digiti minimi,[42] diffusion tensor imaging (DTI) fractional anisotropy,[43] weighted CST lesion load (wCST-LL) in magnetic resonance imaging[44] as well as kinetic and kinematic performance assays of behavioural restitution[45] might improve the accuracy in identifying those patients that will develop wrist hyper-resistance early post stroke and might strengthen evidence on the relationship of wrist hyper-resistance components with upper limb motor recovery, its timeline and underlying pathophysiological concepts. However, these studies require larger sample sizes than presently available.

In our opinion, the observed changes in the neural component reflect neural repair processes early after stroke, further influencing on behavioural restitution, as measured with the FM-UE. The absence of neural and non-neural components of wrist hyper-resistance are conditional for optimal behavioural restitution. Our findings are consistent with a previous study,[36] which suggested that the velocity-dependent increase in muscle tone after damage to the CST due to stroke can be explained by enhanced multisynaptic, reticulospinal pathways in patients with chronic stroke. Confirmation of the enhancement of different multisynaptic pathways using neuroimaging or neurophysiological techniques, such as TMS-MEPs and DTI fractional anisotropy, and its role in the development in wrist hyper-resistance requires further investigation.

Interestingly, the NC further increased after the time window of spontaneous motor recovery, between weeks 12 and 26, which implies that the development of the NC is not influenced by motor recovery alone. This increase of NC may result from non-neural tissue property alterations, as shown by the high correlation between NC and EC from 12 weeks onward. Besides the increase in velocity-dependent wrist hyper-resistance, as represented by the NC, pathological neuromuscular activation may also comprise increased involuntary

background activation. This involuntary background activation, which is measured by resting torque by the NeuroFlexor, may also cause an increase in the elastic component.[46]

Our findings of increased neural and non-neural components of wrist hyper-resistance in patients with poor motor recovery are in line with the results of a previous study,[15] using a haptic robot device with a validated EMG-driven wrist model in 36 patients in the first 6 months post stroke. The results of both the present and aforementioned study[15] suggest that components of wrist hyper resistance show large interindividual variability which suggests that the level of motor recovery as well as additional factors, such as genetic factors, lesion location and premorbid muscle morphology, play a role.

As the NC mainly increases within the time-window of spontaneous neurobiological recovery, it is of interest to know whether the development of the NC restricts motor recovery, and if early reduction of the NC, for example using botulinum toxin, would positively influence motor recovery post stroke. The influence of the development of NC on motor recovery, and the effect of early reduction by botulinum toxin, should be further investigated.

As expected, our group of patients with good motor recovery (i.e. those presenting with VFE at baseline) showed no change in wrist hyper-resistance over time. However, against our expectations, the NC in this group 6 months after stroke onset was significantly higher than the values of healthy controls, whereas the EC approached reference values within 6 months post stroke. These data suggest that some degree of CST intactness, represented by the presence of VFE at baseline, is needed for motor recovery, apparently without interference from a slightly increased NC. In contrast to the NC and EC, the VC in the patients with poor motor recovery showed equivalent values to the healthy controls, whereas it showed decreased values compared with healthy controls in patients with good motor recovery. It should be noted that VC has hardly been investigated early post stroke, and in our study it contributed only 3% to the total wrist hyper-resistance measured with the NeuroFlexor. De Vlugt et al.[47] found comparable results with higher viscosity in the ankle in patients after stroke with higher Ashworth scale values. The decreased VC values in patients with VFE at baseline compared with healthy reference values might result from antagonistic muscle tension, problems of the biomechanical model handling these data or lack of responsiveness.[23]

The NeuroFlexor model includes four slow and nine fast wrist extension movements in the analysis of the components of wrist hyper-resistance. Analysis of the separate fast movements of one measurement session for all patients at baseline revealed a significant reduction of 17% in the NC between the first and last fast movement (paired t-test, mean

difference -0.95 N, 95% confidence interval -1.81 to -0.10 N, $P = 0.031$) (Supplement 5E). This reduced resistance over repeated movements may be due to, for example, an effect of time dependent viscosity,[48,49] varying background activation over time or mechanical hysteresis. To handle these still unknown non-linear effects, it is important to use standardized measurement protocols with a detailed description of the fixed number of repeated movements, the position and instruction of the participants, and extensive training for assessors. Moreover, the underlying mechanisms that contribute to the nonlinear behaviour of resistance to passive movement after stroke need further investigation.[50]

Study limitations

It should be noted that our study included only a small number of subjects. Nevertheless, the findings were robust enough to show significant changes in components of wrist hyper-resistance over time and significant differences between two subgroups of patients. Being sensitive to outliers in this small sample, nonparametric statistics led to the same conclusions when compared with current linear mixed model analyses. Furthermore, due to the different components of wrist hyper-resistance tested in this explorative study, we are also aware of multiple comparisons applied, suggesting that replication of current findings in a larger sample is needed.

Furthermore, the NC in both groups at baseline was already increased compared with healthy controls. With that, the exact moment of onset remains unclear in absence of measurements applied in the first days after stroke onset.[32] Further research in a larger population with more and earlier started measurements serially applied at fixed time-points within the first 12 weeks post stroke is needed to provide independent confirmation of our findings. Finally, this study only included patients with ischemic stroke, a generalization of study results to patients with haemorrhagic stroke should therefore be cautioned.

In recent years, several instrumented measurement techniques have been developed to quantify neural and non-neural components of hyper-resistance, which differ in complexity and modelling method.[51-55] In the absence of an appropriate gold standard, no single most valid method can be identified. Being interested in serially applied, within-subjects' measurements, we used the commercially available and portable NeuroFlexor method to quantify neural and non-neural components of wrist hyper-resistance in a clinical setting. However, the biomechanical model used for discriminating between neural and non-neural components of hyper-resistance has some limitations. First, the underlying biomechanical model assumes linearity, however, this approach does not address the nonlinear features as

length and velocity-dependent threshold of the stretch reflex,[56] and the velocity-dependent VC. Second, it should be noted that the wrist was extended at two arbitrarily selected velocities (5 and 236°/second, respectively), which are assumed to be below and above expected reflex threshold velocities, respectively.[47] Third, the wrist and finger flexor muscles were extended over a fixed 50° range around the neutral position of the wrist, regardless of the individual's passive range of motion. The device might therefore be insensitive to small changes in EC, as well as early muscle shortening.[57] Fourth, since it does not measure EMG but only resting torque of the hand before stretch onset, the NeuroFlexor is not able to specifically control and correct for the influence of increased involuntary background activation on wrist hyper-resistance.[46] Fifth, this involuntary background activation, that is the non-velocity-dependent part of neural activity, may also manifest in the non-velocity, length-dependent component of the total wrist joint resistance which is assumed to reflect the non-neural EC component according to the underlying biomechanical model of the NeuroFlexor.[22] Finally, the NeuroFlexor protocol requires a minimal passive wrist extension of 40°. In our study, one patient with poor motor recovery developed restriction of the passive wrist range of motion with extended fingers to less than 40°, and was therefore unable to comply with the protocol and could not be followed longitudinally from 12 weeks onward.

Future research

The present findings require further replication and validation in a larger population adopting a multimodal approach to better understand the mechanisms underlying the increase in neural and non-neural components of wrist hyper-resistance in patients with poor upper limb motor recovery. This knowledge about the underlying mechanisms might improve our understanding in the distinction between neural repair processes and its interaction with behavioural restitution in recovery of quality of movement early after stroke.[45] Second, further investigation is needed into the role of different multisynaptic pathways, such as the reticulospinal tract, in the development of spasticity, for instance using acoustic startle reflexes (i.e. StartReact phenomenon).[58] Third, further research is needed to investigate other predisposing between-subject factors explaining the heterogeneity between subjects in the development of wrist hyper-resistance post stroke, next to severity of upper limb paresis alone, such as genetic factors, lesion location and premorbid muscle morphology. Additionally, further refinement of the quantification of the neural component of wrist hyper-resistance, using EMG activity, is needed to differentiate between an increase in velocity-dependent spasticity and non-velocity-dependent involuntary background

activation,[59] and to reveal more about the moment of change. Last, the quantification of neural and non-neural components of wrist hyper-resistance, including the velocity-dependent VC that did contribute less than 3% of the total wrist resistance, requires further validation of the NeuroFlexor method with more sophisticated system identification techniques in the next future.

ACKNOWLEDGEMENTS

We would like to thank all patients and healthy volunteers for their participation in the study. We are grateful to Sarah Zandvliet for her contribution to the recruitment and data collection, and to Mique Saes for her contribution to the data collection.

FUNDING

This study was supported by the European Research Council (grant no. 291339, 4D-EEG project) and the Netherlands Organisation for Health Research and Development (ZonMw, grant no. 104003008, PROFITS project) and an unrestricted grant from IPSEN.

REFERENCES

1. Winters C, van Wegen EE, Daffertshofer A, Kwakkel G. Generalizability of the Proportional Recovery Model for the Upper Extremity After an Ischemic Stroke. *Neurorehabil Neural Repair.* 2015;29(7):614-622.
2. Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabil Neural Repair.* 2008;22(1):64-71.
3. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet.* 2011;377(9778):1693-1702.
4. Smania N, Paolucci S, Tinazzi M, et al. Active finger extension: a simple movement predicting recovery of arm function in patients with acute stroke. *Stroke.* 2007;38(3):1088-1090.
5. Nijland R, van Wegen E, Verbunt J, van Wijk R, van Kordelaar J, Kwakkel G. A comparison of two validated tests for upper limb function after stroke: The Wolf Motor Function Test and the Action Research Arm Test. *J Rehabil Med.* 2010;42(7):694-696.
6. Sommerfeld DK, Gripenstedt U, Welmer AK. Spasticity after stroke: an overview of prevalence, test instruments, and treatments. *Am J Phys Med Rehabil.* 2012;91(9):814-820.

7. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Early prediction of long-term upper limb spasticity after stroke: part of the SALGOT study. *Neurology.* 2015;85(10):873-880.
8. Pandyan AD, Cameron M, Powell J, Stott DJ, Granat MH. Contractures in the post-stroke wrist: a pilot study of its time course of development and its association with upper limb recovery. *Clin Rehabil.* 2003;17(1):88-95.
9. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil.* 1989;70(2):144-155.
10. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol.* 2007;6(8):725-733.
11. Van den Noort JC, Bar-On L, Aertbelien E, et al. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. *Eur J Neurol.* 2017;24(7):981-989.
12. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koelle WP, eds. *Spasticity: disordered motor control.* Chicago: Year Book Medical Publishers; 1980:485-94.
13. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry.* 2005;76(1):47-54.
14. Lieber RL, Roberts TJ, Blemker SS, Lee SSM, Herzog W. Skeletal muscle mechanics, energetics and plasticity. *J Neuroeng Rehabil.* 2017;14(1):108.
15. De Gooijer-van de Groep KL, de Groot JH, van der Krogt H, de Vlugt E, Arendzen JH, Meskers CGM. Early Shortening of Wrist Flexor Muscles Coincides With Poor Recovery After Stroke. *Neurorehabil Neural Repair.* 2018;32(6-7):645-654.
16. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci.* 2004;22(3-5):281-299.
17. Winters C, Kwakkel G, van Wegen EEH, Nijland RHM, Veerbeek JM, Meskers CGM. Moving stroke rehabilitation forward: The need to change research. *NeuroRehabilitation.* 2018;43(1):19-30.
18. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. *Restor Neurol Neurosci.* 2013;31(6):707-722.
19. Rosales RL, Balcaitiene J, Berard H, et al. Early AbobotulinumtoxinA (Dysport) in Post-Stroke Adult Upper Limb Spasticity: ONTIME Pilot Study. *Toxins.* 2018;10(7):253.
20. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of Botulinum Toxin Treatment for Upper Limb Spasticity Poststroke Over Different ICF Domains: A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil.* 2019;100(9):1703-1725.

21. Cousins E, Ward A, Roffe C, Rimington L, Pandyan A. Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size. *Clin Rehabil.* 2010;24(6):501-513.
22. Lindberg PG, Gaverth 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(7):617-625.
23. Andringa A, van Wegen E, van de Port I, Kwakkel G, Meskers C. Measurement properties of the NeuroFlexor device for quantifying neural and non-neural components of wrist hyper-resistance in chronic stroke. *Front Neurol.* 2019;10:730.
24. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med.* 2013;45(7):630-636.
25. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc.* 1992;40(9):922-935.
26. Kwakkel G, Lannin NA, Borschmann K, et al. Standardized Measurement of Sensorimotor Recovery in Stroke Trials: Consensus-Based Core Recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Neurorehabil Neural Repair.* 2017;31(9):784-792.
27. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med.* 1975;7(1):13-31.
28. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther.* 1983;63(10):1606-1610.
29. Sullivan KJ, Tilson JK, Cen SY, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke.* 2011;42(2):427-432.
30. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67(2):206-207.
31. Portney LG, Watkins MP. *Foundations of clinical research: applications to practice.* 2nd ed. New Jersey: Prentice Hall; 2000.
32. Cortes JC, Goldsmith J, Harran MD, et al. A Short and Distinct Time Window for Recovery of Arm Motor Control Early After Stroke Revealed With a Global Measure of Trajectory Kinematics. *Neurorehabil Neural Repair.* 2017;31(6):552-560.
33. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol.* 2015;78(6):848-859.
34. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke.* 2006;37(9):2348-2353.

35. Hoonhorst MH, Nijland RH, van den Berg JS, Emmelot CH, Kollen BJ, Kwakkel G. How Do Fugl-Meyer Arm Motor Scores Relate to Dexterity According to the Action Research Arm Test at 6 Months Poststroke? *Arch Phys Med Rehabil.* 2015;96(10):1845-1849.
36. Choudhury S, Shobhana A, Singh R, et al. The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. *Neurorehabil Neural Repair.* 2019;33(5):375-383.
37. Brown P. Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry.* 1994;57(7):773-777.
38. Soteropoulos DS, Williams ER, Baker SN. Cells in the monkey ponto-medullary reticular formation modulate their activity with slow finger movements. *J Physiol.* 2012;590(16):4011-4027.
39. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain.* 2012;135(Pt 7):2277-2289.
40. McPherson JG, Chen A, Ellis MD, Yao J, Heckman CJ, Dewald JPA. Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke. *J Physiol.* 2018;596(7):1211-1225.
41. Winters C, Kwakkel G, Nijland R, van Wegen E, consortium EX-s. When Does Return of Voluntary Finger Extension Occur Post-Stroke? A Prospective Cohort Study. *PLoS One.* 2016; 11(8):e0160528.
42. Hoonhorst MHJ, Nijland RHM, van den Berg PJS, Emmelot CH, Kollen BJ, Kwakkel G. Does Transcranial Magnetic Stimulation Have an Added Value to Clinical Assessment in Predicting Upper-Limb Function Very Early After Severe Stroke? *Neurorehabil Neural Repair.* 2018; 32(8):682-690.
43. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain.* 2007;130(Pt 1):170-180.
44. Feng W, Wang J, Chhatbar PY, et al. Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. *Ann Neurol.* 2015;78(6):860-870.
45. Kwakkel G, van Wegen EEH, Burridge JH, et al. Standardized Measurement of Quality of Upper Limb Movement After Stroke: Consensus-Based Core Recommendations From the Second Stroke Recovery and Rehabilitation Roundtable. *Neurorehabil Neural Repair.* 2019;33(11):951-958.
46. Diong J, Gandevia SC, Nguyen D, et al. Small amounts of involuntary muscle activity reduce passive joint range of motion. *J Appl Physiol (1985).* 2019;127(1):229-234.

47. De Vlugt E, de Groot JH, Schenkeveld KE, Arendzen JH, van der Helm FC, Meskers CG. The relation between neuromechanical parameters and Ashworth score in stroke patients. *J Neuroeng Rehabil.* 2010;7:35.
48. Proske U, Morgan DL. Do cross-bridges contribute to the tension during stretch of passive muscle? *J Muscle Res Cell Motil.* 1999;20(5-6):433-442.
49. Lakie M, Campbell KS. Muscle thixotropy-where are we now? *J Appl Physiol (1985).* 2019;126(6): 1790-1799.
50. Herbert RD, Gandevia SC. The passive mechanical properties of muscle. *J Appl Physiol (1985).* 2019;126(5):1442-1444.
51. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech.* 2016;35:93-101.
52. Mirbagheri MM, Barbeau H, Kearney RE. Intrinsic and reflex contributions to human ankle stiffness: variation with activation level and position. *Exp Brain Res.* 2000;135(4):423-436.
53. Chung SG, van Rey E, Bai Z, Rymer WZ, Roth EJ, Zhang LQ. Separate quantification of reflex and nonreflex components of spastic hypertonia in chronic hemiparesis. *Arch Phys Med Rehabil.* 2008;89(4):700-710.
54. Bar-On L, Desloovere K, Molenaers G, Harlaar J, Kindt T, Aertbelien E. Identification of the neural component of torque during manually-applied spasticity assessments in children with cerebral palsy. *Gait Posture.* 2014;40(3):346-351.
55. Lorentzen J, Grey MJ, Crone C, Mazevet D, Biering-Sorensen F, Nielsen JB. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. *Clin Neurophysiol.* 2010;121(11):1939-1951.
56. Levin MF, Feldman AG. The role of stretch reflex threshold regulation in normal and impaired motor control. *Brain Res.* 1994;657(1-2):23-30.
57. Malhotra S, Pandyan AD, Rosewilliam S, Roffe C, Hermens H. Spasticity and contractures at the wrist after stroke: time course of development and their association with functional recovery of the upper limb. *Clin Rehabil.* 2011;25(2):184-191.
58. Valls-Sole J, Sole A, Valldeoriola F, Munoz E, Gonzalez LE, Tolosa ES. Reaction time and acoustic startle in normal human subjects. *Neurosci Lett.* 1995;195(2):97-100.
59. Pandyan AD, Van Wijck FM, Stark S, Vuadens P, Johnson GR, Barnes MP. The construct validity of a spasticity measurement device for clinical practice: an alternative to the Ashworth scales. *Disabil Rehabil.* 2006;28(9):579-585.

SUPPLEMENTARY MATERIAL

Supplement 3A. Biomechanical model of the NeuroFlexor

In the biomechanical model of the NeuroFlexor, previously described by Lindberg et al.,[1] the total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r) and inertial forces of the limb and the moving parts of the device (F_{in}), described as:

$$F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta), \quad (1)$$

where θ denotes a specific angle.

In the model, four force points in the resistance trace of the slow and fast displacements are used to estimate the different components of the total measured passive force. P0 is the resting torque of the hand before onset of stretch. Two force points are defined within the fast passive wrist extension movement (236°/second): P1, the initial peak in resistance, and P2, the late peak in resistance (Figure S5.1A). One force point (P3) is defined at the end position of the slow wrist extension movement (5°/second) (Figure S5.1B). Resting torque (P0) is subtracted from P1, P2 and P3 prior to further calculations. Two slow and two fast movements without the hand and forearm fastened to the device are run as a reference for the mechanical resistance by the hand platform on the force sensor.

The **inertia component (IC)** corresponds to the force resisting the acceleration of the hand and is calculated in the model as:

$$\mathrm{IC} = m \times \alpha, \quad (2)$$

where *m* is the mass of the hand and the movable platform, and a is the angular acceleration (21 m/s^2). The mass of the hand is estimated to be 0.6% of the total body weight.

The **elastic component (EC)** is a length-dependent resisting force which increases when the muscles are stretched, with an exponential increase when the muscle is stretched close to its end range. The EC is recorded 1 second after the end of the slow movement. The EC corresponds to P3, i.e. the fully stretched position during the slow movement (Figure S5.1B).

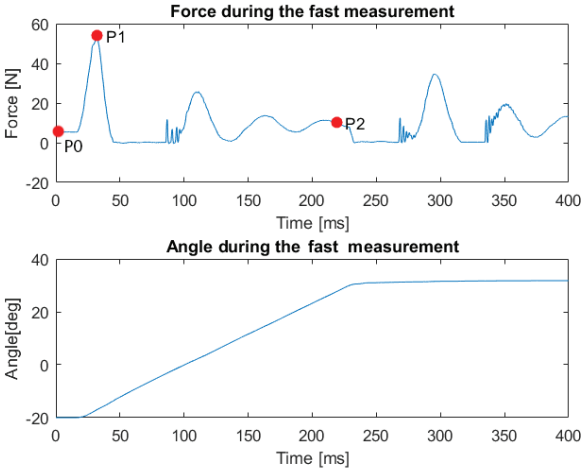


Figure S5.1A. Measured force and wrist angle during fast movement of the NeuroFlexor.

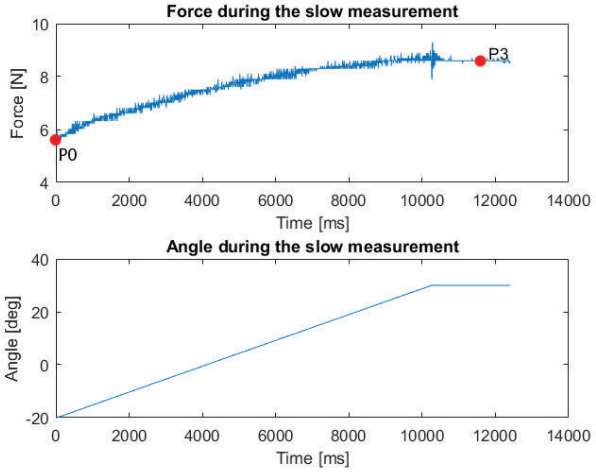


Figure S5.1B. Measured force and wrist angle during slow movement of the NeuroFlexor.

The **viscous component (VC)** is produced by the sliding muscle fibres, and is velocity-dependent. Lindberg et al.[1] assumed that the viscous resistance is highest during the initial acceleration and continues at a lower level during further extension movement. To calculate the viscous component, first, the early viscosity component (VC_{P1}) is calculated.

$$VC_{P1} = Total\ force_{P1} - \mathrm{IC}\,, \tag{3}$$

where Total force$_{P1}$ is the measured force at P1 (Figure S5.1A), and IC the inertial component calculated as above. Since there is a comparatively stable relationship between the early and late viscosity, Lindberg et al.[1] assumed that the late viscosity is approximately 20% of the early viscosity.

$$\mathrm{VC} = VC_{P1} \times 0.2\,. \tag{4}$$

Finally, P2 is defined as the late force peak during the fast wrist extension movement (Figure S5.1A) and consists of the neural, viscous and elastic component together. The velocity-dependent part of the **neural component (NC)** is estimated by:

$$\mathrm{NC} = Total\ force_{P2} - (\mathrm{EC} + \mathrm{VC})\,. \tag{5}$$

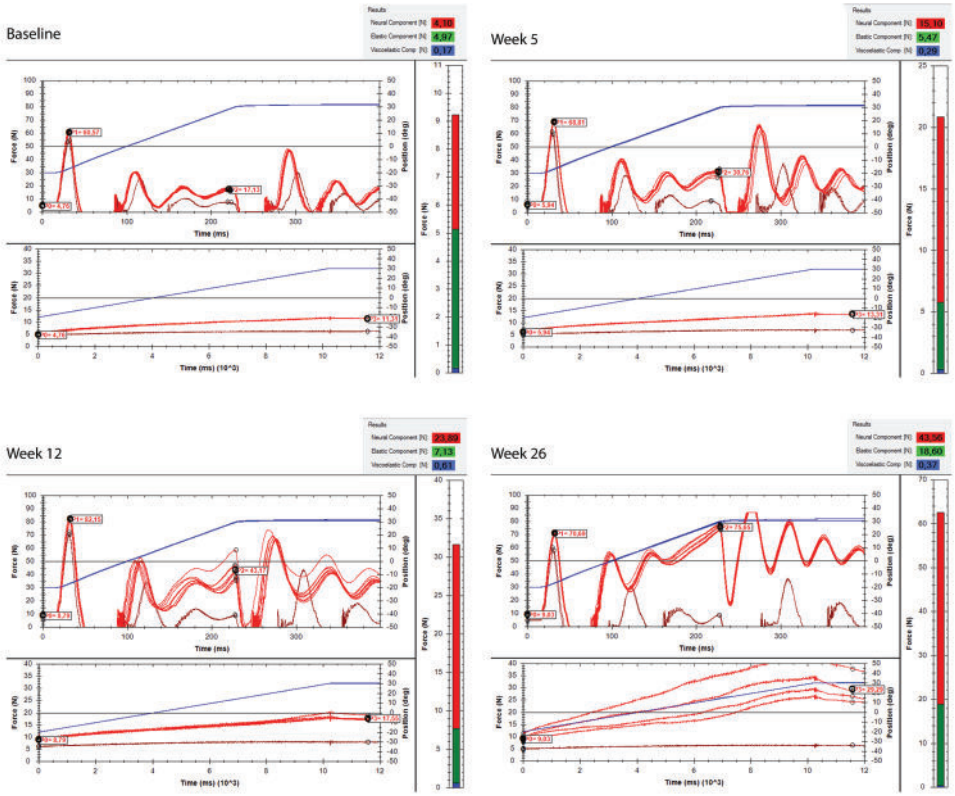


Figure S5.2A. Raw NeuroFlexor data over time of a patient showing no voluntary finger extension at baseline (patient 7).
Red lines represent resistance traces of nine fast and four slow movements; blue lines represent wrist angle during the movements.

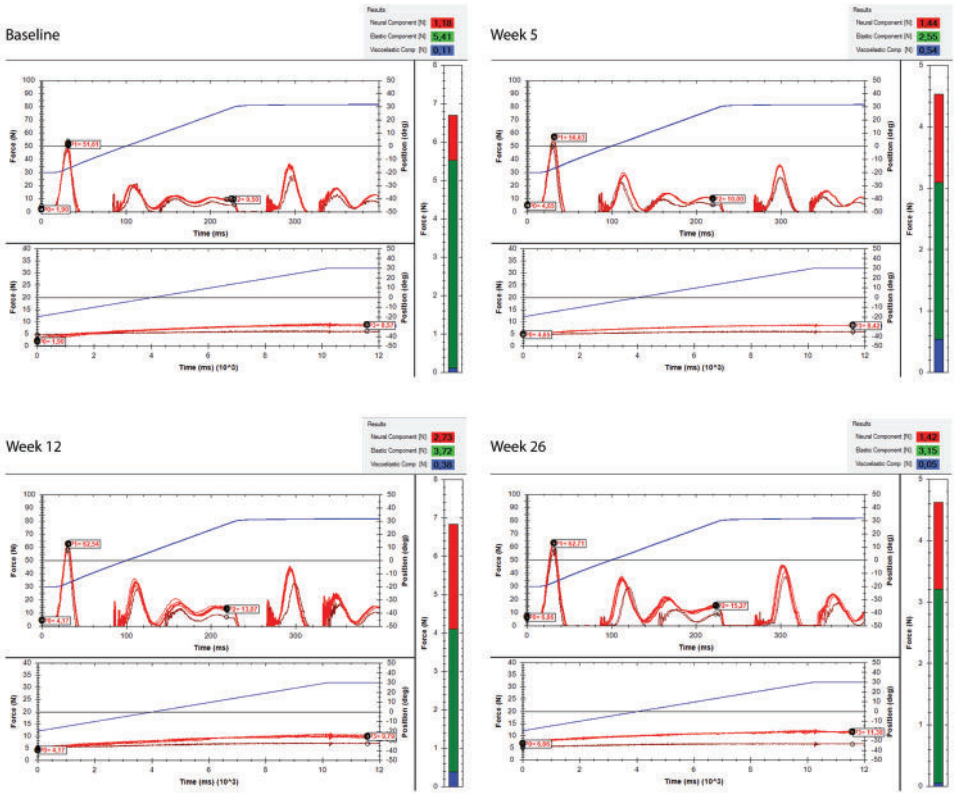


Figure S5.2B. Raw NeuroFlexor data over time of a patient showing voluntary finger extension at baseline (patient 4).
Red lines represent resistance traces of nine fast and four slow movements; blue lines represent wrist angle during the movements.

REFERENCES SUPPLEMENTARY MATERIAL

1. Lindberg PG, Gaverth 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(7):617-625.

Supplement 5B

Table S5.1. Individual data of wrist hyper-resistance components over time

		NC				EC				VC				FM-UE				MAS			
	VFE	b	w5	w12	w26	b	w5	w12	w26	b	w5	w12	w26	b	w5	w12	w26	b	w5	w12	w26
1	0	1.32		0.64	1.39	1.98		4.46	3.97	0.18		0.44	0.24	6		13	33	0		0	0
2	1	2.32	6.46	3.49	10.01	4.07	3.26	4.36	5.85	0.15	0.38	0.27	0.19	43	49	54	56	0	0	0	2
3	1	14.86	18.38	25.81	18.86	5.45	5.55	7.98	4.66	0.31	0.78	0.85	-0.12	40	56	63	62	1+	1	1	1
4	1	1.57	1.57	2.91	1.69	4.36	2.54	3.78	2.71	-0.12	0.56	0.28	0.28	50	55	60	59	0	0	0	0
5	1	4.78	3.10	1.73	1.63	4.00	4.26	5.32	2.89	0.15	0.23	0.20	-0.10	42	51	63	62	0	0	0	0
6	1	0.31	1.67			7.48	6.28			-0.07	0.10			18	34			0	1		
7	0	4.00	13.38	23.20	43.98	5.28	6.05	6.19	17.25	0.05	0.22	0.54	0.37	6	14	14	16	1+	1+	1+	3
8	0	11.17	31.55			3.25	4.94			0.22	0.24			7	13	13	13	2	2	3	3
9	0	24.35	28.03			3.90	3.59			0.30	0.18			34	41			1	1		
10	1	0.33	1.73	4.95	2.05	2.34	1.97	1.73	1.90	0.22	0.13	0.11	0.22	52	60	60	62	0	0	0	0
11	1	2.54	8.08	6.14	6.69	3.93	4.05	4.18	3.89	0.35	0.38	0.26	0.34	9	18	23	48	1	1	1	1
12	1	1.42	8.73	7.86	7.92	3.54	3.79	4.14	3.02	-0.05	0.27	0.35	0.16	33	60	64	63	0	0	1+	1+
13	0	0.42	3.04	10.72	11.76	4.72	3.95	6.48	8.65	0.46	0.59	1.06	1.00	8	10	17	20	0	0	1	1
14	1	1.95	1.84	-1.17	-0.83	1.19	1.84	2.34	2.56	-0.38	0.02	0.34	0.15	58	57	61	64	0	0	0	0
15	0	0.72	4.19	2.68	12.67	3.48	2.34	3.22	6.13	0.20	0.27	0.45	0.55	7	7	12	18	0	1	1+	1+
16	0	1.79	5.38			3.64	5.00			0.30	0.61			13	32			1	1+		
17	0	7.21	10.72	20.35	29.70	4.83	5.18	6.08	4.05	1.29	1.04	0.90	1.36	21	27	37	42	1	1+	1+	1+

Abbreviations: EC, elastic component (N); FM-UE, Fugl-Meyer upper extremity scale; MAS, modified Ashworth score wrist and finger flexor muscles; NC, velocity-dependent part of the neural component (N); VC, viscous component (N); VFE, voluntary finger extension (1, VFE at baseline; 0, no VFE at baseline).

Supplement 5C

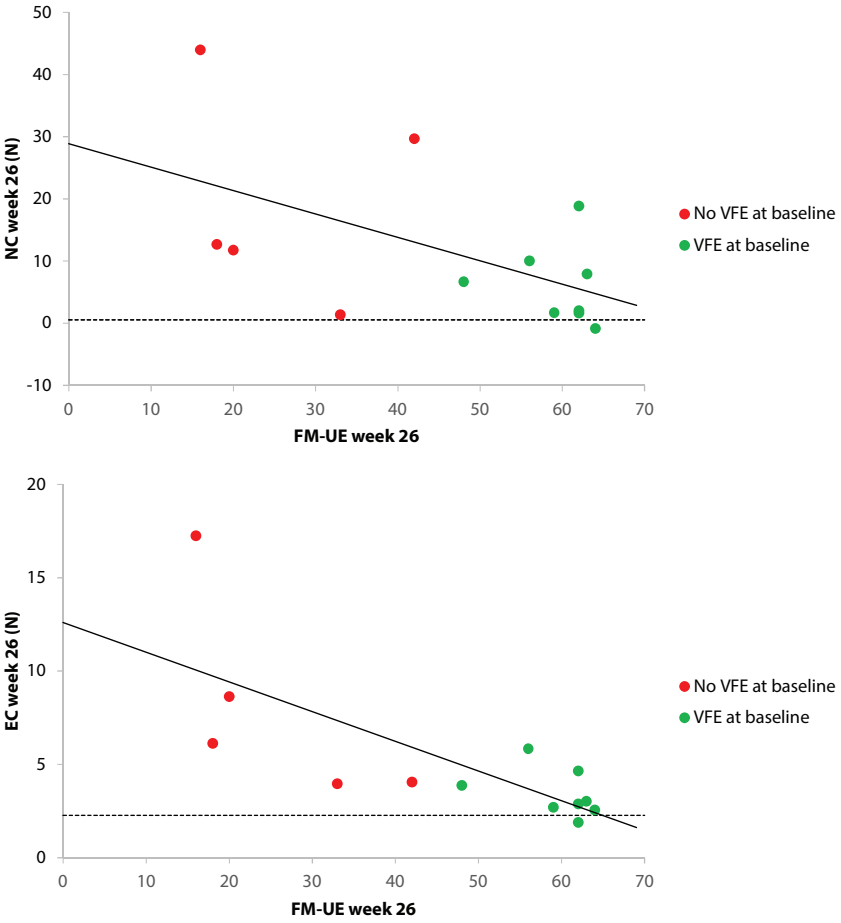


Figure S5.3. Association between the Fugl-Meyer motor upper extremity scale and components of wrist hyper-resistance at 26 weeks post stroke.
Dotted line: healthy reference value. Abbreviations: EC: elastic component; FM-UE, Fugl-Meyer upper extremity scale; NC, velocity-dependent part of the neural component.

Supplement 5D

Table S5.2. Pearson correlation coefficients for neural and non-neural elastic and viscous components of wrist hyper-resistance in the first 6 months post stroke

	NCb	NC5	NC12	NC26	ECb	EC5	EC12	EC26	VCb	VC5	VC12	VC26
NCb	1	**0.85 .000**	0.73 .005				0.72 .006					
NC5	-	1	**0.88 .000**	0.72 .009			0.73 .007					
NC12	-	-	1	**0.85 .000**	**0.76 .003**	**0.87 .000**	**0.78 .002**			0.61 .034	0.67 .012	
NC26	-	-	-	1	0.68 .011	**0.79 .002**	0.60 .029	**0.80 .001**				
ECb	-	-	-	-	1	**0.77 .000**	**0.81 .001**					
EC5	-	-	-	-	-	1	**0.89 .000**					
EC12	-	-	-	-	-	-	1			0.68 .016	**0.76 .003**	
EC26	-	-	-	-	-	-	-	1				
VCb	-	-	-	-	-	-	-	-	1	0.74 .001	0.59 .035	**0.75 .004**
VC5	-	-	-	-	-	-	-	-	-	1	0.72 .008	
VC12	-	-	-	-	-	-	-	-	-	-	1	0.63 .022
VC26	-	-	-	-	-	-	-	-	-	-	-	1

Values are Pearson correlation coefficients with *P*-values. Only significant correlation coefficients are shown. In bold good to excellent associations ($r > 0.75$). Abbreviations: EC, elastic component; NC, velocity-dependent part of the neural component VC, viscous component.

Supplement 5E

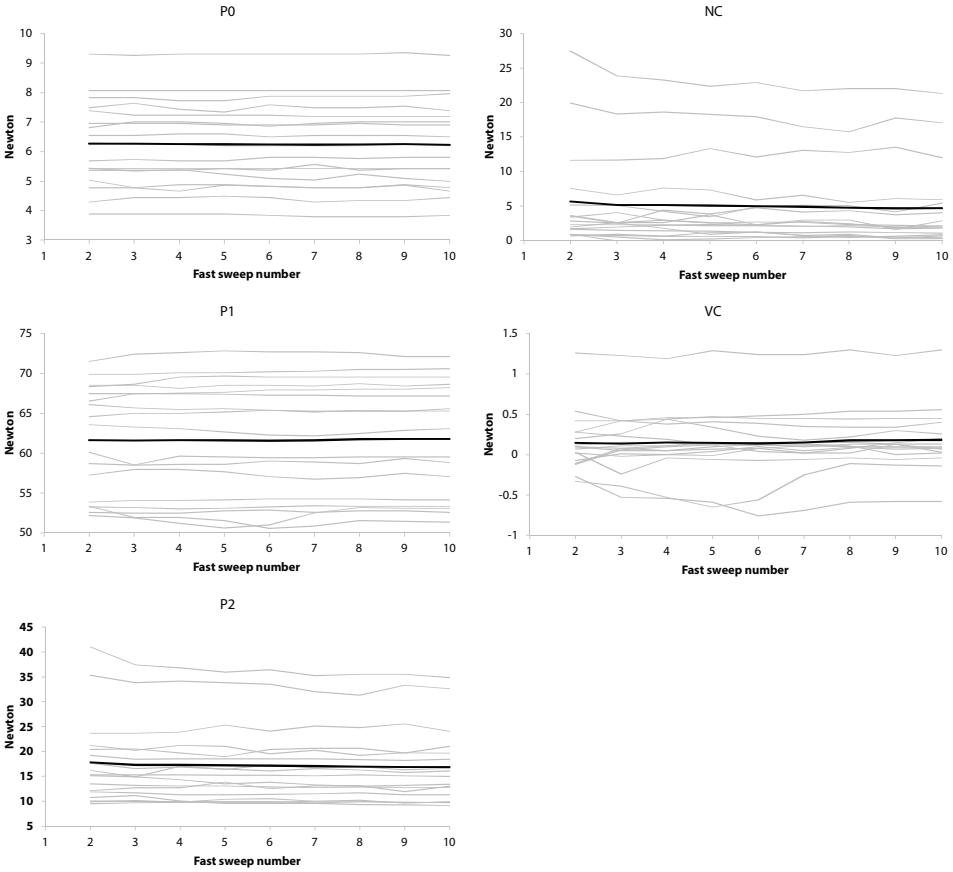


Figure S5.4. Individual and mean results of nine repetitive fast movements of one NeuroFlexor measurement session at baseline for resting torque (P0), initial resistance peak (P1), late resistance peak (P2), velocity-dependent part of the neural component (NC) and viscous component (VC).
Each grey line represents one subject and the black line represents the mean value. Note that the elastic component is not affected by the resistance force of the fast movements.

CHAPTER 6

The effect of botulinum toxin-A on neural and non-neural components of wrist hyper-resistance in adults with stroke or cerebral palsy

Aukje S. Andringa
Erwin E.H. van Wegen
Ingrid G.L. van de Port
Lisette Guit
Wojtek P. Polomski
Gert Kwakkel
Carel G.M. Meskers

PM R. 2021

ABSTRACT

Background: Botulinum toxin-A (BoNT) is widely used to manage focal upper limb spasticity and is effective in reducing resistance to passive movement, as measured with the modified Ashworth scale. Discrimination and quantification of the underlying neural and non-neural components of hyper-resistance may further improve understanding of the effect of BoNT.

Objective: To explore the effects of BoNT on neural (NC), non-neural elastic (EC) and viscous (VC) components of resistance to passive wrist extension in adults with stroke or cerebral palsy and the association between the effects on wrist hyper-resistance components and clinical spasticity, pain and motor function scales.

Design: Pre-experimental study with pre- and post-intervention measurements at 6 and 12 weeks.

Setting: An outpatient clinic of a hospital.

Participants: Adults with chronic stroke or cerebral palsy indicated for BoNT treatment for hyper-resistance in the wrist (n = 18).

Interventions: BoNT injections in the wrist and/or finger flexor muscles.

Main outcome measures: Wrist hyper-resistance components, using the NeuroFlexor, and clinical scales (modified Ashworth scale, Tardieu scale, passive wrist extension, pain, Fugl-Meyer motor assessment of the upper extremity and action research arm test).

Results: NC was significantly reduced 6 and 12 weeks post-intervention (median -11.96 Newton, $P < 0.001$ and median -9.34 Newton, $P = 0.001$, respectively); non-neural EC and VC showed no change. NC reduction 6 weeks post-intervention correlated significantly with BoNT dose (Pearson correlation coefficient $r_p = -0.56$). No significant correlations were found between change scores in wrist hyper-resistance components and clinical scales.

Conclusions: BoNT affected the neural component of resistance to passive wrist extension, while leaving the non-neural elastic and viscous components unaffected. This instrumented approach to quantify the effects of BoNT in the wrist and finger flexor muscles on the components of wrist hyper-resistance may have an added value for BoNT treatment evaluation in clinical practice.

INTRODUCTION

Botulinum toxin-A (BoNT) therapy is the treatment of choice for focal upper limb spasticity. BoNT causes a temporary reduction of muscle activity by blocking the release of acetylcholine at the neuromuscular junction.[1] A recent systematic review[2] has shown robust evidence for the effectiveness of BoNT treatment for upper limb spasticity after stroke in reducing resistance to passive movement at the International Classification of Functioning, Disability and Health (ICF) level[3] of body functions, measured with the modified Ashworth scale (MAS), and improving self-care ability of the affected limb at the ICF activities level. A favourable effect of BoNT treatment on other body functions is suggested in reducing spasticity-related pain and involuntary movements, and improving passive range of motion, whereas no effects were found regarding improvement of arm and hand use, at both body functions and activities levels. The underlying mechanisms and evidence for the generalizability of effectiveness of BoNT in the upper limb need further underpinning.[4-6]

Since the 1990s,[7] many studies question the validity of the MAS as an adequate measure for the evaluation of spasticity and more specifically BoNT treatment on an individual level.[2] The ordinal scaled MAS provides only a subjective estimate of the total perceived resistance to passive movement whereas increased resistance, that is hyper-resistance, is hypothesized to be caused by a complex interaction between pathological neuromuscular activation, including spasticity[8] and involuntary baseline activation,[9] and altered viscoelastic tissue properties of the muscles spanning the joint.[10,11] Moreover, the contribution of aforementioned neural and non-neural tissue components might vary between individual patients with upper limb hyper-resistance[12] and may change over time.[13-15] BoNT treatment is expected to primarily affect the neural component. This latter assumption suggests that the cost-effectiveness of this expensive BoNT treatment may be improved by a better selection of patients, dependent on which component dominates. Aforementioned problems in BoNT treatment indication and evaluation may be overcome by using instrumented measurement techniques that can discriminate between neural and non-neural components of hyper-resistance and that are clinically applicable.

The commercially available NeuroFlexor (Aggero MedTech AB, Älta, Sweden) is developed to quantify neural (NC), non-neural elastic (EC) and viscous (VC) components of hyper-resistance in the wrist and finger flexor muscles in clinical practice. This measurement technique was shown to be valid,[16,17] reliable[17,18] and responsive to change.[15] In a first study[19] it was shown that the NC, as measured with the NeuroFlexor, was responsive to monitor mean change after BoNT treatment in patients post stroke.

The aim of the present pre-experimental study was to explore: (1) the effects of BoNT treatment in the wrist and/or finger flexor muscles on the NC, EC and VC of resistance to passive wrist extension measured by the NeuroFlexor in adults with stroke or cerebral palsy (CP) and (2) the association between the effects on wrist hyper-resistance components and recommended clinical scales at the ICF level of body functions, that is MAS, Tardieu scale (TS), passive wrist extension, numeric rating scale for self-reporting of pain and Fugl-Meyer motor assessment of the upper extremity (FM-UE), and at the level of activities, that is action research arm test (ARAT).

METHODS

Patients

All patients scheduled for BoNT treatment between January 2018 and June 2019 at the outpatient rehabilitation department of a teaching hospital (Spaarne Gasthuis, Hoofddorp, The Netherlands) were screened for eligibility. Inclusion criteria were (1) patients greater than three months post stroke or with a diagnosis of CP, (2) clinically appropriate for botulinum toxin-A treatment in the wrist and/or finger flexor muscles by an experienced rehabilitation physician, (3) at least 18 years old and (4) able to understand test instructions. Exclusion criteria were (1) less than 0° passive wrist extension with extended fingers and (2) other medical disorders, such as osteoarthritis, influencing wrist hyper-resistance. The need for medical ethical certification was waived by the Medical Ethics Committee of the Vrije Universiteit medical centre, Amsterdam, The Netherlands (2017.440) as this study was performed within the context of usual care. In accordance with the Declaration of Helsinki, all participating patients gave written informed consent.

Study design and BoNT treatment

In this prospective clinical cohort study with longitudinal measurements, patients were examined on three occasions: pre-intervention (in the hour before BoNT treatment) and at 6 and 12 weeks post-intervention. All measurements were performed by a trained physiotherapist or occupational therapist, who was unaware of the BoNT treatment dose.

All patients received intramuscular onabotulinum toxin-A injections (Botox, Allergan, Irvine, CA, USA) with the exception of one patient who received incobotulinum toxin-A (Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany) in one or more wrist and/

or finger flexor muscles. All injections were performed under ultrasound guidance by the same physician (W.P.). Injected muscles, dosage and injection sides of the BoNT were individualized for each patient based on the patient's clinical presentation and treatment goals, the physician's clinical experience and on the national guideline for cerebral and/or spinal spasticity of the Federation of Medical Specialists. Results of the NeuroFlexor measurements were not presented to the physician during the study to avoid influence on the individual treatment plan. No additional therapy was prescribed outside usual care.

Outcome measures

Neural and non-neural components of wrist hyper-resistance

The NeuroFlexor, as shown in Figure 6.1, applies isokinetic positional perturbations to the wrist with extended fingers from 20° flexion toward 30° extension at two controlled velocities (5 and 236°/second). When passive wrist extension was less than 40°, the perturbation range was adjusted to a 50° range ending 10° before maximal extension. Total resistance during wrist extension was measured in Newton (N) using a force sensor mounted underneath the moveable hand platform. The patient was seated comfortably parallel to the NeuroFlexor with the shoulder in 45° abduction, 0° flexion, the elbow in 90° flexion and the forearm in pronation fixated to the device. The hand was Velcro-strapped onto the hand platform. The wrist joint was visually aligned to the rotation axis of the device. A measurement session consisted of five slow followed by ten fast movements. The first movement at both velocities was excluded from analysis to avoid bias from startle reflexes and mechanical hysteresis. A biomechanical, unidirectional wrist model[16] using a force-relationship method based on the mean resistance trace of the slow and the fast movements, was applied to calculate the components of wrist hyper-resistance, that is NC, EC and VC, directly after each measurement (software program NeuroFlexor Scientific v0.06, Supplement 6A). Resting force (RF) is the force of the hand on the hand platform before onset of stretch, with wrist angle equals 20° flexion, as depicted as P0 in Figure 6.1 B, C.

Clinical assessments

Total resistance to passive wrist extension was measured for wrist and finger flexor muscles using the MAS,[20] an ordinal scale with scores ranging from 0, no increased tone, to 4, total joint rigidity. Wrist movement with flexed fingers was regarded representative of resistance mostly caused by the wrist flexor muscles, wrist movement with extended fingers as representative of resistance mostly caused by the finger flexor muscles. The TS[21] was used to

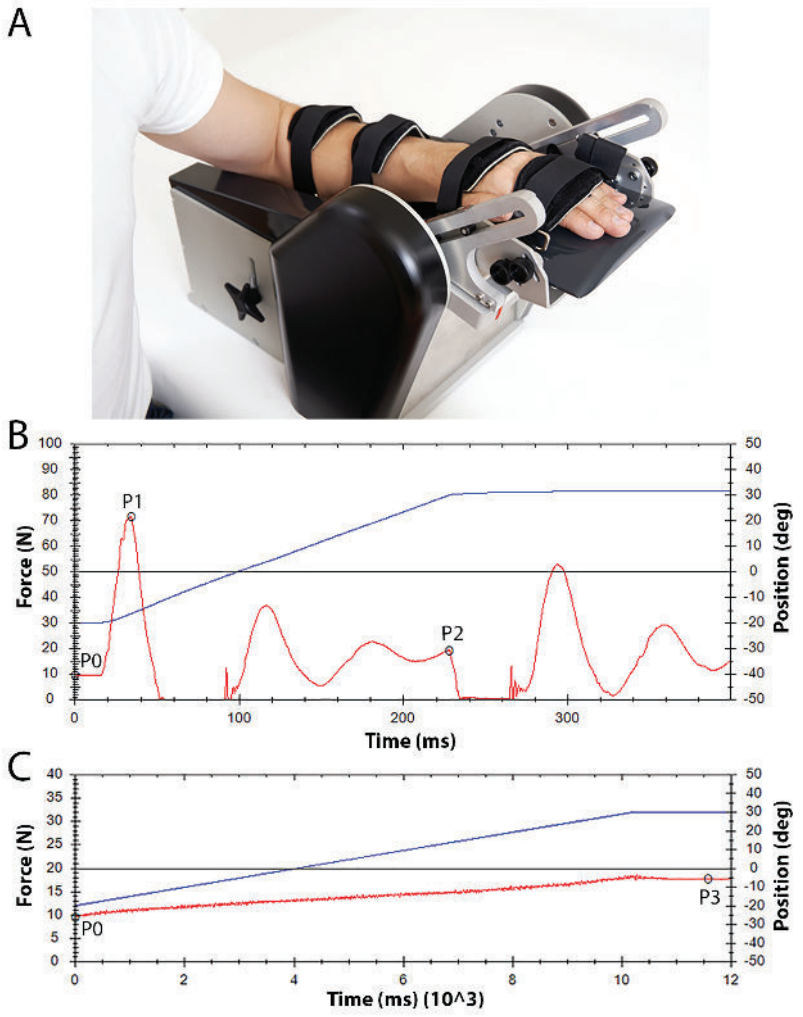


Figure 6.1. NeuroFlexor method.
(A) Measurement set-up. (B-C) An example of the force traces (red line) from a patient (NC: 13.91 N, EC: 6.03 N, RF: 6.64 N, MAS: 1+) obtained during (B) a fast passive wrist extension movement (236°/second) and (C) a slow passive wrist extension movement (5°/second). The blue line represents the angle of the wrist joint. The recorded force traces, measured in Newton (N), are analysed by a biomechanical model, which results in the quantification of the neural component (NC), elastic component (EC) and viscous component (VC) of wrist hyper-resistance. The total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r), and inertial forces of the limb and the moving parts of the device (F_{in}), described as: $F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta)$, where θ denotes a specific angle. In the model, four force magnitudes, identified in the force-time-traces of the slow and fast movements, are used to estimate the different components of the total measured passive force. P0 is the resting force (RF) of the hand before onset of stretch, with wrist angle equals 20° flexion. Two force magnitudes are defined within the fast passive wrist extension movement (236°/second): P1, the initial force peak, and P2, the late force peak (at the end of the movement). One force magnitude (P3) is defined at the end position of the slow wrist extension movement (5°/second). Resting force (P0) is subtracted from P1, P2 and P3 prior to further calculations. Detailed information about the biomechanical model can be found in Supplement 6A. Abbreviations: MAS, modified Ashworth scale; RF, resting force.

assess passive wrist extension at one slow velocity (R2, "as slow as possible"), joint angle of muscle reaction at one fast velocity stretch (R1, "as fast as possible"), and quality of muscle response at fast speed. Passive wrist extension angle at fast velocity (R1) subtracted from passive wrist extension at slow velocity (R2) represents the velocity-dependent resistance element (TS_{R2-R1}). Quality of the muscle response at fast speed (TS_Q) is described on an ordinal five-point scale, where 0 means no resistance to passive movement and 4 means a clonus that does not cease within 10 seconds. Passive wrist extension with fingers flexed and extended was assessed using goniometry at a constant torque of 2 Nm applied at the hand palm controlled by a handheld dynamometer. Pain in the upper limb was assessed by a numeric rating scale (range 0–10). The FM-UE[22] was used to assess motor performance of the affected arm and hand with a scoring range from 0 to 66 points. The ARAT[23] was used to assess arm and hand capacity with a scoring range from 0 to 57 points. Both the FM-UE[24] and ARAT[23] are valid and reliable tests in stroke patients.

Statistical analysis

Study data were analysed using SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical characteristics. For all variables, normality was assessed by inspecting histograms and Q-Q plots. A Shapiro-Wilks test was carried out on all outcome variables on the three different time-points. The majority of data was non-normally distributed. Differences between the measurements over time for the wrist hyper-resistance components and the clinical scales were calculated using Friedman one-way repeated measures analysis. *Post-hoc* Wilcoxon signed-ranks tests with Bonferroni correction were used to identify where the statistical differences occurred between the three time-points. Correlation coefficients between change of wrist hyper-resistance components and the ratio scaled clinical scales, as well as the correlation coefficients with the injected BoNT dose were calculated using Pearson Product Moment correlation coefficients (r_p). Spearman's rank correlation coefficients (r_s) were calculated to assess the relationship between change of wrist hyper-resistance components and the change scores of the ordinal scaled clinical scales. Correlation coefficients below 0.20 were classified as very weak, between 0.20 and 0.39 as weak, between 0.40 and 0.59 as moderate, between 0.60 and 0.79 as strong and above 0.80 as very strong.[25] The level of significance was set at 0.05.

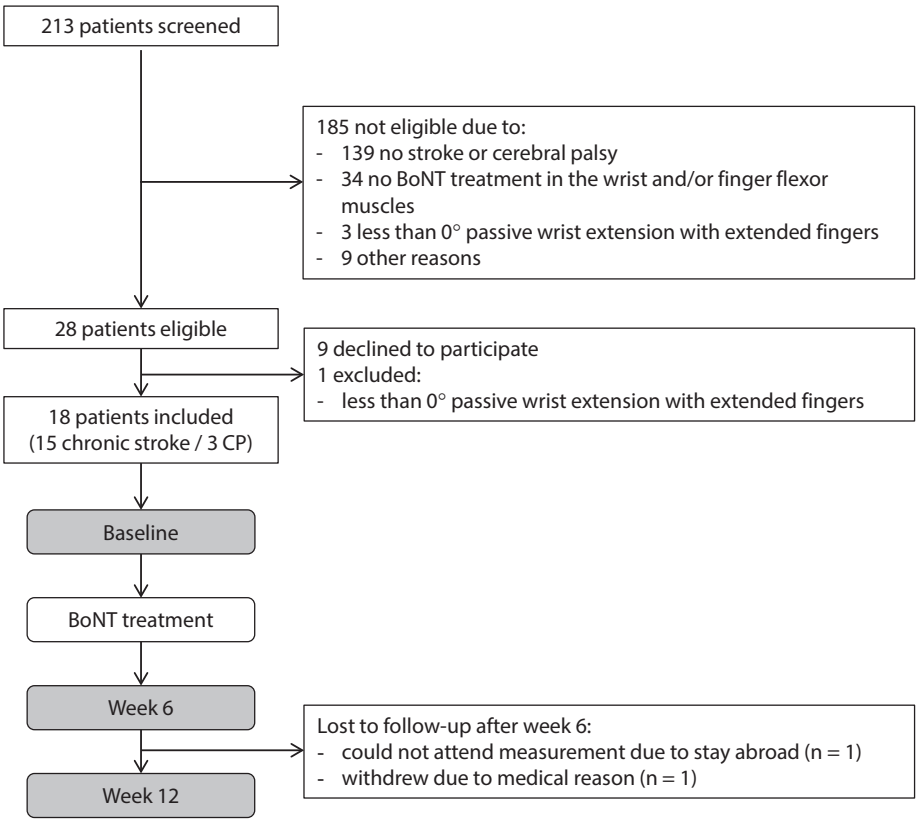


Figure 6.2. Flowchart.

RESULTS

A total of 213 patients scheduled for BoNT treatment were screened for eligibility, and 19 patients were included in the study. Of those 19 there were 16 patients with chronic stroke and three patients with CP (Figure 6.2). One patient with chronic stroke was excluded after the screening procedure as, in contrast to the primary clinical measure, passive wrist extension with fingers extended using goniometry at a constant torque of 2 Nm was less than 0°. Two patients were lost to follow-up after week 6. Table 6.1 presents an overview of the demographic and clinical characteristics of the study population pre-intervention. Patients received a mean total dose of 394 ± 176 units of BoNT (Botox or Xeomin), of which 288 ± 123 units in muscles affecting wrist and/or finger joints (Table 6.2 and Supplement 6B). Patients with chronic stroke received a higher dose of BoNT compared to patients with CP (total dose: 442 ± 151 vs 158 ± 52, and dose in muscles affecting wrist and/or finger joints:

Table 6.1. Demographic and clinical characteristics of the study population (n = 18)

Age, years	57.8 ± 13.3
Gender, male/female (n)	11/7
Diagnose, iCVA/hCVA/CP (n)	12/3/3
Time post stroke, years (n = 15)	7.2 ± 5.4
NIHSS score	4.6 ± 3.0
Affected side, left/right (n)	7/11
Previous BoNT treatments (n)	
0 treatments	2
1 to 5 treatments	1
6 to 10 treatments	8
More than 10 treatments	7
Wrist flexor muscles	
MAS	1.5 [1–2]
TS_Q	2 [1–2]
$TS_{R2\text{-}R1}$ (°)	50.7 ± 42.3
WE_{FF} (°)	57.7 ± 22.7
Finger flexor muscles	
MAS	1.5 [1–2]
TS_Q	2 [1–2]
$TS_{R2\text{-}R1}$ (°)	43.0 ± 42.5
WE_{FE} (°)	51.6 ± 23.1
FM-UE	14 [7–22]
ARAT	3 [0–6]

Values are mean ± SD or median [25th–75th percentile].
Abbreviations: ARAT, action research arm test [range 0–57]; BoNT, botulinum toxin-A; CP, cerebral palsy; FM-UE, Fugl-Meyer motor assessment of the upper extremity [range: 0–66]; hCVA, haemorrhagic stroke; iCVA, ischemic stroke; MAS, modified Ashworth scale [range 0–4], (score 1+ is reported as 1.5); NIHSS, National Institutes of Health Stroke Scale [range: 0–42]; TS_Q, Tardieu scale, quality score; $TS_{R2\text{-}R1}$, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1); WE_{FE}, passive wrist extension, fingers extended; WE_{FF}, passive wrist extension, fingers flexed.

323 ± 101 vs 108 ± 14 units). No serious adverse events related to the BoNT treatment were reported during the study. Post-intervention measurements were performed on average (± SD) 44 ± 5 days and 87 ± 7 days after treatment, respectively.

Table 6.3 shows the pre- and post-intervention scores for all outcome parameters. The individual and median scores for the NC, EC and VC of wrist hyper-resistance over time can be found in Figure 6.3 and Supplement 6B. Friedman one-way repeated measures analysis for the three time points showed a significant difference in NC (χ^2 [2] = 16.625, $P < 0.001$), EC (χ^2 [2] = 6.125, $P = 0.047$) and in RF (χ^2 [2] = 14.625, $P = 0.001$). *Post-hoc* analyses showed significant reductions of the NC and RF 6 weeks post-intervention (NC: Z = -3.549, $P < 0.001$; RF: Z = -3.419, $P = 0.001$), a significant increase of the NC between

Table 6.2. Botulinum toxin-A treatment

Muscle	Patients injected (n)	Dose, unit (median)
m. flexor digitorum superficialis	16	75
m. flexor digitorum profundus	16	75
m. flexor carpi radialis	10	75
m. flexor carpi ulnaris	8	50
m. lumbricalis	10	50
m. palmaris longus	6	25
m. flexor pollicis longus	9	50
m. flexor pollicis brevis	7	25
m. opponens pollicis	7	25
m. extensor carpi radialis	1	25
m. extensor carpi ulnaris	1	40
m. extensor digitorum	1	50
m. extensor pollicis brevis	1	25
m. abductor digiti minimi	1	25
m. pronator teres	8	50
m. pronator quadratus	1	25
m. brachialis	9	50
m. brachioradialis	3	50
m. biceps brachii	6	75
m. triceps brachii	2	37.5
m. pectoralis	3	100

Grey coloured injected muscles affect wrist hyper-resistance, as measured by the NeuroFlexor.

week 6 and week 12 (Z = -2.844, $P = 0.004$), and overall significant reductions of the NC and RF 12 weeks post-intervention (NC: Z = -3.206, $P = 0.001$; RF: Z = -2.896, $P = 0.004$). The median NC was 20.47 N pre-intervention, 8.51 N at 6 weeks post-intervention, and 11.13 N at 12 weeks post-intervention. The median RF was 8.84 N pre-intervention, 7.59 N at 6 weeks post-intervention, and 8.00 N at 12 weeks post-intervention. Wilcoxon signed-rank tests did not yield any significant difference of the EC between the time points. No significant change over time was found for the VC. Patients with CP showed a similar effect of BoNT as patients with stroke.

For the clinical scales, significant differences between repeated measurements were found for the MAS and TS_Q for the wrist flexor muscles (χ^2 [2] = 11.730, $P = 0.003$ and χ^2 [2] = 6.348, $P = 0.042$, respectively), passive wrist extension with extended fingers (χ^2 [2] = 6.419, $P = 0.040$), and FM-UE (χ^2 [2] = 10.360, $P = 0.006$). *Post-hoc* analysis with Bonferroni correction showed a significant increase in FM-UE score between week 6 and week 12 post-intervention (median + 2, Z = -2.680, $P = 0.007$).

Table 6.3. Pre- and post-intervention scores of neural and non-neural components of wrist hyper-resistance and clinical scales

	Pre-intervention week 0 (n = 18)	Post-intervention week 6 (n = 18)	Post-intervention week 12 (n = 16)	*P*-value
NeuroFlexor				
NC	20.47 [10.29–33.00]	8.51 [3.40–15.04] [a]	11.13 [6.21–21.68] [a b]	< 0.001
EC	6.84 [4.11–14.97]	4.95 [3.29–10.26]	7.74 [4.34–10.11]	0.047
VC	0.29 [0.10–0.53]	0.45 [0.02–0.68]	0.36 [-0.09–0.80]	0.646
RF	8.84 [7.59–10.81]	7.59 [5.07–8.53] [a]	8.00 [6.09–9.48] [a]	0.001
Wrist flexor muscles				
MAS	1.5 [1–2]	1 [0–1.5]	1.5 [1–2]	0.003
TS_Q	2 [1–2]	1 [0–2]	2 [1–2]	0.042
TS_{R2-R1}	54 [0–96]	0 [0–66]	4 [0–60]	0.099
WE_{FF}	61 [38–76]	79 [61–90]	67 [54–80]	0.129
Finger flexor muscles				
MAS	1.5 [1–2]	1 [0–1.5]	2 [1–2]	0.058
TS_Q	2 [1–2]	2 [0–2]	2 [1–2]	0.143
TS_{R2-R1}	42 [0–85]	10 [0–69]	50 [0–79]	0.544
WE_{FE}	52 [37–71]	68 [54–86]	60 [48–76]	0.040
Pain average	2 [0–5]	0 [0–4]	1 [0–5]	0.710
Pain worst	4 [0–7]	0 [0–5]	2 [0–7]	0.201
FM-UE	14 [7–22]	14 [7–21]	16 [8–23] [b]	0.006
ARAT	3 [0–6]	3 [2–15]	3 [1–9]	0.862

Values are median [25th–75th percentile].
Friedman's test P-value and post-hoc Wilcoxon signed ranks tests are reported.
[a] Indicates a significant difference compared to baseline ($P < 0.050/3$).
[b] Indicates a significant difference compared to week 6 ($P < 0.050/3$). Grey-filled boxes indicate significant values after Bonferroni correction.
Abbreviations: ARAT, action research arm test; EC, elastic component (N); FM-UE, Fugl-Meyer motor assessment of the upper extremity; MAS, modified Ashworth scale; NC, neural component (N); Pain, range 0–10; RF, resting force (P0); TS_Q, Tardieu scale, quality score; TS_{R2-R1}, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1) (°);VC, viscous component (N); WE_{FE}:, passive wrist extension, fingers extended (°); WE_{FF}, passive wrist extension, fingers flexed (°).

No significant correlation coefficients were found between the change scores within the first 6 weeks on the NC and EC of wrist hyper-resistance and the change scores on the clinical scales (Table 6.4). NC reduction within the first 6 weeks post-intervention showed a significant negative Pearson correlation coefficient to BoNT dose in the muscles affecting wrist and/or finger joints (r_p [17] = -0.56, $P = 0.016$) (Table 6.4 and Supplement 6C).

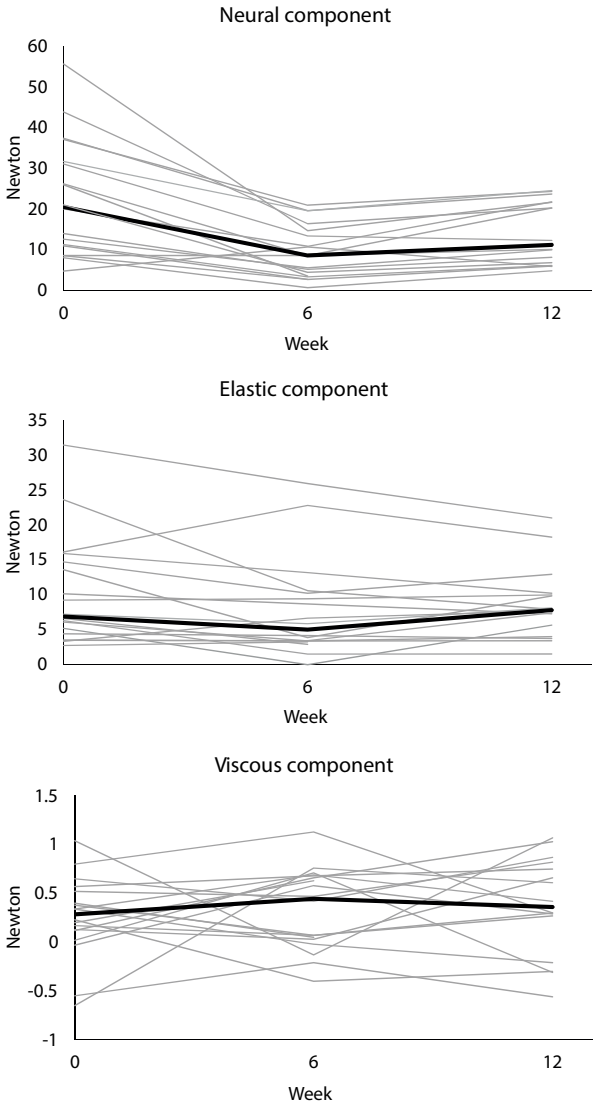


Figure 6.3. Neural and non-neural components of wrist hyper-resistance pre-intervention and at 6 and 12 weeks post-intervention. Bold line is median.

DISCUSSION

In this pre-experimental longitudinal study in a clinical cohort of adults with chronic stroke or CP with severe motor impairments,[26] we found that BoNT treatment in the wrist and/or finger flexor muscles significantly reduced the NC of resistance to passive wrist extension

Table 6.4. Correlation coefficients between changes scores within the first 6 weeks of the wrist hyper-resistance components and clinical scales, and botulinum toxin dose

		ΔNC		ΔEC		BoNT dose wrist/finger	
	Analysis	*r*	*P*	*r*	*P*	*r*	*P*
ΔNC	Pearson	1.00		0.11	0.662	-0.56	0.016
ΔEC	Pearson	0.11	0.662	1.00		-0.28	0.261
Wrist flexor muscles							
ΔMAS	Spearman	0.41	0.093	0.19	0.452	-0.10	0.696
ΔTS_{Q}	Spearman	0.04	0.986	-0.15	0.551	0.35	0.153
$\Delta TS_{R2\text{-}R1}$	Pearson	0.25	0.320	-0.22	0.386	0.38	0.120
ΔWE_{FF}	Pearson	-0.39	0.111	-0.11	0.675	0.10	0.698
Finger flexor muscles							
ΔMAS	Spearman	0.33	0.177	-0.02	0.924	-0.19	0.448
ΔTS_{Q}	Spearman	-0.08	0.754	-0.21	0.396	0.36	0.142
$\Delta TS_{R2\text{-}R1}$	Pearson	-0.21	0.395	-0.24	0.349	0.45	0.060
ΔWE_{FE}	Pearson	-0.29	0.238	-0.01	0.981	0.00	0.993
ΔPain average	Spearman	0.11	0.675	0.20	0.439	-0.35	0.161
ΔPain worst	Spearman	0.12	0.650	0.07	0.780	-0.30	0.220
ΔFM-UE	Spearman	-0.16	0.529	-0.01	0.967	0.42	0.082
ΔARAT	Spearman	0.07	0.799	0.15	0.555	0.05	0.844

Values are *r*: Pearson Product Moment or Spearman's rank correlation coefficients; *P*: probability estimate, Δ outcome at week 6 post-intervention minus outcome pre-intervention. Grey-filled boxes indicate significant values.

Abbreviations: ARAT, action research arm test; BoNT dose wrist/finger, total dose botulinum toxin-A injected in muscles affecting wrist and/or finger joints; EC, elastic component; FM-UE, Fugl-Meyer motor assessment of the upper extremity; MAS, modified Ashworth scale; NC, neural component; TS_{Q}, Tardieu scale, quality score; $TS_{R2\text{-}R1}$, Tardieu scale, passive wrist extension angle at slow velocity (R2) minus passive wrist extension angle at fast velocity (R1); WE_{FE}, passive wrist extension, fingers extended (°); WE_{FF}, passive wrist extension, fingers flexed (°).

6 and 12 weeks after treatment, while leaving the non-neural EC and VC unaffected. The reduction in NC within the first 6 weeks was moderately associated with the injected BoNT dose in the muscles affecting wrist and/or finger joints. Motor function of the upper paretic limb measured with FM-UE showed a significant increase between week 6 and 12 after BoNT treatment. Overall, no associations between the changes in NC and EC and the changes on clinical scales were found. No significant effects of BoNT were found in terms of upper limb capacity. These findings are in line with the previous systematic review[2] showing no association between the effects on the ICF level of body functions with the activities level by treatment of BoNT. Importantly, the present study suggests that in contrast to MAS and other clinical scales at body functions level, the NeuroFlexor quantifies the separate effects of BoNT in the wrist and finger flexor muscles on the NC of wrist hyper-resistance. This

instrumented measurement technique may have an added value in clinical practice for the precise evaluation of BoNT treatment in addition to recommended clinical scales.

Compared to a previous study by Gäverth et al.[19] investigating the sensitivity of the NeuroFlexor to changes induced by BoNT treatment, we found a greater reduction in NC within 6 weeks post-intervention, which may be owing to a higher dosage of BoNT (present study: mean dose 288 ± 123 units Botox or Xeomin; Gäverth: mean dose 111 ± 54 units Botox). Evidence of a dose-response effect in the present study provides a further underpinning of aforementioned difference in reported treatment effects at the group level.

In contrast to the study of Gäverth et al.,[19] we also investigated the resting force of the hand on the hand platform before onset of applied stretch with the NeuroFlexor and found significant reductions in this resting force at 6 and 12 weeks post-intervention. This resting force is assumed to be affected by gender and body length.[27] The resting force may also be influenced by the non-velocity dependent part of neural activation, that is involuntary background activation.[9] Our results suggest that BoNT treatment not only reduces the velocity-dependent NC of wrist hyper-resistance but may also decrease the non-velocity dependent involuntary background activation. Note that the NeuroFlexor does not use electromyography (EMG) measurements, which prevents direct assessment of muscle activation. Construct validity of the NC was previously suggested in three ways, that is by reduction of the NC after an ischemic nerve block, by showing a significant association with integrated EMG and by its velocity-dependency.[16] The NeuroFlexor method appeared to be construct valid with respect to the clinical modified Ashworth and Tardieu scales.[17]

The reduction of NC measured after 6 weeks, showing a clear dose-response relationship, was consistent with the non-significant reductions in the MAS and the Tardieu scale as well as with the increase of passive wrist extension within the first 6 weeks after treatment. Note that the NeuroFlexor may provide for quantitative effect determination of the NC in time beyond commonly used clinical scales. Clinical measures using ordinal scales, such as the MAS and Tardieu scales, may not capture small differences and with that probably underestimate associations in our small sample of participants. Moreover, the absence of significant associations between change scores of wrist hyper-resistance components and clinical scales suggests that the NeuroFlexor measures different constructs compared to currently used clinical scales. Measurements using the NeuroFlexor complement the clinical scales on the body functions level and offer quantitative outcome measures that associate with injected BoNT dose. Individual assessment of relative NC and EC contributions to wrist hyper-resistance may guide treatment/no treatment choices and a quantitative follow-up may allow for refining of BoNT

dosing. The level of NC appears to be predictive for the treatment effect, however, this requires confirmation in a larger population. NeuroFlexor-based measurements and comparable instrumented measurement techniques may allow for a better understanding of the effects of BoNT with respect to different domains of the ICF, that is the distinct effects on the level of body functions and the absence of effects on the activities level.[2] This is confirmed by results in the present study, although it should be noted that the present population of patients showed hardly any arm and hand function, resulting in floor effects of the ARAT measuring arm and hand capacity on the activities level. We found a small significant increase in FM-UE score between 6 and 12 weeks post-intervention. This increase, however, is below the smallest detectable difference of approximately 7 points on the FM-UE.[24,28] Whether BoNT affects voluntary movements in patients with a range of motor impairments was not addressed in this study.

Study limitations

We conducted a pre-experimental, non-blinded observational study in a small mixed population, presenting severe motor impairments, without a control group. Lack of blinding may affect the MAS and Tardieu scale scores, but is unlikely to affect the outcomes of wrist hyper-resistance components. Moreover, only two patients had first-ever BoNT treatment, whereas the other 16 patients received multiple previous BoNT injections. Despite the limitations, we were able identify changes of individual components of wrist hyper-resistance after BoNT treatment.

A possible drawback of the NeuroFlexor for the evaluation of BoNT treatment is that 40° passive wrist extension is needed to comply with the original measurement protocol using a fixed 50° wrist extension range, regardless of the patients' passive range of motion. Further research is needed into the applicability of this device, as well as the validity and reliability of the outcomes, in a population with restrictions of the passive range of wrist extension.

CONCLUSIONS

Using an instrumented approach quantifying the separate components of wrist hyper-resistance, BoNT treatment in the wrist and/or finger flexor muscles in adults with stroke or CP is suggested to provide a dose-dependent reduction of the NC of resistance to passive wrist extension, while leaving the non-neural EC and VC unaffected. Instrumented quantification of wrist hyper-resistance components may have an added value for BoNT treatment indication and evaluation in clinical practice.

More data are required to conclude on the predictive value of NeuroFlexor-based measurements for BoNT outcome. Identifying responders and non-responders of BoNT treatment based on the components of hyper-resistance, allows for the effects of BoNT on NC to be further investigated in a double-blinded, randomized, stratified, placebo-controlled trial with repeated measurements. Stratification at baseline should be based on the neural and non-neural components of wrist hyper-resistance. Frequent, serially applied repeated measurements at fixed time points within the first 6 weeks are needed to better understand the mechanisms underlying the longitudinal reductions in neural and non-neural components of wrist hyper-resistance caused by BoNT and to further address its precision and responsiveness to change in order to conclude on its potential for individual tuning of dose. In addition, further research is needed to examine the effect of BoNT on wrist hyper-resistance of different origins, for example, chronic stroke versus CP. Further work on the construct validity of the NeuroFlexor with respect to the underlying components of wrist hyper-resistance and its translation into velocity-dependent and non-velocity-dependent neural and non-neural components is also needed, for example, by comparing of the NeuroFlexor with methods that encompass EMG enabling direct measurements of muscle activity.

ACKNOWLEDGEMENTS

We would like to thank all patients for their participation in the study. We are grateful to Natasja Wouda and Wanda van Gaal for their contribution to the data collection.

FUNDING

This study was supported by the European Research Council (grant no. 291339, 4D-EEG project), the Netherlands Organisation for Health Research and Development (ZonMw grant no. 104003008, PROFITS program), a grant from the Spaarne Gasthuis Academy and an unrestricted grant from IPSEN.

REFERENCES

1. Wheeler A, Smith HS. Botulinum toxins: mechanisms of action, antinociception and clinical applications. *Toxicology*. 2013;306:124-146.

2. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of Botulinum Toxin Treatment for Upper Limb Spasticity Poststroke Over Different ICF Domains: A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil*. 2019;100(9):1703-1725.
3. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization: 2001. Updated March, 2018. www.who.int/classifications/icf/en/
4. Malhotra S, Cousins E, Ward A, et al. An investigation into the agreement between clinical, biomechanical and neurophysiological measures of spasticity. *Clin Rehabil*. 2008;22(12):1105-1115.
5. Pandyan AD, Vuadens P, van Wijck FM, Stark S, Johnson GR, Barnes MP. Are we underestimating the clinical efficacy of botulinum toxin (type A)? Quantifying changes in spasticity, strength and upper limb function after injections of Botox to the elbow flexors in a unilateral stroke population. *Clin Rehabil*. 2002;16(6):654-660.
6. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil*. 2009;23(7):651-658.
7. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil*. 1999;13(5):373-383.
8. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koelle WP, eds. *Spasticity: disordered motor control*. Chicago (IL): Year Book Medical Publishers; 1980:485-494.
9. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry*. 2005;76(1):47-54.
10. Lieber RL, Roberts TJ, Blemker SS, Lee SSM, Herzog W. Skeletal muscle mechanics, energetics and plasticity. *J Neuroeng Rehabil*. 2017;14(1):108.
11. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil*. 1989;70(2):144-155.
12. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech*. 2016;35:93-101.
13. De Gooijer-van de Groep KL, de Groot JH, van der Krogt H, de Vlugt E, Arendzen JH, Meskers CGM. Early Shortening of Wrist Flexor Muscles Coincides With Poor Recovery After Stroke. *Neurorehabil Neural Repair*. 2018;32(6-7):645-654.
14. Mirbagheri MM, Tsao C, Rymer WZ. Natural history of neuromuscular properties after stroke: a longitudinal study. *J Neurol Neurosurg Psychiatry*. 2009;80(11):1212-1217.

15. Andringa A, Meskers C, van de Port I, van Wegen E, Kwakkel G. Time Course of Wrist Hyper-Resistance in Relation to Upper Limb Motor Recovery Early Post Stroke. *Neurorehabil Neural Repair*. 2020:34(8):690-701.
16. Lindberg PG, Gaverth 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(7):617-625.
17. Andringa A, van Wegen E, van de Port I, Kwakkel G, Meskers C. Measurement Properties of the NeuroFlexor Device for Quantifying Neural and Non-neural Components of Wrist Hyper-Resistance in Chronic Stroke. *Front Neurol*. 2019;10:730.
18. Gaverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson AC. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *J Rehabil Med*. 2013;45(7):630-636.
19. Gaverth J, Eliasson AC, 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. *J Rehabil Med*. 2014;46(7):629-634.
20. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 1987;67(2):206-207.
21. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. *Disabil Rehabil*. 2006;28(15):899-907.
22. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7(1):13-31.
23. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair*. 2008;22(1):78-90.
24. Gladstone DJ, Danells CJ, Black SE. The fugl-meyer assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabil Neural Repair*. 2002;16(3):232-240.
25. Evans JD. *Straightforward statistics for the behavioral sciences*. Pacific Grove (CA): Brooks/Cole Publishing Company; 1996.
26. Woytowicz EJ, Rietschel JC, Goodman RN, et al. Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. *Arch Phys Med Rehabil*. 2017;98(3):456-462.
27. Pennati GV, Plantin J, Borg J, Lindberg PG. Normative NeuroFlexor data for detection of spasticity after stroke: a cross-sectional study. *J Neuroeng Rehabil*. 2016;13:30.
28. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther*. 1993;73(7):447-454.

SUPPLEMENTARY MATERIAL

Supplement 6A. Biomechanical model of the NeuroFlexor

In the biomechanical model of the NeuroFlexor, previously described by Lindberg et al.,[1] the total measured resisting force (F_m) during passive wrist extension is a summation of passive elastic force (F_p), viscous force (F_v), reflexive force (F_r) and inertial forces of the limb and the moving parts of the device (F_{in}), described as:

$$F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta), \quad (1)$$

where θ denotes a specific angle.

In the model, four force magnitudes, identified in the force-time-traces of the slow and fast movements, are used to estimate the different components of the total measured passive force. P0 is the resting force of the hand before onset of stretch, with wrist angle equals 20° flexion. One force magnitude (P3) is defined at the end position of the slow wrist extension movement (5°/second) (Figure S6.1A). Two force magnitudes are defined within the fast passive wrist extension movement (236°/second): P1, the initial force peak, and P2, the late force peak (at the end of the movement) (Figure S6.1B). Resting force (P0) is subtracted from P1, P2 and P3 prior to further calculations. Two slow and two fast movements without the hand and forearm fastened to the device are run as a reference for the mechanical resistance by the hand platform on the force sensor.

The **inertia component (IC)** corresponds to the force resisting the acceleration of the hand and is calculated in the model as:

$$\mathrm{IC} = m \times \alpha, \quad (2)$$

where *m* is the mass of the hand and the movable platform, and *a* is the angular acceleration (21 m/s^2). The mass of the hand is estimated to be 0.6% of the total body weight.

The **elastic component (EC)** is a length-dependent resisting force which increases when the wrist flexor muscles are stretched (and the wrist extensor muscles are shortened), with an exponential increase when the muscle is stretched close to its end range. The EC is recorded 1 second after the end of the slow movement. The EC corresponds to P3, i.e. the fully stretched position during the slow movement, minus resting force (P0) (Figure S6.1A).

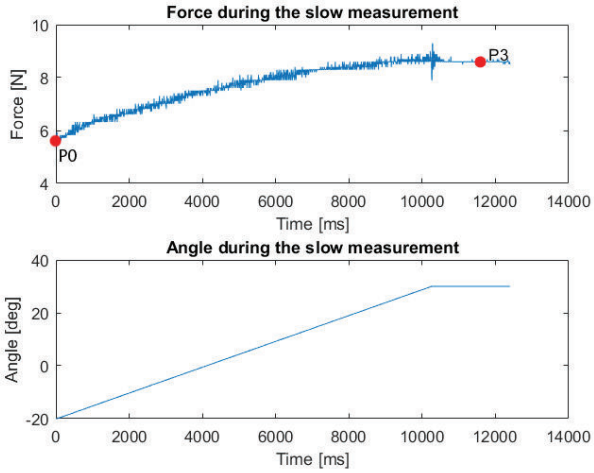


Figure S6.1A. Measured force and wrist angle during slow movement of the NeuroFlexor.

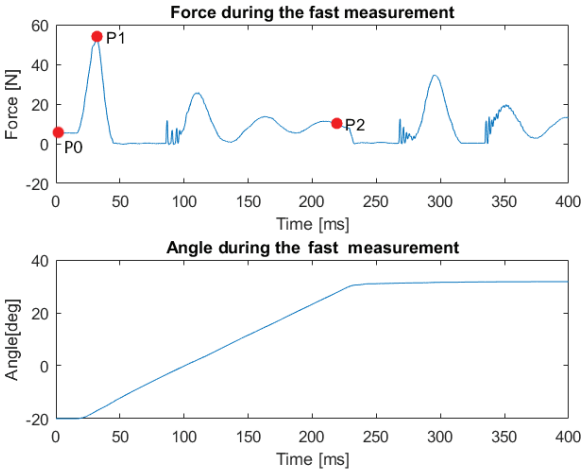


Figure S6.1B. Measured force and wrist angle during fast movement of the NeuroFlexor.

The **viscous component (VC)** is a velocity-dependent resisting force of soft tissues to stretch. Lindberg et al.[1] assumed that the viscous resistance is highest during the initial acceleration and continues at a lower level during further extension movement. To calculate the viscous component, first, the early viscosity component (VC_{P1}) is calculated.

$$VC_{P1} = Total\ force_{P1} - \mathrm{IC}\,, \tag{3}$$

where Total $force_{P1}$ is the measured force at P1 (Figure S6.1B), and IC the inertial component calculated as above. Since there is a comparatively stable relationship between the early and late viscosity, Lindberg et al.[1] assumed that the late viscosity is approximately 20% of the early viscosity.

$$\mathrm{VC} = VC_{P1} \times 0.2\,. \tag{4}$$

Finally, P2 is defined as the late force peak at maximal extension at the end of the passive fast wrist extension movement (Figure S6.1B) and consists of the neural, viscous and elastic component together. The **neural component (NC)** is estimated by:

$$\mathrm{NC} = Total\ force_{P2} - (\mathrm{EC} + \mathrm{VC})\,. \tag{5}$$

REFERENCES SUPPLEMENTARY MATERIAL

1. Lindberg PG, Gaverth 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(7):617-625.

Supplement 6B

Table S6.1. Individual data

Pt	Stroke/ CP	BoNT dose total	BoNT dose wrist-finger joints	Injected muscles and BoNT dose affecting wrist and/or finger joints	Baseline NC	ΔNC at week 6	Baseline EC	ΔEC at week 6	Baseline MAS WF	ΔMAS WF at week 6	Baseline MAS FF	ΔMAS FF at week 6
1	CP	100	100	FCU-35, ECU-40, ADM-25	20.97	-16.60	10.09	-1.46	1+	-0.5	1	+0.5
2	CP	200	100	FCR-50, FCU-50	10.89	-8.27	3.42	-0.10	0	0	1	-1
3	CP	175	125	FDS-50, FDP-25, ED-50	8.45	-5.81	2.67	0.53	0	0	0	+1
4	Stroke	250	150	FDS-50, FDP-50, L-25, EPB-25	19.97	-9.19	3.27	3.32	1	-1	1	-1
5	Stroke	475	175	FDS-75, FDP-75, ECR-25	4.67	5.96	5.13	-5.22	0	0	0	0
6	Stroke	225	225	FDS-75, FDP-50, FPL-50, FPB-25, OP-25	7.95	-7.34	6.23	-4.79	1+	-0.5	1+	-0.5
7	Stroke	400	250	FDS-75, FDP-75, L-50, FPL-50	13.91	-8.81	6.03	-2.70	1+	-0.5	1+	-0.5
8	Stroke	275	275	FDS-100, FDP-100, L-75	12.53	-7.05	7.14	-1.34	1+	-1.5	3	-3
9	Stroke	375	325	FDS-75, FDP-75, FCR-50, PL-25, FPL-50, FPB-25, OP-25	25.91	-22.46	6.54	-3.71	1+	-1+	2	-2
10	Stroke	350	275	FDS-75, FDP-100, FCR-75, FPL-25	31.64	-12.13	3.43	-0.07	2	-0.5	2	0
11	Stroke	350	300	FDS-75, FDP-75, FCR-50, FCU-25, L-50, PL-25	11.21	-7.95	14.67	-4.51	2	-1	2	-0.5

12	Stroke	350	350	FDS-100, FDP-100, L-50, FPL-50, FPB-25, OP-25	8.50	0.02	15.87	-2.75	0	+1,5	1	+0.5
13	Stroke	600	375	FDS-75, FDP-75, FCR-75, L-50, PL-25, FPL-50, FPB-12.5, OP-12.5	26.14	-17.64	13.55	-9.74	1+	0	1+	0
14	Stroke	700	375	FDS-75, FDP-75, FCR-75, FCU-75, L-25, PL-50	37.36	-17.82	31.43	-5.53	3	-1	3	0
15	Stroke	625	400	FDS-75, FDP-75, FCR-75, FCU-50, L-50, FPL-25, FPB-25, OP-25	55.62	-41.01	4.34	-0.25	2	-1	2	-1
16	Stroke	600	425	FDS-100, FDP-100, FCR-100, FCU-75, PL-50	31.03	-17.72	9.18	0.19	2	0	2	-1
17	Stroke	450	450	FDS-75, FDP-100, FCR-75, FCU-50, L-50, FPL-50, FPB-25, OP-25	37.07	-16.18	16.09	6.68	1+	0	1+	0
18	Stroke	600	500	FDS-100, FDP-100, FCR-100, FCU-50, L-50, PL-25, FPL-50, FPB-12.5, OP-12.5	43.83	-27.50	23.59	-13.05	3	-1	3	-1

Abbreviations: ADM, m. abductor digiti minimi; EC, elastic component (N); ECR, m. extensor carpi radialis; ECU, m. extensor carpi ulnaris; ED, m. extensor digitorum; EPB, m. extensor pollicis brevis; FCR, m. flexor carpi radialis; FCU, m. flexor carpi ulnaris; FDP, m. flexor digitorum profundus; FDS, m. flexor digitorum superficialis; FPB, m. flexor pollicis brevis; FPL, m. flexor pollicis longus; L, m. lumbricalis; MAS FF, modified Ashworth scale, finger flexor muscles; MAS WF, modified Ashworth scale, wrist flexor muscles; NC, neural component (N); OP, m. opponens pollicis; PL, m. palmaris longus; Δ, change between baseline and week 6 after treatment.

Supplement 6C

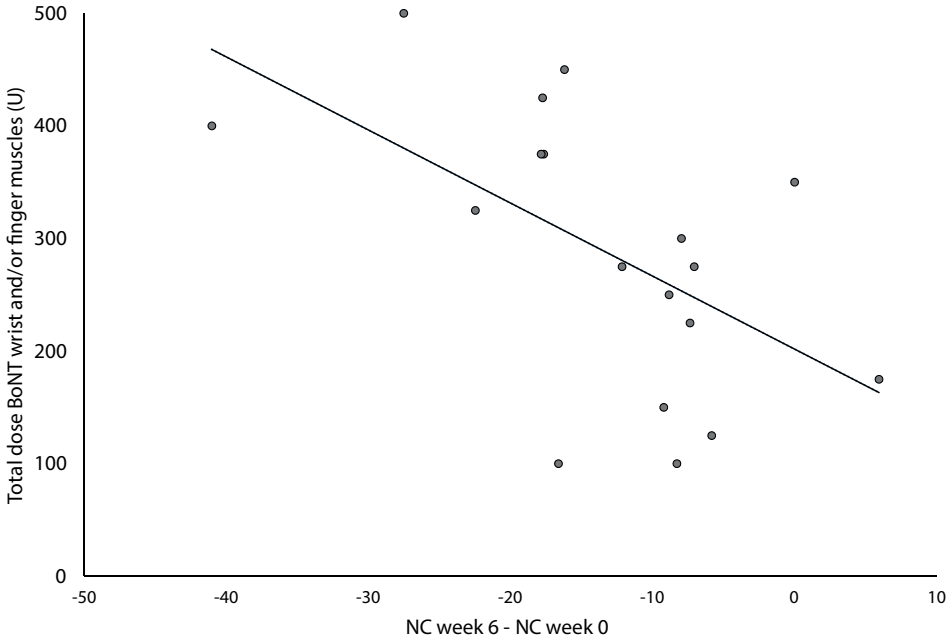


Figure S6.2. Scatterplot of change in neural component (NC) from pre-intervention to week 6 post-intervention, and botulinum toxin-A (BoNT) dose in muscles affecting wrist and finger joints.

CHAPTER 7

General discussion

Increased resistance to passive joint movement (i.e. joint hyper-resistance) is, next to the loss of motor function, one of the clinical characteristics of spastic paresis post stroke. This joint hyper-resistance is hypothesised to be caused by a poorly understood and complex interaction between pathological muscle overactivity and tissue alterations, as outlined in **chapter 1** (Figure 1.2). The current thesis aimed to investigate instrumented assessment to clinically quantify the underlying neural and non-neural components of wrist hyper-resistance in patients in the subacute and chronic phase post stroke and to explore its potential value for timely and patient-specific management of upper limb spastic paresis post stroke. In this chapter, the main findings of this thesis are discussed and recommendations for future research are provided.

MAIN FINDINGS

- Botulinum toxin (BoNT) treatment in the upper limb post stroke was found effective in reducing the total resistance to passive joint movement, as measured with the modified Ashworth scale (MAS), at the International Classification of Functioning, Disability and Health (ICF) level of body functions, and improving self-care ability for the affected arm and hand at the ICF level of activity. However, how BoNT affects the underlying components of increased resistance to passive joint movement remains unknown in the absence of a construct valid outcome measure (**chapter 2**).
- Robust evidence was found indicating that BoNT treatment alone has no effect on arm and hand capacity post stroke at the ICF level of activity, suggesting that the temporary reduction of muscle activity by BoNT, leading to improvements in passive tasks, cannot be extrapolated to active movements performed during functional tasks (**chapter 2**).
- Instrumented assessment using the NeuroFlexor was shown to provide a test-retest reliable, construct-valid and responsive estimate of the underlying neural and non-neural components of wrist hyper-resistance post stroke (**chapter 3 and 4**).
- Patients with severe upper limb motor deficits early post stroke, showing no voluntary finger extension (VFE) within 3 weeks post stroke, demonstrated a gradual increment in the neural and non-neural elastic and viscous components of wrist hyper-resistance within the first 26 weeks post stroke. The main increase of the neural component occurred within the first 5 weeks post stroke, paralleling the time window of spontaneous motor recovery, and was accompanied by a gradual increase in the non-neural elastic component after stroke (**chapter 5**). These findings suggest that the development of the neural and

non-neural components of wrist hyper-resistance is determined by lack of spontaneous neurobiological recovery in absence of corticospinal tract intactness early post stroke.

- In a population of 18 adults with chronic stroke or cerebral palsy, pre- and post-BoNT treatment measurements showed a dose-dependent reduction of the neural component of wrist hyper-resistance while the non-neural elastic and viscous components were unaffected, suggesting a specific effect of BoNT on the neural component (**chapter 6**).

INSTRUMENTED ASSESSMENT METHOD TO QUANTIFY UNDERLYING COMPONENTS OF WRIST HYPER-RESISTANCE

The commercially available NeuroFlexor (Aggero Medtech AB, Älta, Sweden)[1] was developed to address the drawbacks of current clinical manual spasticity assessment[2, 3] and claims to objectively quantify the neural and non-neural elastic and viscous components underlying increased resistance to passive wrist extension movement in a standardized way. In **chapters 3 and 4**, the measurement properties of this device were evaluated in a heterogeneous population of patients with chronic stroke and healthy, age-matched adults.

Test-retest reliability of the NeuroFlexor for the neural and non-neural elastic components was shown to be excellent and good for the viscous component in patients with chronic stroke (**chapter 3**). Despite these promising results, the smallest detectable change (SDC) for all components was large compared to the median values of the population (70-140% of the median). These findings suggest that the NeuroFlexor is a reliable device for research purposes at group level, however, less suitable for detecting changes within individual patients over time. To our knowledge, the NeuroFlexor is the first device available without direct assessment of muscle activation by electromyography (EMG), which may have been of positive influence on the reliability values of the neural component. Similar instrumented assessment methods that encompass EMG have shown comparable reliability for the non-neural components, but poorer reliability for the neural component.[4, 5]

Due to the lack of an appropriate gold standard, the construct validity of the NeuroFlexor outcomes was assessed. In this thesis, construct validity was demonstrated in three ways. First, the NeuroFlexor was able to discriminate between healthy adults and patients with chronic stroke, and between subgroups of patients based on the MAS (**chapter 3**). Second, NeuroFlexor outcomes associated as expected to the clinical scales MAS, Tardieu scale, passive range of wrist extension, Fugl-Meyer motor assessment of the upper extremity (FM-UE) and action research arm test (ARAT) (**chapter 3**). Lastly, the outcomes of the

NeuroFlexor were similar compared to another instrumented assessment method that encompasses EMG, enabling direct measurement of muscle activity, i.e. the experimental EMG-based Wristalyzer (**chapter 4**). However, the neural component assessed by the NeuroFlexor showed unexpectedly high associations with the non-neural elastic components of both devices, suggesting that discrimination between the neural and non-neural elastic components in absence of the direct determination of muscle activity may be less adequate.

The findings of this thesis emphasize the importance to discriminate between the underlying components of wrist hyper-resistance, as patients showed different magnitudes and distribution of components (**chapters 3 and 4**), different time courses of development early post stroke (**chapter 5**) and different responses to BoNT treatment (**chapter 6**). Consequently, instrumented assessment of the underlying components of wrist hyper-resistance may contribute to timely and patient-specific treatment decision-making for upper limb spastic paresis management in rehabilitation. Moreover, quantification of the neural component of wrist hyper-resistance, as a reflection of spasticity, can help to optimise current BoNT injection protocols and to define the most efficient dosing regimens, injection sites and technique, and concurrent treatments. A possible drawback of the NeuroFlexor for treatment evaluation purposes is, however, that 40° passive wrist extension is needed to comply with the measurement protocol.

It should be noted that instrumented assessment by the NeuroFlexor is limited to a passive task, that is with the neuromuscular system at rest, where velocity-dependent spasticity, involuntary background activation and tissue alterations are hypothesised to be the major contributors to the measured increased resistance to passive movement. Moreover, these measurements under passive conditions do not reflect the impact of the various components underlying spastic paresis in active movements and leave the paresis component and other forms of muscle overactivity, such as co-contraction and associated reactions, unexplored. Therefore, the impact of all components of spastic paresis that contribute to the patients' limitations requires careful clinical evaluation under both passive and active measurement conditions. Combining NeuroFlexor assessment under passive conditions with the assessment of motor function, for instance using the FM-UE[6] and kinematic measurements,[7] may allow for assessing the role of the paresis component in relation to muscle overactivity and altered tissue properties on the quality of movement.

UNDERSTANDING THE DYNAMICS OF UPPER LIMB SPASTIC PARESIS EARLY AFTER STROKE

A complex interaction between paresis, various forms of muscle overactivity and tissue property alterations is considered to be responsible for the highly diverse and dynamic clinical presentation of spastic paresis, especially early after stroke. However, the pathophysiological mechanism underlying the development of muscle overactivity, as well as its relationship with tissue property alterations and motor recovery over time post stroke, is not yet well investigated as longitudinal studies with repeated measurements in time, allowing to investigate the time-course, are lacking. Moreover, other predisposing factors leading to the inter-individual variability of the clinical diverse presentation of spastic paresis, such as the role of genetics,[8] are still poorly investigated. Each of these knowledge gaps will be further discussed below.

The pathophysiological mechanism underlying spasticity

Spasticity, one of the positive features of spastic paresis, is often used beyond its original definition to refer to all forms of muscle overactivity, or even in combination with the negative features post stroke. In this thesis, the term spasticity is used in 'sensu stricto' for the velocity- and muscle length-dependent increase of muscle activity in response to an externally imposed stretch following the definition of Lance.[9] In recent years, fundamental research contributed to a better understanding of spasticity. Normally, the stretch reflex is regulated by supraspinal and spinal mechanisms. The supraspinal control is modulated by the inhibitory corticospinal tract (CST) and dorsal reticulospinal tracts (RST), and by the excitatory medial RST and vestibulospinal tracts (VST),[10] while the spinal control depends on the interaction between the muscle spindle, the spinal cord and interneurons. The hyper-excitability of the stretch reflex post stroke, with a reduced reflex threshold and increased reflex gain,[11] is attributed to neural plasticity at both the supraspinal and the spinal level.[12, 13]

It is known that isolated lesions of the pyramidal tract result in weakness and loss of dexterity, in particular in the distal muscles that act directly on the hand, without any sign of spasticity.[14] Instead, neural damage to the corticoreticular fibers that connect the premotor cortex with the medullar reticular formation, from which the dorsal RST originates, is associated with the presence of spasticity.[12] The decrease of the inhibitory influence of the dorsal RST leaves the excitatory effects of the medial RST and VST to the stretch reflex unopposed.[12, 15] Moreover, recent studies suggest that the medial RST receives increased ipsilateral input from the contralesional cortex post stroke.[16] These findings suggest that

the enhancement of the medial RST may be the major supraspinal mechanism leading to the hyper-excitability of the stretch reflex.[12] Likewise, upregulation of the medial RST is also supposed to be the main contributor to other positive features seen post stroke, as it is associated with finger enslaving, mirror movements and flexor synergies.[17] In addition to its role in the positive features, the RST is also associated with residual motor function in patients with severe paresis.[17] However, the exact mechanism of the RST in contributing to both positive and negative features post stroke requires further investigation, for instance using the acoustic startle reflex, a brainstem-mediated reflex via the RST (i.e. StartReact phenomenon).[18-20]

The imbalanced (sub)cortical descending input after stroke is hypothesised to further result in rearrangements at the spinal level.[13, 21] With that, the enhanced influence of the Ia afferent from the muscle spindle on alpha motor neuron activity is believed to be the main contributor to the velocity-dependent increase in motor neuron hyper-excitability. The main spinal mechanisms thought to be involved in hyper-excitability of the stretch reflex post stroke are decreased homosynaptic depression at the synapse between the Ia afferent and the motor neuron (postactivation depression)[13, 22] and decreased reciprocal inhibition from muscle spindle Ia afferents from the antagonist muscles.[23] Moreover, there are indications that recurrent Renshaw cell inhibition and Ib inhibition may be decreased, however, these explanations are still hypothetical by lack of sufficient neurophysiological and anatomical underpinning.[21]

The aforementioned plastic rearrangements at (sub)cortical and spinal levels leading to altered neural input to the muscles will not be limited to the central nervous system alone, but will also lead to altered structural and functional properties of the muscles and soft tissues in terms of muscle atrophy,[24] number and length of serial sarcomeres,[25] and muscle and tendon stiffness.[26, 27] However, evidence for the different alterations in tissue properties are inconsistent as measurement of the separate properties is challenging.[25, 28] Advanced non-invasive measurement tools are needed to gain knowledge of the exact tissue properties that change post stroke, which may provide essential information for treatment decision-making.

Our findings from **chapter 5** are in line with current pathophysiological knowledge of spasticity. The development of the neural component of wrist hyper-resistance, as a reflection of spasticity, seen early post stroke in patients without voluntary finger extension (VFE) within 3 weeks post stroke, as a proxy for the absence of CST intactness, might be driven by enhanced multi-synaptic descending pathways such as the RST, when CST integrity is compromised.[29-31] The main increase of the neural component occurred within the first 5

weeks post stroke, paralleling the time window of spontaneous motor recovery as reflected by improvements on the FM-UE.[32-34] Interestingly, the neural component showed further increase between weeks 12 and 26 post stroke, which emphasizes that 'plasticity' is not restricted to the central nervous system alone. This increase may result from the interaction with peripheral tissue alterations, which showed a gradual increase over time post stroke, and the loss of motor function (Figure 1.2). The mechanisms behind this complex interaction are, however, still poorly understood and remain to be further elucidated.

Understanding the interrelationship between spasticity and motor recovery in time post stroke

Theoretically, spasticity is always accompanied by the presence of paresis. However, the relationship between spasticity and paresis in association with a reduced descending inhibitory control is poorly understood. A possible neuroanatomical explanation for the combination of the negative and positive features of spastic paresis may be that the 1% pyramidal and 99% para- or extrapyramidal descending tracts from the cortical motor areas are intertwined during their descending pathways at hemispheric level. Damage due to stroke will always affect both tracts, leading to respectively deficit and excess symptoms or likewise negative and positive features of spastic paresis. However, the above neuroanatomical explanation for the simultaneous occurrence of spasticity and paresis fails to explain the time-dependency of both components, that is the slow occurrence of spasticity after the immediate loss of motor function. Neurological damage due to stroke leads to an immediate loss of motor function, while, as motor recovery proceeds, spasticity develops gradually in the first weeks following stroke, and continues beyond the first 3 months post stroke as shown in Figure 5.3 in **chapter 5**. This finding suggests that, next to the mainly metabolic driven mechanisms of behavioural recovery such as salvation of penumbral tissue and alleviation of diaschisis mainly restricted to the first weeks post stroke,[35, 36] reactive neuronal plasticity resulting into hyper-excitability of the stretch reflex[21] should be seen as a major mechanism for the gradual development of spasticity. This mechanism seems to continue beyond the window of spontaneous neurobiological recovery within the first 10 weeks post stroke, in particular in those patients with lack of intactness of CST and poor upper limb motor recovery.[35, 37]

Interestingly, it appeared that patients without significant spontaneous neurobiological recovery due to damage of the CST early post stroke, as reflected by the absence of VFE within the first 3 weeks with a low FM-UE baseline start (< 20 points), also are more likely

to show higher magnitudes of the neural component of wrist hyper-resistance, when compared to those presenting VFE with high baseline FM-UE values (> 20 points) (**chapter 5**). This finding supports the hypothesis that the development of the neural component of wrist hyper-resistance, as a proxy for spasticity, develops particularly in those patients where the CST integrity is lacking,[33, 38] and may interfere with the degree of spontaneous neurobiological recovery.

Inter-individual variability in the spastic paresis phenotype post stroke

Our data of patients in both the subacute and chronic phase of stroke demonstrated large inter-individual variability in the magnitude and distribution of neural and non-neural components of wrist hyper-resistance (**chapters 3 and 5**). This inter-individual variability was larger in patients post stroke compared to healthy adults (**chapter 3**), reflecting the heterogeneity in symptomatology after hemispheric stroke.

A considerable number of studies investigated predictive markers for upper limb spasticity, however, all relied on the MAS as the outcome measure.[39-44] These studies identified motor and sensory impairments as the main markers for increased resistance to passive movement in upper limb joints post stroke.[39, 40] Recent studies investigated MRI data of lesion location and size as possible predictive markers,[41-44] and found lesion volume involving motor network structures to be highly associated with increased resistance to passive joint movement. In line with these findings, our results suggested a negative significant association between upper limb motor function, as measured by the FM-UE, and the neural component of wrist hyper-resistance (**chapters 3 and 5**). However, there was still a considerable amount of unexplained variance, suggesting that other predisposing factors may play a role in the development of, and interaction between, muscle overactivity and altered tissue properties. Personal factors, such as genetic characteristics,[8] premorbid muscle morphology,[45, 46] hand dominance,[47] emotional stress level, young age and smoking behaviour, as well as environmental factors, such as task, external temperature and climate, are mentioned as possible factors that contribute to the time-dependent and inter-individual variability.[48-53] Understanding of the complex and multimodal interaction between paresis, the various forms of muscle overactivity and tissue alterations under both passive and active conditions post stroke leading to the dynamic and heterogenetic clinical presentation of spastic paresis is needed to improve patient-specific treatment decision-making.

MANAGEMENT OF UPPER LIMB SPASTIC PARESIS POST STROKE

Patient-specific treatment decision-making

Management of upper limb spastic paresis post stroke is challenging due to its dynamic and multifactorial character. Multiple impairments, that is paresis, various forms of muscle overactivity and altered tissue properties, may be present simultaneously and may be interrelated. In addition, there is a tremendous intra- and inter-individual variability in the magnitude and distribution of underlying impairments. It is hypothesised that different treatment approaches are required for the underlying impairments. As these impairments may arise together, combinations of interventions may be of value. Consequently, interventions for upper limb spastic paresis should be patient-specific, regarding the patients' impairments and their clinical treatment goals. Adequate clinical assessment is needed to examine how the different impairments contribute to the patients' upper limb limitations. Differentiation and quantification of the neural and non-neural components underlying wrist hyper-resistance using instrumented assessment, as studied in this thesis, is of added value to evaluate spasticity and tissue alterations in passive tasks.

Early reduction of spasticity to improve motor recovery post stroke

Twitchell[54] and Brunnstrom[55] empirically described motor recovery over different stereotypical stages which parallel the emergence and disappearance of spasticity.[17] Based on their description, patients recover orderly from stage to stage and recovery will end at any one of these stages. This description suggests that spasticity decreases as motor recovery progresses throughout the stages. Moreover, it might suggest that early reduction of spasticity could improve motor recovery. Recent studies showed that reduction of spasticity, using BoNT, in the early stages post stroke did not lead to improvements in the recovery of arm motor function.[56, 57] Whereas a small study of Cousins et al.[58] suggested that early BoNT treatment may be beneficial for the improvement of arm and hand capacity, measured with the ARAT, in patients who have no arm function within the first 3 weeks post stroke. From these results, it remains unclear whether the development of spasticity may interfere with true neurological recovery,[59] as adequate measures of behavioural restitution are lacking. The influence of the development of spasticity and the effect of early reduction by BoNT on true neurological recovery, using kinematic measures,[7] as well as on behavioural compensation of function should be further investigated.

Early reduction of spasticity to prevent tissue alterations post stroke

Based on current knowledge, patients with a lesion affecting the motor network structures leading to moderate to severe motor impairment[41-44] or those showing no VFE within 3 weeks post stroke (**chapter 5**) are at risk to develop spasticity. Moreover, the relative immobilization of the muscles in a shortened position due to severe paresis in combination with muscle overactivity may cause alterations in tissue properties, as shown by the gradual increase in non-neural elastic component of wrist hyper-resistance (**chapter 5**). Early reduction of the muscle overactivity in these patients at risk may decrease the early-onset problems, such as muscle shortening and stiffness,[27] and may achieve better long-term results.[60] The early use of BoNT has been shown to prevent the deterioration of passive range of motion,[56-58, 61] suggesting that reduction of muscle overactivity may limit secondary tissue alterations. However, the positive effect on passive range of motion was found to disappear six weeks after treatment, once the effects of BoNT on muscle activity diminished. These findings may suggest that, particularly in patients that do not show upper limb motor recovery, muscle overactivity should be treated repeatedly by BoNT to maintain the preventive effect on the unwanted tissue alterations.[56]

Treatment of upper limb spastic paresis in the chronic phase of stroke

For treatment decisions in the chronic phase of stroke, there are two main scenarios based on the patients' level of impairments and the associated clinical treatment goal. Patients with severe paresis suffering from passive limitations on the activity level, such as limited self-care ability of the affected arm and hand, might benefit from interventions that primarily aim to reduce muscle overactivity and tissue properties that underlie increased resistance to passive movement and decreased passive range of motion (**chapter 2**). Muscle overactivity is expected to primarily be influenced by treatments such as BoNT (**chapter 6**) and baclofen, whereas the tissue alterations are expected to be mainly influenced by splints, casts, or surgical lengthening.[62, 63] Patients with some arm function suffering from reduced upper limb capacity, might benefit from an active therapy program possibly combined with the reduction of muscle overactivity. The meta-analysis in **chapter 2** yielded robust evidence that BoNT alone does not improve arm-hand capacity 12 weeks post-injection. These results are in line with our current knowledge of the working mechanism of BoNT, as it causes a temporary and local paresis to the injected muscles without influencing the actual voluntary control. Adjunctive therapies after BoNT treatment within a multidisciplinary rehabilitation program might help to optimize voluntary control during the temporary period of paralysis

in the overactive injected muscles. However, findings from a large trial[64] showed that BoNT followed by an intensive upper limb rehabilitation program did not improve motor function, as measured by the Box and Block Test, in a group of patients showing no active arm and hand function at baseline, suggesting that intensive therapy program after BoNT treatment may only be beneficial in patients showing any active movement.

FUTURE PERSPECTIVES FOR RESEARCH

Need for consensus on definitions concerning spastic paresis

Although spastic paresis is well recognized in clinical practice, both researchers and clinicians still use a variety of definitions together with diverse outcome measures for the underlying impairments and clinical features associated with spastic paresis. Consensus is needed on definitions concerning all separate impairments and clinical features related to upper limb spastic paresis, based on the model presented in Figure 1.2 (**chapter 1**). In addition, a core set of construct-valid, clinical outcome measures is needed, following the ICF model.[65]

Need for better understanding underlying pathophysiological mechanisms and interrelationships leading to spastic paresis post stroke

Translational research in a longitudinal way with multimodal intensive repeated measurements is urgently needed to further understand the pathophysiological mechanisms underlying the development of spastic paresis in time post stroke. In particular, the longitudinal interaction between brain injury with respect to sensorimotor impairments, neuroplasticity and observed changes in tissue properties requires further investigation. First, longitudinal studies using, for instance, the acoustic startle reflex (i.e. StartReact phenomenon)[18-20] or diffusion tensor imaging (DTI) fractional anisotrophy,[66, 67] are needed to further improve the understanding of the role of the enhancement of the RST and VST in the gradual development of the various forms of muscle overactivity. Second, the aforementioned measures should preferably be combined with kinematic and kinetic measurements to relate neurophysiological adaptations to motor recovery, including both changes in behavioural restitution and behavioural compensation.[7] Third, further research is needed to investigate the interrelationships between the various forms of muscle overactivity and tissue alterations over time post stroke, using non-invasive methods such as ultrasound[68] or shear wave elastography.[69] Lastly, multimodal longitudinal studies are needed to investigate

other predisposing inter-individual factors, such as genetic characteristics and premorbid muscle morphology, explaining the heterogeneity in the presentation of spastic paresis between patients post stroke.

Additionally, further research is needed to compare the mechanisms underlying the development of spastic paresis post stroke with neurological diseases of different origins, e.g. multiple sclerosis (MS) and cerebral palsy (CP). It is still unknown how the underlying pathophysiology such as demyelination in patients with MS, or white matter lesion in children with CP, may lead to different phenotypes of spastic paresis with more or less dominance of the muscle overactivity component when compared to the paretic component.

Need for optimizing instrumented assessment methods for clinical use

Further refinement of the NeuroFlexor, investigated in this thesis, is needed to further improve the understanding of the underlying wrist hyper-resistance components and for its use for patient-tailored treatment decisions and evaluation in clinical practice. First, it should be investigated whether the direct measurement of muscle activity using EMG is needed to gain a more valid and accurate distinction between the neural and non-neural components, as well as to differentiate between spasticity and involuntary background activation. However, it is important to maintain the good to excellent test-retest reliability of the current method without EMG, as this is essential in longitudinal repeated measurements. Second, the method may be refined by assessing the resistance over the patients' full range of passive wrist extension to gain better insight into the small changes in tissue alterations early post stroke. Third, to use the method for individual treatment decisions, the method needs improvement in terms of standardization of the assessment protocol to reduce SDC values. Muscle overactivity has shown to be under influence of multiple factors, such as posture, external temperature and emotional status,[70] and is variable in time. To account for the fluctuations in the level of a patients' muscle overactivity, repeated measurements under highly standardized conditions within one session may be of added value.[71] Moreover, EMG can be used to strive for equivalent levels of involuntary background activation at the start of each measurement.[72] Fourth, the NeuroFlexor uses a unidirectional (i.e. extension) biomechanical modelling method without taking muscle activity and tissue properties of the extensor muscles into account, whereas the experimental Wristalyzer uses a more extensive EMG-based and bidirectional optimization model, from which more parameters can be extracted, such as optimal muscle length and slack length of connective tissue, as

well as the characteristics of the extensor muscles.[73] Further research is needed to examine the value of these additional parameters for patient-specific treatment decision-making. Lastly, to enhance applicability in a larger population, the current device and model should be modified for patients with a passive range of wrist extension of < 40°, since these are the patients who require treatment. The current method is only applicable to the wrist joint. For future use in clinical practice, the method needs to be developed for other joints, such as the elbow, knee and ankle.

Need for timely and patient-specific interventions for upper limb spastic paresis

Patient phenotyping based on the distribution and magnitude of the underlying impairments of spastic paresis, that is paresis, various forms of muscle overactivity and altered tissue properties, can guide treatment decision-making and allows for stratification in phase II and III trials. First of all, this requires high-quality phase II trials that improve and extend the evidence for effective treatment modalities for the separate underlying impairments, as well as the associated cut-off values that can be used for patient selection. In addition, the effects of combined interventions should be evaluated in future studies. BoNT treatment can be followed by, for instance, a splint protocol or dynamic orthosis[74] in patients with both increased neural and non-neural components of wrist hyper-resistance. Furthermore, the effect of the early reduction of muscle overactivity on true neurobiological recovery and behavioural compensation of function may merit further considerations. Additionally, further research should focus on interventions that lead to long-term reduction of muscle overactivity, because BoNT, as is the current standard, only leads to a temporary reduction of muscle overactivity and, with that, a temporary preventive effect on the unwanted tissue alterations. In general, attention should be paid to the generalization of the positive effects of different interventions on the ICF level of body functions to the effects on the clinically important ICF levels of activity and participation.

CLINICAL IMPLICATIONS

- Instrumented assessment using the NeuroFlexor provides an objective and standardized alternative for the currently used and often-criticized MAS,[2, 3] and allows for quantification of the underlying neural and non-neural components of wrist hyper-resistance post stroke.

- Instrumented assessment under passive conditions, such as the NeuroFlexor, should be accompanied by the assessment of motor function, for instance using the FM-UE[6] or kinematic measurements,[7] to understand the impact of all underlying components of spastic paresis that contribute to the patients' disability.
- Quantifying the neural and non-neural wrist hyper-resistance components offers a more precise evaluation of treatment and may be of added value for decision-making in when and how to treat patients with spastic paresis post stroke, as what lacks in current clinical assessment.
- Patients with a large neural component of wrist hyper-resistance are expected to benefit most from BoNT treatment. However, further studies are needed to identify responders and non-responders of BoNT treatment based on the underlying components of wrist hyper-resistance.

REFERENCES

1. Lindberg PG, Gaverth 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(7):617-625.
2. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosurg Psychiatry*. 2010;81(1):46-52.
3. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil*. 1999;13(5):373-383.
4. Van der Krogt H, Klomp A, de Groot JH, et al. Comprehensive neuromechanical assessment in stroke patients: reliability and responsiveness of a protocol to measure neural and non-neural wrist properties. *J Neuroeng Rehabil*. 2015;12:28.
5. Sloot LH, van der Krogt MM, de Gooijer-van de Groep KL, et al. The validity and reliability of modelled neural and tissue properties of the ankle muscles in children with cerebral palsy. *Gait Posture*. 2015;42(1):7-15.
6. Pohl J, Held JPO, Verheyden G, et al. Consensus-Based Core Set of Outcome Measures for Clinical Motor Rehabilitation After Stroke-A Delphi Study. *Front Neurol*. 2020;11:875.
7. Kwakkel G, Van Wegen E, Burridge JH, et al. Standardized measurement of quality of upper limb movement after stroke: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. *Int J Stroke*. 2019;14(8):783-791.

8. Pearson-Fuhrhop KM, Burke E, Cramer SC. The influence of genetic factors on brain plasticity and recovery after neural injury. *Curr Opin Neurol*. 2012;25(6):682-688.
9. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koelle WP, eds. *Spasticity: disordered motor control*. Chicago (IL): Year Book Medical Publishers; 1980:485-494.
10. Ganguly J, Kulshreshtha D, Almotiri M, Jog M. Muscle Tone Physiology and Abnormalities. *Toxins*. 2021;13(4):282.
11. Katz RT, Rymer WZ. Spastic hypertonia: mechanisms and measurement. *Arch Phys Med Rehabil*. 1989;70(2):144-155.
12. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. *Front Hum Neurosci*. 2015;9:192.
13. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. *Neurology*. 2013;80(3 Suppl 2):S20-6.
14. Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain*. 1968;91(1):1-14.
15. Brown P. Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry*. 1994;57(7):773-777.
16. McPherson JG, Chen A, Ellis MD, Yao J, Heckman CJ, Dewald JPA. Progressive recruitment of contralesional cortico-reticulospinal pathways drives motor impairment post stroke. *J Physiol*. 2018;596(7):1211-1225.
17. Krakauer JW, Carmichael ST. *Broken movement. The neurobiology of motor recovery after stroke*. Cambridge (MA): The MIT Press; 2017.
18. Valls-Sole J, Sole A, Valldeoriola F, Munoz E, Gonzalez LE, Tolosa ES. Reaction time and acoustic startle in normal human subjects. *Neurosci Lett*. 1995;195(2):97-100.
19. Jankelowitz SK, Colebatch JG. The acoustic startle reflex in ischemic stroke. *Neurology*. 2004;62(1):114-116.
20. Li S, Chang SH, Francisco GE, Verduzco-Gutierrez M. Acoustic startle reflex in patients with chronic stroke at different stages of motor recovery: a pilot study. *Top Stroke Rehabil*. 2014;21(4):358-370.
21. Nielsen JB, Crone C, Hultborn H. The spinal pathophysiology of spasticity--from a basic science point of view. *Acta Physiol*. 2007;189(2):171-180.
22. Aymard C, Katz R, Lafitte C, et al. Presynaptic inhibition and homosynaptic depression: a comparison between lower and upper limbs in normal human subjects and patients with hemiplegia. *Brain*. 2000;123 (Pt 8):1688-1702.
23. Yanagisawa N, Tanaka R, Ito Z. Reciprocal Ia inhibition in spastic hemiplegia of man. *Brain*. 1976;99(3):555-574.

24. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle Nerve*. 2005;31(5):535-551.
25. Lieber RL, Roberts TJ, Blemker SS, Lee SSM, Herzog W. Skeletal muscle mechanics, energetics and plasticity. *J Neuroeng Rehabil*. 2017;14(1):108.
26. Paudyal A, Degens H, Baan GC, et al. Changes in muscle-tendon unit length-force characteristics following experimentally induced photothrombotic stroke cannot be explained by changes in muscle belly structure. *Eur J Appl Physiol*. 2021;121(9):2509-2519.
27. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. *Muscle Nerve*. 2004;29(5):615-627.
28. Foran JR, Steinman S, Barash I, Chambers HG, Lieber RL. Structural and mechanical alterations in spastic skeletal muscle. *Dev Med Child Neurol*. 2005;47(10):713-717.
29. Choudhury S, Shobhana A, Singh R, et al. The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. *Neurorehabil Neural Repair*. 2019;33(5):375-383.
30. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain*. 2012;135(Pt 7):2277-2289.
31. Plantin J, Pennati GV, Roca P, et al. Quantitative Assessment of Hand Spasticity After Stroke: Imaging Correlates and Impact on Motor Recovery. *Front Neurol*. 2019;10:836.
32. Cortes JC, Goldsmith J, Harran MD, et al. A Short and Distinct Time Window for Recovery of Arm Motor Control Early After Stroke Revealed With a Global Measure of Trajectory Kinematics. *Neurorehabil Neural Repair*. 2017;31(6):552-560.
33. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol*. 2015;78(6):848-859.
34. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. *Stroke*. 2006;37(9):2348-2353.
35. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. *Restor Neurol Neurosci*. 2013;31(6):707-722.
36. O'Dwyer NJ, Ada L. Reflex hyperexcitability and muscle contracture in relation to spastic hypertonia. *Curr Opin Neurol*. 1996;9(6):451-455.
37. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci*. 2004;22(3-5):281-299.
38. Lin DJ, Cloutier AM, Erler KS, et al. Corticospinal Tract Injury Estimated From Acute Stroke Imaging Predicts Upper Extremity Motor Recovery After Stroke. *Stroke*. 2019;50(12):3569-3577.

39. Zeng H, Chen J, Guo Y, Tan S. Prevalence and Risk Factors for Spasticity After Stroke: A Systematic Review and Meta-Analysis. *Front Neurol*. 2020;11:616097.
40. Tedesco Triccas L, Kennedy N, Smith T, Pomeroy V. Predictors of upper limb spasticity after stroke? A systematic review and meta-analysis. *Physiotherapy*. 2019;105(2):163-173.
41. Ri S, Kivi A, Urban PP, Wolf T, Wissel J. Site and size of lesion predict post-stroke spasticity: A retrospective magnetic resonance imaging study. *J Rehabil Med*. 2020;52(5):jrm00065.
42. Ri S, Glaess-Leistner S, Wissel J. Early brain imaging predictors of post-stroke spasticity. *J Rehabil Med*. 2021;53(3):jrm00169.
43. Lee KB, Hong BY, Kim JS, et al. Which brain lesions produce spasticity? An observational study on 45 stroke patients. *PLoS One*. 2019;14(1):e0210038.
44. Barlow SJ. Identifying the brain regions associated with acute spasticity in patients diagnosed with an ischemic stroke. *Somatosens Mot Res*. 2016;33(2):104-111.
45. Hafer-Macko CE, Ryan AS, Ivey FM, Macko RF. Skeletal muscle changes after hemiparetic stroke and potential beneficial effects of exercise intervention strategies. *J Rehabil Res Dev*. 2008;45(2):261-272.
46. Sions JM, Tyrell CM, Knarr BA, Jancosko A, Binder-Macleod SA. Age- and stroke-related skeletal muscle changes: a review for the geriatric clinician. *J Geriatr Phys Ther*. 2012;35(3):155-161.
47. Harris JE, Eng JJ. Individuals with the dominant hand affected following stroke demonstrate less impairment than those with the nondominant hand affected. *Neurorehabil Neural Repair*. 2006;20(3):380-389.
48. Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK, Watkins CL. Predicting spasticity after stroke in those surviving to 12 months. *Clin Rehabil*. 2004;18(4):438-443.
49. Wissel J, Schelosky LD, Scott J, Christe W, Faiss JH, Mueller J. Early development of spasticity following stroke: a prospective, observational trial. *J Neurol*. 2010;257(7):1067-1072.
50. Urban PP, Wolf T, Uebele M, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke*. 2010;41(9):2016-2020.
51. Picelli A, Tamburin S, Dambruoso F, et al. Topical distribution of initial paresis of the limbs to predict clinically relevant spasticity after ischemic stroke: a retrospective cohort study. *Eur J Phys Rehabil Med*. 2014;50(5):489-494.
52. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Early prediction of long-term upper limb spasticity after stroke: part of the SALGOT study. *Neurology*. 2015;85(10):873-880.
53. Lundstrom E, Smits A, Terent A, Borg J. Time-course and determinants of spasticity during the first six months following first-ever stroke. *J Rehabil Med*. 2010;42(4):296-301.

54. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74(4): 443-480.
55. Brunnstrom S. *Movement therapy in hemiplegia. A neurophysiological approach*. San Francisco: Harper & Row; 1970.
56. Lindsay C, Ispoglou S, Helliwell B, Hicklin D, Sturman S, Pandyan A. Can the early use of botulinum toxin in post stroke spasticity reduce contracture development? A randomised controlled trial. *Clin Rehabil*. 2021;35(3):399-409.
57. Rosales RL, Kong KH, Goh KJ, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. *Neurorehabil Neural Repair*. 2012;26(7):812-821.
58. Cousins E, Ward A, Roffe C, Rimington L, Pandyan A. Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size. *Clin Rehabil*. 2010;24(6):501-513.
59. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke*. 2017;12(5):444-450.
60. Rosales RL, Efendy F, Teleg ES, et al. Botulinum toxin as early intervention for spasticity after stroke or non-progressive brain lesion: A meta-analysis. *J Neurol Sci*. 2016;371:6-14.
61. Hesse S, Mach H, Frohlich S, Behrend S, Werner C, Melzer I. An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. *Clin Rehabil*. 2012;26(3):237-245.
62. Lannin NA, Novak I, Cusick A. A systematic review of upper extremity casting for children and adults with central nervous system motor disorders. *Clin Rehabil*. 2007;21(11):963-976.
63. Renzenbrink GJ, Buurke JH, Nene AV, Geurts AC, Kwakkel G, Rietman JS. Improving walking capacity by surgical correction of equinovarus foot deformity in adult patients with stroke or traumatic brain injury: a systematic review. *J Rehabil Med*. 2012;44(8):614-623.
64. Lannin NA, Ada L, English C, et al. Effect of Additional Rehabilitation After Botulinum Toxin-A on Upper Limb Activity in Chronic Stroke: The InTENSE Trial. *Stroke*. 2020;51(2):556-562.
65. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva: World Health Organization: 2001. Updated March, 2018. www.who.int/classifications/icf/en/
66. Owen M, Ingo C, Dewald JPA. Upper Extremity Motor Impairments and Microstructural Changes in Bulbospinal Pathways in Chronic Hemiparetic *Stroke. Front Neurol*. 2017;8:257.

67. Jang SH, Kwon JW, Yeo SS. Three Dimensional Identification of Medial and Lateral Vestibulospinal Tract in the Human Brain: A Diffusion Tensor Imaging Study. *Front Hum Neurosci*. 2018;12:229.
68. Gao F, Grant TH, Roth EJ, Zhang LQ. Changes in passive mechanical properties of the gastrocnemius muscle at the muscle fascicle and joint levels in stroke survivors. *Arch Phys Med Rehabil*. 2009;90(5):819-826.
69. Brandenburg JE, Eby SF, Song P, et al. Ultrasound elastography: the new frontier in direct measurement of muscle stiffness. *Arch Phys Med Rehabil*. Nov 2014;95(11):2207-2219.
70. Phadke CP, Balasubramanian CK, Ismail F, Boulias C. Revisiting physiologic and psychologic triggers that increase spasticity. *Am J Phys Med Rehabil*. 2013;92(4):357-369.
71. Starsky AJ, Sangani SG, McGuire JR, Logan B, Schmit BD. Reliability of biomechanical spasticity measurements at the elbow of people poststroke. *Arch Phys Med Rehabil*. 2005;86(8):1648-1654.
72. Diong J, Gandevia SC, Nguyen D, et al. Small amounts of involuntary muscle activity reduce passive joint range of motion. *J Appl Physiol (1985)*. 2019;127(1):229-234.
73. De Gooijer-van de Groep KL, de Vlugt E, van der Krogt HJ, et al. Estimation of tissue stiffness, reflex activity, optimal muscle length and slack length in stroke patients using an electromyography driven antagonistic wrist model. *Clin Biomech*. 2016;35:93-101.
74. Andringa AS, Van de Port IG, Meijer JW. Tolerance and effectiveness of a new dynamic hand-wrist orthosis in chronic stroke patients. *NeuroRehabilitation*. 2013;33(2):225-231.

List of abbreviations

ARAT	action research arm test
AS	Ashworth scale
BoNT	botulinum toxin-A
CI	confidence interval
CP	cerebral palsy
CST	corticospinal tract
EC	elastic component of wrist hyper-resistance
ECR	extensor carpi radialis muscle
EMG	electromyography
FCR	flexor carpi radialis muscle
FM-UE	Fugl-Meyer motor assessment of the upper extremity
ICF	International Classification of Functioning, Disability and Health
MAS	modified Ashworth scale
MD	mean difference
MMSE	mini mental state examination
N	Newton
NC	neural component of wrist hyper-resistance
NF	NeuroFlexor
NIHSS	National Institutes of Health Stroke Scale
PEDro	Physiotherapy Evidence Database
PRoM	passive range of motion
RCT	randomized controlled trial
RST	reticulospinal tract
SDC	smallest detectable change
SES	summary effect size
SMD	standardized mean difference
TS	Tardieu scale
UMN	upper motor neuron
VC	viscous component of wrist hyper-resistance
VFE	voluntary finger extension
VST	vestibulospinal tract
WA	Wristalyzer

Summary

Upper limb motor impairments are one of the most common impairments post stroke and occur in up to 80% of all patients. Motor impairments post stroke comprise negative and positive upper motor neuron features. The negative features involve deficit symptoms, such as loss of voluntary motor function, i.e. paresis, and the positive features encompass involuntary muscle overactivity. The combination of negative and positive features leads to the typical clinical presentation of spastic paresis, which shows a considerable, still unexplained, variability between patients and changes over time post stroke. Spastic paresis is hypothesised to be the result of a complex and poorly understood interaction between paresis, various forms of muscle overactivity and altered tissue properties, possibly influenced by personal and environmental factors. Clinically, spastic paresis is characterized at the International Classification of Functioning, Disability and Health (ICF) level of body functions by a loss of motor function, increased resistance to passive joint movement (i.e. joint hyper-resistance), reduced passive range of motion and postural change. These impairments lead to diverse limitations on the activity level, such as a limited arm and hand capacity and problems with self-care ability of the impaired arm and hand (e.g. hygiene maintenance and dressing), further influencing the patients' quality of life.

Spasticity is an important topic in stroke rehabilitation and is considered to be one of the forms of involuntary muscle overactivity that develops gradually post stroke. Although considerable research has been devoted to spasticity, the term on itself is inconsistently defined in both literature and clinical practice, and its pathophysiology is still poorly understood. Moreover, agreement on construct-valid outcome measures and effective evidence-based interventions is still lacking in the literature. In this thesis, the term spasticity is used, in 'sensu stricto', for the velocity- and muscle length-dependent increase of muscle activity in response to an externally imposed stretch, as one of the separate positive upper motor neuron features post stroke.

Current clinical assessment of post-stroke spasticity is restricted to subjective ordinal rating scales, such as the modified Ashworth and Tardieu scales, assessing the total resistance to a manually applied passive joint movement. Unfortunately, these clinical scales are unable to distinguish between muscle overactivity, including spasticity and involuntary background activation, and altered tissue properties, the so-called neural and non-neural components influencing the perceived resistance to passive movement under passive conditions. Moreover, these scales show poor measurement properties with respect to reliability and responsiveness to change. To disentangle increased resistance to passive joint movement, i.e. joint hyper-resistance, in terms of neural and non-neural components

is important for understanding underlying neurophysiological mechanisms during upper limb motor recovery and may impact treatment decisions. Therefore, there is an urgent need for an objective, reliable and valid quantitative measurement technique with a standardized assessment protocol, feasible for serially use in clinical practice to discriminate between the neural and non-neural components underlying joint hyper-resistance. Instrumented assessment methods have been developed to address the drawbacks of current clinical scales. These methods allow for standardized assessment and can provide objective and quantitative information of the underlying neural and non-neural components of joint hyper-resistance. This thesis investigates instrumented assessment to clinically quantify the underlying neural and non-neural components of wrist hyper-resistance in patients in the subacute and chronic phase post stroke and explores its potential value for timely and patient-specific management of upper limb spastic paresis post stroke.

Chapter 2 presents a systematic review and meta-analysis in which the effectiveness of botulinum toxin (BoNT) on the main clinical goals related to upper limb spastic paresis post stroke was investigated. Data from 40 trials, including 2718 patients with stroke, provide a comprehensive overview of reported effects and the scientific robustness of BoNT. The results of the meta-analysis demonstrate robust evidence for the effectiveness of BoNT on the passive clinical goals in reducing resistance to passive movement (joint hyper-resistance), as measured with the modified Ashworth scale (MAS), and improving self-care ability for the affected arm and hand. In addition, the meta-analysis yields robust evidence that BoNT treatment alone does not affect the active arm and hand capacity. Our robust findings show that no further trials are needed to investigate BoNT for its favourable effects on resistance to passive movement and on the self-care ability of the affected upper limb. Additionally, no trials are needed to further confirm the lack of effect of BoNT on arm-hand capacity after stroke. Despite the demonstrated robust positive effect of BoNT on the MAS, the underlying mechanisms of how BoNT affects resistance to passive movement remain unclear. Moreover, due to the low responsiveness to change of this ordinal rating scale, it offers insufficient precision to measure the effectiveness of BoNT and therefore to define the most effective injection protocols. These findings emphasize the need for instrumented methods that allow for standardized assessment and quantification of the underlying neural and non-neural components of joint hyper-resistance.

The portable and commercially available NeuroFlexor (Aggero Medtech AB, Älta, Sweden) was developed for objective quantification of neural and non-neural elastic and viscous

components underlying increased resistance to passive wrist extension, i.e. wrist hyper-resistance, in upper limb spastic paresis. This motor-driven device imposes isokinetic wrist extensions over a fixed 50° range around the neutral position at two controlled velocities (5 and 236°/second). Biomechanical modelling allows for direct estimation of the neural and non-neural elastic and viscous components of wrist hyper-resistance. The neural component is considered as a reflection of the velocity-dependent spasticity. **Chapters 3 and 4** of this thesis, focus on the measurement properties of this device for the paretic upper limb.

In **chapter 3**, the test-retest reliability and construct validity of the NeuroFlexor are investigated in a heterogeneous population of 46 patients with chronic stroke and 30 healthy age-matched adults. Test-retest reliability of the NeuroFlexor for the neural and non-neural elastic components was excellent and good for the viscous component. However, the smallest detectable change values for all components are relatively high compared to the median value of our study population. Our data suggest that this device is a test-retest reliable method for research purposes at group level and is able to differentiate between patients, but is less suited for detecting changes within individual patients over time. The NeuroFlexor quantifies neural and non-neural components of hyper-resistance without the assessment of electromyography (EMG) of the muscles involved, which may have had a positive influence on the reliability values.

In lack of a gold standard for the assessment of the underlying components of wrist hyper-resistance, the NeuroFlexor outcomes are compared with the outcomes on clinical scales to investigate its construct validity. The NeuroFlexor outcomes for the neural and non-neural elastic and viscous components associate as expected to the clinical scales MAS, Tardieu scale, passive range of wrist extension, Fugl-Meyer motor assessment of the upper extremity (FM-UE) and action research arm test. These findings suggest that the outcomes of the NeuroFlexor were construct-valid compared to clinical scales.

The construct validity of the NeuroFlexor is further investigated in **chapter 4**. In a cross-sectional study, including 43 patients with chronic stroke, the outcomes of two instrumented assessment methods, i.e. the NeuroFlexor and the experimental EMG-based Wristalyzer, are compared. Additionally, the outcomes of both devices are compared with the MAS and range of passive wrist extension, obtained by goniometry and the Wristalyzer. The results show similarity between the two instrumented assessment methods for the quantification of neural and non-neural components underlying increased resistance to passive wrist extension in patients with chronic stroke and upper limb spastic paresis. However, the neural component assessed by the NeuroFlexor shows unexpectedly high associations with the non-neural

elastic components of both devices, which may suggest that the discrimination between the neural and non-neural elastic component in the NeuroFlexor is less adequate in absence of a direct measurement of muscle activity by EMG. The possible added value of EMG in the discrimination between the neural and non-neural components requires further investigation.

The results of **chapters 3 and 4** confirm that instrumented assessment provides reliable and construct-valid quantification of the underlying neural and non-neural components of wrist hyper-resistance in a standardized matter and may have an added value above current clinical assessments. Knowledge of the underlying components of wrist hyper-resistance may contribute to patient-specific treatment decision-making in when and how to treat patients with spastic paresis. Moreover, objective quantification of the underlying components contributes to a more precise effect evaluation of interventions that target joint hyper-resistance. Additionally, the portable NeuroFlexor allows for clinically repeated measurements, which is important to understand the development of the underlying components over time as well as into the interrelationships between the components.

Chapter 5 aims to investigate the time course of neural and non-neural elastic and viscous components of wrist hyper-resistance in relation to upper limb motor recovery in the first 6 months post stroke. This longitudinal study included 17 patients with a first-ever ischemic stroke and initial arm paresis. Patients were stratified into two groups based on the presence or absence of voluntary finger extension (VFE) within 3 weeks post stroke, as a proxy for corticospinal tract (CST) intactness. Neural and non-neural elastic and viscous components of wrist hyper-resistance, obtained by the NeuroFlexor, and synergy-dependent motor recovery of the upper limb, measured by the FM-UE, were assessed within 3 weeks and at 5, 12 and 26 weeks post stroke. On average, patients without VFE within 3 weeks (n = 8) show a gradual increase of the neural component and subsequently also in the non-neural elastic and viscous components of wrist hyper-resistance within the first 26 weeks post stroke. The main increase in the neural component occurred within the first 5 weeks post stroke and preceded the increase in the elastic component after 12 weeks. The group of patients with VFE within 3 weeks (n = 9) shows no significant change in either of the components of wrist hyper-resistance over time. In agreement with previous studies, we found that the absence of VFE at baseline is associated with the absence of spontaneous neurobiological recovery, as the group of patients showing no VFE demonstrate poor upper limb motor recovery, as reflected by the small increase in FM-UE score from 13 to 26 points within the first 26 weeks. In contrast, the group of patients showing VFE demonstrate good upper limb motor recovery, as reflected by the improvement

from 38 to 60 points on the FM-UE. Our findings suggest that the development of the neural component in patients with severe baseline motor deficits might be driven by enhanced multi-synaptic descending pathways when CST integrity is compromised. Interestingly, the neural component showed further increases between weeks 12 and 26 post stroke, which suggests that plasticity is not restricted to the central nervous system alone. This increase of neural component may result from peripheral tissue alterations, as shown by the high correlation between the neural and non-neural elastic components from 12 weeks onward.

In **chapter 6**, instrumented assessment is used to investigate the effects of BoNT treatment in the wrist and/or finger flexor muscles on neural and non-neural elastic and viscous components of wrist hyper-resistance. This pre-experimental study with pre- and post-intervention measurements at 6 and 12 weeks included 18 adults with chronic stroke or cerebral palsy. Our findings show a dose-dependent reduction of the neural component 6 and 12 weeks after intervention, while the non-neural components show no change. Our study suggests that instrumented quantification of wrist hyper-resistance components may have an added value for BoNT treatment indication and evaluation in clinical practice.

In **chapter 7**, the main results of this thesis are discussed and recommendations for future research are given. Overall, the present thesis shows that instrumented assessment of the underlying components of wrist hyper-resistance is of added value to current clinical assessment. Instrumented assessment of wrist hyper-resistance gives more insight into the mechanisms underlying the clinical increased resistance to passive movement and provides a first step in further unravelling upper limb spastic paresis. To move forward in the research and management of upper limb spastic paresis, consensus is needed on definitions concerning all underlying impairments and clinical features related to upper limb spastic paresis, together with construct-valid clinical outcome measures. Future longitudinal studies with multimodal repeated measurements are needed into the pathophysiological mechanisms and interrelationships underlying spastic paresis in time post stroke. Moreover, further refinement of the NeuroFlexor, investigated in this thesis, is needed to further improve the understanding of the underlying wrist hyper-resistance components and for its use for patient-tailored treatment decisions and evaluation in clinical practice. Additionally, future studies are needed to improve and extend the evidence for effective treatment modalities for the separate components underlying spastic paresis, as well as the effect of combined interventions, and the associated cut-off values that can be used for patient selection.