Functional muscle characteristics after stroke and unloading

Astrid M.H. Horstman
The research presented in this thesis was carried out at the Research Institute MOVE, Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands.

Reading committee:
Prof.dr. M. Narici
Dr. N. A. Maffiuletti
Prof.dr. A.C.H. Geurts
Prof.dr. F. Nollet
Dr. H. Houdijk

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Functional muscle characteristics after stroke and unloading

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Astrid Maria Hermina Horstman
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promotoren: prof.dr. A. de Haan
            prof.dr.ir. D.F. Stegeman
copromotor: dr. H.L. Gerrits
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Chapter 1

General introduction
'Rest rusts' is a Dutch saying, meaning that lack of sufficient physical activity has negative consequences for the neuromuscular system (including all parts of the body that contribute to inducing movement). Normally, a movement starts with an action in the central nervous system (CNS). The CNS sends signals via peripheral nerves to muscles, which contract and generate force and/or cause movement. This combination of brain, nerves and muscles constitutes what we call ‘the neuromuscular system’. It is well known that the maximal strength of a muscle is determined by its structural properties. That is, the larger the physiological cross sectional area, the higher the force capacity of a muscle. Moreover, maximal force is dependent on the actual length of the muscle, muscle fiber type composition, contraction history, etc. In addition, the number of fibers recruited, as well as the frequency of recruitment, which are regulated by activation from the CNS, dictate the output of the activated muscle. Thus, maximal force generating capacity of the muscle is dependent on the properties of the muscle, which we refer to as intrinsic muscle properties or contractile properties, and on the voluntary central activation. One way to distinguish between these two factors is to use electrical stimulation. Electrical stimulation, for example via electrodes on the thigh (quadriceps muscles), can evoke knee extensor muscle contractions without intervention of the CNS in order to investigate how much force the involved muscle can generate regardless of central activation. If, for instance, muscle mass is reduced after 6 weeks of immobilization by a plaster cast, one can see that the electrically evoked force is also reduced. This decrement in force is due to changes in intrinsic muscle properties, such as a decreased muscle mass (atrophy) or parts of the contraction mechanism which can be affected, e.g. excitation-contraction coupling.

Roughly, human muscles consist of two kinds of fibers: slow (type I, red) muscle fibers and fast (type II, white) muscle fibers. Fast muscle fibers have a high contraction speed and are mainly used during fast, explosive movements. However, these fibers will fatigue relatively fast. Slow fibers develop force more slowly but are less fatigable. The proportion of slow and fast fibers varies between different muscles and can change after altered use, which will also influence the intrinsic muscle properties and therefore muscle function.
In response to resistance exercise, the maximum force increases. This can be the result of an increase in muscle mass and/or an increased voluntary activation because the subject has trained the CNS to activate the muscles. In contrast, if an astronaut would travel to Mars and lacks gravitational loading for a long time or if a patient ends up in a wheelchair after stroke, muscles will be less loaded than normal and will decrease in size and function. Additionally, voluntary activation usually decreases. So, ‘rest rusts’; it is well documented that inactivity has an influence on the neuromuscular system. Unfortunately, unloading is a frequently occurring phenomenon, not only during a stay in space by astronauts, but also in people who are bedridden as a result of illness. Under these circumstances muscles suffer from disuse. This holds especially for those muscles that normally work against gravity, such as the calf and thigh muscles, which will adapt to the unloading state by losing mass and strength. The origin of reduction in muscle function can be bipartite. On the one hand, inactivity causes a decline in activation from the CNS to the muscles. On the other hand, the muscle itself deteriorates because of the lower daily activity level.

We are primarily interested in functional muscle properties after stroke, such as strength, speed and fatigability, in order to provide scientific knowledge for developing specific intervention or rehabilitation programs after stroke. Information about the relative contribution of impaired neural control as a direct consequence of stroke and adaptations in intrinsic muscle characteristics to the muscle weakness in patients with stroke is lacking. Therefore we aimed to study changes in functional intrinsic muscle properties and neural activation as a result of stroke. To gain further insight in the generic adaptations in the functional characteristics of the lower extremity muscles, we used two different unloading models in healthy subjects: unilateral lower limb suspension and bed rest. We further investigated whether prevention or attenuation of the reduction in muscle function can be counteracted by training during bed rest. Besides measuring functional muscle characteristics such as force development, contraction speed and fatigue-resistance, we were interested in more functional tasks, such as walking and balancing, which were studied to
determine whether changes in muscle characteristics correlate with these indices of functional performance.

**Aim**

To conclude, the **main aim** of this thesis is to investigate muscle adaptations occurring in patients after a cerebral vascular accident (stroke). Therefore, we investigated the nature of muscle adaptations in both legs after stroke compared with able-bodied subjects. However, in patients with stroke not only the direct effects of the disorder can affect the working muscles, but also the indirect effect of lower activity levels. To be able to differentiate between these effects, we performed two studies in healthy people to examine the effects of purely decreased activity on muscles and to investigate whether these can be prevented or attenuated by training. Thus, the second aim was to investigate which muscle adaptations can be (partly) attributed to the reduced physical activity, which accompanies stroke mainly as a consequence of hemiparesis. The specific objectives of this thesis are to assess how the maximal muscle strength and speed, and fatigue properties of the knee extensor muscles of both legs have changed in patients with subacute stroke and to investigate whether strength is more impaired at shorter muscle lengths. This was previously shown in elbow flexors and extensors\(^2\,^{27,36}\), but was not yet investigated in lower limb muscles. We aimed to gather more insight in the relative contribution of neural activation on the one hand and changes in intrinsic muscle properties on the other hand. Furthermore, we wanted to correlate activation capacity, contractile speed and muscle strength with functional performance in subacute patients and investigate how these parameters developed during the first year after stroke. Moreover, we aimed to assess what happens with the maximal muscle strength and speed after decreased activity.
Stroke

Stroke, also called a cerebro vascular accident (CVA), follows a problem with the blood circulation in the brain. This can either be due to ischemia (lack of blood supply caused by a blood clot in an artery or vein) or to a brain hemorrhage. As a result, the affected area of the brain is unable to function. Depending on the part of the brain that is damaged by stroke, loss of abilities will follow. The consequences of stroke can affect almost all parts of the body. Right-sided hemiparesis (weakness on the right side of the body) involves injury to the left side of the brain, which also controls language and speech. Injury to the right side of the brain, which controls the process of how we learn, non-verbal communication and certain types of behavior, may lead to left-sided hemiparesis. With respect to the neuromuscular system, people with hemiparesis may have trouble moving one or more limbs, have difficulty walking and may also experience a loss of balance and affected coordination. As a result, doing simple everyday activities like walking, grasping objects, dressing and eating can be very problematic.

Around 80-90% of patients with stroke experience acute problems with movements and have a spastic paresis (paralysis that presents as weakness with abnormally high tone) in at least one of the limbs shortly after stroke. After 6 months, half of this patient population still suffers from motor impairments revealed by hemiparesis. They are the chronic stroke patients (>6 months after stroke).

Given the importance of locomotor muscles in daily life, we focus on the muscles of the thigh. Muscle weakness in knee extensors (front thigh) and flexors (back thigh) on the paretic side (contralateral to the brain lesion) is a well-known phenomenon. Reduced muscle strength is also reported for the non-paretic limb (ipsilateral to the lesion, i.e. the limb at the same side as the lesion). Moreover, several studies report correlations between muscle strength of the knee extensors and flexors and functional performance, such as gait and stair climbing speeds, transfer capacity, short- and long distance walking and standing-up performance. There is clear evidence that both impaired neural control as a direct consequence of the stroke...
and adaptations in intrinsic muscle characteristics\textsuperscript{45,14,10,23} underlie the weakness and consequently impaired functional performance after stroke. The relative contributions of these factors are, however, largely unknown. Therefore, to provide scientific background information for optimizing rehabilitation programs, we studied the nature of muscle weakness in both legs after stroke compared to able-bodies subjects. We examined whether the muscle weakness in the paretic and non-paretic lower limb has the same underlying mechanism. Moreover, we investigated whether there is a relationship between changes in motor control and muscle function with functional performance. Therefore, subjects performed the following seven functional performance tests: Timed get-up-and-go test, 10 meter walk test, Berg Balance Scale, Motricity Index, Functional Ambulation Categories-score, Brunnstrom Fugl-Meyer (lower extremity) and the Rivermead Mobility Index. This study is described in Chapter 2.

Since the knee extensor muscles are exposed to altered patterns of activity and function after stroke, their contractile properties are assumed to change. A change in muscle fiber composition has been shown in paretic muscles, characterized by selective fast fiber type (II) atrophy and predominance of slow twitch oxidative type I fibers\textsuperscript{45,14,10,23,18} which would lead to concomitant changes in fatigue resistance. Results concerning fatigability are inconsistent\textsuperscript{52,56,21} and it is unclear whether the fatigue properties of muscles in \textit{subacute} stroke patients have altered. This is evaluated in Chapter 3.

Given the altered muscle fiber composition combined with impaired neural drive, the ability to develop force as rapidly as possible (the (maximal) rate of torque development) may be even more deteriorated than peak steady force. This maximal rate of torque development appears to be important for balance control and fall prevention\textsuperscript{42,48} and is reduced in people with stroke\textsuperscript{8,37,54,5}. Nevertheless, information about the relative contribution of both central neural and local muscular changes is still lacking. Therefore, in Chapter 3 we also compare fatigue characteristics and voluntary and electrically evoked contractile speed of the knee extensors of subacute stroke patients with those of able-bodied controls.
In addition to a reduction in muscle strength, muscle length-dependency of strength is an important feature, since a whole range of muscle lengths, depending on the joint angle, is used during daily activities such as climbing stairs, cycling and standing up from a chair. This muscle length-dependency of strength implies that with the knee almost stretched (short knee extensor muscles), or with knee joint bended (long knee extensor muscles), the force of the thigh muscle is less than with a knee angle in between\textsuperscript{38}. For arm muscles, this angle-dependent difference is even larger in patients with stroke than in healthy individuals. More specifically, it is known that after stroke, muscle weakness is more prominent at relatively short muscle lengths for elbow flexors and extensors\textsuperscript{1,27,36}. Whether this also is true for the thigh muscles and what the underlying mechanisms are, is currently unknown. The knee extensor and flexor muscles are very important for locomotion and work at different muscle lengths. Therefore it is important to investigate if and to what extent muscle weakness predominates at a certain joint angle. In addition, information about the mechanisms responsible may help to optimize rehabilitation strategies. For instance, one can recommend strengthening the muscle at a certain (long or short) length. Therefore, in Chapter 4 we describe experiments in which we assessed muscle strength in the lower limbs at different knee angles and we measured muscle activity to determine whether impaired function of the knee extensors and flexors is associated with impaired neural activation at short muscle lengths.

As indicated above, 6 months after stroke half of the population still experiences some extent of hemi paresis\textsuperscript{7}. Longitudinal studies have shown that almost all patients with stroke experience a certain degree of functional recovery within those first six months after stroke and that recovering from motor impairments and developing behavioral compensation strategies even extend beyond 6 months post stroke\textsuperscript{33}. Little is known about whether changes in functional performance are related to changes in activation capacity and neuromuscular function of the lower limbs in patients with stroke. It is essential for rehabilitation to get more clarity on longitudinal improvements in (intrinsic) muscle strength, activation ability and fast torque development during the first year after stroke. This may allow optimizing
rehabilitation strategies for patients with stroke, with the ultimate goal to achieve a level of functional independence that enables the patient to return home and optimally reintegrate into community life. We investigated changes in functional performance in relation to muscle function during first year after stroke. For this, we studied maximal voluntary isometric torques of knee extensors and flexors, maximal triplet response (thigh; 3 electrical pulses applied at 300Hz as a measure of intrinsic muscle strength), maximal rate of torque development during voluntary and electrically evoked contractions and the degree of voluntary activation of the knee extensors 3.5±2 months after stroke and 3, 6 and 12 months thereafter. This is described in Chapter 5.

Unloading

Unilateral lower limb suspension

In the above mentioned stroke studies, a cerebro vascular accident changed the brain’s function. An indirect consequence is a lower activity level of the patients, mainly as a consequence of hemi paresis after stroke. Thus, decreased use is an indirect effect of stroke. In the following two studies, we looked into direct effects of inactivity without interference of CNS abnormalities due to ischemia or hemorrhage to get a purer look at unloading effects.

In the first study, we used unilateral lower limb suspension which is a human model that promotes disuse with intact joint mobility, relatively low costs and only moderate encroachment on daily physical activities. This model is described by Berg et al.3. In brief, the subjects are wearing a left shoe with a 7.5 cm thick sole, the right leg is suspended via a strap around foot and ankle and subjects use crutches for daily live activities. Subjects are instructed not to load the suspended limb (e.g. no touching the ground, no car driving etc). In Chapter 6 we describe a study using this model in which the subjects underwent 3 weeks of unloading. Maximal voluntary plantar flexor (calf) and knee extensor (thigh) contraction torque, voluntary activation, maximal triplet
torque, maximal rate of torque development and 1- and 2-leg squat jump height were measured. We investigated whether changes in maximal voluntary and electrically evoked torque and rate of torque development during single joint isometric muscle contractions, as a result of limb unloading are related to changes in jump performance involving dynamic muscle contractions and several joints.

**Bed rest**

In the second study, we used a bed rest model for unloading, which is often used to simulate antigravity muscle usage during space flight. We participated in the second Berlin Bed Rest study (BBR2), which main aim was to identify additive effects of vibration to resistance training to prevent changes in muscle and bone adaptations as a result of unloading. Mulder *et al.*\(^{38}\) report that gravity-independent resistance training augmented by whole body vibration substantially attenuated changes in thigh muscle size and maintained isometric strength after 8 weeks of bed rest. During side-alternating whole body vibration exercise, skeletal muscles of the lower limb undergo small changes in muscle length due to the oscillatory displacements of the vibration platform. When superimposed during a voluntary contraction, vibration may peripherally reinforce activation of motor neurons excited by descending pathways of the central nervous system\(^{22,49}\). However, neither single contributions of vibration training or resistance training, nor the complementary effects of both training modes could be identified by the approach of Mulder *et al.*\(^{38}\).

An additional aim for the bed rest study was to understand the underlying mechanisms responsible for changes in maximal isometric muscle strength and indices of rate of torque development during bed rest. A number of such studies have been performed, ranging from \(3^{50}\) to \(120^{19,30,25,31}\) days of bed rest. From those studies, it is known that decrements in maximal motor performance typically outweigh the changes in muscle mass\(^{19}\), which can be related to a reduced ability of the central nervous system to maximally drive the muscles voluntarily after bed rest\(^{2,46}\).

In BBR2, subjects underwent 56 days of 6° head down tilt bed rest, during which they were not allowed to sit or stand up. The study consisted of four campaigns, each composed of six male subjects. Three pairs of subjects were formed, according to
psychological criteria before the start of the study. The formed pairs were then randomly assigned to either a resistance exercise group (RE), a resistance exercise + vibration group (RVE) or to an inactive control group (CTR). Only subjects assigned to the RE and RVE group performed resistance training 3 times per week which was a clearly lower number compared to the first Berlin Bed Rest study, which incorporated 11 sessions a week\textsuperscript{38}. The exercise device was novel and developed exclusively for the second Berlin Bed Rest study (Galileo Space, Novotec Medical, Pforzheim, Germany).

In Chapter 7, the experiments related to the underlying mechanisms responsible for potential differences between training regimes (resistance exercise and resistance exercise with vibrations) are described. We measured indices for muscle size (cross sectional area) and strength and neural activation (electromyography) and assessed the differential influence of bed rest and the two training regimes on indices of rate of torque development.

In the last chapter (Chapter 8), all findings concerning adaptations in functional muscle characteristics and performance after stroke and unloading are discussed with respect to their methodological and scientific implications and their implications for (stroke) rehabilitation.

References

Chapter 1: General introduction

Chapter 1: General introduction


Chapter 2

Intrinsic muscle strength and voluntary activation of both lower limbs and functional performance after stroke

Astrid M. Horstman
Marijke J. Beltman
Karin H. Gerrits
Peter Koppe
Thomas W. Janssen
Peter Elich
Arnold de Haan

Summary

Objective was to assess the nature of muscle weakness in both legs after stroke compared to able-bodied control individuals and to examine whether there is a relationship between the degree of muscle weakness and coactivation of knee extensors and flexors as well as voluntary activation capacity of knee extensors of both paretic and non-paretic legs and indices of functional performance.

Maximal voluntary isometric torques of knee extensors (MVCe) and flexors (MVCf) were determined in 14 patients (bilaterally) and 12 able-bodied controls. Simultaneous measurements were made of torque and surface EMG from agonist and antagonist muscles. Coactivation was calculated. Supra maximal triplets were evoked with electrical stimulation to estimate maximal torque capacity and degree of voluntary activation of knee extensors. MVC’s, activation and coactivation parameters were correlated to scores of 7 functional performance tests. MVCe, MVCf and voluntary activation were lower in paretic lower limb (PL) compared to both non-paretic lower limb (NL) and control. Besides, all these parameters of NL were also lower than control. Electrically evoked torque capacity of knee extensors of PL was about 60% of both NL and control, which were not significantly different from each other. Strong significant correlations between strength, as well as voluntary activation, and functional performance were found. Coactivation did not correlate well with functional performance. Thus, whereas for NL activation failure can explain weakness, for PL both activation failure and reduced intrinsic torque capacity are responsible for the severe weakness. Activation capacity and muscle strength correlated strongly to functional performance, while coactivation did not.
Introduction

About 80-90% of patients after stroke has a spastic paresis in at least one of the limbs shortly after the stroke\textsuperscript{10}. After six months, half of the patient population still suffer from motor impairments revealed by hemiparesis (partial paralysis that is manifested by decreased muscle strength) or hemiplegy (taking into account both spastic and paretic components contribute to motor functional loss)\textsuperscript{11}. Furthermore, Bohannon\textsuperscript{7,9} showed that the severity of the paresis strongly relates to the loss of functional performance in stroke. Given the importance of the locomotor muscles in daily life, this study will focus on the muscles of the thigh. Muscle weakness in hamstrings and quadriceps on the paretic side (contralateral to the lesion) is a well known phenomenon\textsuperscript{49,22}. In addition, reduced muscle strength was also reported for the non-paretic limbs (ipsilateral to the lesion)\textsuperscript{22,8,33} and this weakness develops already in the first week following acute ischaemic hemiplegic stroke\textsuperscript{33}. Moreover, several studies reported correlations between muscle strength of knee extensors and knee flexors of both paretic and non- paretic lower limbs and functional performance\textsuperscript{9} such as gait and stair-climbing speeds\textsuperscript{39}, short and long distance walking\textsuperscript{51}, transfer capacity\textsuperscript{6} and standing-up performance\textsuperscript{19}. The common goal of rehabilitation of stroke patients is to retrain functional performance skills (e.g. locomotion, balance, stair climbing ability and transfer capacity). Clearly, muscle strength seems an important determinant for improving locomotor performance in stroke patients and Ouellette et al.\textsuperscript{50}, Ada et al.\textsuperscript{1} and Yang et al.\textsuperscript{64} suggested that strength training should be an important part of the rehabilitation program. To do this effectively and to optimize interventions or adaptation in rehabilitation programs of stroke patients it is important to elucidate which parameters may underlie muscle weakness (and impaired functional performance) and therefore are of most interest to improve. Previous studies have shown an overall loss of muscle mass, type II fiber atrophy and predominance of type I fibers in paretic muscles after stroke\textsuperscript{21,26,30,55}. It is therefore...
expected that at least part of the muscle weakness relates to adaptations in the intrinsic muscle properties. However, Bourbonnais and Vanden Noven\textsuperscript{11} and Newham and Hsiao\textsuperscript{49} showed that stroke patients have a disturbed central activation, which would lead to an impairment of the ability to maximally drive their muscles and most probably also to altered coordination of muscles involved. A disturbed neural control in the sense of abnormal coactivation of antagonist muscles during maximal voluntary extension and flexion contractions might be indicative for a decreased neural control during locomotor tasks such as walking or stair climbing. Moreover, excessive coactivation of antagonist muscles, in addition to reduced voluntary activation of agonist muscles might further reduce the net torques around the joints and are therefore also expected to contribute significantly to the impaired use of the muscles of the thigh. Some of these parameters indeed have been associated with functional performance. For example, Chae \textit{et al.}\textsuperscript{14} found significant correlations between coactivation and motor impairment in upper limb hemiplegia. To our best knowledge, it is not known if such relationship also holds for the lower limbs in stroke patients.

Thus, there is clear evidence suggesting that both impaired neural control as a direct consequence of the stroke and adaptations in intrinsic muscle characteristics underlie the weakness and therefore impaired functional performance in patients after stroke. Information about the relative contribution of these factors is, however, lacking. Therefore, to provide scientific background information for developing specific intervention or rehabilitation programs, the purpose of this study was to assess the nature of muscle weakness in both legs after stroke compared to able-bodied control individuals. Furthermore, we wanted to examine whether there is a relationship between the degree of muscle weakness and coactivation of the knee extensors and flexors as well as voluntary activation capacity of knee extensors of both paretic and non-paretic lower limbs and indices of functional performance. Our hypothesis is that both limbs show reduced intrinsic muscle strength, impaired voluntary activation capacity and disturbed coactivation, which correlate significantly with indices of functional performance after stroke.
Methods

Subjects
Fourteen stroke patients and twelve able-bodied control subjects volunteered in this study. Patients (characteristics, see Table 2.1) with a wide range of motor impairments from very severe to very mild, based on the scores at the tests of functional performance, were recruited for this study. They entered the study on average 3.5 months after stroke and 2 months after admission in the rehabilitation centre. Controls were matched as much as possible for age, length and weight (mean ± standard deviation: see Table 2.1).

Before participation, each subject was thoroughly informed about the procedures, filled out a health questionnaire and signed an informed consent. Inclusion criteria for patients were a minimum age of 18 years and a hemiparesis of the lower extremity as a result of first ever-stroke.

Table 2.1: Characteristics of the subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr) ± SD</th>
<th>Weight (kg) ± SD</th>
<th>Length (cm) ± SD</th>
<th>Lesion side (Left/Right)</th>
<th>Stroke type (Hemorrhagic/Ischaemic)</th>
<th>Time after stroke (days) ± SD</th>
<th>Time after admission (days) ± SD</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>55.9 ± 10.4</td>
<td>74.9 ± 14.3</td>
<td>174.2 ± 10.1</td>
<td>(6L/8R)</td>
<td>(5H/9I)</td>
<td>109 ± 46</td>
<td>67 ± 33</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>58.1 ± 12.2</td>
<td>75.7 ± 11.9</td>
<td>175.6 ± 6.5</td>
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The exclusion criteria were medical complications (such as unstable cardiovascular problems), severe cognitive and/or communicative problems preventing the ability to follow verbal instructions or limiting the ability to perform the requested tasks (e.g. aphasia, hemineglect) and contra-indications for electrical stimulation (unstable epilepsy, cancer, skin abnormalities, pacemaker). The project carried the approval of
the institutional review board (Medical Ethical Committee) of the VU University Medical Centre, Amsterdam, The Netherlands.

**Experimental set-up**

Contractile properties and functional performance were measured. For the present study only a selection of muscle function characteristics (strength, voluntary activation and coactivation) were used. The experiments were spread over four different days (sessions) with at least one day of rest in between.

**Force measurements**

Maximal voluntary and electrically evoked forces of the knee extensors and knee flexors were measured on a custom built Lower EXtremity System (LEXS). This set-up can be used in both supine and sitting position. Subjects were placed on the LEXS in a supine position (Figure 2.1, left) and were tilted to the measuring position (Figure 2.1, right): they were seated with their back 10° backwards and a hip angle of 100° (180° being fully stretched hips) and knee angle 60° (0° = full extension). This semi-supine position is comfortable for patients either with or without balance problems. The position of the LEXS was adjusted to establish these angles and to enable alignment of the knee axis (during maximal voluntary contraction) with the rotation-axis of the LEXS. A hip belt (Figure 2.1, right, C) was fixed tightly to avoid changes in hip and knee angle during (isometric) contractions and a trunk belt (Figure 2.1, right, A) was fixed for stabilisation. The lower leg was strapped tightly to a force transducer (KAP, E/200Hz, Bienfait B.V Haarlem, The Netherlands, range: 0-2 kN) just above the ankle by means of a cuff (Figure 2.1, D). Left-right translation of the force transducer was adapted. Active knee angle was determined with a handheld goniometer (model G300, Whitehall Manufacturing, California, USA) using the greater trochanter, the lateral epicondyle of the femur and the lateral malleolus of the fibula as references. The distance between the lateral femur epicondyle and a fixed point at the force transducer was measured representing the external moment arm.
For the maximal voluntary contractions (MVC’s) of the knee flexors, the leg was fixed tightly by a top restraining bar that was secured on the thigh, just proximal to the knee joint to minimize the movement of the leg and to avoid changes in hip and knee angles during force generation (Figure 2.1, right, B). An ankle brace was placed to keep the ankle in plantar flexion position, reducing the contribution of the gastrocnemius medialis muscle to the knee flexion. During voluntary contractions the skin was shaved and cleaned with alcohol for EMG-measurements (Biotel 99, The Netherlands). After that, surface Ag-AgCl electrodes were placed in a bipolar figuration, in line with the muscle fiber direction, with a centre to centre inter-electrode distance of 25 mm on the muscle bellies of the vastus lateralis muscle (VL), rectus femoris muscle (RF), vastus medialis muscle (VM), biceps femoris muscle (BF) and gastrocnemius medialis muscle (GM). One reference electrode was placed on the patella of the measured lower limb.

**Experimental procedures**

**Familiarization session**

The measurements of the familiarization session were performed with the non-
paretic lower limb to check whether the instructions were understood by the subject. After a warming-up (existing of 5 submaximal contractions) subjects were trained to perform maximally isometric knee flexion and extension contractions. Subsequently, the subjects were familiarized with electrical stimulation.

Muscle strength
Subjects were asked to maximally generate isometric knee extensions for 3-4 s to determine maximal voluntary knee extension torque (MVCe). Alternately, MVC’s with the knee flexors (MVCf) were performed. Two to four attempts were allowed for both MVCf’s and MVCe’s, separated by 2 min of rest. MVC was taken as the highest value of these attempts, which did not exceed preceding attempts by >10%, allowing a maximum of four attempts. Real-time force was visible on a computer screen. Subjects were vigorously encouraged to exceed their previous maximal value, which was also displayed to confirm the subject’s achievement throughout the test. EMG was measured as described above (see section Force measurements). The same measurements performed on the paretic lower limb were repeated with the non-paretic lower limb, carried out on a separate day. Control subjects only performed one of these sessions, with the right leg.

Voluntary activation
Volitional tests rely heavily on the patient’s motivation and the ability to maximally recruit their muscles and are often not an accurate reflection of the maximal torque generating capacity of the muscle. Electrically evoked contractions are independent of the patient’s effort. Therefore, a modified super-imposed stimulation technique was used in which electrically evoked triplets (pulse train of three rectangular 200 μs pulses applied at 300 Hz) were used to establish the subjects’ capacity to voluntarily activate their muscles 41.

After explanation of the procedure, the skin of the thigh of the subject was shaved (when necessary) and a pair of self-adhesive surface electrodes (13 x 8 cm, Schwa-Medico, The Netherlands) was placed over the proximal and distal part of the anterior
thigh and moment arm was measured as described above. The knee extensors were electrically stimulated using a computer-controlled constant current stimulator (Digitimer DSH7, Digitimer Ltd., Welwyn Garden City, UK). Measurements started with the paretic lower limb, knee angle 60°. First, stimulation current was increased until torque measured in response to a triplet levelled off. The current (in mA) was then increased by a further 20 mA to ensure supramaximal stimulation. It was assumed that at this point all muscle fibers of the knee extensors were activated. These high frequency stimulations (triplets) produce maximal responses in terms of torque production\textsuperscript{23}, thereby limiting the sensitivity to, for instance, length-dependent changes in calcium sensitivity and post-tetanic potentiation and improving the signal-to-noise ratio. Subjects underwent measurements consisting of a triplet superimposed on the plateau of the force signal of the MVC. Subsequently, these measurements were performed with the non-paretic lower limb. Control subjects performed this session with only the right leg.

**Functional performance**

To determine the relationship of changes in motor control and muscle function with functional performance, the following tests were performed by the subjects under supervision of a physiotherapist (except for the Rivermead Mobility Index, which was carried out by one of the researchers):

- *Timed “get-up-and-go” test* (TUG) requires patients to stand up from a chair, walk 3m, turn around, return, and sit down again. Time to fulfil this test is measured\textsuperscript{52}.
  - *10 meter walk test (10m)* is performed at comfortable (self selected) walking speed by patients who are able to walk independent with or without mobility aid and/or orthosis. Time to walk 10 m is measured and averaged over three trials\textsuperscript{58}.
  - *Berg Balance Scale (BBS)* assesses sitting and standing balance and exists of 14 test-items, scored on an ordinal 5-point scale (0-4). It gives an estimation of the chance that patients with stroke will fall\textsuperscript{3-5}.
  - *Motricity Index (MI)* evaluates the arbitrary movement activity and maximum
isometric muscle force. Possible scores are 0-9-14-19-25-33 at each of the three parts of the test for lower extremities.24,18,13

- **Functional Ambulation Categories-score (FAC)** evaluates the measure of independence of walking of the patient. Categories are scored on a six-point scale (0-5).34,35
- **Brunnstrom Fugl-Meyer (FM), lower extremity,** is a test for evaluation of patellar, knee flexor and Achilles reflexes, flexor and extensor synergies, isolated movements of knee flexor and ankle dorsal flexor function and normal reflex activity of the quadriceps and triceps surae muscles in hemiplegic patients.29
- **Rivermead Mobility Index (RMI)** comprises a series of 14 questions and 1 direct observation, and covers a range of activities from turning over in bed to running. It is a measure of mobility disability which concentrates on body mobility.17

**Data analysis**

Real-time force applied to the force transducer was displayed online on a computer monitor and digitally stored (1 kHz) on computer disc. The force signals were automatically corrected for gravity of the leg. All force signals were low-pass filtered (4th order, 50 Hz, Butterworth). 

* MVC torque *(Nm)* was determined as the peak force from the force plateau multiplied by the external moment arm. Ratio’s of MVCf and MVCe are used to indicate which muscle group is most affected.

* Voluntary activation* is defined as the completeness of skeletal muscle activity during voluntary contractions and was calculated by means of a modified interpolated twitch technique.41

Voluntary activation (%) = [ 1 – (superimposed triplet/control triplet)] * 100.

Here the superimposed triplet is the force increment during a maximal contraction at the time of stimulation and the control triplet is that evoked in the relaxed muscle.57

EMG-signals of the voluntary maximal knee extensions and flexions were amplified
(x100), digitized (1 kHz) and stored with the synchronized force signal on computer disc. All EMG-signals were band-pass filtered (10-400 Hz) and rectified. Rectified surface EMG amplitude (rsEMG) was calculated for the RF, VL, VM, BF and GM for 1000 ms of the plateau of the force signal. rsEMG served to assess activation levels of the knee extensors and flexors during MVC as well as to determine the coactivation of the thigh muscles during MVC. To assess the level of coactivation, rsEMG of the antagonist muscles was normalized to the maximum rsEMG during their primary function (working as agonists). For instance, the level of coactivation of knee flexors during knee extension was expressed as a percentage of the maximal knee flexion rsEMG (rsEMG/rsEMG\text{max})^46.

Correlations were calculated between the coactivation parameters and the tests of functional performance, between MVC’s and the tests and between voluntary activation and the tests.

Statistics

All results were presented as means ± standard deviations. For the comparison of MVC, MVCf:MVCe-ratio, triplet torque, activation level, and rsEMG/rsEMG\text{max} between non-paretic, paretic and control lower limbs, one-way analysis of variance (ANOVA) was used. In case of significance Bonferroni post hoc tests were used. To assess the relation between coactivation, activation level and strength and outcome measurements of the tests of functional performance, non parametric Spearman correlation was used because of the ordinal scale of most of the tests. For each statistical analysis, the level of significance was set at p<0.05.

Results

All subjects of whom the data were included for analysis could tolerate the electrical stimulation. Subjects performed some MVC’s without stimulation during the familiarization session. Only when MVC’s with expected superimposed stimulation matched those without expected stimulation, data were used for analysis. Data were
not complete for some of the patients due to discomfort (duration of the experiments, electrical stimulation) or unreliable data. The number of patients analysed are indicated in the text.

**Muscle strength**

Both MVCe-torque and MVCf-torque (Table 2.2) were significantly lower in the paretic lower limb as well as the non-paretic lower limb compared to control. Furthermore, MVCe and MVCf of the paretic limb were also significantly lower than the non-paretic limb. The ratio MVCf:MVCe (Table 2.2) was significantly lower for the paretic limb compared to both the non-paretic limb and control, which in turn were not different from each other.

The extension torque evoked by a triplet for the paretic lower limb was about 60% (p<0.05) of both the non-paretic lower limb and control, which were not different (Table 2.2). Maximal voluntary activation of both paretic and non-paretic lower limb was significantly lower than control and that of the paretic lower limb was significantly lower than the non-paretic lower limb (Table 2.2).

*Table 2.2: MVC during extension (MVCe) and flexion (MVCf), ratio MVCf:MVCe, voluntary activation and triplet torque of knee extensors of the paretic lower limb (PL), non-paretic lower limb (NL) and control (mean ± standard deviation).*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NL</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVCe (Nm)</td>
<td>223.2 ± 47.8</td>
<td>151.8 ± 54.8</td>
<td>62.1 ± 47.9</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 13</td>
<td>n = 14</td>
<td></td>
</tr>
<tr>
<td>MVCf (Nm)</td>
<td>89.5 ± 29.0</td>
<td>56.3 ± 26.9</td>
<td>10.3 ± 16.1</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 13</td>
<td>n = 14</td>
<td></td>
</tr>
<tr>
<td>Ratio MVCf:MVCe</td>
<td>0.40 ± 0.07</td>
<td>0.36 ± 0.09</td>
<td>0.14 ± 0.19</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 13</td>
<td>n = 12</td>
<td></td>
</tr>
<tr>
<td>Voluntary activation (%)</td>
<td>93.6 ± 4.1</td>
<td>75.1 ± 7.3</td>
<td>57.8 ± 24.6</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 10</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td>Triplet torque (Nm)</td>
<td>99.1 ± 12.6</td>
<td>93.7 ± 25.6</td>
<td>55.8 ± 26.8</td>
</tr>
<tr>
<td>n = 12</td>
<td>n = 12</td>
<td>n = 10</td>
<td></td>
</tr>
</tbody>
</table>

† significantly lower than control, ‡ significantly lower than NL
rsEMG for activation and coactivation
During maximal knee extension, rsEMG of VL, RF and VM was significantly lower for the paretic limb (n=13) compared to both the non-paretic limb (n=12) and control (n=12) (Figure 2.2A), whereas no differences were observed across groups for rsEMG of the antagonist muscles (BF and GM, Figure 2.2D).
During maximal knee flexion, the paretic lower limb (n=12) showed reduced rsEMG (p<0.05) of all five muscles studied (agonist and antagonists, Figure 2.2B and C) compared to control (n=12) and when compared to the non-paretic lower limb (n=12) this was true for all muscles except for VL. No differences in rsEMG were found between the non-paretic limb and control, neither during MVCe nor during MVCf. The ratio rsEMG/rsEMGmax was used as a measure of coactivation. This ratio (the level of coactivation) of the knee-extensors (VL, RF, and VM) during knee- flexion was not significantly different across groups (Figure 2.3A). However, as can be observed in Figure 2.3B, a significantly higher ratio for BF and GM during maximal voluntary knee extension was found in the paretic compared to the non-paretic lower limb and controls. The ratio in the non-paretic lower limb did not differ from controls.

Functional performance
Results of the tests of functional performance are shown in Table 2.3. Three subjects could not perform the 10 meter walk test (10m) and the Timed “get-up-and-go” test (TUG). They were not used for data-analysis for these two tests. One of them scored zero at the Fugl Meyer (FM) and Functional Ambulation Categories (FAC). Note that significant correlations or trends were found between MVCe and MVCf of the paretic lower limb and all tests of functional performance (Table 2.4). Other significant correlations and trends are also shown in Table 2.4.
Figure 2.2: rsEMG values of knee extensors vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) during maximal voluntary knee extension (A) and flexion (C) and absolute EMG values of knee flexors biceps femoris (BF) and gastrocnemius medialis (GM) during maximal voluntary knee flexion (B) and knee extension (D) for controls, non-paretic lower limb and paretic lower limb. * significantly different from control, + significantly different from non-paretic lower limb.
Figure 2.3: Coactivation ratio rsEMG/reEMGmax of vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) during maximal voluntary knee flexion (A) and coactivation of biceps femoris (BF) and gastrocnemius medialis (GM) during maximal voluntary knee extension (B) for controls, non-paretic lower limb and paretic lower limb. Note the unrealistic coactivation values above 1 for the paretic lower limb during extension (B) which is mainly due to problems with activation of muscles in this group. * significantly different from control, + significantly different from non-paretic lower limb.

Table 2.3: Maximal possible scores (if applicable) and mean scores and standard deviations (SD) of stroke patients of the present study at the tests of functional performance: Rivermead Mobility Index (RMI), 10 meter walk test (10m), Functional Ambulation Categories (FAC), Berg Balance Scale (BBS), Timed get-Up-and-Go (TUG), Fugl Meyer (FM) and Motricity Index (MI)

<table>
<thead>
<tr>
<th></th>
<th>RMI</th>
<th>10m</th>
<th>FAC</th>
<th>BBS</th>
<th>TUG</th>
<th>FM</th>
<th>MI</th>
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<tr>
<td>Max. possible</td>
<td>15</td>
<td>-</td>
<td>5</td>
<td>56</td>
<td>-</td>
<td>34</td>
<td>100</td>
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<tr>
<td>Mean</td>
<td>8.1</td>
<td>33.8s</td>
<td>3.3</td>
<td>37.7</td>
<td>44.4s</td>
<td>16.5</td>
<td>46.0</td>
</tr>
<tr>
<td>SD</td>
<td>3.8</td>
<td>19.1s</td>
<td>1.4</td>
<td>13.3</td>
<td>22.6s</td>
<td>8.5</td>
<td>20.9</td>
</tr>
<tr>
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<td>14</td>
<td>14</td>
<td>11</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 2.4: Significant correlations (bold) and trends were found between the tests of functional performance and MVCe’s, MVCf’s, some of the rsEMG/rsEMGmax parameters of the measured muscles (RF = rectus femoris, BF = biceps femoris and GM = gastrocnemius medialis) and activation measured in the paretic (PL) and non-paretic lower limb (NL).

<table>
<thead>
<tr>
<th></th>
<th>RMI</th>
<th>10m</th>
<th>FAC</th>
<th>BBS</th>
<th>TUG</th>
<th>FM</th>
<th>MI</th>
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<tbody>
<tr>
<td>MVCe PL</td>
<td>.744(*)</td>
<td>- .545(†)</td>
<td>.780(‡‡)</td>
<td>.764(‡‡)</td>
<td>- .573(†)</td>
<td>.746(*)</td>
<td>.761(*)</td>
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<td>n=11</td>
<td>n=14</td>
<td>n=14</td>
<td>n=14</td>
</tr>
<tr>
<td>MVCf PL</td>
<td>.643(‡)</td>
<td>- .763(*)</td>
<td>.463(†)</td>
<td>.527(†)</td>
<td>- .858(‡‡)</td>
<td>.687(*)</td>
<td>.727(*)</td>
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</tr>
<tr>
<td>MVCe NL</td>
<td>.510(†)</td>
<td>- .699(‡)</td>
<td>X</td>
<td>.504(†)</td>
<td>X</td>
<td>.647(‡)</td>
<td>.615(‡)</td>
</tr>
<tr>
<td>n=13</td>
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<tr>
<td>MVCf NL</td>
<td>X</td>
<td>- .634(‡)</td>
<td>.485(†)</td>
<td>.516(†)</td>
<td>- .622(†)</td>
<td>.597(‡)</td>
<td>.570(‡)</td>
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<td>n=10</td>
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</tr>
<tr>
<td>rsEMG/rsEMGmax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RF PL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>BF PL</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
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<td></td>
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</tr>
<tr>
<td>GM PL</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<td>n=8</td>
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<tr>
<td>rsEMG/rsEMGmax</td>
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<td></td>
</tr>
<tr>
<td>GM NL</td>
<td>X</td>
<td></td>
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<td>X</td>
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<tr>
<td>n=11</td>
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<tr>
<td>Activation PL</td>
<td>.841(‡)</td>
<td>.845(‡)</td>
<td>.829(‡)</td>
<td></td>
<td>.883(‡)</td>
<td></td>
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</tr>
<tr>
<td>n=6</td>
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<td>n=6</td>
<td>X</td>
<td>n=6</td>
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</tr>
<tr>
<td>Activation NL</td>
<td>.665(‡)</td>
<td>- .964(‡‡)</td>
<td>X</td>
<td>X</td>
<td>- .893(*)</td>
<td>.828(*)</td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td>n=7</td>
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<td>X</td>
<td>n=10</td>
</tr>
</tbody>
</table>

† Trend 0.054 < p < 0.096,
‡ Correlation is significant at the 0.05 level (2-tailed),
§ Correlation is significant at the 0.01 level (2-tailed),
‡‡ Correlation is significant at the 0.001 level (2-tailed),
X No significant correlation or trend.
Discussion

The present report shows significant adaptations in both central neural activation and more intrinsic muscle properties in individuals 4 months after stroke. Weakness was observed in both paretic and non-paretic knee-extensors and -flexors. However, in the non-paretic lower limb this reduced strength seemed primarily due to impaired voluntary activation whereas in the paretic lower limb both impaired voluntary activation as well as reduced intrinsic torque capacity seemed responsible. An interesting and new observation is the strong significant correlation between functional performance and voluntary activation capacity of both lower limbs in stroke patients.

Strength

MVC

The results of the present study demonstrate that muscle strength of knee flexors and extensors is reduced after stroke in both legs with the greatest reduction in voluntary strength observed in the paretic lower limb muscles (Table 2.2), which is in accordance with previous studies\(^\text{22,33,8,49}\). The finding by Harris et al.\(^\text{33}\) that muscle strength of the non-paretic lower limb was already reduced in the first week after stroke, suggests that the direct consequences of stroke are the most likely cause of this muscle weakness.

Furthermore, the lower MVCf:MVCe-ratio’s in the paretic lower limb compared to control (Table 2.2) indicate a more pronounced weakness of the flexor muscles compared to extensors after stroke. This was also reported by Newham and Hsiao\(^\text{49}\), although they found a higher ratio for the paretic lower limb (0.31) compared to our results (0.14), which might be explained by possible differences in severity of stroke. Overall, the results suggest that the knee flexors are more affected than knee extensors after stroke. Alternatively, it may be possible that both muscle groups are equally affected by the stroke itself, but that the difference appeared because during
rehabilitation, training of knee extensors is more emphasized than that of knee flexors. Moreover, Twitchell\textsuperscript{61} described predictable spontaneous motor recovery with a fixed sequence after (initial paralysis after) stroke. It was stated that extensor movement is the first movement to recover. Accordingly, as our subjects were studied within 4 months after stroke such sequential spontaneous recovery could explain why knee extensors of the paretic lower limb seem less affected than knee flexors. Also the presence of synergies might be a possible explanation for the lower MVCf:MVCe ratio in the paretic limb compared to the non-paretic limb and control. Some patients have lost independent control over certain muscle groups after stroke, which results in coupled joint movements which are often inappropriate for daily tasks. These coupled movements or inability to master individual joint movements are known as synergies. Although Brunnström\textsuperscript{12} and Welmer \textit{et al.}\textsuperscript{63} demonstrated that the presence of synergies can negatively affect functional performance, Neckel \textit{et al.}\textsuperscript{48} showed little evidence of abnormal synergy patterns in lower limbs in isometric conditions. In the present study, scores at the (Brunnström) Fugl Meyer test show that as much flexor as extensor synergies are present in the paretic lower limb. Thus, it seems that, in line with the results of Neckel \textit{et al.}\textsuperscript{48}, the presence of synergies are not a likely explanation for a lower MVCf:MVCe ratio in the paretic lower limb.

\textbf{Voluntary activation}

The present results show that maximal voluntary activation capacity of the knee extensors is reduced in both lower limbs after stroke (Table 2.2), which can be attributed to damage of the descending motor tracts following stroke\textsuperscript{62}. Voluntary activation of 58, 75 and 94\% for respectively paretic, non-paretic and control lower limb was found. This means activation \textit{failure} (defined as 100 - voluntary activation (\%)) of 42\% for the paretic lower limb, 25\% for the non-paretic lower limb and 6\% for control which is very comparable with the values of Newham and Hsiao\textsuperscript{49}. It was shown before that the ability to maximally drive the knee extensor muscles is usually overestimated and that the level of overestimation increases with lower activation capacity\textsuperscript{42}. This would suggest that as the stroke patients have a lower activation capacity compared with controls, the difference in the ability to access the muscles’
potential between limbs is most likely underestimated. In other words, the real differences in maximal voluntary activation between paretic lower limb and control in the present study will be even more pronounced than calculated here.

Unfortunately, from pilot experiments we concluded that presently it is difficult to obtain reliable maximal voluntary activation values in the knee flexors and therefore we are presently unable to estimate the possible influence of voluntary activation on strength of the knee flexors. On the other hand, interestingly, the higher values found for EMG of flexor muscles during extension (Figure 2.2D, paretic lower limb (PL)) than during flexion (Figure 2.2B, PL) suggest that the voluntary activation capacity of the knee flexors is possibly severely affected.

**Maximal torque capacity**

Triplet torque is a measure for the maximal (intrinsic) torque capacity of the muscle, independent of voluntary activation. While all muscle fibers were assumed to be recruited with the used supramaximal stimulation, the muscle fibers of the paretic knee extensors only generated about half of the torque of controls (Table 2.2). Thus, besides reduced voluntary activation there is a reduction in the intrinsic torque capacity of the paretic knee extensors. In contrast, torque capacity of the non‐paretic lower limb did not differ from control (Table 2.2). This is different from Harris et al.\(^{33}\) who demonstrated that apart from reduced central activation there is an additional reduction in the twitch torque of the non‐paretic quadriceps muscles.

Part of the reduction of the torque capacity in the paretic lower limb might be explained by muscle atrophy. For instance, Metoki et al.\(^{47}\) and Ryan et al.\(^{54}\) found hemiparetic skeletal thigh muscle atrophy more than six months after stroke that might contribute to functional disability in chronic hemiparetic stroke patients. Atrophy is not induced by upper neuromotor lesion itself, but may be attributed to the sedentary lifestyle as a result of functional disability (e.g. hemiparesis), immobilisation (e.g. lying in bed or sitting in a wheelchair) and malnutrition after stroke\(^{33,47}\). Therefore, although muscle size or volume was not directly measured in
the present study, the reduced torque capacity in the paretic limb is likely due to muscle atrophy, especially in view of the period of 4 months of relative disuse after stroke before patients were measured. Nevertheless, the found fifty percent reduction in torque capacity reported in our study would indicate a similar degree of atrophy which seems very excessive if attributed solely to changes in muscle volume. Therefore, it seems reasonable to expect that other factors, like for example a disturbed excitation contraction coupling mechanism, may additionally contribute to the specific reduction of torque capacity\textsuperscript{20}.

\textit{Coactivation}

Excessive coactivation, for instance as a result of impaired reciprocal inhibition\textsuperscript{36}, may underlie the lower torques as measured in the paretic and non-paretic lower limb compared to control. Conflicting results are found between and within several muscle groups regarding coactivation after stroke. For instance, Knutsson and Martensson\textsuperscript{40} and Neckel \textit{et al.}\textsuperscript{48} have indeed found increased coactivation of thigh muscles in hemiplegia following stroke, while Davies \textit{et al.}\textsuperscript{22} and Newham and Hsiao\textsuperscript{49} did not. Some studies\textsuperscript{45,25,31}, but not all\textsuperscript{16,28} showed excessive coactivation in the hemiparetic elbow and shoulder muscles. Chae \textit{et al.}\textsuperscript{14} even found correlation between coactivation in upper limb hemiparesis and functional measures. Levin and Hui-Chan\textsuperscript{44} found high coactivation ratio’s for the paretic dorsiflexors, while Becher \textit{et al.}\textsuperscript{2} found a low level of coactivation in gastrocnemius muscle in spastic hemiplegia. The results of the present study show a higher rsEMG/rsEMGmax ratio of the knee flexors during extension in the paretic compared to the non-paretic lower limb. These findings may suggest that enhanced coactivation of knee flexor muscles might (partly) explain the lower MVC\textsubscript{e} in the paretic lower limb compared to the non-paretic lower limb and control, which is in agreement with Neckel \textit{et al.}\textsuperscript{48}. Remarkably, however, rsEMG of the flexors (BF and GM) during extension was the same for the three groups, while maximal rsEMG of these muscles during flexion (i.e., working as agonists), was significantly lower for the paretic lower limb compared to control and the non-paretic lower limb. Consequently, the ratio might be exaggerated by reduced agonist activity in the
presence of normal antagonist activity\textsuperscript{15} since the antagonist activity of the flexors is scaled to a lower ‘maximum’ agonist value in the paretic lower limb. Thus, although it seems tempting to interpret our data such that the reduced torques around the knee joint result from enhanced coactivation of antagonist muscles, the high rsEMG/rsEMGmax ratio’s most likely result from the low rsEMG for BF and GM during MVCf, which would argue against the existence of real excessive coactivation.

**Functional performance**

*Strength and functional performance*

The results show that isometric extensor as well as flexor torque of especially the paretic lower limb but also of the non-paretic lower limb is strongly related to a broad spectrum of functional performance (Table 2.4), which is in accordance with reported findings\textsuperscript{8,51}.

Thus, deteriorated functional performance is related to limitations in muscle strength of both extensors and flexors of both lower limbs, but the exact nature of that reduced functional performance is not completely clear yet. Given the nature of the disorder (cerebro vascular accident) a disturbed neural control is also a very likely explanation for impaired functional performance.

*Neural control and functional performance*

Most interestingly and to our best knowledge never investigated before, maximal voluntary activation of the paretic lower limb correlated significantly with RMI, FAC, BBS and FM, while activation of the non-paretic lower limb correlated significantly with RMI, MI, 10 m walk test and TUG (Table 2.4). The lower the activation, the longer the time to walk 10 m or perform the TUG and the lower the score at the RMI and MI. The very high correlation coefficient for the relationship between activation of the knee extensor muscles of the non-paretic lower limb and the 10m walk time means that about 93\% (r\textsuperscript{2}) of the time of the 10 m walk test could be explained by the voluntary activation capacity of these muscles. In other words activation capacity of the non-paretic knee extensor muscles seems to be very important in predicting
functional performance. A possible cause for this strong correlation might be behavioural compensation strategies, for instance enhanced use of the non-ataxic lower limb, to counterbalance the motor impairment of the ataxic lower limb⁴³,⁵³.

The underlying nature of the reduced maximal voluntary activation could be impairments in either motor unit recruitment and/or rate of motor unit firing⁵⁷,⁵₂. This disturbance in central drive might not only cause a limited voluntary activation capacity during maximal isometric contractions, but might also lead to a disturbed neuromuscular control and coordination during more submaximal contractions while performing the functional performance tests. Hence, although the sample size is limited, the findings tend to reinforce measures as strength and activation as indicative of function and identify intrinsic muscle strength and voluntary activation as important targets of intervention for stroke patients. Moreover, we believe that improving voluntary activation might result in better functional performance, like increasing strength results in gains in measures of impairments and disabilities⁵⁹, gait performance⁶⁰ and velocity⁵⁶. Besides, it is known that voluntary activation can be improved by strength training in healthy subjects²⁷,⁴⁸,⁵₂. Therefore, involving strength training in rehabilitation programs for stroke patients is recommended for both increasing muscle strength⁹,⁵⁰,¹,⁶⁴ and improving voluntary activation in order to improve functional performance after stroke.

The question remains whether our measure for the degree of coactivation correlates with functional performance. In the present study indeed some significant correlations were found between the measured ratio during extension and functional performance. However, hardly any correlation between functional performance and the ratio during flexion was found. This supports our idea that, high ratio’s were obtained due to low maximal rsEMG instead of high coactivation. Another possible explanation might be that the degree of coactivation during an isolated task such as maximal voluntary contraction is different than that during more complex functional tasks, thereby possibly not being representative to assess the influence of coactivation during functional performance.
Conclusions
Both paretic and non-paretic knee extensor and knee flexor muscle torques are reduced after stroke. Whereas for the non-paretic lower limb failure of activation can fully explain the weakness, for the paretic lower limb both reduced activation and reduced torque capacity are responsible for the severe weakness. There are no indications that coactivation during maximal contractions play a significant role in the observed weakness. The high correlations found between strength, as well as voluntary activation, and functional performance, indicate that these parameters have a determinant influence on performance. These results clearly indicate that both muscle strength and voluntary activation are important parameters which can potentially be fruitful objects for rehabilitation programs after stroke.

References
Chapter 2: Muscle strength and functional performance after stroke


Chapter 2: Muscle strength and functional performance after stroke
Chapter 3

Intrinsic properties of the knee extensor muscles after subacute stroke

Astrid M. Horstman
Karin H. Gerrits
Marijke J. Beltman
Peter A. Koppe
Thomas W. Janssen
Arnold de Haan

Summary

For optimizing rehabilitation programs, a better understanding is needed of the nature of weakness and fatigability of muscles of patients with stroke. Our aim was to characterize muscle properties of paretic (PL) and non-paretic (NL) knee extensors in patients with subacute stroke. Therefore we included 14 patients with subacute stroke and 12 able-bodied age-matched control subjects. Half relaxation times (HRT) and maximal rates of torque development (MRTD) were assessed as indicators of contractile speed using both voluntary and electrically evoked contractions. Moreover, changes in torque were measured during a fatigue protocol (35 electrically evoked intermittent contractions; 1.5 s on, 2 s off) and recovery. No differences among groups were found for normalized MRTD during electrically evoked contractions (p=0.117). However, during voluntary contractions both PL (53% of control, p=0.022) and NL (71% of control, p<0.001) had significantly lower MRTD compared to control. Both PL (134% of control, p=0.001) and NL (123% of control, p=0.032) had significantly higher HRTs than control, indicating muscle ‘slowing’ in patients with subacute stroke. PL fatigued more and faster than control (p=0.011) and both PL and NL recovered slower (p<0.001).

In conclusion, the changes in half relaxation times and fatigue suggest adaptations in muscle properties towards slower, more fatigable muscle shortly after stroke. The inability to make use of contractile speed due to impaired neural activation seems the most limiting factor during the initial phase of torque development in PL. Thus, besides strengthening, also muscle endurance and speed should be addressed during rehabilitation.
Introduction

Stroke leads to significant muscle weakness in both the lower limb contralateral (paretic, PL)\textsuperscript{5,22,17} and ipsilateral (non-paretic, NL) to the lesion\textsuperscript{5,2,13}. In a previous study with the same group of patients\textsuperscript{17} we have reported that in patients with subacute stroke muscle weakness of NL (torque was 68% of control) could be explained by activation failure (voluntary activation capacity was 75% compared to 94% in control), whereas in PL, muscle weakness (torque was 28% of control) could not only be attributed to a reduced activation (58% of control), but also to an impaired intrinsic torque capacity (56% of control).

Since the knee extensor muscles are exposed to altered patterns of activity and function after stroke, their contractile properties are assumed to change. A change in muscle fiber composition, characterized by selective type II fiber atrophy and predominance of (slow twitch, oxidative) type I fibers has been shown in paretic muscles\textsuperscript{26,8,4,12,9}, which would lead to concomitant changes in contractile speed of the muscle fibers towards those of slow muscles, accompanied by more fatigue resistance, as found by Toffola\textsuperscript{29} in patients with chronic stroke. Results are inconsistent as others\textsuperscript{33,11} found enhanced neuromuscular fatigue in patients with chronic stroke which may partly relate to methodologies used to study fatigue resistance. Moreover, it is unclear whether the fatigue properties of muscles in subacute stroke patients have altered. We anticipate that shortly after stroke people are more inactive and therefore are likely to develop a lower oxidative capacity. Together with impaired blood flow and capillarization\textsuperscript{19,1,32,24} this is expected to lead to a higher fatigability.

Given the altered muscle fiber composition combined with impaired neural drive, the rate of torque development may be even more deteriorated. This ability to develop torque rapidly seems important for balance control and fall prevention\textsuperscript{23,27}. Indeed, individuals with stroke seem to perform slower during voluntary contractions of both upper and lower limb muscles\textsuperscript{2,3,21,30}. Other studies, using electrically evoked
contractions\textsuperscript{31,11}, suggest that the time course of torque development has changed, due to changes in contractile muscle properties, making it intrinsically slower. Nevertheless, as these studies did not compare electrically induced with voluntary contractions, information about the relative contribution of both neural and more local muscular changes is still lacking. More specifically, it is presently unknown to what extent patients with stroke are able to make use of the muscles’ maximal torque capacity during \textit{fast voluntary contractions} of the knee extensors and whether this differs between the paretic and non-paretic side. Accordingly, we were interested whether this muscle slowing was due to the inability to maximally drive the muscles to perform fast contractions and/ or that the slowing was due to changed intrinsic muscle properties. Therefore both voluntary and electrically evoked contractions were used to determine maximal rate of torque development.

For optimizing rehabilitation programs a better understanding of the degree and nature of impaired muscle function of the knee extensor muscles in patients with subacute stroke is needed. Therefore, the aim of the present study was to compare contractile speed and fatigue characteristics of the knee extensor muscles of subacute stroke patients with those of able-bodied controls. We hypothesized that patients with subacute stroke have slower, more fatigable muscles and are less able to make use of the muscles’ maximal torque capacity during \textit{fast voluntary contractions}, mainly due to impaired neural control.

\section*{Methods}

\subsection*{Subjects}

Fourteen patients after their first stroke and with lower-extremity hemiparesis entered the study on average 3.5 months after stroke and 2 months after admission to the rehabilitation center (Table 3.1). They were in- or outpatients and all (except one) ambulatory. From this patient group, data on knee extensor and flexor torque (at different knee angles) and voluntary activation have been published
The median and quartiles on the Functional Ambulation Categories (FAC)-score were 4 (2.25-4.00), evaluating the measure of independence of walking on a six-point scale (0-5)\textsuperscript{14,15}. Twelve able-bodied control subjects volunteered to participate in this study. They were matched (0.470<p<0.954) for age, height and weight. Each subject was informed about the procedures. They all filled out a health questionnaire and gave written informed consent. Exclusion criteria were medical complications, severe cognitive and/or communicative problems preventing the ability to follow verbal instructions or limiting the ability to perform the requested tasks and contra-indications for electrical stimulation. The study was approved by the institutional review board of the VU University Medical Centre, Amsterdam, The Netherlands.

### Table 3.1: Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age (years) (mean ± SD)</th>
<th>Height (m) (mean ± SD)</th>
<th>Weight (kg) (mean ± SD)</th>
<th>Sex (Men, Women)</th>
<th>Stroke type (Hemorrhagic, Ischaemic)</th>
<th>Side of lesion (Left, Right)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke patients</td>
<td>56 ± 10</td>
<td>1.74 ± 0.10</td>
<td>74.9 ± 14.3</td>
<td>10M, 4W</td>
<td>5H, 9I</td>
<td>6L, 8R</td>
</tr>
<tr>
<td>Control</td>
<td>58 ± 12</td>
<td>1.76 ± 0.06</td>
<td>75.7 ± 11.9</td>
<td>7M, 5W</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Experimental set-up and procedures

The measurements described in the present paper were part of a protocol spread over 4 measurement days (separated by at least 24 hours). On the first day, electrically evoked contractions and a fatigue protocol (see below) were performed with both legs, starting with PL and then NL. The second day subjects underwent supramaximal stimulation and superimposed triplets, also starting with PL, followed by NL. The third day, torque-angle relationships were recorded from the PL and on the fourth day for NL. Control subjects only performed the measurements with their right leg.

In a familiarization session, subjects started with a warm-up (consisting of 5 submaximal contractions) with NL to check whether the instructions were
understood. Subsequently, they were trained to perform maximal isometric knee extension contractions. Thereafter, they were familiarized with electrical stimulation. Using a frequency of 150 Hz, the current was increased in steps of 10mA until the torque reached 50% of their maximal voluntary contraction torque.

**Torque measurements**

Measurements were performed on a custom built (VU University Amsterdam, The Netherlands) Lower EXTremity System (LEXS)\(^{17}\). Subjects were placed on the LEXS in a supine position and were tilted to the measuring position: seated with their back 10° backwards from upright, 80°-hip angle and 60°-knee angle (0°=full extension). To avoid changes in hip and knee angle during isometric contractions, subjects were restrained with a hip and trunk belt. Their shank was strapped tightly to a force transducer (KAP, E/200 Hz, Bienfait B.V., Haarlem, The Netherlands, range: 0-2 kN) with a cuff just above the ankle. Active knee angle was determined with a handheld goniometer (model G300, Whitehall Manufacturing, California, USA) using the greater trochanter, the lateral femoral epicondyle and the lateral malleolus as references\(^{20}\). The distance between the epicondyle and a fixed point on the force transducer was used as external moment arm.

Each session started with maximal isometric knee extensions for 3-4 seconds to determine maximal voluntary knee extension contraction (MVC) torque separated by 2 minutes of rest. MVC was taken as the highest value that did not exceed preceding attempts by >10%, allowing a maximum of four attempts. Subjects were vigorously encouraged to exceed their previous maximal value, displayed on a computer screen to confirm the subject’s achievement throughout the test. After explanation of the procedure for electrical stimulation, the skin of the thigh of the subject was shaved (when necessary) and a pair of self-adhesive surface electrodes (13 x 8 cm, Schwa Medico, Nieuw Leusden, The Netherlands) was placed over the proximal and distal part of the anterior thigh. A computer-controlled constant current stimulator (Digitimer, Welwyn Garden City, UK) was used with rectangular pulses of 200 μs. Current amplitude was increased at 150 Hz until 50% of subjects’ MVC torque was
reached, assuming that then 50% of the knee extensor muscle mass, which could be voluntary recruited for healthy subjects, was activated. This current was subsequently used in the following procedures: an electrically evoked 80 ms-contraction at 300 Hz to determine the maximal rate of torque development and at 150 Hz (700 ms) to determine maximal torque at this intensity. The fatigue protocol lasted 2 minutes and existed of 35 electrically evoked intermittent contractions (1.5 s on, 2 s off) at 50 Hz. At this 50 Hz frequency, torque was ~90% of the maximal torque and high frequency fatigue was prevented. Recovery measurements occurred at 15, 30, 45, 60, 90 and 180 s after the last contraction of the fatigue protocol using the same current amplitude and stimulation frequency to check if and how fast the muscle recovered from fatigue. Half relaxation time was measured from the torque trace at 50 Hz stimulation (700 ms). Pilot data have shown that responses at this 50 Hz frequency showed the least disturbance in the relaxation phase, which is a prerequisite for appropriate calculations of half relaxation times (HRT).

**Fast voluntary isometric contractions**

Subjects were asked to perform knee extensions as fast as possible without a countermovement (flexion). The command was: 3, 2, 1 GO! Subjects performed these fast contractions until they had 2 attempts without countermovement or an enhanced pretension just before the fast extension with a maximum of 5 attempts to avoid fatigue. After each attempt (1 minute rest in between), subjects received feedback by means of a histogram with the reciprocal value of the time between 10 and 100 N and were encouraged to exceed this value.

**Data analysis**

Real-time force applied to the force transducer was digitally stored (1kHz) on computer disc. Force signals were automatically corrected for gravity of the leg: average force applied by the limb weight to the transducer during the first 50ms after start of a recording, with the subject seated in a relaxed manner, was set to zero by the computer program. All force signals were low-pass filtered (4th order, 50 Hz,
Butterworth). MVC torque (Nm) was defined as the peak force from the force plateau multiplied by the external moment arm.

Maximal rate of torque development (MRTD) was defined as the steepest slope of torque development during both fast voluntary contractions (vol)\(^6\) and during 80 ms pulse trains at 300 Hz (stim). The MRTD as such not only depends on speed properties of the muscle but also on its maximal torque generating capacity. Therefore, to get a fair comparison of contractile speed of muscles between different subjects independent of absolute maximal torques, MRTD\(_{\text{vol}}\) was normalized to MVC torque and MRTD\(_{\text{stim}}\) to the 150 Hz torque (obtained at the same stimulation intensity as the 300 Hz pulse train).

HRT was the time taken for the force decline from the maximal torque at the end of the 50Hz-stimulation to 50% of that torque value.

The course and degree of torque decrease during the stimulated fatiguing contractions was taken as measure of fatigue. Absolute torque values during the fatiguing contractions were normalized to the torque of the first contraction to correct for torque differences among subjects.

For the recovery measurements we normalized the degree of recovery (absolute torque value during the concerning recovery contraction compared to the last fatiguing contraction) to the degree of fatigue (torque of the first minus the last fatiguing contraction = 100%) to correct for different fatigue states per group.

**Statistics**

All results are presented as means ± SD. For the comparison of MRTD\(_{\text{vol}}\), MRTD\(_{\text{stim}}\) and HRT among PL, NL and control, one-way analysis of variance (ANOVA) was used. For fatigue and recovery parameters, a repeated-measures-ANOVA with ‘time’ as the within subject factor and ‘group’ (3 levels) as the between subject factor was used. In case of significance, Bonferroni post hoc tests were used. The level of significance was set at p<0.05 for each statistical analysis.
Chapter 3: Intrinsic muscle properties after stroke

Results

Some patients were excluded from data analysis, due to unreliable data (e.g. concentration problems, one subject dozed off a few times during the measurements) or incomplete data because of discomfort (electrical stimulation, duration of the experiments). In addition, two of the 14 patients with stroke were not able to extend their paretic lower limb at all and were therefore not able to generate torque as fast as possible. The number of patients analysed are indicated in the text.

Maximal rate of torque development

Figure 3.1A shows that MRTD\textsubscript{stim} in PL (n=10) was 78% and in NL (n=9) 95% of control (n=13), but there were no significant differences among groups (p=0.117). However, PL (n=8) and NL (n=10) had a significantly lower MRTD\textsubscript{vol} (Figure 3.1B) compared to control (n=12) (PL: 53% (p=0.022) and NL: 71% (p<0.001) of control, respectively).

![Figure 3.1: Normalized (%-ms\textsuperscript{-1}) maximal rate of torque development (MRTD) during fast voluntary isometric contractions (vol) and during 300 Hz stimulation (stim) for controls, non-paretic and paretic lower limb. * significantly different from control]
**Half relaxation times (HRT)**

HRTs in PL (n=10) and NL (n=10) were significantly longer than control (n=13), 134% (p=0.001) and 123% respectively (p=0.032) (Figure 3.2), so the knee extensor muscles of patients with subacute stroke relaxed slower than controls.

![Half relaxation times](image)

*Figure 3.2: Half relaxation times of controls, non-paretic and paretic lower limb during 50 Hz contractions. *significantly different from control*

**Fatigue and recovery**

Figure 3.3 shows the course of fatigue and recovery in the three groups. A significant interaction (fatigue x group) effect was found (p<0.001) for the fatigue protocol, indicating that the course of fatigue differed among groups. Also a significant main effect was found for group (p=0.013). Bonferroni post hoc tests showed a significant difference in fatigue between PL (n=10) and control (n=13) (p=0.011). Thus, PL fatigued more and faster than control, but no differences in the course of fatigue were found between PL and NL (n=9, p=0.174) or between NL and control (p=0.996). The course of recovery was not different among groups (Figure 3.3, p=0.289). However a main effect for group (p=0.003) showed that NL and PL recovered less than
control. This was also found when corrected for the different fatigue states per group. Control showed 89 ± 16%, NL 71 ± 21% and PL 77 ± 20% recovery (interaction effect: p=0.510, main effect group: p<0.001).

Figure 3.3: Torque (normalized to torque of first contraction) course of control, non-paretic (NL) and paretic lower limb (PL) during the fatigue protocol and six recovery measurements. A significant interaction (fatigue x group) effect was found as well as a significant main effect for group: PL and control differed significantly, but no differences in the course of fatigue were found between PL and NL or between NL and control.

**Discussion**

The present study has clearly shown that in addition to a severe reduction in maximal isometric strength as reported previously\(^1\), the knee extensors of patients with subacute stroke also demonstrated severe impairment in the rate of torque development. Interestingly, whereas in the paretic limb both changes in the intrinsic muscle (fiber) characteristics and impaired neural activation seem responsible, in the non-paretic limb reduced rate of torque development seems primarily related to
neural activation changes. In addition, both PL and NL muscles relaxed more slowly than control as indicated by significantly higher half relaxation times. PL fatigued more and faster than control and both PL and NL recovered slower.

**Maximal rate of torque development and half relaxation times**

During voluntary contractions, MRTDvol was lower for PL and NL than for control. Thus, the capacity to develop adequate torque rapidly is severely decreased shortly after stroke, as previously found in the knee extensors\(^2,30\) and elbow flexors and extensors\(^3\). During the stimulated contractions, MRTDstim in NL was comparable with control. However, in PL, MRTDstim was only 78% of control albeit failure to reach statistical significance (\(p=0.117\)), probably due to the high variability among subjects. From previous work of our group\(^10\) we know this variable shows a high variability among subjects despite the use of well controlled electrically induced contractions, and only relatively large differences can be detected. This intrinsically slower muscle would be in accordance with the longer HRTs we found in PL compared with control, similar as found in chronic stroke patients\(^11\). In the present study, the HRTs were also longer in NL compared to control. This overall muscle slowing is presumably caused by an altered muscle fiber composition after stroke with selective type II fiber atrophy and predominance of (slow twitch) type I fibers\(^26,8,4,12,9\). Since we determined both the stimulated and voluntary MRTD, this is to our best knowledge the first time that intrinsic muscle properties and voluntary activation can be distinguished with regard to fast torque development. Our results suggest that the inability to make use of the contractile speed of the muscle due to impaired neural activation seems the most limiting factor during the initial phase of torque development in the non‐paretic knee extensors in patients with subacute stroke, whereas in the paretic lower limb both changes in the intrinsic muscle (fiber) characteristics and impaired neural activation seem responsible for the reduced rate of torque development. This reduced MRTD in both lower limbs may have significant functional implications for individuals with (subacute) stroke, especially in situations where torques do not have to be maximal, but need to be generated quickly (e.g. avoiding an obstacle).
Chapter 3: Intrinsic muscle properties after stroke

Fatigue

The knee extensor muscles of PL shortly after stroke fatigued more rapidly than those of NL and controls. This was characterized by a greater force decline, which is in agreement with Gerrits et al.\textsuperscript{11} who found enhanced fatigability in the paretic knee extensors of patients with chronic stroke. This reduced resistance to fatigue seems to be in contrast with our finding of slowing of contractile properties and the previously reported selective type II fiber atrophy and predominance of type I fibers in paretic muscles after stroke\textsuperscript{9,26,4,12,8}. However, it agrees with previously reported appearance of slow-twitch fatigable motor units, a type which is generally not found in neurologically healthy subjects\textsuperscript{33}. In addition, it is likely that, despite the possible predominance of type I fibers, the faster and greater development of fatigue partly results from an impaired blood flow and lower oxidative metabolism in paretic limbs of patients with both subacute and chronic stroke\textsuperscript{19,1,32,24}. The difference between fatigue response in the present study and the higher fatigue resistance reported in other studies\textsuperscript{29,18,25,28} may originate from the type of contractions being studied. In previous studies mostly voluntary contractions were used, which largely depend on the neural activation which in turn is known to be reduced after stroke\textsuperscript{17,13}. This reduced maximal voluntary activation capacity in patients with stroke leads to an overestimation of the relative level of muscle recruitment at a given (submaximal) workload. Accordingly, the muscle is metabolically less loaded than expected resulting in a reduced fatigue. This was avoided in the present study by using electrically evoked contractions during the fatigue protocol, allowing studying intrinsic muscle characteristics apart from activation properties. Apparently already shortly after stroke, a reduction in fatigue resistance of the knee extensor muscles occurs.

Conclusions

The capacity to develop adequate torque rapidly is decreased (lower voluntary MRTD) already shortly after stroke in both lower limbs, mainly due to decreased voluntary activation and in PL also as a result of reduced intrinsic speed characteristics. Slower relaxation in both PL and NL also indicate intrinsic muscle ‘slowing’ in patients with subacute stroke although no significant differences were found in electrically evoked
MRTD. These changes suggest adaptations in muscle properties towards slower, less fatigue resistant muscle which develop shortly after stroke. Moreover, these abnormalities were bilateral. Thus, besides strengthening, also muscle endurance and speed should be addressed in both lower limbs during rehabilitation to reverse adaptations in the neuromuscular system after stroke.

References


Chapter 3: Intrinsic muscle properties after stroke
Chapter 4

Muscle function of knee extensors and flexors after stroke is selectively impaired at shorter muscle lengths

Astrid Horstman
Karin Gerrits
Marijke Beltman
Thomas Janssen
Manin Konijnenbelt
Arnold de Haan

Summary

Our objective was to investigate whether muscle strength is selectively more affected at shorter lengths of thigh muscles as result of stroke and to determine whether this is associated with impaired neural activation at shorter muscle lengths. In 14 patients with sub acute stroke (bilaterally) and 12 able-bodied controls torque and activation was measured during maximal voluntary isometric contractions of knee extensors and flexors at 30, 60 and 90° knee flexion. The paretic knee extensors showed lower normalized maximal torques (73%) and lower normalized activation (71%) compared to control at 30°. The paretic knee flexors showed lower normalized maximal torques at 60° (64%) and 90° (45%) with non-significantly lower normalized activation (~79% and ~67%, respectively).

In conclusion, as a result of stroke lower muscle torque at shorter muscle lengths of the knee extensors is associated with a length-dependent lower voluntary activation, which may also be the case for the flexor muscles, but not with altered co-activation. We recommend investigating the role of specific training of paretic knee extensors and flexors in especially shortened positions to improve recovery of function after stroke.
Chapter 4: Muscle weakness at shorter muscle lengths after stroke

Introduction

The majority of people after stroke has motor impairments, e.g. hemiparesis, muscle weakness of the upper and lower limbs contralateral to the brain lesion. This causes problems in functional tasks like balancing, climbing stairs, walking and transfers. Therefore, the severity of strength loss after stroke is an important consideration in regaining locomotor skills and improving functional performance during rehabilitation.10

In addition to a reduction in muscle strength, length-dependency of strength is an important feature, since a whole range of muscle lengths is used during daily activities. This length-dependency of force generation is reflected in the torque angle relationship as found in healthy humans.6 In patients with stroke, muscle weakness is present to a greater extent at relatively short muscle lengths for elbow extensors and flexors.2,12,13 However, the mechanisms responsible for the impaired strength at short muscle length after stroke are presently unknown. Ada et al.2 excluded contracture as a major contributing factor to selective weakness at short elbow muscle lengths. Apart from possible changes in biomechanical properties of muscles, Koo et al.12 showed for arm muscles that a reduced central drive to the agonist muscles could be responsible for the lower torque at shorter muscle lengths. According to Ada et al.1, a differential effect of muscle length on strength after stroke may contribute to the problem of poorer muscle function at shorter muscle lengths rather than loss of control.

To our best knowledge, the length-dependency of torque of knee flexors and extensors of individuals after stroke has never been investigated before. In fact, the consequences of this length-dependent weakness could be much larger in the lower limb muscles compared to e.g. elbow muscles, since it is impossible to walk with one leg. Besides, in the upper limbs, more degrees of freedom are available so the unfavorable lengths could be avoided or the other arm could be used for certain movements. This is, except for some compensation strategies, impossible with the lower limb muscles during locomotion. Moreover, it is known that individuals after
stroke have difficulties functioning when the affected knee is in the last 0-15° of extension. This possible length-dependent muscle weakness could explain the clinical observation of an inability to stand with a straight knee (short muscle length of knee extensors) despite the ability to bear weight when the knee is slightly flexed (longer knee extensor muscles). As said, the quadriceps muscles, and also the hamstrings during the swing phase of gait are very important for locomotion. The knowledge that force is more impaired after stroke at a certain thigh muscle length, and moreover which mechanisms are responsible for this, may help to further improve the rehabilitation after stroke. Therefore, the aim of the present study is to investigate whether muscle strength is impaired at particular lengths of the thigh muscles as result of stroke. We hypothesized patients with stroke show selective muscle weakness at relatively short lengths of knee extensor and flexor muscles of the contralateral paretic lower limb. Because the ipsilateral non-paretic limb also shows muscle weakness and may thus not be valid as control, we assessed muscle strength in both lower limbs at different knee angles and compared this with able-bodied control subjects. We further measured muscle activity from both knee extensor and flexor muscles to determine whether impaired function was associated with neural activation at knee angles in which muscles were at short length.

Methods

Subjects

Fourteen patients after their first-ever stroke (side of lesion: 6 left and 8 right, type of stroke: 5 haemorrhagic and 9 ischemic, sex: 4 women and 10 men) with a minimum age of 18 years and a hemiparesis of the lower extremity (55.9 ± 10.4 years, 1.74 ± 0.10 m and 74.9 ± 14.3 kg) and twelve able-bodied control subjects (58.1 ± 12.2 years, 1.76 ± 0.06 m and 75.7 ± 11.9 kg, 5 women) volunteered in this study. The patients entered the study on average 3.5 months after stroke and 2 months after admission to the rehabilitation centre. They were all inpatient and all (except one) ambulatory. The median and quartiles on the Functional Ambulation Categories (FAC)-score were 4
(2.25-4), evaluating the measure of independence of walking of the patient and categories are scored on a six-point scale (0-5)\(^8,9\) in our study. The exclusion criteria were medical complications severe cognitive and/or communicative problems preventing the ability to follow verbal instructions or limiting the ability to perform the requested tasks, e.g. aphasia, hemineglect, and contra-indications for electrical stimulation like unstable epilepsy, cancer, skin abnormalities, pacemaker. The project carried the approval of the institutional review board of the VU University Medical Centre, Amsterdam, The Netherlands and all subjects signed an informed consent before participation.

**Experimental design**

Maximal voluntary isometric knee extensions and flexions in 30, 60 and 90° knee angles were performed. The studies were spread over two days, one day the familiarization session was performed and the other day the real measurements took place, with at least one day of rest in between.

**Torque measurements**

Maximal voluntary isometric forces of the knee extensors and knee flexors at different knee angles were measured on a custom built Lower EXtremity System (LEXS). Subjects were placed in a supine position and were tilted to the measuring position: back 10° backwards from upright position and a hip angle of 100° (180° being fully extended hips). The position of LEXS was adjusted, subjects were stabilized with a hip and trunk belt to avoid changes in hip and knee angle during isometric contractions and the external moment arm was measured as described in Horstman *et al.*\(^{10}\). Briefly, the lower leg was strapped tightly to a force transducer (KAP, E/200 Hz, Bienfalt B.V., Haarlem, The Netherlands, range: 0-2 kN) just above the ankle by means of a cuff and active knee angle was determined with a handheld goniometer (model G300, Whitehall Manufacturing, California, USA). The three different knee angles were 30, 60 and 90° (0° corresponds with fully extended knee).
**EMG measurements**

To assess the potential effect of neural activation on the torque-angle relationship we obtained EMG from both extensor and flexor muscles. For these EMG-measurements (Biotel 99, The Netherlands) the skin was shaved and cleaned with alcohol. Subsequently, surface Ag-AgCl electrodes were placed in a bipolar figuration, consistent with the muscle’s overall direction of pull, with a centre to centre inter-electrode distance of 25 mm on the muscle bellies of the vastus lateralis muscle (VL), rectus femoris muscle (RF), vastus medialis muscle (VM), biceps femoris muscle (BF) and gastrocnemius medialis muscle (GM). One reference electrode was placed on the patella of the corresponding lower limb.

**Experimental procedures**

**Familiarization session**

The measurements of the familiarization session were performed with the non-paretic lower limb to check whether the subjects understood the instructions. After a warm up (existing of 5 submaximal contractions) subjects were trained to perform maximal isometric knee flexion and extension contractions.

**Muscle torque**

Subjects started with their paretic lower limb (PL) and were asked to maximally generate isometric knee extensions for 3-4 s to determine maximal voluntary knee extension torque (MVCe). Two to four attempts were allowed, separated by 2 min of rest. MVC was taken as the highest value of these attempts, which did not exceed preceding attempts by >10%, allowing a maximum of four attempts. Real-time force production was visible on a computer screen. Subjects were vigorously encouraged to exceed their maximal value, which was also displayed to confirm the subject’s achievement throughout the test. Alternately, MVC’s with the knee flexors (MVCf) were performed. For this purpose, the lower limb was fixed tightly by a top restraining bar that was secured on the thigh, just proximal to the knee joint to minimize the movement of the leg and to avoid changes in hip and knee angles during
isometric flexion contractions\textsuperscript{10}. Besides, an ankle brace was placed to keep the ankle in plantar flexion position, reducing the contribution of the gastrocnemius medialis muscle to the knee flexion.

Muscle activity was measured by means of EMG as described above (see \textit{Torque measurements}). Measurements always started at 60° knee angle, at which angle usually the highest torque is produced\textsuperscript{5}. Subsequently, measurements were repeated at 30° and 90° knee angles, which were randomly assigned. At the end of the session, 1 or 2 maximal attempts were carried out again at 60° to assure that fatigue, which could have influenced the maximal force values at the previous knee angle as well, had not occurred.

The measurements performed on the PL were repeated with the non-paretic lower limb (NL), carried out on a separate day. Control subjects only performed 1 of these sessions, with the right lower limb.

\textbf{Data analysis}

Real-time force applied to the force transducer was digitally stored (1 kHz) on computer disc. The force signals were automatically corrected for gravity of the leg; the average force applied to the transducer during the first 50 ms after the start of the recording, was set to zero force by the computer program. All force signals were low-pass filtered (4\textsuperscript{th} order Butterworth, 50 Hz). MVC torque (Nm) was defined as the peak force from the stable part of the force plateau multiplied by the external moment arm. Overall, all torques (and accompanying EMG signals) higher than 0.3 Nm are included.

To assess the potential effect of neural activation on the torque-angle relationship we obtained EMG from both extensor and flexor muscles during MVCf’s and MVCe’s at the three knee angles. EMG signals of the voluntary maximal knee extensions and flexions were amplified (x100), digitized (1 kHz) and stored with the synchronised force signal on computer disc. All EMG signals were band-pass filtered (10-400 Hz) and rectified. Rectified surface EMG amplitude (rsEMG) was calculated for the RF, VL, VM, BF and GM for 1000 ms of the plateau of the force signal. rsEMG signals served to
assess activation levels of the knee extensors (summed rsEMG of VL, VM and RF) and flexors (summed rsEMG of BF and GM) during MVC’s in the different knee angles. Moreover, rsEMG signals served to determine the co-activation of the thigh muscles during those MVC’s, to check whether an increased neural drive to antagonist muscles causes reduced net torques. To determine whether activation was selectively more affected after a stroke at different muscle lengths, absolute rsEMG was normalized to maximum rsEMG at the angle with the highest torque, making the results independent from absolute rsEMG-values. To evaluate the level of co-activation, rsEMG of the antagonist muscles was normalized to the maximum rsEMG during its primary function (working as an agonist). For instance, co-activation during flexion was defined as the ratio of rsEMG flexors during extension divided by maximal rsEMG flexors during maximal flexion (rsEMG/rsEMGmax)\(^{14}\).

**Statistics**

All results are presented as means and standard deviations (SD). Repeated measures analysis of variance (ANOVA) were used (group x knee angle) for the comparison of normalized MVCe and MVCf, agonist and antagonist rsEMG in the 30°, 60° and 90° knee angle and between NL, PL and control lower limb. In case of significance, Bonferroni post hoc tests were used. In each statistical analysis, the level of significance was set at p<0.05. For our main hypothesis a sample size calculation was done and the design, given a large effect size (\(\Delta^2=0.9\)) and a power of 70% would result in 13 participants per group to be able to show a significant, relevant difference within angles between groups. A post hoc power analysis showed a power of 99%.

**Results**

Data were not complete for some patients due to discomfort or unreliable data, e.g. concentration problems, one subject dozed off a few times during the measurements. These were excluded from the data. In addition, one of the 14 patients with stroke was not able to flex the non-paretic lower limb in any of the angles. One subject could
not perform a knee extension with the non-paretic lower limb in 30°. With the paretic lower limb, 7 subjects were unable to perform a knee flexion in all angles and were therefore not included. One subject could not perform a knee flexion with the paretic leg only in the 90° knee angle. The number of patients analysed are indicated in the text or in the figure legends.

**Torque-angle relationship**

For both knee extensors and flexors, significant main effects for group (p<0.001, p<0.001) and angle (p<0.001, p<0.001) were found (Figure 4.1, A and B). More important, significant interaction effects (angle x group) were found for the absolute maximal voluntary torque of the knee extensors (p<0.001) and knee flexors (p=0.002). Thus, for both extensors and flexors a significant difference is found in the angle-torque relationships between groups. To compare angle effects among groups independent of absolute torque we normalized torques for torque at the ‘optimum’ knee angle (i.e., angle at which torque was highest) (Figure 4.1, C and D). Most important, a main effect for group was found (p=0.001): at 30° knee angle (at short muscle length) normalized knee extensor torque in PL (n=12) was significantly lower than in NL (n=13) and control (n=12) (Figure 4.1C). NL did not differ significantly from control. Also for knee flexors, at shorter muscle lengths (60 and 90° knee angle), normalized torque in PL (n=7) was significantly lower than in NL (n=13) and control (n=12) (Figure 4.1D main effect group, p=0.001). NL again did not differ significantly from control.

Thus, lower normalized torques at shorter muscle lengths were found for both knee extensors (73% of control in 30°) and knee flexors (64% and 45% of control in 60 and 90°, respectively) in PL compared to control. No significant differences were found between NL and control.

**Agonists muscle activity**

For absolute rsEMG of the knee extensors (sum of VL, VM and RF) during extension an interaction effect (angle x group) was found (p=0.05), while for absolute rsEMG of the knee flexors (sum of BF and GM) during knee flexion no significant interaction effect
was found ($p=0.876$). Thus, the angle-rsEMG relation of the knee extensors is different among groups, whereas no differences were found for knee flexors.

Figure 4.1: Left: Absolute maximal voluntary torques of controls ($n=12$), non-paretic lower limb ($n=13$) and paretic lower limb ($n=12$ for extension and $n=7$ for flexion) at three different knee angles (30, 60 and 90°) for knee extensors (A) and knee flexors (B). An interaction-effect (knee angle x group) was found. Right: Normalized knee extensor (C) and knee flexor (D) torque at the three knee angles for the three groups. ^ lower than non-paretic lower limb and control, # lower than control, * lower than 30°, + lower than 60°, x lower than 90°
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Normalized knee extensor rsEMG values (Figure 4.2 upper) were significantly lower in PL than in controls (~71%) at 30° knee angle (p=0.006), indicating lower activation at short muscle lengths compared to controls. Mean values for the knee flexors muscles in PL (Figure 4.2 lower) at 60° and 90° were 79% and 67% of control, respectively, but were not significantly different from control (p=0.226). No significant differences between control and NL were found.

**Figure 4.2:** Normalized rsEMG at the three knee angles (30°, 60° and 90°) for the three groups (control (n=12), non-paretic lower limb (n=13) and paretic lower limb (n=12 for extension and n=7 for flexion) for knee extensors (upper) and knee flexors (lower). * lower than control
Co-activation

No interaction effects (angle x group) were found for co-activation values during extension (p=0.419) or flexion (p=0.052), hence no differences among PL, NL and control in the different angles were found (rsEMG/rsEMGmax). So, the level of co-activation was not different between PL, NL and controls and this was not different among knee angles.

Discussion

The most important finding of the present study was the selectively impaired muscle function at shorter muscle lengths of both knee extensors and flexors of the paretic lower limb, but not the non-paretic lower limb of individuals after stroke. For the knee extensors, this may be attributed to a length-dependent lower voluntary activation capacity, which may also be the case for the flexor muscles. Co-activation did not seem to play a significant role herein.

Normalized angle-torque relationship

After normalization, lower torques at shorter muscle lengths were found for both knee extensors (73% of control in 30°) and knee flexors (64% and 45% of control in 60° and 90°, respectively) in PL compared to control. Bohannon3 found lower knee flexion torque in supine position (shorter knee flexor muscle length) compared to sitting position. The sitting-to-supine ratio was .56 for the non-paretic lower limb and .70 for the paretic side, but this difference was not significant.

As said, in the present study patients with stroke seem to show relative muscle weakness of knee extensors at more extended knee angle (shorter knee extensor muscle lengths) of the paretic lower limb. This is in agreement with Koo et al.12, who found smaller extension torques of the upper limb at shorter muscle lengths in patients with stroke compared to controls. They also found slightly smaller maximal flexion torques in the more flexed positions (shorter muscle lengths) for the paretic
compared with the control (upper) limb. In addition, the non-paretic lower limb was weaker than control, but no length-dependent differences in extensor and flexor strength were observed.

**Activation**

An impaired drive to voluntarily activate the quadriceps muscles in patients with stroke\(^{15,7,10}\) might be a cause of the length-dependent weakness after stroke. Indeed, our results (Figure 4.2) show that normalized knee extensor rsEMG in PL was significantly lower compared with controls (~71%) at 30° knee angle, which corresponds with the 73% lower torque. Although not significantly different, mean values for the PL knee flexors muscles in 60° and 90° were 79% and 67% of control, respectively, which may explain the torque decreases of 64 and 45%. Note that our patients have a wide range of motor impairments from very severe to very mild, based on the scores at tests of functional performance\(^{10}\). This leads to a large variation within the subject group which may explain the lack of significance. Another reason for the lower torque at shorter muscle length could be more co-activation. Despite a tendency during flexion we did not find significant differences in co-activation between groups during the maximal voluntary contractions in isometric conditions. However, during (submaximal) dynamic contractions, this may be different.

Thus, the voluntary activation capacity is more impaired at shorter lengths of paretic knee extensor muscle compared to control, which may also be the case for the flexor muscles. This is in agreement with Koo et al.\(^{12}\), who found smaller elbow extension torques at shorter muscle lengths in patients with stroke compared to controls, also accompanied by a reduced central drive (rsEMG) to agonist muscles at extended positions. Besides, Koo et al.\(^{12}\) also found that during maximal flexion contraction, the rsEMG of patients with stroke tended to be lower than control as elbow joint was flexed beyond 90° (short muscle lengths). During submaximal contractions, Tang et al.\(^{17}\) found more EMG per force level in shortened paretic elbow flexors. The authors conclude that this did not result from co-activation, but most likely from a reduction of mean motor unit discharge rate.
A possible explanation for the disproportionate reduction of muscle strength at short lengths might be differentially affected (impaired) excitability – muscle length relation in patients with stroke, which corresponds with difficulties in producing higher motor unit firing rates required to produce fusion of twitches, and therefore maximum torque, at shorter muscle lengths after stroke. This decreased neural activation is a primary result of the stroke and explains why already 3.5 months after stroke, muscle weakness at especially short lengths is found, in contrast to adaptations in intrinsic muscle properties, which are often used as an explanation in chronic patients with stroke with spastic upper limbs.

**Conclusions**

As result of stroke the lower muscle torque at shorter muscle lengths of the knee extensors is associated with a length-dependent lower voluntary activation capacity, which may also be the case for the flexor muscles. Co-activation does not seem to play a role in the length-dependency of muscle weakness after stroke. From these results, we recommend to investigate the role of specific training of the knee flexors and extensors of the (paretic) lower limb in especially the shortened position to improve the recovery of function after stroke. Hence, it may be important not only to strengthen muscles after stroke, but to strengthen them at shortened lengths to counterbalance the impaired voluntary activation at those muscle lengths.

**References**

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