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

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Issue Date: 2018-11-06

Chapter 7

Discussion

The aim of this thesis was to explore the neuromechanics of recovery of arm-hand function after stroke by assessing neural and non-neural contributors to movement disorders in the acute and chronic phase after stroke. Key questions were: How and to what extent does endpoint wrist joint behavior, as measured with neuromechanical parameters, change in the first 6 months after stroke? And how do those changes relate to functional outcome? For this purpose, an assessment protocol with valid and sensitive parameters had to be developed, based on clear pathophysiological concepts. With the assessment protocol, a prospective study with repeated measurements of neuromechanical parameters in the first 6 months after stroke was conducted.

Developing a neuromechanical assessment protocol

A literature review revealed a number of initiatives to quantify and objectify movement disorders after stroke. In 19 out of the 37 articles describing the use of biomechanical and/or EMG outcome measures to analyze post-stroke movement disorder, the authors strived to separate neural contributors (motor control and stretch reflexes) from non-neural contributors (tissue properties). The most frequently used pathophysiological constructs were spasticity, muscle tone and muscle overactivity. However, definitions of these constructs were not uniform and the distinction between neural and non-neural contributors to movement disorders after stroke was not commonplace yet. Only 6 of the articles measured biomechanical and electromyographical outcome measures simultaneously, while applying the active and passive tasks and multiple movement velocities necessary to separate neural and non-neural contributors to movement disorders after stroke (chapter 2).

The overview of pathophysiological constructs and required measurement conditions generated a methodology to assess endpoint joint behavior around a single axis. This methodology was translated into a comprehensive assessment protocol to quantify endpoint wrist joint behavior i.e. motor control, stretch reflex properties and tissue properties during flexion-extension movement under different task instructions and with different external perturbations, resulting in passive, active and reflexive neuromechanical parameters (chapter 3).

The neuromechanical parameters were responsive to clinical status, i.e. results demonstrated differences between a cohort of healthy participants and a cohort of chronic stroke patients. Test-retest reliability was assessed: passive and active parameters could be assessed with excellent reliability. The passive parameter rest angle and all but one of the reflexive parameters had fair to good reliability (chapter 4).

Evaluation of selective muscle activation by means of Activation Ratios (AR) of flexor carpi radialis (FCR) and extensor carpi radialis communis (ECR) was supported by high measurement reliability in participants with any voluntary muscle activation. AR were significantly lower in chronic stroke patients compared to healthy participants, indicating loss of selective muscle activation in the chronic stroke patients. Based on the ability for voluntary muscle activation and selective muscle activation, three clinical phenotypes were confirmed, i.e. patients with flaccid paresis and therefore insufficient voluntary muscle activation to determine selective muscle activation; patients with some loss of selective muscle activation; and patients with selective muscle activation comparable to healthy volunteers, despite not reaching maximum voluntary torque comparable to healthy volunteers (chapter 5).

Neuromechanical parameters in the first 6 months after stroke

In the longitudinal study, neuromechanical parameters were repeatedly assessed with the comprehensive assessment protocol in the first 6 months after stroke in the two groups stratified within the EXPLICIT-stroke trial according to the finger extension algorithm [1]. In the group of patients with an initial favorable prognosis for recovery of arm-hand function, passive parameters did not change over time, while active parameters recuperated most before week 5. However, on average, maximal voluntary contraction and control over joint torque at week 26 did not recover to values measured in healthy volunteers. Reflexive parameters demonstrated small reflex magnitudes and an ability to modulate reflexes in a changing environment.

In patients with an initial unfavorable prognosis for recovery of arm-hand function, two subgroups could be distinguished: those with a positive functional outcome (≥10 points on the Action Research Arm Test (ARAT) at 6 months) and those with a poor functional outcome (ARAT <10 points) [2]. In the group with an initial unfavorable prognosis and a positive functional outcome, there was no change in passive parameters except for a reduction in passive range of motion. Active parameters recuperated, but at a later moment in time than observed in the group with an initial favorable prognosis. The ability to modulate reflexes in a changing environment did not change over time. In patients with an initial unfavorable prognosis and a poor functional outcome, there was a marked shift in rest angle towards flexion as early as the first week after stroke, little or no improvement in active parameters, higher reflex magnitudes and a diminished ability to modulate reflexes in a changing environment. Moreover, if there was any increase in function, it was not observed until week 5-8. A catch or clonus during measurements of reflexive parameters was only observed in the groups with an initial unfavorable prognosis, in 8% of participants with a positive functional outcome and in 44% of participants with an poor functional outcome, the earliest at week 5 (chapter 6).

The relation between neuromechanical parameters and functional outcome

All participants with an initial favorable prognosis for recovery of arm-hand function after stroke reached a positive functional outcome of ARAT ≥10 points at 26 weeks. Within the group of patients with an unfavorable prognosis for functional outcome, 57% reached a positive functional outcome at 26 weeks. A diminished ability for maximal voluntary contraction and a diminished ability to modulate reflexes at 26 weeks were significantly related to poor outcome. Stiffness (as measured around the rest angle) at 26 weeks was not significantly related to poor outcome. However, structural changes in tissue properties were represented by a changed rest angle towards wrist flexion and a diminished passive range of motion. Prediction of functional outcome on activity level was mostly determined by an increase in active range of motion and a stable rest angle (chapter 6).

Clinical implications

The precision diagnostics provided by a neuromechanical assessment protocol could support clinical decision making. To enhance prediction of recovery of arm-hand function after stroke and better represent endpoint joint behavior [3,4], neuromechanical parameters could be added to the current set of biomarkers of stroke recovery [5]. Furthermore, implementation of the use of neuromechanical parameters such as selective muscle activation, rest angle and active range of motion in future intervention trials concerning e.g. botulinum toxin, surgery or robot therapy will support both stratifying the patients most likely to benefit from an intervention and evaluating the results of a given therapy in a more objective manner. Moreover, neuromechanical parameters allow for a connection to be made between pathophysiology and treatment goals within the framework of the International Classification of Functioning, Disability and Health (ICF) [6].

To achieve an improvement in activities or participation, it is sometimes, but not always, necessary to intervene at the level of body functions and structures first. This decision should be based on clear patient-related information concerning which pathophysiological entity is most constraining for arm-hand function at that moment in time and in the context of a prediction model. For example, to optimize the period in which neural repair is possible and prevent secondary complications, neuromechanical parameters such as rest angle and/or active range of motion could be monitored systematically in the first months after stroke and treatment adapted accordingly. In the group of patients with a favorable prognosis for recovery of arm-hand function, active task oriented training can start right away, while in patients with an unfavorable prognosis, the focus should be on passive movement to prevent contractures until there is an increase in active range of motion (which can take up to 5-8 weeks after stroke). If there is no improvement in active function after 5-8 weeks, compensation strategies should be considered [7] and efforts to prevent contractures can be monitored by repeated assessment of rest angle.

Methodological considerations

The neuromechanical assessment protocol aimed to identify neural and non-neural contributors to movement disorders by differences in task and measurement conditions. For example: the protocol was designed to minimize the effects of neural contributors during non-neural tasks and vice versa. However, this might not yet give a complete reflection of endpoint joint behavior, as system behavior under active task conditions involves a combination of both neural and non-neural contributors. The same goes for passive conditions, where neural contributors may be present through increased baseline activation [8]. Further development of System Identification and Parameter Estimation techniques might help to differentiate even better between neural and non-neural contributors to movement disorders after stroke, e.g. further differentiation between passive and reflexive stiffness [9].

The studies in this thesis refer to wrist function, a single axis joint function. This could do injustice to arm-hand function in general when not connected to outcome measures on the level of activity or participation. On the other hand, the limitation in freedom of movement gives us a unique insight in function without synergies and compensatory trunk movement. Stratification of patient groups makes it more difficult to generalize the results to the stroke population as a whole; however, as stratification contributes to an increased homogeneity within the subgroup and an increased heterogeneity between subgroups, interpretation of the results in our study is greatly ameliorated by stratification according to the finger extension algorithm [10,11].

Future work

As the comprehensive neuromechanical assessment protocol is only used in a research setting so far, future work should include implementation of the protocol in daily practice. Further research into e.g. the amount of training needed for caregivers to apply the protocol and the applicability of the protocol in the general stroke population could help remove the behavioral and economical barriers often seen in implementation of robot-assisted assessments [12]. Interpretation of the results could be enhanced by developing a flowchart containing distinctive neuromechanical parameters for different patient categories and treatment questions. To assemble such a flowchart, systematic measurement of neuromechanical parameters should be incorporated in intervention trials, to answer e.g. the following questions:

- Can a shift in rest angle be prevented? For example by passive (possibly robot assisted) movement, splinting, oral spasmolytics or botulinum toxin?
- If a shift in rest angle is prevented, does this help in recovery of arm-hand function?
- In the presence of selective muscle activation and a suboptimal maximal voluntary contraction, is an exercise program aimed at strength beneficial in recovery of arm-hand function?
- Does botulinum toxin have an effect on active range of motion or on arm-hand function in terms of activity or participation if there is no selective muscle activation?
- How can additional therapy (e.g. splinting, passive movement) maximize the possible effect of botulinum toxin on passive range of motion and/or stiffness? Can additional therapy help to prevent a relapse once the effect of botulinum toxin wanes?

- If there is no selective muscle activation in a transposed muscle, is surgery aimed at creating a functional joint beneficial?
- Are neural contributors to movement disorders after stroke a risk for pressure sores or even losing the desired position of the joint after surgery to stabilize a joint?
- Which stretch reflex properties help in selecting patients for surgery aimed at interruption of the stretch reflex loop?

These examples may seem very plain, but objective and reproducible assessment of neural and non-neural contributors to movement disorders after stroke are not commonplace yet. Neuromechanical parameters should be used in prediction models and as biomarkers to support clinical decision making in recovery of arm-hand function after stroke, for example by improving the time-window and selection of patients. Thus, rehabilitation strategies can be optimized.

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