Recovery of arm-hand function after stroke: developing neuromechanical biomarkers to optimize rehabilitation strategies.

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Chapter

6

Early increase in active range of motion and a steady rest angle at the wrist are associated with better arm-hand function after stroke: a longitudinal study

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ABSTRACT

In stroke patients, pathophysiological mechanisms of functional recovery are largely unknown. The aims of this study were to quantify neural and non-neural contributors to endpoint wrist joint behavior under both passive and active task conditions, and to relate these neuromechanical parameters to the recovery of arm-hand function.

Methods

Wrist neuromechanical parameters (measured with haptic robotics and surface electromyography) and Action Research Arm Test (ARAT) were assessed prospectively in 36 stroke patients on 8 occasions during the first 6 months after stroke. At 6 months, maximum voluntary contraction, passive stiffness at rest angle and reflex modulation were related to ARAT by linear regression. Predictors of positive functional outcome (ARAT ≥ 10) were determined by a repeated measures model.

Results

At 6 months after stroke, a lower maximum voluntary contraction and impaired reflex modulation were significantly related to poor functional outcome ($p < 0.001$ and $p = 0.047$). A steady rest angle and increasing active range of motion contributed most to prediction of positive functional outcome.

Conclusion

Longitudinally measured neuromechanical parameters relate to arm-hand function during the first 6 months after stroke and, as a reflection of pathophysiological dynamics of recovery, may assist clinicians in triage and assignment of optimally individualized therapy.

INTRODUCTION

Impairment in function of the upper extremity is common after stroke [1,2] and has a profound impact on activities and participation in daily life [1,3-5]. Despite an increased attention for measuring outcome on multiple levels of the International Classification of Functioning, Disability and Health (ICF), the relationship between pathophysiological mechanisms of recovery and functional outcome as measured with clinical scales, is still largely unknown [6-8]. Furthermore, the relationship between pathophysiological mechanisms of recovery and time after stroke is still uncharted territory, as longitudinal data in the acute phase after stroke are still scarce [9,10].

In translational research, the connection between pathophysiological changes and functional outcome is typically addressed by relating neural imaging techniques (e.g. functional MRI, transcranial magnetic stimulation) and movement analysis (e.g. kinematics) to clinical scales [11] on the ICF-levels of impairment (e.g. Fugl Meyer Assessment), activity (e.g. Action Research Arm Test (ARAT), Motor Activity Log) and participation (e.g. Health Related Quality of Life). Neuromechanics [12] may contribute to this framework of assessments by providing a quantitative high resolution assessment of neural and non-neural contributors to endpoint joint behavior under passive and active conditions and as a reaction to external mechanical perturbations [13-15] by use of biomechanical and neurophysiological techniques [6,16]. Measuring neuromechanical parameters around a single joint excludes interference of compensatory movements as seen in multi-joint tasks. Previous studies in stroke indicate a large contribution of paresis, stiffness and a decreased ability to modulate reflexes in a changing environment to poor functional outcome [6,14,16-20]. To further explore this, a longitudinal study was conducted. We hypothesize that a poor functional outcome (less than 10 points on ARAT at 6 months after stroke [11]) is associated with a more pronounced paresis, a higher degree of stiffness and absence of reflex modulation at 6 months post stroke. Furthermore, using our earlier described comprehensive neuromechanical assessment protocol [21], we systematically describe the course of passive, active and reflexive parameters at the wrist joint during the first 6 months after stroke and, with this information, identify neuromechanical predictors of functional outcome.

METHODS

Participants

This study was conducted as an observational study within the EXplaining PLastICITy after stroke trial (EXPLICIT-stroke, Dutch Trial register NTR1424, part B3). EXPLICIT-stroke is a multicenter research program, consisting of a randomized clinical trial on the effects of early rehabilitation intervention on arm-hand function after stroke and a longitudinal survey into the dynamics of post-stroke recovery [11]. Participants were assessed for eligibility within one week after stroke according to the following criteria: first-ever ischemic stroke in area of middle cerebral artery; impairment of the arm (National Institutes of Health Stroke Severity (NIHSS) item 5a or 5b score 1 – 4); age 18 to 80 years; able to travel to Leiden University Medical Center (LUMC) or University Medical Center Utrecht (UMCU).

Participants were excluded in case of previous upper extremity orthopedic limitations on affected side; insufficient communication (Utrecht Communication Observation item 19: score less than 4 points) [22]; and/or severe cognitive impairment (Mini Mental State Examination: score 22 points or less) [23]. Participants were then stratified into 2 prognostic groups according to National Institutes of Health Stroke Severity (NIHSS) item 5a or 5b; group F with a favorable prognosis (score 1 – 2) and group U with an unfavorable prognosis (score 3 – 4). The study was approved by the Medical Ethical Committees of the LUMC and UMCU. Written informed consent was given by all participants in the first week after stroke. All participants started with inpatient rehabilitation and were discharged home as soon as this was safe. This was followed by ambulant/outpatient rehabilitation according to usual care. In addition to usual care, the intervention therapies of the main trial were applied according to stratification (favorable prognosis: modified Constrained Induced Movement Therapy; unfavorable prognosis: electromyography-triggered Neuromuscular Stimulation) and randomization. Participants were compensated for travel expenses.

Measurement set up and protocol

Measurements consisted of a neuromechanical assessment protocol and the ARAT, which were administered on eight occasions at fixed time points within the first 6 months after stroke: weekly in the first 5 weeks after stroke and subsequently at 8, 12 and 26 weeks after stroke. The neuromechanical assessment protocol was performed at the department of Rehabilitation at the LUMC and UMCU. A haptic robot (Wristalyzer[a]) delivered precise torque or position perturbations to a handle[b] via a vertically positioned servomotor[a]. Muscle activity of m. flexor carpi radialis and m. extensor carpi radialis brevis and longus was recorded by a surface EMG-system[c]. Participants were seated upright in front of a screen, with their hand fixed to the handle. The handle had an ellipsoidal shape to prevent finger flexion (Figure 1). The arm and elbow were stabilized in an arm rest. The motor axis was aligned with the rotation axis of the wrist joint, therefore rotation of the motor was directly

coupled to flexion/extension movement of the wrist. Participants were provided with visual feedback on torque, angle or EMG-level, depending on the task instruction.
Each test within the measurement protocol was aimed at quantification of either non-neural contributors (passive parameters) or neural contributors (active and reflexive parameters) to movement disorder after stroke. Passive parameters were measured at low velocity to minimize muscle activation and stretch reflexes, and included a task instruction to "do nothing". Measurement of active parameters included task instructions to "move/push/hold", i.e. exert a voluntary torque or complete a prescribed movement trajectory. Reflexive parameters were measured at higher wrist rotation velocities, to elicit reflexes, with either passive or active task instructions [24]. Measurements took 45 minutes.
Observers of neuromechanical parameters (HK and AK) and ARAT (RN) were blinded for each other's outcome.

Data analysis

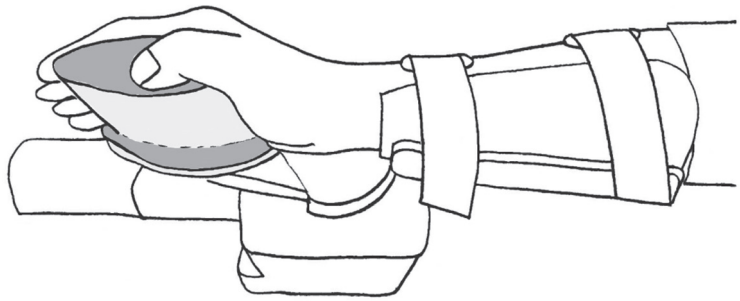
Data were retrieved and processed with customized software written in Matlab 2007b[d]. The following neuromechanical parameters were extracted [24]:
Passive parameters:

- *Passive Range of Motion (P_{ROM}):* range between maximal flexion and extension wrist angles during a slow sinusoidal passive movement with a maximal torque of 2 Nm.
- *Rest Angle (P_{RA}):* angle within passive range of motion where the angle-torque curve crosses 0 Nm, during a slow, position controlled, passive movement.
- *Stiffness in Rest (P_K):* resistance to passive movement during a slow, position controlled, passive movement through passive range of motion. The average negative tangent of the angle-torque curve over 0.2 rad around P_{RA} was calculated.

Active parameters:

- *Active Range of Motion (A_{ROM}):* range between maximal flexion and extension wrist angles obtained during a voluntary movement through range of motion without external resistance.
- *Maximal Voluntary Contraction (A_{MVC}):* maximal isometric torque generated by participants in direction of flexion ($A_{MVC\ flex}$) and extension ($A_{MVC\ ext}$). The handle of the haptic robot was fixed at the Rest Angle (P_{RA}).
- *Control over Joint Torque (A_{CJT}):* ability of participant to achieve steadily increasing target torque in direction of flexion ($A_{CJT\ flex}$) and extension ($A_{CJT\ ext}$). The handle of the haptic robot was fixed at P_{RA}.

Figure 1 | Illustration of Wristalyzer handle and arm-rest.
For a better view of the hand position, the hand straps are not represented in this illustration.



Reflexive parameters:

- *Reflexive Loop Time (R_{lt}):* time from start of ramp and hold perturbation to short latency reflex onset. Participants were asked either to relax ("do nothing") ($R_{lt\ pas}$) or to deliver 10% of maximum EMG-activity as measured during A_{MVC} ($R_{lt\ act}$). Perturbations consisted of position controlled angular displacements over 0.14 rad at a velocity of 2 rad/s.
- *Reflex Magnitude (R_{AUC}):* area under EMG-time curve in window of 0.02 – 0.05s after perturbation. Participants were asked either to relax ("do nothing") ($R_{AUC\ pas}$) or to deliver 10% of maximum EMG-activity as measured during A_{MVC} ($R_{AUC\ act}$). Perturbations consisted of position controlled angular displacements over 0.14 rad at a velocity of 2 rad/s. EMG was normalized, rectified and low pass filtered (80Hz Butterworth).
- *Reflexive Contribution to Joint Resistance (R_{kv}):* participants were asked to resist fast multisine force perturbations ("hold position"). Velocity dependent reflex gain was computed using system identification methods [25].
- *Reflex Modulation due to Environmental Changes (R_{m_env}):* participants were asked to resist fast multisine force perturbations ("hold position") in a damped environment (i.e. a viscous environment was simulated by the haptic robot). Velocity dependent reflex gain in this altered environment was computed [17].

Parameter changes over time were separately analyzed for three groups of participants, defined on both initial prognosis: group F with a favorable prognosis (NIHSS item 5 score 1-2) and group U with an unfavorable prognosis (NIHSS item 5 score 3 – 4); and functional outcome post stroke: ARAT ≥ or < 10 points at 26 weeks [11]. This led to the following groups: favorable prognosis-positive functional outcome ($F\text{-}_{positive}$); unfavorable prognosis-positive functional outcome ($U\text{-}_{positive}$) and unfavorable prognosis-poor functional outcome ($U\text{-}_{poor}$).

Statistical analysis

Parameters were inspected for normality of distribution. The relation between stiffness (Stiffness in Rest = P_k) at 26 weeks and positive functional outcome (i.e. ARAT ≥ 10 at 26 weeks) was described by linear regression. The same applied for paresis (Maximal Voluntary Contraction = $A_{MVC\ flex}$) and reflex modulation (Reflex Modulation due to Environmental Changes = R_{m_env}).

Changes over time and between groups were visually inspected and screened per parameter by a generalized estimating equation with the outcome group ($F\text{-}_{positive}$, $U\text{-}_{positive}$, $U\text{-}_{poor}$) as a between participants factor and time as a within participants factor, and the interaction of time with outcome included in the model. Post-hoc testing per week was then performed by ANOVA and Tukey (or Dennett when parameters were not equally distributed per group as tested with Levene's test).

To determine predictors of a positive functional outcome on the ARAT, a multivariate repeated measures model was fitted by means of a generalized estimating equation. Within this model, the stratified group (F- or U-group) was modeled as a factor, and time (i.e. # weeks after stroke) was modeled as a within participants factor. Descriptive parameters (age, affected hand and gender) and outcome parameters (P_{ROM}, P_k, P_{RA}, $A_{ROM,}$ A_{MVC}, A_{CJT}, R_{lt}, R_{AUC}, R_{kv}, R_{m_env}) were added stepwise. Statistics were performed in SPSS Statistics 20[e].

RESULTS

Out of an eligible cohort of 68 patients, 36 participants were included between April 1th 2009 and March 1th 2012: 15 participants were stratified into the F-group and 21 participants were stratified into the U-group. A description of the study population is presented in Table 1. Due to medical factors associated with stroke (e.g. fatigue, co-morbidity) and logistic difficulties inherent to a multicenter trial (e.g. transport of participants between facilities), 41 out of 288 scheduled visits were cancelled. Sixty visits were missed because of late enrollment; participants were enrolled in EXPLICIT-stroke, but could not participate in part B3 yet, due to location or co-morbidity. An additional 20 visits were cancelled on account of loss to follow up. With an average of 4.7 visits per participant (SD 1.9) in the F-group and 4.6 (SD 1.9) in the U-group, participation in both groups was comparable (p = 0.941, 95% confidence interval -1.2 to 1.3 visits) (Figure 2 Flow Diagram).

All 15 participants in the group with an initial favorable prognosis (F-group) achieved a positive functional outcome of an ARAT score of 10 points or higher at 26 weeks ($F\text{-}_{positive}$). In the group with an initial unfavorable prognosis (U-group), 12 participants (57%) achieved an ARAT of 10 or higher ($U\text{-}_{positive}$) and 9 participants did not (43%) ($U\text{-}_{poor}$).

Table 1 | Descriptive data of the study population.

Overall descriptive data and separate descriptives per group. Groups based on prognosis (NIHSS score item 5) and functional outcome (Action Research Arm Test): F-$_{positive}$: favorable prognosis-positive functional outcome; U-$_{positive}$: unfavorable prognosis-positive functional outcome, and U-$_{poor}$: unfavorable prognosis-poor functional outcome. All variables presented as n (%), unless otherwise indicated. IQR: interquartile range.

	Overall	F-$_{positive}$	U-$_{positive}$	U-$_{poor}$
Participants	36	15	12	9
Age, years (mean, (SD))	59.8 (10.6)	60.7 (8.2)	59.6 (14.6)	58.6 (8.6)
Gender (male)	27 (75)	12 (80)	8 (67)	7 (78)
Hand preference: right hand	30 (83)	13 (87)	11 (91)	7 (78)
Affected hand: right hand	12 (33)	3 (20)	5 (42)	4 (44)
Affected hand = preferred hand	10 (28)	4 (27)	4 (33)	2 (22)
ARAT week 1 (median [IQR])		9 [6 – 31]	0 [0 – 0]	0 [0 – 0]
ARAT week 26 (median [IQR])		40 [38 – 57]	39 [31 – 53]	0 [0 – 3]

Functional outcome related to stiffness, paresis and reflex modulation

At week 26, P_k was not significantly related to functional outcome ($p = 0.940$; Standard Error of the Estimate (SE) 0.055) (Figure 3 top panel). $A_{MVC\ flex}$ at 26 weeks did have a significant relation with functional outcome (Figure 3 middle panel): participants that did not reach 10 points on the ARAT at 26 weeks produced less torque compared to participants with an ARAT score ≥ 10 points at 26 weeks ($p < 0.001$; SE 0.391). R_{m_env} at 26 weeks had a less outspoken, but still significant relation with functional outcome ($p = 0.047$; SE 0.005). In participants that did not reach 10 points on the ARAT, the ability for reflex modulation was diminished (Figure 3 lower panel).

Longitudinal changes

In the first 6 months after stroke, P_{ROM}, P_{RA}, A_{ROM}, $A_{MVCflex}$, A_{MVCext}, $A_{CJTflex}$, A_{CJText}, and $R_{AUCactflex}$ had a significant change in outcome over time and/or between groups as tested with the generalized estimating equation and post-hoc test with ANOVA and Tukey or Dennett. The time course of these parameters is illustrated in Figure 4 and Table 2.

In the F-$_{positive}$ group, passive parameters did not change over time. Active parameters recuperated most before week 4. On average, maximal voluntary contraction (A_{MVC}) and control over joint torque (A_{CJT}) at week 26 did not recover to values measured in healthy volunteers [21]. Reflexive parameters demonstrated small reflex magnitudes and an ability to modulate reflexes in a changing environment.

The U$_{-positive}$ group showed no change in passive parameters except for a reduction in passive range of motion (P_{ROM}). Active parameters recuperated, but at a later moment in time than observed in the F-$_{positive}$ group. The ability to modulate reflexes in a changing environment (R_{m_env}) did not change over time.

The U_{-poor} group had a marked shift in rest angle (P_{RA}) towards flexion as early as the first week after stroke (this could only be quantified from week 8 onwards because of small groups/ missing values), little or no improvement in active parameters, higher reflex magnitudes (R_{AUC}) and a diminished ability to modulate reflexes in a changing environment (R_{m_env}).
A marked increase in A_{ROM} in the $F\text{-}_{positive}$ and $U\text{-}_{positive}$ group was observed before week 4, while an increase in A_{ROM} in the $U\text{-}_{poor}$ group was not observed until week 8. The increase in Maximal Voluntary Contraction ($A_{MVC\ flex}$) in the U-group started at 5 weeks. Improvement in Control over Joint Torque ($A_{CJT\ flex}$) in the U-group started at 5 weeks or later.

Figure 2 | Flow Diagram.

Progress of participants through our observational study. Flow diagram based on CONSORT statement [26]. F-group = favorable prognosis, U-group = unfavorable prognosis.

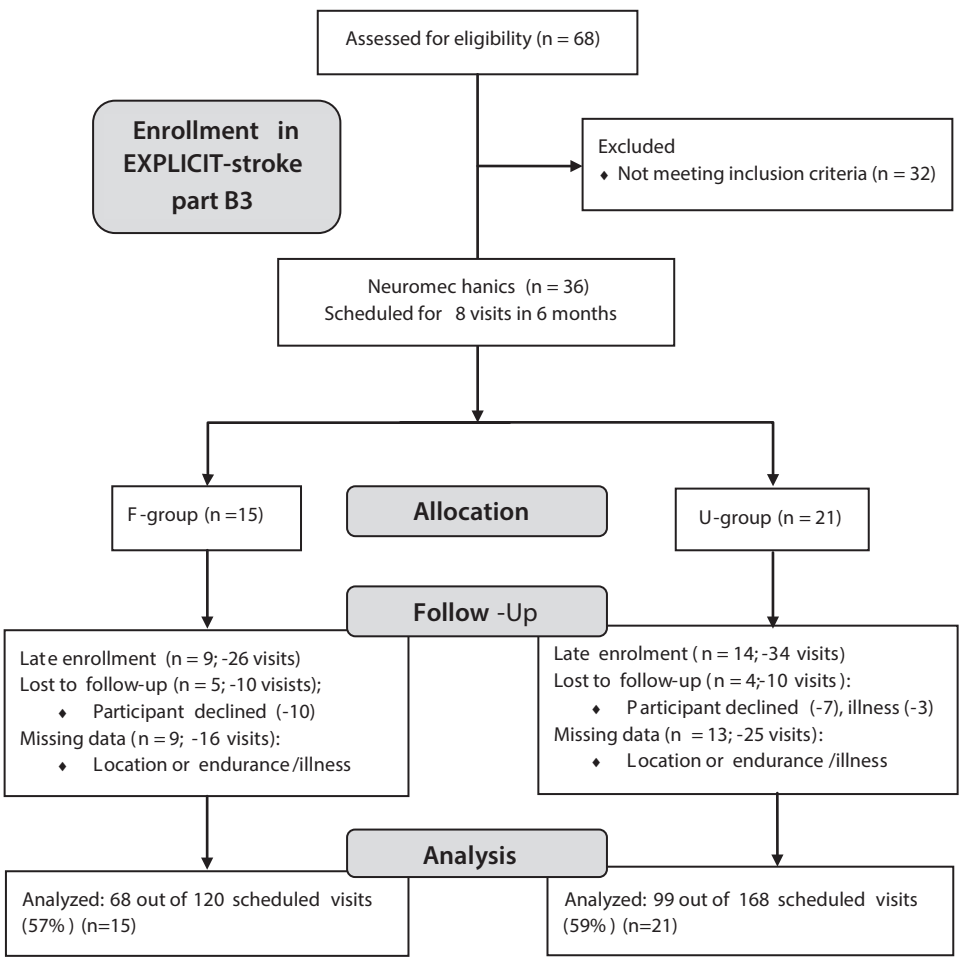
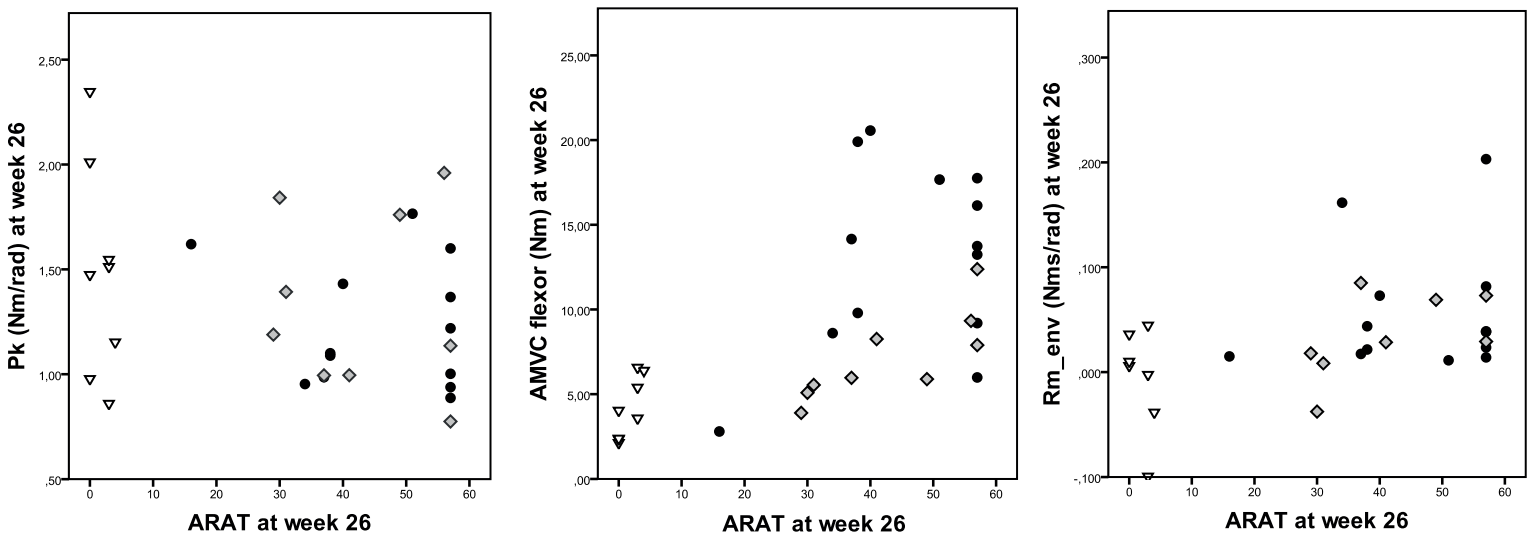


Figure 3 | Stiffness in Rest, paresis and reflex modulation related to ARAT at 26 weeks post stroke: scatter plot.

Top panel: P_k = Stiffness in Rest; Middle panel: A_{MVC}=Maximal Voluntary Contraction; Lower panel: R_{m_env}= Reflex Modulation due to Environmental Changes. Black dots: $F_{-positive}$ group, Grey squares: $U_{-positive}$ group, White triangles: U_{-poor} group. ARAT= Action Research Arm Test.



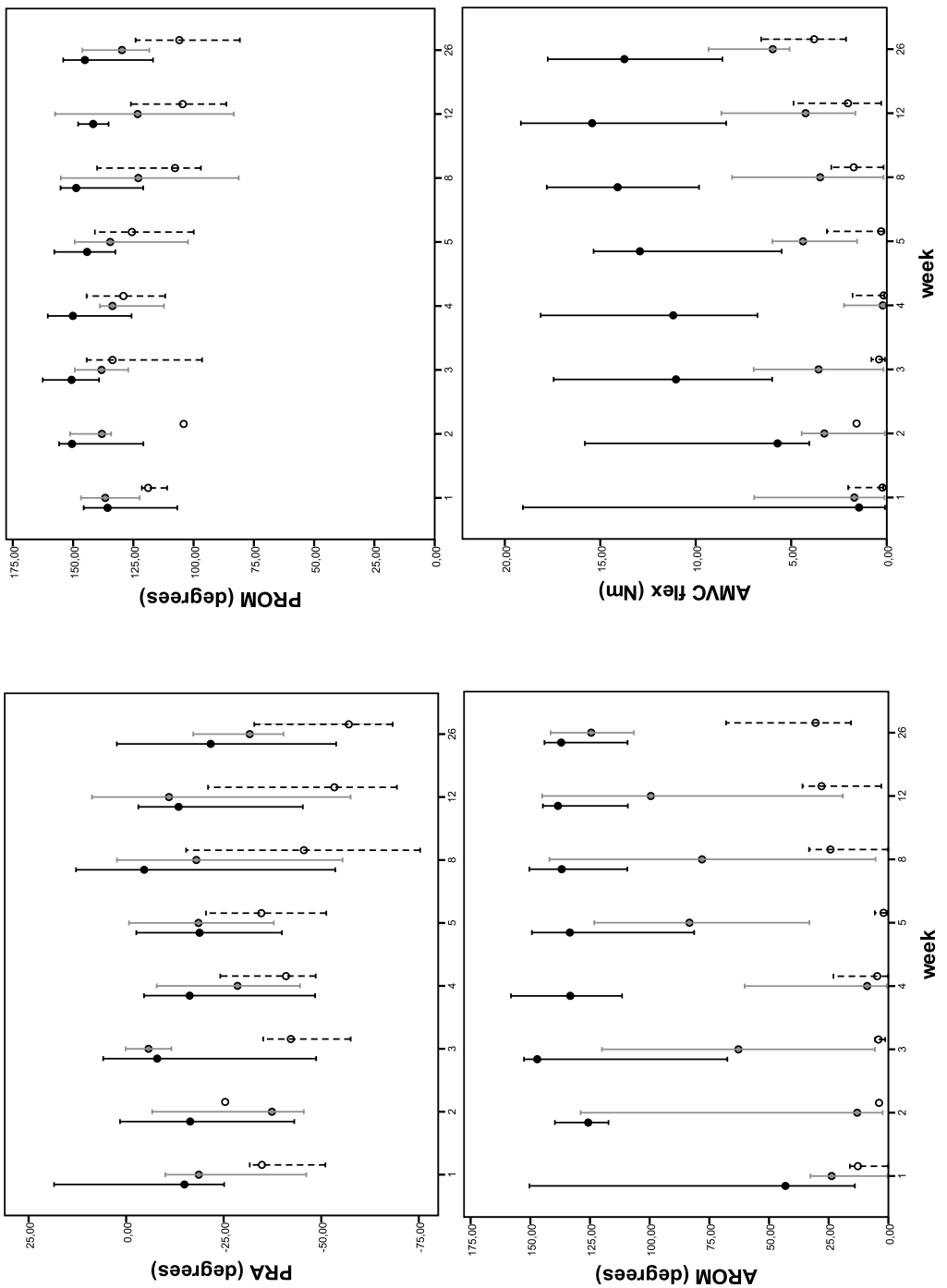


Figure 4 | Passive, active and reflexive parameters from week 1 to week 26 after stroke.

Figure 4 | Passive, active and reflexive parameters from week 1 to week 26 after stroke.

Bar charts with median and 95% confidence interval for parameters with a significant change over time or between groups. Black bars: $F_{-positive}$ group, Grey bars: $U_{-positive}$ group, Striped bars: U_{-poor} group. P_{ROM} = Passive Range of Motion, P_{RA} = Rest Angle, A_{ROM} = Active Range of Motion, A_{MVC} = Maximal Voluntary Contraction, A_{CJT} = Control over Joint Torque, R_{AUC} = Reflex Magnitude and R_{m_env} = Reflex Modulation due to Environmental Changes. A more detailed description of changes in outcome parameters over time can be found in Appendix A. Wrist flexion angles were defined as negative angles.

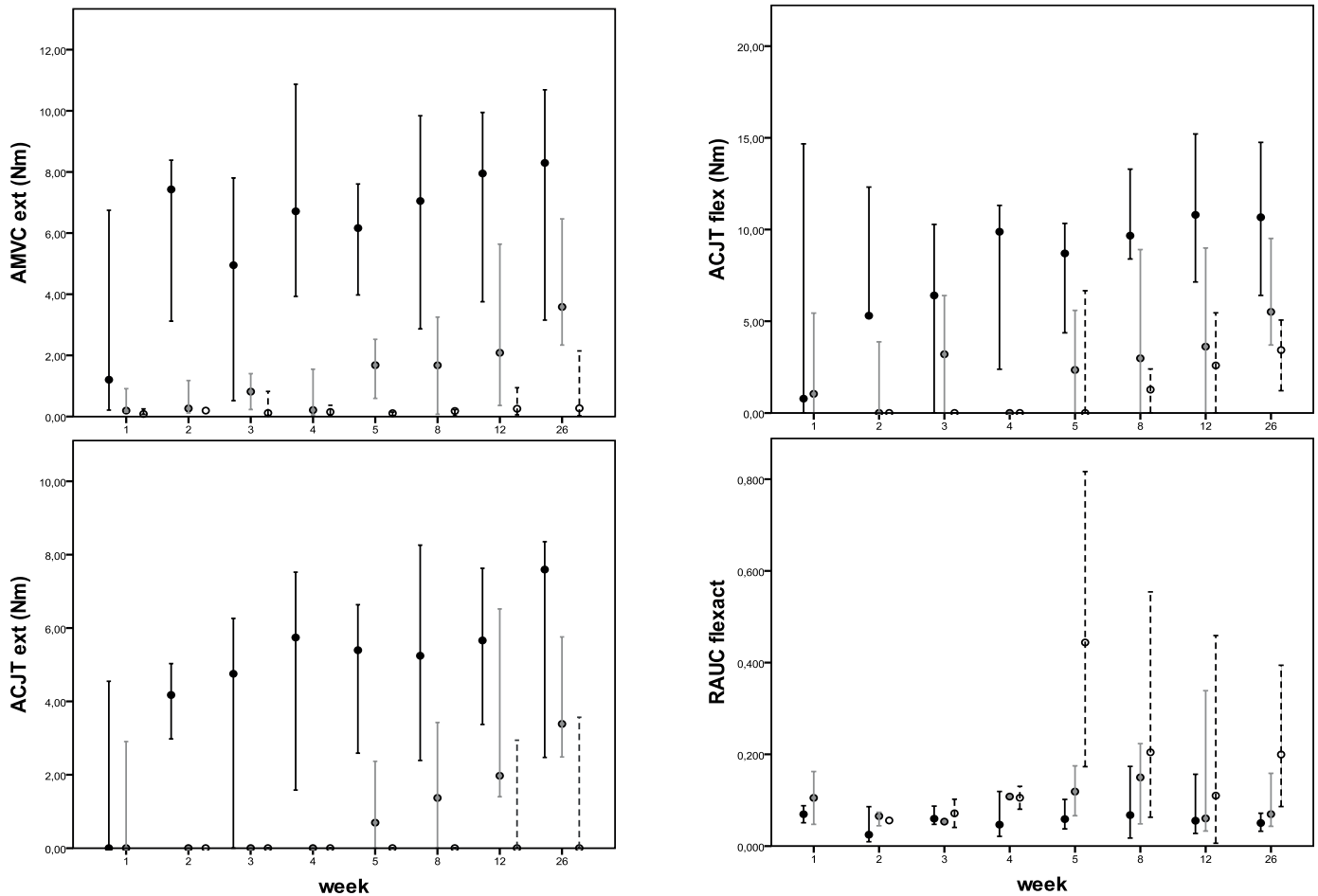


Table 2 | Analysis of changes over time and between groups per parameter.

Group and time effect and the interaction between group and time as tested with a generalized estimating equation. Group was modelled as a between participants factor and time (i.e. # weeks after stroke) as a within participants factor; p-values of the Wald Chi Square are represented. Post-hoc analysis by ANOVA and Tukey (or Dennett when parameters were not equally distributed per group as tested with Levene's test). P_{RA} = Rest Angle, P_{ROM}= Passive Range of Motion, P_k = Stiffness in Rest, A_{ROM} = Active Range of Motion, A_{MVC} = Maximal Voluntary Contraction, A_{CJT} = Control over Joint Torque, R_{lt} = Reflexive Loop Time, R_{AUC} = Reflex Magnitude, R_{kv} = Reflexive Contribution to Joint Resistance, R_{m_env} = Reflex Modulation due to Environmental Changes. F = F-$_{positive}$ group, U+ = U-$_{positive}$ group, U- = U-$_{poor}$ group.(continues on next page)

Parameter	Generalized estimating equation			Post hoc analysis				
	Group	Time	Inter-action	Week 4	Week 5	Week 8	Week 12	Week26
P_{RA}	< 0.001	0,217	< 0.001	n.s.	n.s.	U-/F 0.041	U-/F 0.043	U-/F 0.007 U-/U+ 0.037
P_{ROM}	< 0.001	< 0.001	< 0.001	n.s.	U-/F 0.028	U-/F 0.003	U-/F 0.001 U+/F 0.044	U-/F 0.001 U-/U+ 0.012
P_k	0.525	0.487	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
A_{ROM}	< 0.001	< 0.001	< 0.001	U-/F <0.001 U+/F <0.001	U-/F <0.001 U-/U+ <0.001 U+/F 0.020	U-/F <0.001 U-/U+ <0.001 U+/F <0.001	U-/F <0.001 U-/U+ <0.001 U+/F 0.010	U-/F <0.001 U-/U+ <0.001
$A_{MVC\ flex}$	< 0.001	< 0.001	0.015	U-/F 0.005 U+/F 0.005	U-/F <0.001 U+/F 0.004	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F <0.001	U-/F <0.001 U-/U+ 0.039 U+/F 0.010
$A_{MVC\ ext}$	< 0.001	< 0.001	< 0.001	U-/F 0.005 U+/F 0.005	U-/F <0.001 U-/U+ 0.001 U+/F <0.001	U-/F <0.001 U-/U+ 0.007 U+/F <0.001	U-/F <0.001 U-/U+ 0.035 U+/F 0.001	U-/F <0.001 U-/U+ 0.001 U+/F 0.021
$A_{CTJ\ flex}$	< 0.001	< 0.001	0.001	U-/F 0.006 U+/F 0.006	U-/F <0.001 U+/F 0.011	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F 0.001	U-/F <0.001 U+/F 0.026
$A_{CTJ\ ext}$	< 0.001	< 0.001	< 0.001	U-/F 0.003 U+/F 0.003	U-/F <0.001 U+/F <0.001	U-/F <0.001 U+/F 0.001	U-/F 0.001 U+/F 0.050	U-/F <0.001
$R_{lt\ flex\ pas}$	0.765	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ ext\ pas}$	0.141	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ flex\ act}$	0.660	0.001	0.002	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{lt\ ext\ act}$	0.577	< 0.001	0.097	n.s.	n.s.	n.s.	n.s.	n.s.
$R_{AUC\ flex\ act}$	< 0.001	< 0.001	< 0.001	n.s.	U-/F <0.001 U+/F <0.001	n.s.	n.s.	U-/F 0.012
$R_{AUC\ ext\ act}$	0.501	< 0.001	0.105	n.s.	n.s.	n.s.	n.s.	n.s.
R_{kv}	0.199	0.076	0.009	n.s.	n.s.	n.s.	n.s.	n.s.
R_{m_env}	0.828	< 0.001	< 0.001	n.s.	n.s.	n.s.	n.s.	n.s.

A catch or clonus during measurements of reflexive parameters with the haptic robot was observed in 1 out of 12 participants in the U-$_{positive}$ group (8%) and 4 out of 9 participants in the U-$_{poor}$ group (44%), the earliest at week 5.

Prediction of positive functional outcome

In the repeated measures model, descriptive parameters (age, affected hand and gender) were not influential. Co-linearity was observed between the active parameters A_{ROM}, A_{MVC} and A_{CJT}. Of these parameters, A_{ROM} was included in the model as most influential. R_{AUC} was identified as a confounder for P_k, and therefore kept in the model, although not reaching significance. Therefore, the definitive model included passive parameters P_k and P_{RA}; active parameter A_{ROM}; and reflexive parameters R_{m_env} and R_{AUC}. Quasi Likelihood under Independence Model Criterion (QIC) of the definitive model was 50 (in a smaller-is-better format). Adding more parameters worsened the QIC, while not altering beta-coefficients and p-values of parameters mentioned above.

From this model it can be concluded that a steady P_{RA} and an increasing A_{ROM} were the best predictors of reaching a score of 10 points or higher at the ARAT at 26 weeks after stroke (p 0.039 and $p < 0.001$ respectively), but only when outcomes of the reflexive parameters R_{m_env} and R_{AUC} were included in the model. See Table 3 for model parameters and confidence intervals.

Table 3 | Repeated measures model.

To identify predictors of a positive functional outcome (ARAT ≥10 (per week), a multivariate repeated measures model was fitted by means of a generalized estimating equation. Within this model, the stratified group (F- or U-group) was modeled as a between participants factor, and time (i.e. # weeks after stroke) was modeled as a within participants factor. Parameters were added stepwise.

*F-group = favorable prognosis, U-group = unfavorable prognosis. P_{RA} = Rest Angle, A_{ROM} = Active Range of Motion, R_{AUC} = Reflex Magnitude, R_{m_env} = Reflex Modulation due to Environmental Changes. * significant p<0.05 †F is set to zero because this is the reference category, i.e. functional outcome of U-group is compared to F-group. Wrist flexion angles were defined as negative angles.*

Parameter	Beta	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p-value
(Intercept)	0.293	1.3829	-2.418	3.003	0.045	1	0.832
F- group	0†						
U- group	-3.378	1.8903	-7.083	0.327	3.192	1	0.074
P_{RA}	0.040	0.0194	0.002	0.078	4.257	1	0.039*
A_{ROM}	0.046	0.0131	0.021	0.072	12.510	1	0.000*
R_{AUC}	-0.657	4.2594	-9.006	7.691	0.024	1	0.877
R_{m_env}	1.369	3.3986	-5.292	8.030	0.162	1	0.687
(Scale)	1						

DISCUSSION

As hypothesized, paresis and diminished ability to modulate reflexes (quantified by reduced A_{MVC} and lower R_{m_env}) were significantly related to poor functional outcome (ARAT less than 10 points at 26 weeks after stroke). Stiffness (P_k at rest angle), was not significantly related to poor outcome.

Repeated measurements with a neuromechanical assessment protocol in this cohort of acute stroke patients showed changes in two out of three passive parameters, changes in active parameters even before week 4, and small to no changes in reflexive parameters.

A steady rest angle (P_{RA}) and an increasing active range of motion (A_{ROM}) were the best predictors for functional outcome at 26 weeks after stroke (ARAT ≥ 10 points).

Clinical implications

In this study, changes in tissue properties in the U-group with a poor functional outcome (U_{-poor} group) were represented by a shift in rest angle (P_{RA}) and passive range of motion (P_{ROM}), and not by a change in stiffness in rest (P_k). Apparently, when objectively measuring these separate properties under standardized measurement conditions, shortening of elastic structures is represented by a shift in operating point (rest angle) and a limitation in the movement trajectory (passive range of motion). This is supplementary to previous findings [27,28].

Functional recovery in the group with an initial unfavorable prognosis is first heralded by an increase in active range of motion. It should be noted that recovery in time can differ between patients and it may take at least 5 – 8 weeks for an increase in active range of motion to become apparent in patients with an initial unfavorable prognosis. This is in accordance with earlier published research [9,10]. A marked shift in rest angle towards flexion is apparent from the start in the group with an initial unfavorable prognosis. These combined outcomes lead to the recommendation of regular (e.g. weekly) measurements of A_{ROM}, P_{ROM} and rest angle in the first 8 weeks after stroke, ideally in a standardized environment.

Strengths and limitations

Studies on longitudinal assessment in the acute phase after stroke are scarce. We comprehensively and prospectively assessed neuromechanics by means of passive, active and reflexive parameters at fixed time points after stroke with a validated neuromechanical assessment protocol [21] and related them to functional outcome in a stratified cohort of stroke patients in the early phase after stroke. Despite all efforts to complete all visits, missing data were unavoidable and occurred predominantly in the early phase after stroke. Due to the stratification based on early prediction of outcome the effects of selection bias were limited.

Division in passive and active parameters was based on task instructions. This facilitates clinical assessment and interpretation of parameters, yet does not absolutely discriminate between tissue properties and motor unit recruitment [28,29], as involuntary motor unit recruitment may also be present at rest when measuring passive parameters (e.g. elevated baseline activation). Also, reflex magnitude measurement was calculated relative to the baseline EMG of the participant. Some underestimation of stretch reflex activation might therefore be expected [29]. Possible variance in EMG caused by daily fluctuations in reflex thresholds may introduce additional variance in reflexive parameters. Sophisticated system identification techniques are required to further discriminate neural and non-neural contributors to movement disorder after stroke, e.g. to discern baseline activity from reflexive activity [29,30].

CONCLUSION

In this observational study, longitudinally measured neuromechanical parameters were combined with data on arm-hand function after stroke. Paresis (i.e. low maximal voluntary contraction) and a diminished ability to modulate reflexes are associated with poor functional outcome at 6 months after stroke. Changes in tissue properties were represented by a shift in wrist rest angle towards flexion and a decline in passive range of motion, rather than by passive stiffness measured around the rest angle. Passive, active and reflexive neuromechanical parameters significantly changed over time and showed group effects based on favorable/unfavorable prognosis versus positive/poor functional outcome 6 months after stroke. An increase in active range of motion and a steady rest angle contributed most to prediction of functional outcome at 6 months after stroke. These neuromechanical parameters show potential as biomarkers for prediction of arm-hand function after stroke and may contribute to the translation of neural repair at the level of body function and structures to recovery on the level of activities and participation.

Abbreviations

ARAT: Action Research Arm Test;

EMG: Electromyography;

EXPLICIT-stroke: the EXplaining PLastICITy after stroke trial;

ICF: International Classification of Functioning, Disability and Health (WHO, Geneva 2001);

LUMC: Leiden University Medical Center;

QIC: Quasi Likelihood under Independence Model Criterion;

UMCU: University Medical Center Utrecht;

SE: Standard Error.

Suppliers

a. Haptic wrist manipulator "Wristalyzer" containing a Parker SMH100 series servo motor: Moog FCS, PO Box 187, 2150 AD Nieuw-Vennep, the Netherlands.
b. Handle production: Meester techniek, Dorus Rijkersweg 23, 2315 WC Leiden, the Netherlands
c. Bagnoli 8 channel surface electromyography acquisition equipment and surface EMG sensors: Delsys Inc. P.O. Box 15734 Boston, MA, 02215, USA.
d. Mathworks, 3 Apple Hill Drive, Natick, MA 01760-2098, USA.
e. SPSS Statistics 20: IBM, 1 New Orchard Rd. Armonk, NY, 10504-1783, USA.

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Conflicts of interest

None

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