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Identification of neural and non-neural contributors to joint stiffness in upper motor neuron disease

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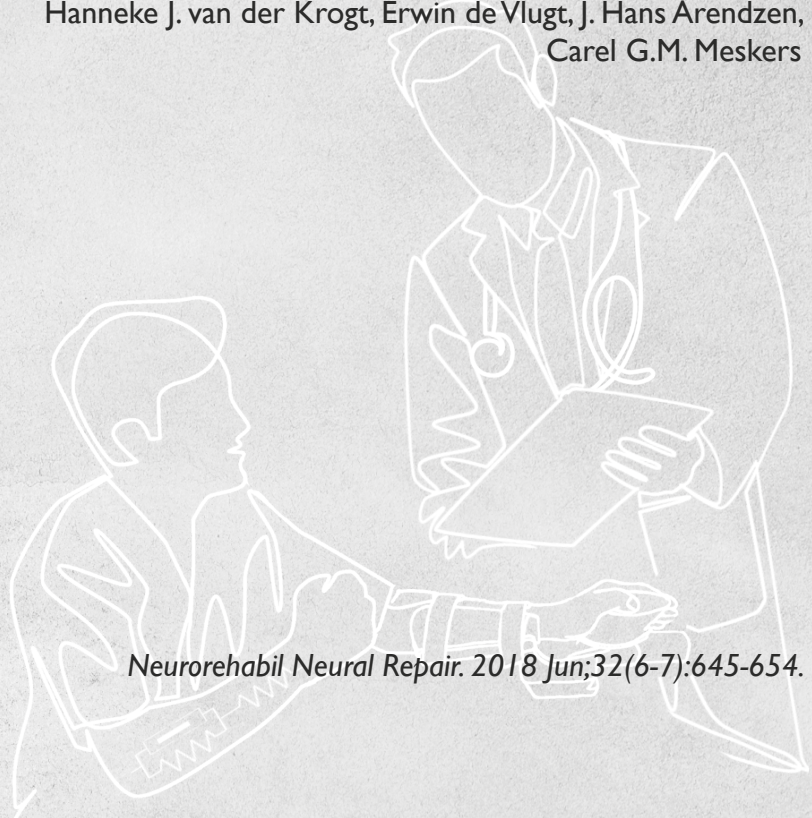
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CHAPTER 5

Early shortening of wrist flexor muscles coincides with poor recovery after stroke

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Abstract

The mechanism and time course of increased wrist joint stiffness post-stroke and clinically observed wrist flexion deformity is still not well understood. The components contributing to increased joint stiffness are of neural reflexive and peripheral tissue origin and quantified by reflexive torque and muscle slack length and stiffness coefficient parameters.

To investigate the time course of the components contributing to wrist joint stiffness during the first twenty-six weeks post-stroke in a group of patients, stratified by prognosis and functional recovery of the upper extremity.

36 stroke patients were measured on eight occasions within the first twenty-six weeks post-stroke using ramp-and-hold rotations applied to the wrist joint by a robot manipulator. Neural reflexive and peripheral tissue components were estimated using an electromyography driven antagonistic wrist model. Outcome was compared between groups cross-sectionally at twenty-six weeks post-stroke and development over time was analyzed longitudinally.

At twenty-six weeks post-stroke, patients with poor recovery ($ARAT \leq 9$ points) showed a higher predicted reflexive torque of the flexors ($P < .001$) and reduced predicted slack length ($P < .001$) indicating shortened muscles contributing to higher peripheral tissue stiffness ($P < .001$), compared to patients with good recovery ($ARAT \geq 10$ points). Significant differences in peripheral tissue stiffness between groups could be identified around week four and five; for neural reflexive stiffness this was the case around week twelve.

We found onset of peripheral tissue stiffness to precede neural reflexive stiffness. Temporal identification of components contributing to joint stiffness after stroke may prompt longitudinal interventional studies to further evaluate and eventually prevent these phenomena.

Introduction

Recovery of motor function of the upper limb after stroke mainly adheres to the first eight weeks post-stroke^{1,2}. These early changes are related to underlying mechanisms of spontaneous neurologic repair³, which is still poorly understood. Most patients with a poor recovery of motor function show increased joint stiffness. The components contributing to increased joint stiffness are of neural reflexive and peripheral tissue origin and quantified by reflexive torque and muscle slack length and tissue stiffness coefficient⁴⁻⁶, determined by e.g. sarcomere length and collagen composition. The timing of developing increased joint stiffness and contribution of its underlying components post-stroke is not clear⁷.

The goal of the current study was to investigate the time course of neural reflexive and peripheral tissue changes in the wrist joint during the first twenty-six weeks post-stroke in three groups of patients, stratified by prognosis and functional recovery of the upper extremity. With a recently developed and validated technique we were able to simulate the wrist torques using muscle activation (electromyography, EMG) and wrist position as input^{8,9}. The time course of the contribution of estimated neural reflexes to wrist joint stiffness and the value of the estimated peripheral tissue parameters (muscle slack length and tissue stiffness coefficient) may ultimately explain the development of wrist joint stiffness over time^{7,8,10,11}. We hypothesize that stroke patients with poor recovery of motor function of the arm have increased reflexive torque and shortened muscles of the flexor muscles at twenty-six weeks resulting in increased joint stiffness and wrist flexion deformity compared to patients with good recovery. As stroke primarily results in a neural paresis and muscle tissue may respond to muscle state changes caused by altered neural input⁴ we presume that neural reflexive changes precede the peripheral tissue changes in the patients with poor recovery.

Knowledge about the time course of changes in the contributors of joint stiffness, i.e. neural reflexes and peripheral tissue stiffness, may significantly contribute to the choice of treatment during the early phase post-stroke and may hand us a key to understand underlying mechanisms of functional recovery.

Methods

Study design

In the multicenter randomized clinical EXPLICIT-stroke trial, the effects of early applied constrained induced movement therapy (CIMT) or EMG triggered neuromuscular stimulation of the finger extensors (EMG-NMS) were compared to usual care on recovery of arm-hand function after stroke^{7;12;13}. A cohort of 36 acute patients was recruited within this EXPLICIT-stroke trial^{7;12;13} (Dutch Trial register NTR1424, part B3). Inclusion criteria comprised first-ever ischemic stroke in the area of middle cerebral artery, impairment of the arm, age 18-80 year and able to travel to the Leiden University Medical Center (LUMC) or University Medical Center Utrecht (UMCU). Exclusion criteria were previous upper extremity orthopedic limitations on the affected side and insufficient communication.

Patients were assessed for eligibility within a week after stroke. Depending on the prognostic presence of finger extension post-stroke and the National Institutes of Health Stroke Score (NIHSS) item 5a or 5b^{7;14;15}, patients were initially stratified in two groups. In the first stratum (finger extension ten degrees or larger at the end of the first week post-stroke and a NIHSS score of 1 or 2 on item 5, good prognosis) patients were randomized to receive constrained-induced movement therapy within their usual care programs¹⁶. In the second stratum (finger extension less than 10 degrees and NIHSS score 3 or 4 on item 5, poor prognosis) patients were randomized to receive electromyography-triggered neuromuscular stimulation of the finger extensors¹⁷ within their usual care programs¹⁶.

Within the measurement framework of EXPLICIT-stroke, patients were measured on eight occasions, i.e. at 1–5, 8, 12, 26 weeks post-stroke. We applied stratification based on the Explicit-stroke study. Therefore, based on both the initial prognosis for functional recovery, i.e. good and poor, and functional outcome at 26 weeks post-stroke, three groups were identified: 1) a GG group of 15 patients with an initially good prognosis for upper extremity motor recovery and showing good recovery at 26 weeks post-stroke, i.e. a score of 10 points or more on the ARAT; 2) a PG group of 12 patients with poor prognosis and good recovery; 3) a PP group of 9 patients with poor prognosis and poor recovery, i.e. a score of 9 points or less on the ARAT at 26 weeks post-stroke.

The study was approved by the medical ethics committee of the LUMC and UMCU. All participants gave their written informed consent prior to the experimental procedure.

Instrumentation and protocol

Subjects were seated upright with the affected arm slightly abducted in the frontal plane. The lower arm was fixed in an arm rest with the elbow at approximately 90 degrees of flexion and the shoulder comfortably relaxed. The hand was fixed into a custom-made handle (Meester Techniek, Leiden, the Netherlands). The wrist joint was aligned to the motor axis of a robot manipulator (Wristalyzer, Moog, Nieuw Vennep, the Netherlands). The robot manipulator delivered precise angular position (rotation) perturbations to the handle via a vertically positioned servomotor (Parker SMH100 series, Parker Hannifin, Charlotte NC, USA) and synchronously recorded the angular position of the handle and torque at the vertical motor axis of the handle, representing the wrist angular position and wrist torque respectively (Figure 5.1)^{9:13:14}.

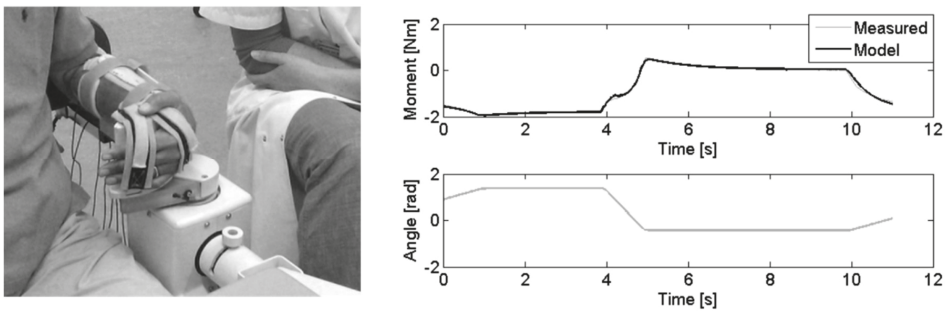


Figure 5.1: Left: *Experimental setup.* The forearm and hand of the subject were fixed to the manipulator (Wristalyzer® by MOOG, the Netherlands). Ramp-and-hold rotations in flexion and extension direction (right) were imposed to the wrist while the subject was instructed to remain relaxed and not react to the rotations. Top right: *measured torque and model fit;* bottom right *measured angle.*

Muscle activation was recorded by means of EMG with bipolar surface electrodes using a Delsys Bagnoli 8 system (Delsys Inc., Boston MA, USA). Electrodes were placed on the flexor carpi radialis (FCR) and on the extensor carpi radialis (ECR) muscles respectively. For the FCR, electrodes were placed on the muscle belly at one third of the line originating from the medial epicondyle of the humerus to the radial styloid process and for the ECR, electrodes were placed on the muscle belly at one third of the line originating from the lateral epicondyle of the humerus to the ulnar styloid process. The EMG signals were sampled at 2048 Hz, online band

pass filtered (20–450 Hz), rectified and low pass filtered (20 Hz, 3rd order Butterworth) to obtain the EMG envelope. EMG at rest was subtracted from the total EMG in order to reduce noise. The filtered and rectified EMG was input for the model. The range of motion (RoM) was determined as the difference between maximal wrist flexion and wrist extension angle resulting from an imposed sinusoidal varying wrist torque starting from 0 Nm and ranging between 2 Nm (extension torque) and –2 Nm (flexion torque) with a duration of about 80-100 seconds. Subsequently, ramp-and-hold (RaH) rotations were imposed onto the wrist over the full (individual) RoM within 1 second. Two RaH trials were imposed per measurement. Each trial encompassed a one second ramp in either extension or in flexion direction, two slow ramps in the opposite direction and three “hold” periods in between the ramps in which the position of the wrist did not change (Figure 5.1). Subjects were asked to remain relaxed during the entire experiment and not to voluntarily react to the imposed wrist movements.

Data analysis

A validated biomechanical EMG driven antagonistic muscle model was used to predict wrist torque from the imposed wrist angle and recorded EMG⁸. The following twelve parameters of the model were predicted through least squares optimization by fitting the predicted torque derived from the model onto the experimentally recorded torque: of both flexor and extensor muscles: the stiffness coefficient, muscle slack length, optimal muscle length, EMG weighting factors and further: mass of the hand and the handle, activation cut-off frequency and parameters related to tissue relaxation, i.e. the tissue relaxation time constant and tissue relaxation factor⁸. The present study focused on four main outcome parameters: 1) The slack muscle length ($l_{p,slack,m}$), which is the minimal muscle (m) length at which passive forces are generated and where m either represents the lumped system of wrist flexors or wrist extensors. 2) The stiffness coefficient (k_m) representing the shape of the force-length curvature of the muscle tissue at lengths exceeding the slack muscle length: the higher the coefficient, the steeper the force-length curvature and the stiffer the muscle; the shorter the slack length, the higher the force at any given length exceeding the slack length. The force-length characteristics of the flexor and extensor muscle models were used to determine 3) the peripheral tissue dependent joint stiffness (peripheral tissue stiffness, K_{joint}) which is both joint angle, i.e. muscle

length, and direction dependent (described for the present study from neutral position towards wrist extension)^{8;9}.

For clinical comparison between subjects, the peripheral tissue stiffness was compared at an identical wrist angle for all subjects. This angle was chosen at zero degrees, i.e. where the robot manipulator handle is in line with the forearm. Besides the peripheral tissue stiffness component of wrist joint stiffness also the neural reflexive stiffness was predicted. As a measure of the amount of reflex activity, the root mean square reflex torques from the flexor and extensor muscles were derived by calculating the integral of the squared instantaneous measurements over the full observation period resulting in the reflexive torque^{8;9} ($T_{reflex,m}$) (4). Trials were excluded from further analysis when the model was not able to predict the measured torque adequately, i.e. variance accounted for (VAF) below 98%. Calculated model parameters were discarded when identified as outlier based on standard deviation when compared to the values at adjacent time points or extraordinary parameter value.

Statistical analysis

A linear mixed model was used to assess the difference in outcome measures at twenty-six weeks post-stroke and each of the other consecutive measured time points between PP, PG and GG groups. A linear model was used to model the within subject correlation structure of the time points as auto-regressive order 1 (AR(1)). There were no random factors in the model. Fixed effects were modelled for the group factor indicating the PP, PG and GG groups, for the time points and for the interaction between the time and group. Alpha was set at .05. For statistical analysis IBM SPSS statistics 22 and GraphPad Prism 6 were used.

Results

The characteristics of the 36 included patients are illustrated in Table 5.1. On average, a patient had 4.6 visits with a total of 163 measurements. Each measurement resulted in a ramp-and-hold trial in flexion direction and a trial in extension direction. Each set of flexion and extension trials resulted in 7 outcome measures. Twenty trials (of 326) were excluded due to poor model

fit (VAF < 98%) and four trials (two measurements) due to corrupt measurement files. For the remaining trials in total 22 outlier outcome measures (~2%) in 11 subjects were identified and excluded for further analysis. Missing measurements exceeded 70% in the first three weeks due e.g. to late enrolment in this part of the EXPLICIT-stroke protocol, medical factors associated with stroke and logistic difficulties. Therefore we focused our statistical analysis on week four and onwards.

Table 5.1: Patient characteristics for patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP).

	GG	PG	PP
Number of patients	15	12	9
Age, years (SD)	6.7 (8.2)	59.6 (14.6)	58.6 (8.6)
Male gender, n (%)	12 (80)	8 (67)	7 (78)
Preferred hand, right, n (%)	13 (87)	11 (91)	7 (78)
Affected hand, right, n (%)	3 (20)	5 (42)	4 (44)
Affected = preferred, n (%)	4 (27)	4 (33)	2 (22)

Cross-sectional group comparison at 26 weeks post-stroke

The PP patient group with poor prognosis and poor recovery of motor function had a significant higher reflexive torque of the flexors ($T_{reflex,flexor}$), a higher peripheral tissue stiffness (K_{joint}) and a smaller slack length of the flexors ($l_{p,slack,flexor}$) compared to patient with good prognosis and good recovery (GG) and patients with poor prognosis and good recovery (PG) (Figure 5.2). The stiffness coefficient of the flexors (k_{flexor}) was lower in the PP group compared to PG group ($P=.029$) and higher in the extensor muscles ($k_{extensor}$) in the PP patient group compared to the PG patient group ($P=.028$). No other differences were observed for the wrist extensor muscles.

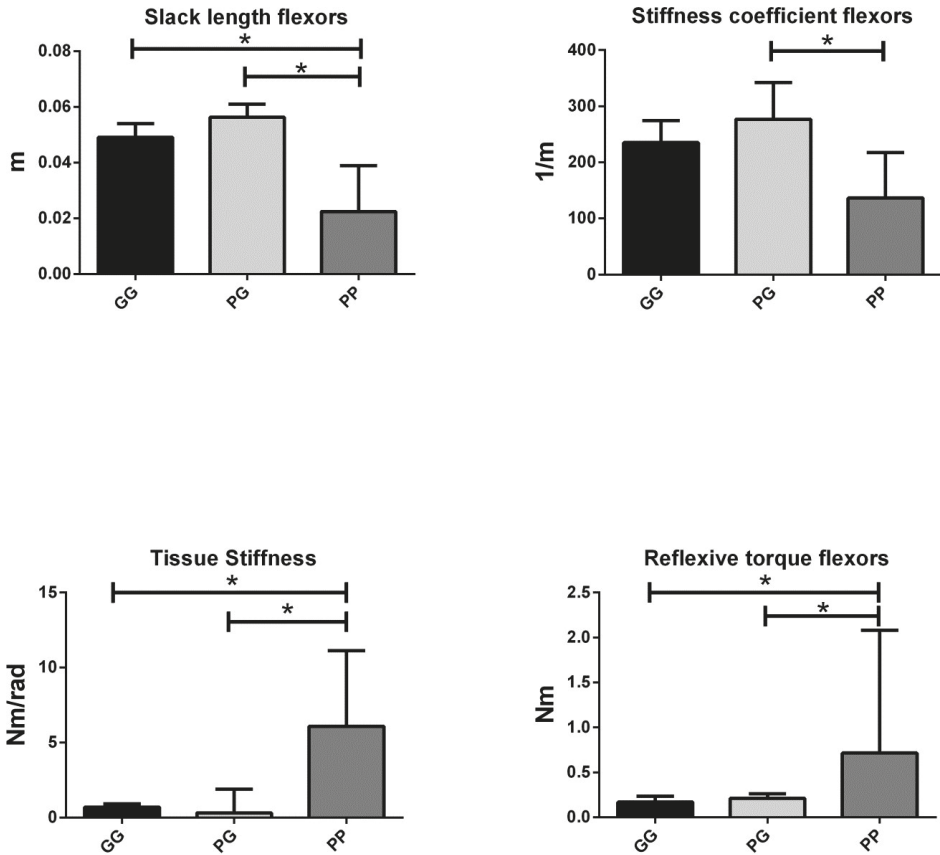


Figure 5.2: Predicted outcome measures for the patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP) at twenty-six weeks post-stroke. Significant differences between groups are indicated with asterisks.

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Table 5.2: Median and interquartile range for the predicted stiffness coefficient (k_m), slack length ($l_{p,slack,m}$), reflexive torque ($T_{reflex,m}$) and peripheral tissue stiffness (K_{joint}) for patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP). In the first three weeks most missing occasions are found. Therefore week four and onwards are shown. Numbers of patients per group and week are shown (n) for parameters related to flexor and extensor muscles. Differences between the two are due to bad model fits (variance accounted for < 98%)

	k_{flex}	$l_{p,slack,flex}$	K_{ext}	$l_{p,slack,ext}$	$T_{Reflex,flex}$	$T_{Reflex,ext}$	K_{joint}	n	n
								(flex)	(ext)
GG									
Week 4	268 (236-391)	.055 (.054-.057)	210 (175-282)	.070 (.061-.075)	.27 (.07-.48)	.066 (.001-.25)	.73 (.30-1.1)	5	6
Week 5	260 (234-329)	.054 (.050-.059)	345 (202-388)	.074 (.064-.078)	.15 (.009-.55)	.088 (.027-.25)	.70 (.26-1.2)	12	11
Week 8	268 (213-321)	.054 (.047-.059)	242 (205-303)	.067 (.058-.070)	.14 (.033-.29)	.16 (.013-.22)	.59 (.33-.84)	10	10
Week 12	244 (174-266)	.052 (.048-.054)	214 (167-319)	.068 (.063-.076)	.085 (.043-.29)	.17 (.083-.35)	.78 (.57-1.3)	12	9
Week 26	235 (196-275)	.049 (.045-.054)	185 (111-290)	.064 (.053-.070)	.17 (.030-.24)	.014 (.000-.089)	.69 (.54-.91)	11	10
PG									
Week 4	251 (239-263)	.054 (.051-.065)	256 (179-382)	.070 (.062-.078)	.23 (.028-.45)	.15 (.000-.36)	.62 (.052-1.0)	3	3
Week 5	217 (187-244)	.053 (.042-.056)	227 (167-279)	.065 (.060-.070)	.19 (.073-.41)	.15 (.052-.41)	.67 (.36-1.8)	12	12
Week 8	244 (234-247)	.052 (.045-.055)	218 (154-239)	.063 (.056-.070)	.20 (.039-.57)	.17 (.13-.33)	1.2 (.57-2.2)	8	8
Week 12	252 (168-385)	.056 (.037-.058)	253 (149-343)	.065 (.051-.074)	.037 (.000-.70)	.20 (.027-.95)	.81 (.36-2.3)	6	6
Week 26	277 (227-342)	.056 (.047-.061)	148 (76-192)	.063 (.052-.071)	.21 (.18-.26)	.078 (.006-.34)	.30 (.28-1.9)	8	8
PP									
Week 4	197 (159-295)	.042 (.036-.056)	242 (189-400)	.072 (.067-.076)	.27 (.14-.39)	.26 (.098-.62)	1.4 (.52-2.5)	5	5
Week 5	187 (132-255)	.042 (.025-.050)	249 (234-320)	.069 (.065-.074)	.34 (.18-.66)	.027 (.003-.40)	2.8 (.82-4.5)	9	9
Week 8	192 (166-267)	.036 (.031-.046)	252 (225-290)	.070 (.062-.072)	.54 (.16-.71)	.015 (.001-.21)	5.8 (4.4-6.9)	6	5
Week 12	152 (121-307)	.029 (.014-.047)	253 (198-330)	.066 (.065-.072)	.71 (.43-1.4)	.14 (.001-.18)	5.0 (2.6-9.0)	5	7
Week 26	137 (119-217)	.023 (.010-.039)	231 (171-340)	.066 (.059-.074)	.71 (.51-2.1)	.027 (.000-.085)	6.1 (4.3-11)	7	7

Longitudinal group comparisons (repeated measures)

Table 5.2 shows the medians with interquartile range (IQR) for the predicted outcome measures. Significant differences initiating at different moments of measurement between the different groups were observed for the reflexive torque of the flexors, the peripheral tissue stiffness (K_{joint}) and the slack length of the flexors (Table 5.3, Figure 5.3).

Table 5.3: Significant differences between patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP) for the predicted slack length of the flexors ($l_{p,slack,flex}$), reflexive torque of the flexors ($T_{reflex,flex}$) and peripheral tissue stiffness (K_{joint}). In the first three weeks most missing occasions are found. Therefore week four and onwards are shown.

	$l_{p,slack,flex}$			$T_{Reflex,flex}$			K_{joint}		
	<i>PP vs</i>	<i>PP vs</i>	<i>GG vs</i>	<i>PP vs</i>	<i>PP vs</i>	<i>GG vs</i>	<i>PP vs</i>	<i>PP vs</i>	<i>GG vs</i>
	GG	PG	PG	GG	PG	PG	GG	PG	PG
<i>Week 4</i>	$P=.025$	$P=.005$	$P=.37$	$P=.94$	$P=.94$	$P=.89$	$P=.577$	$P=.335$	$P=.69$
<i>Week 5</i>	$P<.001$	$P=.013$	$P=.21$	$P=.30$	$P=.35$	$P=.91$	$P=.002$	$P=.069$	$P=.23$
<i>Week 8</i>	$P=.002$	$P=.010$	$P=.72$	$P=.21$	$P=.36$	$P=.74$	$P<.001$	$P<.001$	$P=.51$
<i>Week 12</i>	$P<.001$	$P<.001$	$P=.83$	$P=.001$	$P=.006$	$P=.73$	$P<.001$	$P<.001$	$P=.52$
<i>Week 26</i>	$P<.001$	$P<.001$	$P=.42$	$P<.001$	$P<.001$	$P=.29$	$P<.001$	$P<.001$	$P=.60$

Overall effect of time and group and the interaction effect are shown in Appendix 5. At week four and onwards the slack length of the flexors was significantly smaller in the PP group compared to the GG and PG groups. The peripheral tissue stiffness was increased from week five to week twenty-six for the PP group compared to the GG and PG groups. At week twelve and twenty six the reflexive torque of the flexors was increased in the PP compared to GG and PG.

Extensor reflexive torque differed at week twelve ($P=.019$) between the PG and the PP groups. The extensor slack length was smaller in PG compared to GG ($P=.032$) at week five.

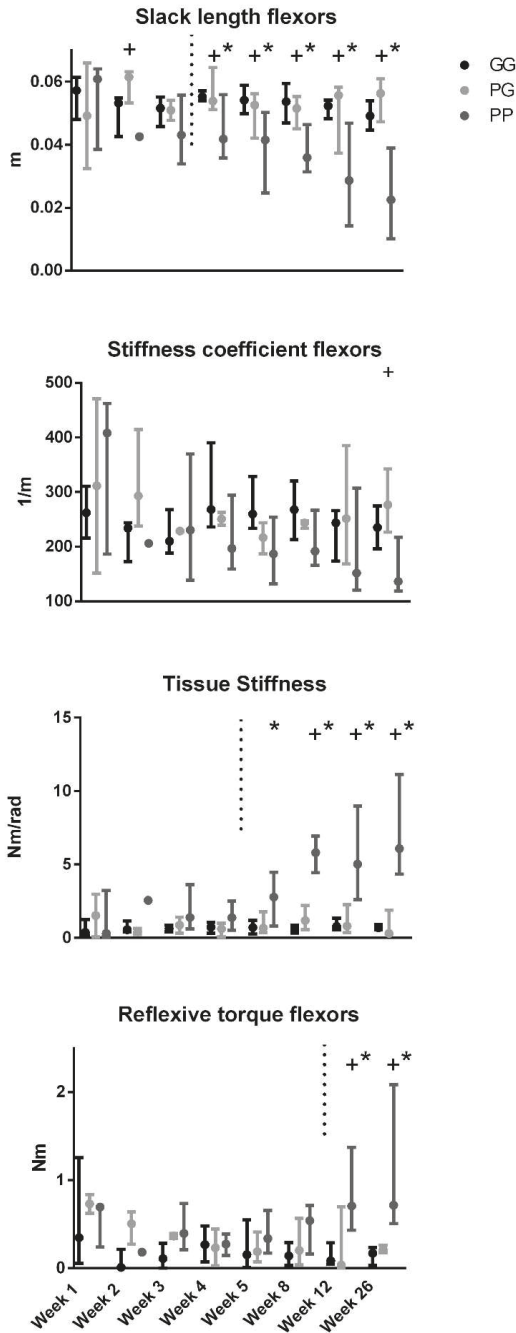


Figure 5.3: Longitudinal observations for the predicted outcome measures for the patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP). Significant differences between the GG and PP groups are indicated with an asterisk () and significant differences between the PG and PP group are indicated with a cross (+). The dashed line denotes the onset of changes between the poor recovery and good recovery groups.*

Discussion

Increased reflexive torque of the flexor muscles and shortened flexor muscles were predicted in patients with poor prognosis and poor recovery of the upper limb (PP, ARAT \leq 9 points) compared to patients with good prognosis and good recovery (GG, ARAT \geq 10 points) and patients with poor prognosis and good recovery (PG, ARAT \geq 10 points) using a validated electromyography driven modeling in 36 stroke patients at twenty-six weeks post-stroke^{8;9}. As expected, patients with an initial poor prognosis and poor recovery showed increased reflexive torque of the flexor muscles ($T_{reflex,flex}$), increased peripheral tissue stiffness (K_{joint}) and shortened flexor muscles, indicated by smaller flexor slack length ($l_{p,slack,flex}$) compared to patients with good recovery, at twenty-six weeks post-stroke. The current study suggests that peripheral tissue changes, i.e. slack length, around week four and five in the PP group preceded the neural reflexive stiffness, i.e. reflexive torque, changes observed around week twelve (Table 5.3).

Cross-sectional group comparison at 26 weeks post-stroke

The PP patient group with poor prognosis and poor recovery had shortened flexor muscles at twenty-six weeks post-stroke, indicated by the smaller slack length of the modelled flexor muscles compared to the good recovery groups (PG and GG). The shortening of the muscle in the PP group is in concordance with the flexion deformity found by van der Krogt et al. (unpublished results), i.e. a marked shift of the wrist rest angle towards flexion, observed in these patients. Note that in the present study the peripheral tissue stiffness (K_{joint}) was measured at a fixed angle of zero degrees. Peripheral tissue stiffness determined at the individual rest angles of patients may reveal a difference with the current study as was previously observed (unpublished results, van der Krogt et al.). This illustrates that peripheral tissue stiffness depends on the angle of observation. Additionally, at the rest position of the wrist (zero torque)³, the stiffness is lowest and contrast between the different groups is minimal. The stiffness coefficient was lower in the PP group compared to the PG group. This could be due to structural changes in the muscle or because of an interaction of the contractile state of passive tissue with the active state of the muscle, e.g. background activation¹⁸ which we currently do not

account for. However, without further substantiating data these physiological explanations are speculative and obviously additional research endeavors and validation are warranted.

The exact mechanism of muscle shortening after an upper motor neuron disease is still unclear¹⁹. A diminished neural input might result in disuse or immobilization and therefore muscle atrophy. Immobilized muscles in a shortened position adapt to their resting length and lose sarcomeres to develop maximal force at their shortened length^{5:20-23}. When stretching the shortened muscles, the diminished number of sarcomeres in series results in a higher tissue stiffness compared to normal muscles. Our data suggest that muscle shortening occurs soon (around week 4) after stroke. Immobilization and muscle over-activity in the sub-acute phase post-stroke may worsen shortening^{5:24}.

Peripheral tissue changes precede neural reflexes changes

The current study suggests that tissue changes in the flexor muscles around week four and five in the poor recovery group (PP) preceded the neural reflexive changes observed around week twelve. The progressive increase in peripheral tissue stiffness and neural reflexive stiffness around the wrist in stroke patients is in accordance with results found by Mirbagheri et al.²⁵ in the elbow joint.

Movement disorders after stroke are the result of a complex interplay between tissue and neural properties^{4:26}. After stroke, central neural drive changes with excessive responses to muscle stretch via several proposed mechanisms which encompass alpha motor neuron hyper excitability, changes in recruitment gain and plateau potentials of motor neurons, loss of presynaptic inhibition and changes in gamma-motor-neuron excitability²⁴. Altered neural input may also comprise increased background muscle activation which may also explain hyper excitability of reflexes^{18:27}. Loss of neural drive also results in flexion synergies at the wrist due to neural coupling with the shoulder and elbow²⁸ which may worsen immobilization of the flexors in a short position. Increased muscle strain in shortened muscles may potentially result in increased spindle responses and subsequent increased spinal reflex activity^{5:29}. This may offer an alternative yet interesting explanation of the temporal delay between tissue changes and reflexive responses. We suppose that tissue changes occur within the first weeks after

stroke. This was confirmed by the large differences between the groups at week four. The onset of shortening within the poor recovery group (PP) is likely to start in the weeks before.

Changes were mainly observed in the flexor muscles. Changes in the extensor muscle were only found for the stiffness coefficient at twenty-six weeks: the stiffness coefficient of the extensors was higher for the PP group compared to the PG group meaning that the extensor muscle was stiffer in the PP group. The different adaptation of the extensor muscle in recovery is not yet clear. At week twenty-six, no differences were found in outcome measures between the GG patients and PG patients. Differences between these groups could arise earlier after stroke. Increased resolution of measurements by increasing the number of observations within these first weeks may reveal differences especially between the PG and PP and GG groups.

Limitations

For this study a validated EMG driven wrist model⁸ was used to predict the peripheral tissue stiffness and neural reflexive components of wrist joint stiffness. Using this method allows us to predict lumped parameters of the flexor and extensor muscle groups. The method can be useful in decisions for treatment and may hand us a key to understand underlying mechanisms of functional recovery^{9;30-34}. However, the method has also some limitations. During the processing of EMG input data, background muscle activation, which is assumed to be noise, was removed from the EMG signal and only the variances in EMG amplitude were used to estimate the reflexive torque. As in stroke patients the rest level EMG may be elevated¹⁸ this elevated additional input is discarded and therefore not included in the active (contractile) contribution to torque. The background activation could not be identified by the model but might be traced back in the overall peripheral tissue stiffness meaning that the peripheral tissue stiffness might have been overestimated in patients with increased background activation. However, analysis of the EMG levels at rest showed no difference between the three groups which made it less likely that differences in background activation explain the observed elevated reflex activity and flexor muscle shortening.

In the EMG driven wrist model⁸ the muscle length at which the highest forces are generated was also included. In the current study this optimal muscle length (i.e. due to the maximal

overlap between contractile filaments) was not presented as reflexive muscle activation in these patients was low in most patients and estimation of contractile muscle properties was therefore unreliable.

The model is a lumped representation of all flexor and extensor muscles. The differences between individual muscles (e.g. flexor carpi radialis and flexor carpi ulnaris) after stroke were therefore not identified.

Most drop-outs were found in the first three weeks. Additional observations, thus increasing statistical power, are needed to obtain reliable information about the neural reflexes and peripheral tissue changes in the first weeks post-stroke for patients with different recovery patterns. Small sample size also prevented further substantiation of the additional effects of treatment. However, subgroup analysis in the present sample showed no substantial differences between intervention and control groups. We chose to use an interaction term in our statistical model, because of plausibility of group and time interaction. Small sample size prevented that this interaction term was significant in all cases.

Clinical implications

Clinically observed changes post-stroke, e.g. the altered wrist flexion deformity, were now further specified by predicting its components explaining increased joint stiffness, i.e. neural reflexive and peripheral tissue stiffness, and characterized over time. Around 4-5 weeks post-stroke significant peripheral tissue changes were observed in a group of patients with initially poor prognosis for functional recovery and a poor recover (i.e. ARAT \leq 9 points) at 26 weeks; changes in reflex torque were only observed after 12 weeks. The exact interplay of properties of neural reflexive stiffness, i.e. reflexive torque and peripheral tissue stiffness, i.e. slack length and stiffness coefficient, background muscle activation and the interplay of both muscle groups need to be studied further to pinpoint the cause-and-effect of increased joint stiffness and whether it can be influenced by therapy shortly after stroke.

Preventing immobilization in a shortening position early after stroke should be an important focus in clinical practice. The effect of therapies on neural reflexive and peripheral tissue stiffness in the acute and sub-acute stroke patients, e.g. neuromuscular electrical stimulation of the wrist extensors (suggested to enhance motor recovery)³⁵, the best timing of physical

therapy³⁶ or the effect of splinting of the wrist³⁷, needs to be studied using longitudinal observations at fixed time points post-stroke.

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Appendix 5: Supplementary Table

Table 5A: Overall effect of time (weeks), overall effect of group (PP, PG, GG) and effect of interaction between group and time for patients with poor prognosis and poor recovery (PP) compared to the good recovery groups for the predicted slack length of the flexors ($I_{p,slack,flex}$), reflexive torque of the flexors ($T_{reflex,flex}$) and peripheral tissue stiffness (K_{joint}). In the first three weeks most missing occasions are found. Therefore week four and onwards are shown.

	$I_{p,slack,flex}$			$T_{Reflex,flex}$			K_{joint}		
	Overall effect of time	Overall effect of group	Interaction effect	Overall effect of time	Overall effect of group	Interaction effect	Overall effect of time	Overall effect of group	Interaction effect
Week 4	F=2.4 (P=0.026)	F=11.9 (P<0.001)	F=1.4 (P=0.17)	F=1.9 (P=0.079)	F=6.2 (P=0.003)	F=1.8 (P=0.043)	F=7.7 (P<0.001)	F=13.7 (P<0.001)	F=5.2 (P<0.001)
Week 5	F=3.5 (P=0.002)	F=10.5 (P<0.001)	F=1.9 (P=0.034)	F=1.9 (P=0.077)	F=6.2 (P=0.003)	F=1.8 (P=0.043)	F=7.1 (P<0.001)	F=13.9 (P<0.001)	F=5.4 (P<0.001)
Week 8	F=3.3 (P=0.004)	F=11.2 (P<0.001)	F=1.9 (P=0.041)	F=1.9 (P=0.079)	F=6.2 (P=0.003)	F=1.8 (P=0.045)	F=5.3 (P<0.001)	F=14.5 (P<0.001)	F=3.8 (P<0.001)
Week 12	F=1.8 (P=0.098)	F=9.8 (P<0.001)	F=1.5 (P=0.13)	F=1.9 (P=0.070)	F=6.4 (P=0.003)	F=1.9 (P=0.038)	F=4.1 (P=0.001)	F=11.6 (P<0.001)	F=3.2 (P=0.001)
Week 26	F=1.7 (P=0.13)	F=10.0 (P<0.001)	F=1.3 (P=0.22)	F=1.8 (P=0.090)	F=5.5 (P=0.006)	F=1.7 (P=0.06)	F=4.5 (P<0.001)	F=10.2 (P<0.001)	F=3.2 (P<0.001)

