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

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Citation
Krogt, J. M. van der. (2018, November 6). *Recovery of arm-hand function after stroke: developing neuromechanical biomarkers to optimize rehabilitation strategies*. Retrieved from https://hdl.handle.net/1887/66816

Version:	Not Applicable (or Unknown)
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Note: To cite this publication please use the final published version (if applicable).

Cover Page

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Issue Date: 2018-11-06

Chapter 1

General introduction

Stroke and impairment in arm-hand function

A cerebrovascular accident, or stroke, is defined by the World Health Organization as "an interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue". The effects of a stroke depend on which part of the brain is injured and how severely it is affected [1]. Mortality directly after stroke is 15% [2].

Only 10% of stroke patients have a complete functional recovery [2]. In the Netherlands, it is estimated that the incidence of stroke is 0.5% [3] with a prevalence of 2.5%. That means that in a population of 17 million, there are around 85,000 new cases of stroke per year and over 400,000 persons living with the consequences of stroke. Among them, 32-60% experience a lasting impairment in arm-hand function [4,5] and movement disorders such as spasticity [6,7], with resulting limitations in activities of daily living or in participation [5,8], e.g. social functioning, sports or work.

Interventions directed at recovery of arm-hand function are either aimed at neural repair or at compensation methods and prevention of secondary complications. On the level of neural repair, early reperfusion with thrombolytic agents or mechanically by thrombectomy aim to minimize the damage in the first hours after stroke [9]; early hand therapy interventions aim to prevent learned non-use in the first days and weeks after stroke [10]. In the chronic phase after stroke, improvement in arm-hand function via neural repair is not to be expected [11]. Therefore, the focus in this phase lies on preventing secondary complications on the level of body structures and function; and on maximizing functioning on the level of activities and participation by compensation methods. Rehabilitation strategies range from task specific arm-hand training, robotics, splinting, stretching and botulinum toxin injections to surgery [12-15].

Clinical decision making

How to choose an appropriate rehabilitation strategy? Abovementioned therapies are often expensive and time consuming for both patients and therapists alike. Assigning the most effective intervention, however, not only depends on money and time, but also on an optimization of the time-window and selection of patients for a given intervention. Prediction models and biomarkers could support clinical decision making in this field [16]. For example: early return of wrist and finger extension and shoulder abduction after stroke is a key prognostic factor for regaining arm-hand function [4,10,17,18]. However, sensitivity and specificity of prediction models is seldom 100%. For example, prediction of proportional recovery fails in 30% of patients [19,20]. In this context, biomarkers of motor outcome play an important role, e.g. neuro-imaging and neurophysiological parameters to assess intactness of the corticospinal tract [16]. But these techniques do not fully bridge the gap towards endpoint joint behavior [21].

Endpoint joint behavior is determined by motor control, stretch reflex properties and tissue properties. Movement disorders after stroke are the result of a complex interaction between neural deficits and changes in non-neural tissue properties [22,23], leading to a recognizable triad of paresis, muscle overactivity and contracture. Paresis is determined by decreased voluntary motor unit recruitment. Muscle overactivity (e.g. over-excitability of stretch reflexes and decreased selectivity of movement) is determined by increased involuntary motor unit recruitment. Contracture is determined by altered tissue properties and a changed position of the joint [24,25]. Biomarkers that accurately represent endpoint joint behavior (i.e. parameters with a high sensitivity and specificity) are required to assign and evaluate therapies both in the acute and chronic phase, and to reduce numbers of patients needed in research [21]. These data need to be collected objective and reproducible, which cannot always be achieved by using clinical scales [26,27].

Neuromechanics

Could neuromechanics be the essential element to represent and further specify endpoint joint behavior? Clinically, endpoint joint behavior is mostly described in terms such as paresis and spasticity, and measured with clinical scales. Neuromechanics provide a quantitative description of joint properties, both under passive and active conditions and as a reaction to external mechanical perturbations [28]. Variation in measurement conditions and tasks allows for the separation of neural contributors (motor control and stretch reflex properties) and non-neural contributors (tissue properties) to movement disorders after stroke, and for a more precise analysis of the non-linear properties of endpoint joint behavior [29] (e.g. for non-linearity: twice as much stretching does not result in twice as much resistance of the joint).

Biomechanical measuring devices (such as haptic robots, force/torque transducers and electrogoniometers) in combination with electromyography [27,30-32] allow variation in measurement conditions to objectify motor control, stretch reflexes and tissue properties in a reproducible manner. Furthermore, degrees of freedom of movement may be controlled, to allow or restrict compensation methods, providing valuable information on the pathophysiological mechanisms underlying functional recovery. For example, neuromechanical parameters can describe paresis not only in terms of force or torque, but also as lack of selective muscle activation or diminished active range of motion. And in case of a clinical phenomenon such as spasticity: tissue stiffness, stiffness due to reflex activity and modulation of reflexes in a changed environment can be distinguished. In summary, neuromechanical parameters may provide a comprehensive description of endpoint joint behavior with a strong link to underlying pathophysiological mechanisms.

EXPLICIT-stroke project

The studies in this thesis were conducted within the framework of the Explaining PLastICITy after stroke (EXPLICIT-stroke) trial. This 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 [10], aimed at improving arm-hand function by utilizing the window of opportunity for neural repair in the acute phase after stroke. Patients were stratified according to active wrist and finger extension within one week after stroke [10], based on the prediction model described earlier [4].

Parallel to clinical tests measuring arm-hand function, a selection of patients was assessed longitudinally by fMRI, TMS, kinematics and neuromechanics. The combination of clinical outcome measures, neuro-imaging, neurophysiological parameters and neuromechanics, aimed to enlarge the understanding of pathophysiological mechanisms of functional recovery after stroke. In short, EXPLICIT-stroke was designed to provide an answer to the key question whether improvement in arm-hand function in the first 6 months after stroke is due to a reduction of basic motor impairment by neural repair or by behavioral compensation methods.

Thesis outline

The aim of this thesis is 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 are: 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? [10]

First, the gap is explored between day-to-day practice (i.e. physical examination) and the biomechanical and electrophysiological techniques recommended by research to support clinical decision making. An overview is given of regularly used pathophysiological concepts and biomechanical and electromyographical outcome measures of movement disorders after stroke (chapter 2).

Then, methodological aspects on how to address the different (nonlinear) neural and non-neural properties of the wrist joint during flexion-extension movement are presented. The recommendations to apply multiple measurement and task conditions are assembled in a comprehensive and clinically applicable assessment protocol, to identify patients within the spectrum of neuromechanics and to understand the underlying pathophysiological mechanism of movement disorders after stroke (chapter 3).

Clinical responsiveness of the newly developed protocol and test-retest reliability are assessed in a cohort of stroke patients with impaired arm-hand function in the chronic phase after stroke and compared to a cohort of healthy participants (chapter 4). Complementary,

the roles of co-contraction and paresis on arm-hand function are investigated by assessing impairment in selective muscle activation. The methodology of measuring selective muscle activity by means of Activation Ratios is described and test-retest reliability and clinical responsiveness of this tool are presented (chapter 5).

Ultimately, changes in wrist neuromechanical parameters in the first 6 months after stroke are quantified by longitudinal data obtained with the comprehensive assessment protocol within the prospective cohort of the EXPLICIT trial. Neural and non-neural contributors to movement disorders after stroke i.e. paresis, stiffness and reflex modulation are related to functional outcome as determined by the Action Research Arm Test (ARAT) at 26 weeks after stroke. It is hypothesized that paresis, a high degree of stiffness and absence of reflex modulation will be related to poor functional outcome (chapter 6).

In the general discussion, the diverse aspects of measurement of impairment in arm-hand function after stroke are summarized, including clinical implications, methodological considerations and recommendations for future work (chapter 7).

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