Original Research Article

Neurorehabilitation and
Neural Repair
2018, Vol. 32(6-7) 645–654

DOI: 10.1177/1545968318779731
journals.sagepub.com/home/nnr

Early Shortening of Wrist Flexor Muscles Coincides With Poor Recovery After Stroke

Karin L. de Gooijer-van de Groep, MSc[1], Jurriaan H. de Groot, PhD[1], Hanneke van der Krogt, MD[1], Erwin de Vlugt, PhD[2], J. Hans Arendzen, MD, PhD[1], and Carel G. M. Meskers, MD, PhD[3,4]

Abstract

Background. The mechanism and time course of increased wrist joint stiffness poststroke 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. *Objective*. To investigate the time course of the components contributing to wrist joint stiffness during the first 26 weeks poststroke in a group of patients, stratified by prognosis and functional recovery of the upper extremity. *Methods*. A total of 36 stroke patients were measured on 8 occasions within the first 26 weeks poststroke 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 26 weeks poststroke and development over time was analyzed longitudinally. *Results*. At 26 weeks poststroke, patients with poor recovery (Action Research Arm Test [ARAT] ≤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 with patients with good recovery (ARAT ≥10 points). Significant differences in peripheral tissue stiffness between groups could be identified around weeks 4 and 5; for neural reflexive stiffness, this was the case around week 12. *Conclusions*. 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.

Keywords

stroke, muscle spasticity, longitudinal study, wrist, biomechanics

Introduction

Recovery of motor function of the upper limb after stroke mainly adheres to the first 8 weeks poststroke.[1,2] These early changes are related to underlying mechanisms of spontaneous neurologic repair,[3] 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 coefficient,[4-6] determined by, for example, sarcomere length and collagen composition. The timing of developing increased joint stiffness and contribution of its underlying components poststroke is not clear.[7]

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 26 weeks poststroke in 3 groups of patients, stratified by prognosis and functional recovery of the upper extremity. With a recently developed

[1]Leiden University Medical Center, Leiden, The Netherlands
[2]Delft University of Technology, Delft, Netherlands
[3]VU Medical Center, Amsterdam, Netherlands
[4]Amsterdam Movement Sciences, Amsterdam, The Netherlands

Supplementary material for this article is available on the *Neurorehabilitation & Neural Repair* website along with the online version of this article.

Corresponding Author:
Karin L. de Gooijer-van de Groep, Department of Rehabilitation Medicine, Leiden University Medical Center, Postzone B0-Q, P.O. Box 9600, 2300 RC Leiden, the Netherlands.
Email: k.l.de_gooijer-van_de_groep@lumc.nl

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 26 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 input[4] 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, that is, neural reflexes and peripheral tissue stiffness, may significantly contribute to the choice of treatment during the early phase poststroke 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 constraint-induced movement therapy (CIMT) or electromyography (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 to 80 years, 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 poststroke and the National Institutes of Health Stroke Score (NIHSS) item 5a or 5b,[7,14,15] patients were initially stratified in 2 groups. In the first stratum (finger extension 10° or larger at the end of the first week poststroke 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 programs.[16] In the second stratum (finger extension less than 10° and NIHSS score 3 or 4 on item 5, poor prognosis) patients were randomized to receive EMG-NMS of the finger extensors[17] within their usual care programs.[16]

Within the measurement framework of EXPLICIT-stroke, patients were measured on 8 occasions, that is, at 1 to 5, 8, 12, and 26 weeks poststroke. We applied stratification based on the EXPLICIT-stroke study. Therefore, based on both the initial prognosis for functional recovery, that is, good and poor, and functional outcome at 26 weeks poststroke, 3 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 poststroke, that is, a score of 10 points or more on the ARAT; (2) a PG group of 12 patients with poor prognosis and good recovery; and (3) a PP group of 9 patients with poor prognosis and poor recovery, that is, a score of 9 points or less on the ARAT at 26 weeks poststroke.

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° 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 1).[9,13,14] 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, third 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

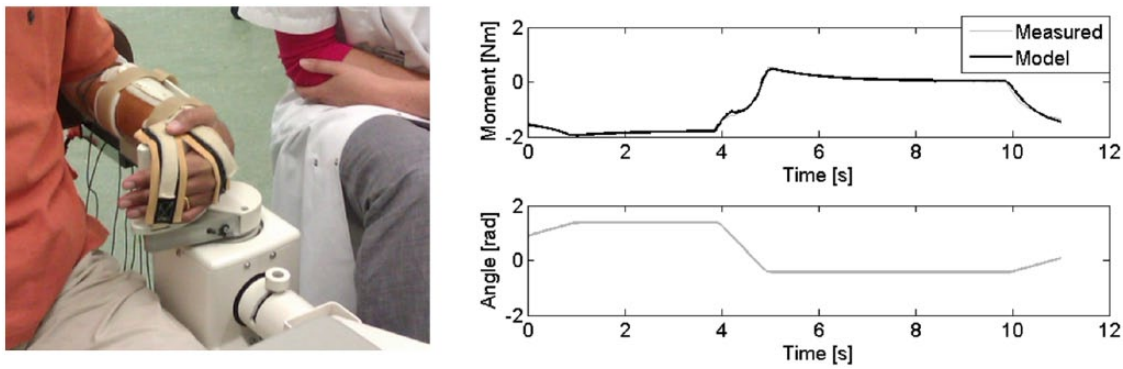

Figure 1. (Left) Experimental setup. The forearm and hand of the subject were fixed to the manipulator (Wristalyzer by MOOG, the Netherlands). Ramp-and-hold rotations in flexion and extension direction (right) were imposed to the wrist while the subject was instructed to remain relaxed and not react to the rotations. (Top right) Measured torque and model fit. (Bottom right) Measured angle.

difference between maximal wrist flexion and wrist extension angle resulting from an imposed sinusoidal varying wrist torque starting from 0 N·m and ranging between 2 N·m (extension torque) and −2 N·m (flexion torque) with a duration of about 80 to 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 1-second ramp in either extension or in flexion direction, 2 slow ramps in the opposite direction, and 3 "hold" periods in between the ramps in which the position of the wrist did not change (Figure 1). Subjects were asked to remain relaxed during the entire experiment and not to voluntary 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 EMG.[8] The following 12 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 cutoff frequency and parameters related to tissue relaxation, that is, the tissue relaxation time constant and tissue relaxation factor.[8] The present study focused on 4 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, that is, muscle length, and direction dependent (described for the present study from neutral position toward 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 0°, that is, 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, that is, variance accounted for (VAF) below 98%. Calculated model parameters were discarded when identified as outlier based on standard deviation when compared with 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 26 weeks poststroke and each of the other consecutive measured time points between PP, PG, and GG groups. A linear model was used to model the

Table 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
No. of patients	15	12	9
Age, years, mean (SD)	60.7 (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)

within-subject correlation structure of the time points as autoregressive 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 0.05. 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 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 4 trials (2 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 3 weeks due to, for example, 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 4 and onward.

Cross-Sectional Group Comparison at 26 Weeks Poststroke

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 2). The stiffness coefficient of the flexors (k_{flexor}) was lower in the PP group compared with the PG group ($P = .029$) and higher in the extensor muscles ($k_{extensor}$) in the PP patient group compared with the PG patient group ($P = .028$). No other differences were observed for the wrist extensor muscles.

Longitudinal Group Comparisons (Repeated Measures)

Table 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 3, Figure 3). Overall effect of time and group and the interaction effect are shown in Supplementary Table A. At week 4 and onward, the slack length of the flexors was significantly smaller in the PP group compared with the GG and PG groups. The peripheral tissue stiffness was increased from week 5 to week 26 for the PP group compared with the GG and PG groups. At weeks 12 and 26, the reflexive torque of the flexors was increased in the PP compared with GG and PG.

Extensor reflexive torque differed at week 12 ($P = .019$) between the PG and the PP groups. The extensor slack length was smaller in PG compared with GG ($P = .032$) at week 5.

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 ≤9 points) compared to patients with good prognosis and good recovery (GG, ARAT ≥10 points) and patients with poor prognosis and good recovery (PG, ARAT ≥10 points) using a validated EMG-driven model in 36 stroke patients at 26 weeks poststroke.[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 26 weeks poststroke. The current study suggests that peripheral tissue changes, that is, slack length, around weeks 4 and 5 in the PP group preceded the neural reflexive stiffness, that is, reflexive torque, changes observed around week 12 (Table 3).

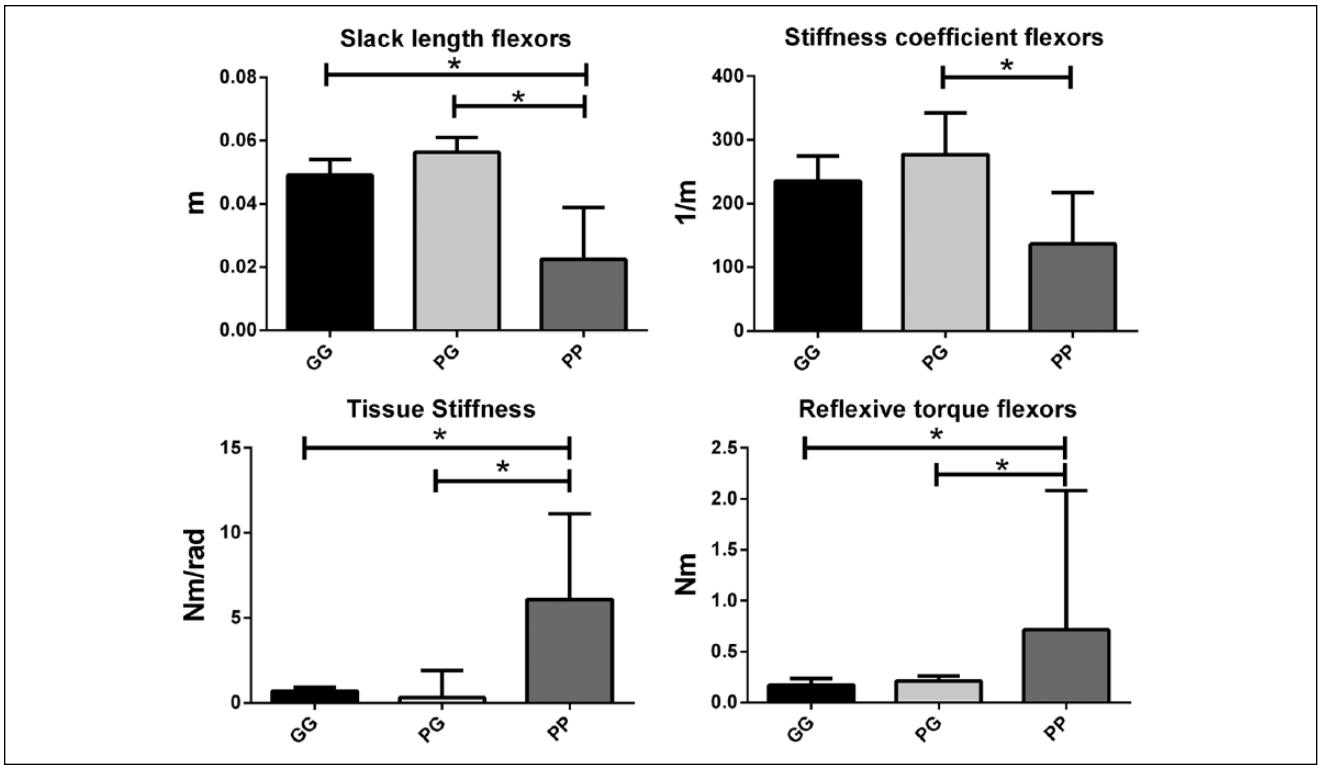

Figure 2. Predicted outcome measures for the patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG) and patients with poor prognosis and poor recovery (PP) at 26 weeks poststroke. Significant differences between groups are indicated with asterisks.

Cross-Sectional Group Comparison at 26 Weeks Poststroke

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), that is, a marked shift of the wrist rest angle toward flexion, observed in these patients. Note that in the present study the peripheral tissue stiffness (K_{joint}) was measured at a fixed angle of 0°. Peripheral tissue stiffness determined at the individual rest angles of patients may reveal a difference with the current study as was previously observed (van der Krogt et al, unpublished results). 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 and interaction of the contractile state of passive tissue with the active state of the muscle, for example, background activation,[18] 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 unclear.[19] 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 overactivity in the subacute phase poststroke may worsen shortening.[5,24]

Peripheral Tissue Changes Precede Neural Reflexes Changes

The current study suggests that tissue changes in the flexor muscles around weeks 4 and 5 in the poor recovery group (PP) preceded the neural reflexive changes observed around

Table 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).[a]

	k_{flex}	$l_{p,slack,flex}$	K_{ext}	$l_{p,slack,ext}$	$T_{Reflex,flex}$	$T_{Reflex,ext}$	K_{joint}	n (flex)	n (ext)
GG									
Week 4	268 (236-391)	0.055 (0.054-0.057)	210 (175-282)	0.070 (0.061-0.075)	0.27 (0.07-0.48)	0.066 (0.001-0.25)	0.73 (0.30-1.1)	5	6
Week 5	260 (234-329)	0.054 (0.050-0.059)	345 (202-388)	0.074 (0.064-0.078)	0.15 (0.009-0.55)	0.088 (0.027-0.25)	0.70 (0.26-1.2)	12	11
Week 8	268 (213-321)	0.054 (0.047-0.059)	242 (205-303)	0.067 (0.058-0.070)	0.14 (0.033-0.29)	0.16 (0.013-0.22)	0.59 (0.33-0.84)	10	10
Week 12	244 (174-266)	0.052 (0.048-0.054)	214 (167-319)	0.068 (0.063-0.076)	0.085 (0.043-0.29)	0.17 (0.083-0.35)	0.78 (0.57-1.3)	12	9
Week 26	235 (196-275)	0.049 (0.045-0.054)	185 (111-290)	0.064 (0.053-0.070)	0.17 (0.030-0.24)	0.014 (0.000-0.089)	0.69 (0.54-0.91)	11	10
PG									
Week 4	251 (239-263)	0.054 (0.051-0.065)	256 (179-382)	0.070 (0.062-0.078)	0.23 (0.028-0.45)	0.15 (0.000-0.36)	0.62 (0.052-1.0)	3	3
Week 5	217 (187-244)	0.053 (0.042-0.056)	227 (167-279)	0.065 (0.060-0.070)	0.19 (0.073-0.41)	0.15 (0.052-0.41)	0.67 (0.36-1.8)	12	12
Week 8	244 (234-247)	0.052 (0.045-0.055)	218 (154-239)	0.063 (0.056-0.070)	0.20 (0.039-0.57)	0.17 (0.13-0.33)	1.2 (0.57-2.2)	8	8
Week 12	252 (168-385)	0.056 (0.037-0.058)	253 (149-343)	0.065 (0.051-0.074)	0.037 (0.000-0.70)	0.20 (0.027-0.95)	0.81 (0.36-2.3)	6	6
Week 26	277 (227-342)	0.056 (0.047-0.061)	148 (76-192)	0.063 (0.052-0.071)	0.21 (0.18-0.26)	0.078 (0.006-0.34)	0.30 (0.28-1.9)	8	8
PP									
Week 4	197 (159-295)	0.042 (0.036-0.056)	242 (189-400)	0.072 (0.067-0.076)	0.27 (0.14-0.39)	0.26 (0.098-0.62)	1.4 (0.52-2.5)	5	5
Week 5	187 (132-255)	0.042 (0.025-0.050)	249 (234-320)	0.069 (0.065-0.074)	0.34 (0.18-0.66)	0.027 (0.003-0.40)	2.8 (0.82-4.5)	9	9
Week 8	192 (166-267)	0.036 (0.031-0.046)	252 (225-290)	0.070 (0.062-0.072)	0.54 (0.16-0.71)	0.015 (0.001-0.21)	5.8 (4.4-6.9)	6	5
Week 12	152 (121-307)	0.029 (0.014-0.047)	253 (198-330)	0.066 (0.065-0.072)	0.71 (0.43-1.4)	0.14 (0.001-0.18)	5.0 (2.6-9.0)	5	7
Week 26	137 (119-217)	0.023 (0.010-0.039)	231 (171-340)	0.066 (0.059-0.074)	0.71 (0.51-2.1)	0.027 (0.000-0.085)	6.1 (4.3-11)	7	7

[a]In the first 3 weeks, most missing occasions are found. Therefore, week 4 and onward are shown. Numbers of patients per group and week are shown (n) for parameters related to flexor and extensor muscles. Differences between the 2 are due to bad model fits (variance accounted for <98%).

Table 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}).[a]

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

[a]Figures shown are *P* values. In the first 3 weeks, most missing occasions are found. Therefore, week 4 and onward are shown.

week 12. 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 hyperexcitability, changes in recruitment gain and plateau potentials of motor neurons, loss of presynaptic inhibition and changes in gamma-motor-neuron excitability.[24] 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 elbow,[28] 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 week 26: The stiffness coefficient of the extensors was higher for the PP group compared with 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 26, 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 model[8] 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 elevated,[18] 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 3 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 model,[8] the muscle length at which the highest forces are generated was also included. In the current study, this optimal muscle length (ie, 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 (eg, flexor carpi radialis and flexor carpi ulnaris) after stroke were therefore not identified.

Most drop-outs were found in the first 3 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

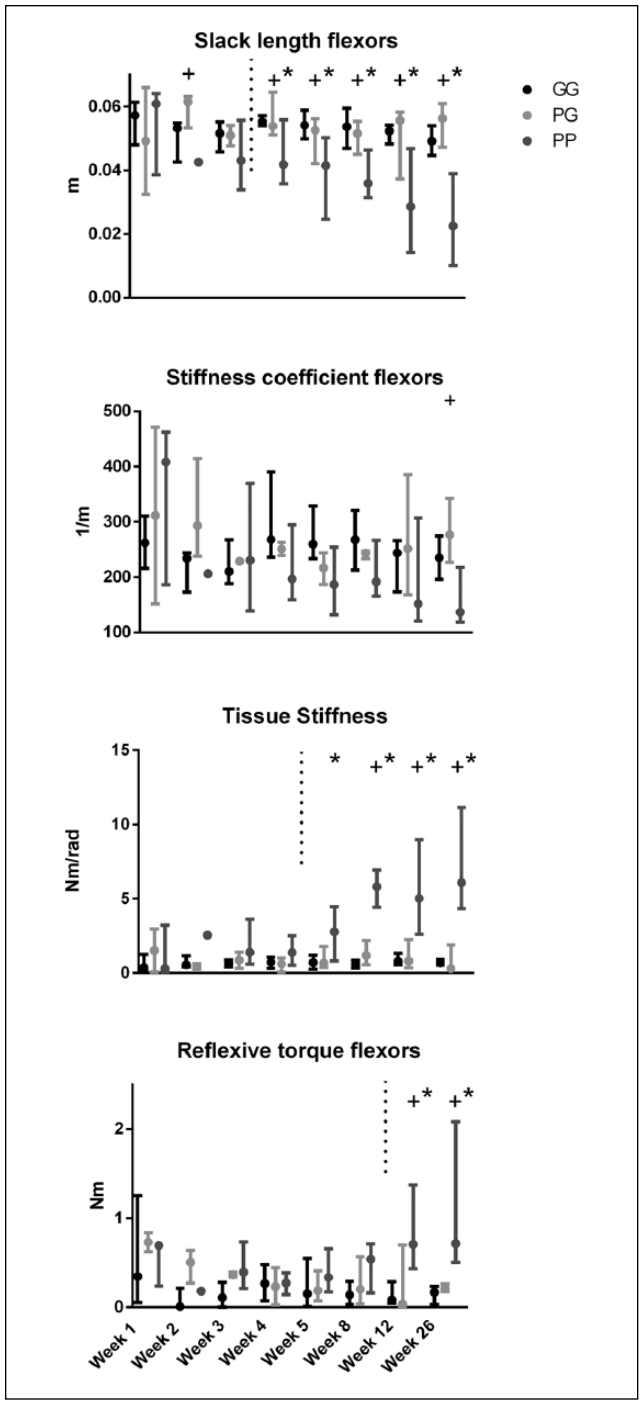

Figure 3. Longitudinal observations for the predicted outcome measures for the patients with good prognosis and good recovery (GG), patients with poor prognosis and good recovery (PG), and patients with poor prognosis and poor recovery (PP). Significant differences between the GG and PP groups are indicated 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.

poststroke 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 poststroke, for example, the altered wrist flexion deformity, were now further specified by predicting its components explaining increased joint stiffness, that is, neural reflexive and peripheral tissue stiffness, and characterized over time. Around 4 to 5 weeks poststroke significant peripheral tissue changes were observed in a group of patients with initially poor prognosis for functional recover and a poor recover (ie, ARAT $\leq$9 points) at week 26; changes in reflex torque were only observed after 12 weeks. The exact interplay of properties of neural reflexive stiffness, that is, reflexive torque and peripheral tissue stiffness, that is, 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 acute and subacute stroke patients, for example, neuromuscular electrical stimulation of the wrist extensors (suggested to enhance motor recovery),[35] the best timing of physical therapy,[36] or the effect of splinting of the wrist,[37] needs to be studied using longitudinal observations at fixed time points poststroke.

Acknowledgments

We thank the Department of Medical Statistics at the LUMC for assistance in statistical analysis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the Dutch Technology Foundation STW (ROBIN project, Grant No. 10733), which is part of the Dutch national organization for scientific research (NWO) and partly

funded by the Ministry of Economic Affairs, Agriculture and Innovation, and the Dutch organization for Health Research and Development ZonMW (Explicit Stroke project, grant nr. 890000001). CGMM is supported by a grant from the Dutch Brain Foundation.

References

1. Kwakkel G, Kollen B. Predicting improvement in the upper paretic limb after stroke: a longitudinal prospective study. *Restor Neurol Neurosci*. 2007;25:453-460.
2. van Kordelaar J, van Wegen E, Kwakkel G. Impact of time on quality of motor control of the paretic upper limb after stroke. *Arch Phys Med Rehabil*. 2014;95:338-344.
3. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci*. 2004;22:281-299.
4. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol*. 2007;6:725-733.
5. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. *Muscle Nerve*. 2005;31:535-551.
6. Diong J, Harvey LA, Kwah LK, et al. Gastrocnemius muscle contracture after spinal cord injury: a longitudinal study. *Am J Phys Med Rehabil*. 2013;92:565-574.
7. Kwakkel G, Meskers CG, van Wegen EE, et al. Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design. *BMC Neurol*. 2008;8:49.
8. de Gooijer-van de Groep K, 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 (Bristol, Avon)*. 2016;35:93-101.
9. 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.
10. Mirbagheri MM, Rymer WZ. Time-course of changes in arm impairment after stroke: variables predicting motor recovery over 12 months. *Arch Phys Med Rehabil*. 2008;89:1507-1513.
11. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. *Restor Neurol Neurosci*. 2013;31: 707-722.
12. 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. doi:10.4172/2155-9538.S1-008.
13. van der Krogt HJ, 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.
14. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G; EPOS Investigators. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke*. 2010;41:745-750.
15. Stinear C. Prediction of recovery of motor function after stroke. *Lancet Neurol*. 2010;9:1228-1232.
16. Van Peppen RP, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehabil*. 2004;18:833-862.
17. Kwakkel G, Winters C, van Wegen EE, et al; EXPLICIT-Stroke Consortium. Effects of unilateral upper limb training in two distinct prognostic groups early after stroke: the EXPLICIT-Stroke randomized clinical trial. *Neurorehabil Neural Repair*. 2016;30:804-816.
18. Burne JA, Carleton VL, O'Dwyer NJ. The spasticity paradox: movement disorder or disorder of resting limbs? *J Neurol Neurosurg Psychiatry*. 2005;76:47-54.
19. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. *Muscle Nerve*. 2004;29:615-627.
20. Tabary JC, Tabary C, Tardieu C, Tardieu G, Goldspink G. Physiological and structural changes in the cat's soleus muscle due to immobilization at different lengths by plaster casts. *J Physiol*. 1972;224:231-244.
21. Williams PE, Goldspink G. Changes in sarcomere length and physiological properties in immobilized muscle. *J Anat*. 1978;127(pt 3):459-468.
22. Wisdom KM, Delp SL, Kuhl E. Use it or lose it: multiscale skeletal muscle adaptation to mechanical stimuli. *Biomech Model Mechanobiol*. 2015;14:195-215.
23. Kelleher AR, Gordon BS, Kimball SR, Jefferson LS. Changes in REDD1, REDD2, and atrogene mRNA expression are prevented in skeletal muscle fixed in a stretched position during hindlimb immobilization. *Physiol Rep*. 2014; 2:e00246.
24. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. *Muscle Nerve*. 2005;31:552-571.
25. Mirbagheri MM, Tsao C, Rymer WZ. Natural history of neuromuscular properties after stroke: a longitudinal study. *J Neurol Neurosurg Psychiatry*. 2009;80:1212-1217.
26. 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.
27. Denny-Brown D, ed. The extrapyramidal cortical system. In: *The Cerebral Control of Movement*. Liverpool, England: University Press; 1966:173.
28. Miller LC, Dewald JP. Involuntary paretic wrist/finger flexion forces and EMG increase with shoulder abduction load in individuals with chronic stroke. *Clin Neurophysiol*. 2012;123:1216-1225.
29. Gioux M, Petit J. Effects of immobilizing the cat peroneus longus muscle on the activity of its own spindles. *J Appl Physiol (1985)*. 1993;75:2629-2635.
30. 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.
31. 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;46:629-634.

32. 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.
33. 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.
34. 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.
35. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke*. 1999;30:1384-1389.
36. Veerbeek JM, van Wegen E, van Peppen R, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One*. 2014;9:e87987.
37. Lannin NA, Cusick A, McCluskey A, Herbert RD. Effects of splinting on wrist contracture after stroke: a randomized controlled trial. *Stroke*. 2007;38:111-116.