General introduction
THE ISCHAEMIC CASCADE IN STROKE

The World Health Organisation (WHO) defines stroke as “rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.” The World Health Organisation (WHO) defines stroke as “rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.”1,2 Strokes can be generally classified as haemorrhagic or ischaemic and lead to hypoperfusion of a part of the brain tissue. Haemorrhagic strokes occur when a vessel ruptures and blood flows into or around the brain tissue. In ischaemic strokes, hypoperfusion is caused by a blood clot which blocks a vessel in or leading to the brain. In this thesis, the focus will be on patients with ischaemic strokes, accounting for 80% of all stroke victims.3-5

The reduced cerebral blood flow (i.e. hypoperfusion) to a brain area will trigger an ischaemic cascade involving a series of neurochemical processes.6 The ischaemic cascade starts with the failure of the energy (adenosine triphosphate) production, subsequently causing dysfunction of depolarisation of neurons, dysfunction of energy-dependent ion transport pumps and inflammation.8,9 Cell death through necrosis will occur in the ischaemic core where cerebral blood flow decreases to less than about 8 ml per 100 g brain tissue per minute.6,10,11 The degree and the duration of the oxygen deprivation are important variables for the amount of permanent damage to the brain tissue.12 The area of permanently damaged tissue will expand when energy failure and ion transport pump failure occur within the brain cells surrounding the core.10,13 This area is often called the perilesional region or penumbra. Initially, the cells in the penumbra are only dysfunctional (i.e. electrical failure) due to the decrease of cerebral blood flow below 20 ml per 100 g per min, however, cell death will occur through delayed apoptosis when the hypoperfusion maintains.10,14 The penumbra is the main focus of early treatment within approximately the first 4.5 hours after stroke onset.15,16 However, a large number of patients is not eligible for this early treatment, because they do not reach the hospital in time.

THE EPIDEMIOLOGY OF STROKE

According to the WHO, the worldwide incidence and prevalence of stroke was respectively 10.3 million and 25.7 million in 2013.5 Stroke is the second-leading cause of disease burden.5 The disease burden, expressed in the absolute number of Disability-Adjusted Life Years (DALYs), was 47.4 million and approximately 3.3 million people died from a stroke.5 The global burden of stroke will continue to increase, mainly due to the ageing population and the increase in DALYs in developing countries.5,17
Stroke survivors present a wide range of clinical symptoms, including cognitive and motor impairments. Motor impairment is one of the most common impairments after stroke and occurs in up to 80% of all stroke survivors.18,19 The face, upper and lower limb on one side of the body are typically affected. The severity of upper limb impairment early after stroke is strongly related to the ability to perform Activities of Daily Living (ADL).20 In addition, upper limb impairment is related to low subjective well-being in stroke survivors.21 Because up to 80% of the individuals with initial severe upper limb motor impairment is still disabled at 3 or 6 months after stroke onset,22,23 upper limb training is an important element of post stroke rehabilitative therapy.

**STROKE REHABILITATION**

Getting out of bed, going to the toilet, taking a shower, grooming, getting dressed, eating breakfast and drinking a cup of coffee; a list of basic ADLs that many people consider as normal and easy. The complexity of these activities becomes clear when motor function and/or cognition are affected by a stroke. Stroke remains a leading cause of long-term disability, despite the continuously advancing emergency medicine, acute and inpatient care.5,24 Hence, there is a need for more efficient stroke prevention and management.5 Stroke rehabilitation involves different steps which are part of a cyclic process, including: identifying and quantifying patients’ needs, setting realistic and attainable goals, supporting to attain those goals (i.e. intervention) and evaluating the process.25 The main goal of stroke rehabilitation is to reduce individuals’ disability and improve health-related quality of life.25

It is evident that knowledge about prognostic variables and time dynamics for predicting neurobiological recovery after stroke is paramount to: (1) make clinical decisions; (2) optimize (early supported) discharge planning; (3) allow patients to receive the most appropriate rehabilitation intervention, dependent on individual abilities; (4) correctly inform patients and relatives about their future perspectives regarding ADLs; and (5) design future Randomised Controlled Trials (RCTs) to investigate the effectiveness of interventions.20,25 In order to optimize therapeutic care within the field of stroke rehabilitation, there is need to increase knowledge about early prediction of outcome after stroke. This is in line with the quickly evolving research field of precision medicine. According to the National Research Council, precision medicine is “the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices
that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Before we can discuss early prediction and intervention after stroke, we first need to define the term ‘recovery’.

WHAT IS RECOVERY?

In this thesis, ‘recovery’ is defined as (1) patients’ overall improvement over time or (2) change over time in the underlying mechanisms of neurobiological recovery. We can further specify ‘recovery’ as improvements of body functions and structures (impairments), activities (disability), and participation (handicap), using the International Classification of Functioning, disability and health (ICF) framework. Generally, mechanisms of skill reacquisition after stroke are classified into behavioural restitution (i.e. true repair) and behavioural compensation of functions. Behavioural restitution is related to the reduction of impairment, for example, return of muscle strength or arm movements outside of the synergistic movement pattern (i.e. normalisation of the coupling between joints toward the level prior to stroke). Behavioural compensation consists of the alternative employment of the same structures, for example, a change in timing and/or increase in co-activation of the antagonist muscles, or even use of the non-affected bodyparts. A key questions in neurorehabilitation is whether we can modulate behavioural restitution through therapy (i.e. experience-dependent plasticity). One of the primary mechanisms underlying patients’ recovery is spontaneous neurobiological recovery. Not yet fully unravelled mechanisms that have been suggested to contribute to spontaneous neurobiological recovery are: recovery of the penumbra, alleviation of diaschisis and homeostatic mechanisms. Unfortunately, spontaneous neurobiological recovery remains a neglected area of research in neurorehabilitation.

A number of longitudinal studies with intensive repeated measurements in time show that most improvements in neurological impairments such as motor function, neglect, aphasia and somatosensory function occur in the first 3 months post stroke. Serial measurements of change scores by intensive repeated measurements suggested that progress of time alone explained 80 to 90% of the neurological improvements observed in the first 8 to 10 weeks after onset, suggesting that spontaneous neurobiological recovery is
largely responsible for the improvements of impairments in the first 3 months after stroke, independent of variables like type of stroke, affected hemisphere, age and gender.\textsuperscript{51} Moreover, the recovery of neurological impairments is a time-dependent, non-linear process.\textsuperscript{23,42-44} Figure 1.1 shows the suggested timing of neural mechanisms, which are related to the progression of stroke damage.\textsuperscript{27,39} Various phases post stroke have been distinguished in the literature.\textsuperscript{27,39,52} In the current thesis the time line of neurobiological recovery is divided into the following 5 phases: (1) hyper-acute: 0–24 hours; (2) acute: 1–7 days; (3) early subacute: 7 days to 3 months; (4) late subacute: 3 to 6 months; and (5) chronic: 6 months or more.\textsuperscript{27} Insight into the timing of underlying mechanisms of neurobiological recovery is important for early prediction of outcome after stroke, which allows improved clinical decision making and optimisation of discharge planning.

**Figure 1.1  Progression of stroke damage and tissue reorganisation.**
Adapted from Bernhardt and co-workers (2017);\textsuperscript{27} previous work of Dobkin and Carmichael (2016).\textsuperscript{39}

**CAN WE PREDICT WHO WILL AND WHO WILL NOT SHOW NEUROBIOLOGICAL RECOVERY?**

A number of prospective cohort studies showed that the initial severity of neurologic impairments within the first days after stroke onset is an important predictor for functional outcome at 3 or 6 months after stroke.\textsuperscript{20,22,23,42,53,54} For example, strength of the hemiparetic lower extremity and sitting balance, measured within 72 hours after stroke onset, were strong predictors for regaining independent gait at 6 months.\textsuperscript{20} In addition, the National Institutes of Health Stroke Scale (NIHSS),\textsuperscript{55} a measure for overall neurological impairment, was found to be highly associated with final outcome in terms of ADL at 6 months after stroke onset when measured within approximately 1 week post stroke.\textsuperscript{56} In terms of upper limb motor...
function, early presence of some Voluntary Finger Extension (VFE) is a strong predictor for recovery of upper limb capacity.\textsuperscript{54,57-59}

Recently, two independently conducted prospective cohort studies showed that early presence of some VFE, combined with presence of some Shoulder Abduction (SA), is a key variable in predicting a favourable outcome of upper limb capacity at 3 and 6 months post stroke.\textsuperscript{54,58} This clinical model known as the SAFE-model showed a high Positive Predictive Value (PPV) when applied within 72 hours to predict outcome at 6 months post stroke (PPV = 0.93, 95\% CI = 0.88-0.96).\textsuperscript{54} However, prediction of upper limb recovery in patients who were not likely to regain some upper limb capacity at 6 months (i.e. based on absence of VFE and SA) was much less accurate (Negative Predictive Value, NPV = 0.76, 95\% CI = 0.67-0.83).\textsuperscript{54} Retesting the SAFE-model at day 5 and 9 post stroke did show an increase of NPV (0.86, 95\% CI = 0.77-0.93) while preserving the high PPV (0.93, 95\% CI = 0.89-0.95), suggesting that the accuracy of early prediction of upper limb capacity in patients without initial voluntary SAFE improves during the time course post stroke.\textsuperscript{51} The relationship between the severity of initial impairment and long-term outcome after stroke may not be unexpected, however, it is remarkable that we can accurately predict outcome within 72 hours post stroke. This finding suggests that the amount of neurobiological recovery is already defined within this early time window and that therapy most likely does not have a major contribution to the recovery of neurological impairments.\textsuperscript{60,61} Moreover, spontaneous neurobiological recovery is estimated to explain up to 70\% of the variance in neurobiological recovery in the first 3 to 6 months after stroke.\textsuperscript{53} Although the majority of patients show improvement of their neurological impairments to some extent, the amount of spontaneous neurobiological recovery after stroke differs greatly between patients.\textsuperscript{53}

In 2008, the maximum proportional recovery rule was introduced by Prabhakaran and colleagues to describe a general principle behind the large heterogeneity in patients’ recovery patterns of upper extremity motor function.\textsuperscript{53} They measured Upper Extremity (UE) motor function with the Fugl-Meyer Assessment (FMA) in a group of 41 first-ever ischaemic stroke patients.\textsuperscript{53} The motor section of the FMA is suggested to reflect behavioural restitution as it assesses patients’ ability to move outside of patterns of abnormal joint coupling.\textsuperscript{32,62,63} Prabhakaran and colleagues (2008) used linear regression analysis to model the change in FMA-UE scores with clinical predictors. Baseline FMA-UE score (FMA-UE_{initial}), subcortical lesion volume, age and time to reassessment were predictors included in the model. They thereafter evaluated the regression model at average subcortical lesion volume, age and time to reassessment, reducing the model to ΔFMA-UE = 0.70 \cdot (66 - \text{FMA-UE}_{initial}).
Moreover, their proportional recovery rule stated that patients would recover to a level that is 70% of their maximum possible improvement measured with the FMA-UE within 72 hours after stroke onset. However, 7 patients (17%) were characterized as ‘outliers’ and excluded from applied linear regression analysis. These patients failed to follow the rule regarding predicted amount of upper extremity motor recovery. As a consequence of the small sample investigated, Prabhakaran and colleagues (2008) were unable to investigate differences between patient who did and did not follow the proportional prediction rule. Advanced knowledge of patients’ potential for neurobiological recovery and understanding how outliers (i.e. non-fitters) differ from other patients (i.e. fitters) with stroke can help optimize early prediction of outcome. In addition, the identification of non-fitters of spontaneous neurobiological recovery will have a huge impact on designing stroke recovery trials, acknowledging that heterogeneity in patients’ recovery is one of the key problems that lead to failure to underpin evidence-based therapies in stroke rehabilitation. Therefore, identification of fitters and non-fitters on this assumed proportional recovery rule should be seen as a major target for moving stroke rehabilitation forward. Additionally, the maximum proportional recovery rule has been found to be also applicable to the recovery of aphasia. The generalisability of the proportional recovery rule to different neurological impairments may reflect common underlying mechanisms of spontaneous neurobiological recovery and needs to be further investigated.

**CAN WE INFLUENCE NEUROBIOLOGICAL RECOVERY WITH EARLY APPLIED INTERVENTIONS?**

At this moment, the most effective curative interventions after ischaemic stroke are early reperfusion of the penumbra using recombinant tissue Plasminogen Activator (rt-PA) and endovascular thrombectomy. Both interventions aim to minimize the final size of the ischaemic core by breakdown or removal of the blood clot within the first 4.5 and 6 hours in the hyper-acute phase, respectively. A smaller time window between onset of stroke and intervention is associated with better long term functional outcome in terms of the modified Rankin Scale (mRS) score. About 70% of all stroke patients are not eligible for intravenous or intra-arterial treatment, primarily due to this small time window. Resulting in a number needed to treat (NNT) of 1:4 for intravenous rt-PA and 1:3 for intra-arterial treatment (e.g. mechanical thrombectomy and/or intra-arterial thrombolysis) in the Netherlands. To elucidate, the results from the MR CLEAN trial suggest that for every
4 patients with ischaemic stroke treated with rt-PA, 1 patient will be saved from death or dependency following the modified Rankin Scale (mRS, 0–2 points), whereas for intra-arterial treatment this will be the case in 1 out of 3 admitted stroke patients. However, in middle and low income countries the NNT will be larger mostly due to lower income levels, less high quality stroke-units and limited urbanisation, which results in increased time from stroke onset to hospital admission. Fortunately, in the Netherlands and in other countries in Europe, the health system is well organized and the distance from patients’ home to a specialized hospital is relatively short.

Stroke rehabilitation starts early after the hyper-acute phase, as soon as patients are medically stable. Evidence-based guidelines may help physiotherapists and occupational therapists to choose the most appropriate treatment for each individual patient. A large number of RCTs focus on testing the effect of new or enhanced therapies to improve self-care, mobility, communication and cognition after stroke. Naturally, the type of treatment is dependent on patients’ level of impairment, time after stroke onset and treatment goals. It is unclear if and how early applied therapies can influence spontaneous neurobiological recovery. In terms of upper limb function, exercise therapy for those patients with no initial voluntary hand function may focus on compensatory techniques and supportive devices. There are currently no effective evidence-based interventions that improve upper limb function in severely impaired patients. There is however evidence that ElectroMyoGraphy-triggered NeuroMuscular Stimulation (EMG-NMS) may improve motor function of the arm in patients with some VFE, measured in the early subacute, late subacute and chronic phase post stroke. Meta-analyses showed significant positive summary effect sizes of EMG-NMS on motor function of the paretic upper limb (3 RCTs, N = 49) and upper limb capacity (14 RCTs, N = 162), respectively. With this, somatosensory stimulation via EMG-NMS may cause changes in neural networks, specifically changes in cortical activation patterns and excitability. Therefore, the value of EMG-NMS in patients without VFE early after stroke should be investigated by applying EMG-NMS in the acute and early subacute phase post stroke to try to influence spontaneous neurobiological recovery and facilitate return of VFE.

Therapies are available for those patients with voluntary movement of the paretic upper limb, including task-specific training and strength training. Constraint-Induced Movement Therapy (CIMT) and its modified versions (mCIMT) have shown to be effective interventions. For example, Wolf and colleagues (2006) investigated the effect of CIMT in a group of 222 patients in the late subacute and chronic phase post stroke. Within the 2 week intervention period, patients in the CIMT group received 6 hours of task-specific
upper limb training per day, on weekdays, and were instrumented to wear a padded safety mitt on their less impaired hand to encourage use of the impaired upper limb in ADLs, daily, during 90% of their waking hours. The results showed that patients displayed significant more improvement of upper limb capacity and performance, in terms of Wolf Motor Function Test performance time and Motor Activity Log (amount of use), when administered 2 weeks of CIMT in comparison to usual care. In contrast, a proof-of-concept trial of Dromerick and colleagues suggested that a higher dose of mCIMT of 2 hours per day may harm upper limb recovery ($N_{\text{experimental}} = 16$), in terms of Action Research Arm Test (ARAT) scores, early post stroke when compared to 1 or 2 hours of mCIMT per day ($N_{\text{experimental}} = 19$) and control treatment ($N_{\text{control}} = 17$). Unfortunately, like other previous RCTs, this VECTORS trial only included a small number of patients with stroke ($N = 52$) and did not include measures like the FMA-UE to investigate the impact of mCIMT on the recovery of neurological impairment. Although above proof-of-concept trials were underpowered, meta-analysis of Nijland and co-workers (2011) showed that low-intensity mCIMT of less than 3 hours of shaping procedures of the affected upper limb per working day (3 RCTs, $N_{\text{experimental}} = 32$) was more beneficial than high-intensity mCIMT applied for more than 3 hours (3 RCTs, $N_{\text{experimental}} = 32$) per day, after pooling the results of 5 trials ($N = 106$) that started within the first 3 months post stroke. However, due to the small number of phase II trials of poor to moderate quality, one may conclude that additional high quality trials are needed to underpin the value of low-intensity mCIMT on upper limb recovery in terms of body functions and structure, activities and participation, following the ICF framework. Finally, a meta-analysis of the efficacy of limb constraint in animals showed conflicting results, and suggests a significantly better cognitive function (12 RCTs, $N = 173$) and trend for worse behavioural scores after constraining (2 RCTs, $N = 28$), whereas no significant group differences were found for infarct volume (13 RCTs, $N = 194$).

At this moment, there are no trials on rehabilitation interventions in humans that show large differential effects of more than 15% on top of the within group changes due to spontaneous neurobiological recovery. Taking a more optimistic point of view of early started stroke rehabilitation, a number of animal studies showed that the first weeks post stroke are characterized by increased levels of brain plasticity. Nonetheless, most of the RCTs investigating the effects of (m)CIMT in humans started in the late subacute or chronic phase after stroke and it remains difficult to translate the results from animal to human trials. The variation between animals can easily be reduced by controlling the experimental environment with measurements at fixed time points post stroke and by
controlling animal characteristics (e.g. same genes, lesion location and size). Unfortunately, this is more difficult in human trials. Although the variation between patients will remain, it is possible to reduce the heterogeneity in patients’ recovery within studies by paying more attention to trial design and patient selection in human studies. A more selected, homogeneous, study population will most likely increase the chance of finding clinically meaningful intervention effects in human stroke rehabilitation trials. In addition, the differences in intervention effects between animal and human trials may be partly explained by the higher treatment intensity in animal studies resulting in sufficient treatment contrast.

Therefore, acknowledging the importance of tailored interventions and precision medicine in stroke rehabilitation, it is important to conduct stratified trials to address heterogeneity in subjects’ recovery (see also recommendations Langhorne and co-workers, 2011).

OUTLINE OF THIS THESIS

The main aims of this thesis are to gain insight into early prediction of neurobiological outcome after stroke and investigate whether we can influence neurobiological recovery with early applied interventions. Therefore, the time window for return of VFE within the first 6 months post stroke onset and the clinical baseline characteristics of those patients who, despite initial absence of VFE, do show some return of upper limb capacity is examined in chapter 2. Next, in chapter 3, early prediction of upper limb motor function in terms of spontaneous neurobiological recovery is investigated. Patients’ upper limb motor function is assessed within 72 hours and 6 months after stroke onset to investigate the generalisability of the ‘maximum proportional recovery rule’, developed in 2008. Thereafter, the generalisability of this rule to the recovery of lower limb motor function and visuospatial neglect is examined in chapters 4 and 5. In addition, differences in patients’ baseline characteristics are investigated to discriminate between patients who follow the rule (i.e. fitters) and patients who do not (i.e. non-fitters). The main results of the EXPLICIT-stroke trial are described in chapter 6. In EXPLICIT-stroke, the effects of upper limb training, in comparison to usual care, are investigated in two distinct prognostic patient groups with a first-ever ischaemic stroke. In chapter 7, the effects of various time intervals for patient randomisation and prognostic stratification on the required sample size to find significant and clinically relevant intervention effects in upper limb trials are investigated. Finally, the thesis concludes with a general discussion (chapter 8), reflecting on the main findings of this thesis and discussing directions for future research.
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REFERENCES


General introduction


