



# **Stiff Knee Gait in Stroke**

Walking down the road of  
different treatment options

Martin J.B. Tenniglo



# **STIFF KNEE GAIT IN STROKE**

**WALKING DOWN THE ROAD OF DIFFERENT TREATMENT OPTIONS**

**Martinus Johannes Bernardus Tenniglo**

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# STIFF KNEE GAIT IN STROKE

## WALKING DOWN THE ROAD OF DIFFERENT TREATMENT OPTIONS

DISSERTATION

to obtain  
the degree of doctor at the University of Twente,  
on the authority of the rector magnificus,  
prof. dr. ir. A. Veldkamp,  
on account of the decision of the Doctorate Board  
to be publicly defended  
on Thursday 7 December 2023 at 14.45 hours

by

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Voor Ellen, Job en Emmy

“A winner is a dreamer who never gives up” (Nelson Mandela)



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# 1

## General Introduction

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*“I can hardly walk. I am stumbling and my leg is shaking. I must be careful not to trip.”*  
(Mw W.)

---

This quote is from a person walking with a stiff knee gait who participated in the research presented in this thesis. It expresses how patients experience the problems of walking with a stiff knee gait.

There are over 12.2 million new strokes each year. Globally, one in four people over age 25 will have a stroke in their lifetime <sup>1</sup>. In the Netherlands every day, 110 persons sustain a stroke <sup>2</sup>. Because populations are ageing, the prevalence and burden of stroke are expected to further increase in the upcoming years <sup>3</sup>. There is a large variety in the clinical presentation of stroke depending on the stroke characteristics such as location, severity and age <sup>4-6</sup>.

A combination of cognitive, emotional, sensory and motor impairments are often present leading to limitations in performing activities of daily living <sup>7</sup>. An important goal in rehabilitation for the stroke patient is regaining the ability to walk again <sup>8</sup>. Approximately 70 - 80% of the stroke patients will recover the ability to walk short distances independently without assistance of another person <sup>9,10</sup>.

However, only 50% of stroke patients achieve limited community ambulation status or better <sup>9,10</sup>. Factors that can limit walking ability are muscle weakness, abnormal muscle activity, and joint deformities. An important alteration in the gait pattern is the ease of clearing the floor in swing or the so called foot clearance. It is, besides stability in stance, prepositioning of the foot for initial contact, adequate step length and energy conservation, one of the five prerequisites of normal gait described by Gage <sup>11,12</sup>. Foot clearance problems <sup>13,14</sup> can lead to tripping and increased risk of falling <sup>15</sup>. Compensatory movements, such as ipsilateral hip circumduction or contralateral vaulting, are performed to clear the foot consequently resulting in an increased energy expenditure <sup>16</sup>.

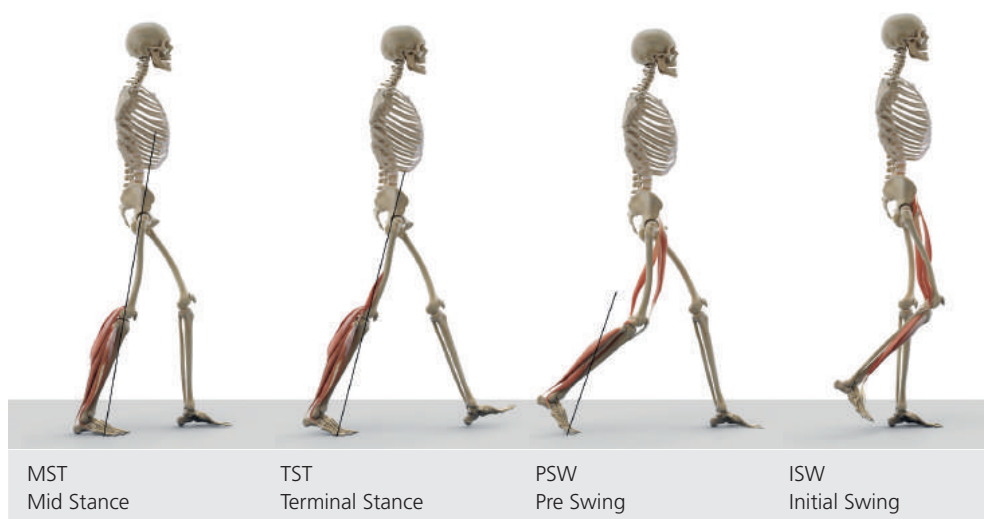
Foot clearance problems can be caused by a decreased ankle dorsiflexion, a decreased knee flexion and/or a decreased hip flexion during swing. A decreased ankle dorsiflexion is often caused by a drop foot/equinus and is most commonly the result of weakness of the dorsiflexors and/or overactivity in the plantar flexors. It is estimated to be present in 20-30% of the stroke population <sup>17</sup>. In clinical practice there are a lot of different treatment options for decreased ankle dorsiflexion. One of the commonly used treatment options is an Ankle Foot Orthosis (AFO)<sup>18</sup>. There are many different AFO designs available from highly rigid to more flexible and from prefabricated to a specially fitted custom-made AFO to the patients. Functional electrical stimulation of the peroneal nerve can also be a treatment option for correction of the drop foot. The stimulation is applied through electrodes on the skin or implanted electrodes and often triggered by a footswitch. If overactivity of calf muscles

plays a role with the equinus, a chemodenervation can be an option. A last treatment option for the equinus can be a surgery of the lower leg or foot. Surgical treatment can focus on fusing bones, such as a talonavicular arthrodesis or focus on soft tissues, such as the splitt anterior tibial tendon transfer or lengthening of the Achilles tendon. It can also be a combination of different surgical procedures.

If foot clearance problems occur due to a decrease in hip flexion during swing a hip flexion assistive device (e.g. Exo band) <sup>19</sup> can be a treatment option. Surgical procedures or functional electrostimulation to increase hip flexion are not available.

Finally, a frequently mentioned cause for foot clearance problems is a diminished knee flexion in swing also known as stiff knee gait or stiff legged gait <sup>20</sup>. It affects approximately 60% of the stroke patients with gait disorders <sup>21</sup> and is one of the most commonly observed gait disorders <sup>22,23</sup>.

In healthy subjects, knee flexion in swing occurs due to push off from the calf muscles in combination with pull off from the hip flexors. The amount of knee flexion is fine-tuned by activity from the rectus femoris <sup>24</sup> as a knee extensor (see figure 1). The pathophysiology of stiff knee gait is only partly understood and several hypotheses involving the ankle, knee and hip joint are postulated in the literature. It could be related to a lack of push-off power at the end of the stance phase due to weakness of the calf muscle <sup>22,25-27</sup>. Insufficient hip pull-off power at toe off due to a weakness of the hip flexors <sup>28,29</sup> and increased forces generated by the vastii <sup>29</sup>, are also mentioned. Although, the exact mechanisms of stiff knee gait remains unclear and seems to be multifactorial, stiff knee gait is thought to be mainly caused by abnormal activity of the rectus femoris during swing <sup>30-32</sup>.



**Figure 1.** The amount of knee flexion is fine-tuned by activity from the rectus femoris. Adapted from Streifeneder ortho production.

Different treatment options aimed at reducing stiff knee gait are described in literature, including electrical stimulation of the calf and/or hamstring muscles<sup>33,34</sup>, chemodenervation of the rectus femoris<sup>35</sup>, and the rectus femoris transfer<sup>36,37</sup>.

Electrical stimulation of the calf and/ or hamstrings is a treatment option for stiff knee gait, that might be suitable for patients irrespective of the cause of stiff knee gait, as it might directly assist in achieving sufficient knee flexion.

Studies on the effect of electrical stimulation of the calf or hamstrings on the hemiplegic gait pattern are scarce. The available studies<sup>33,34,38</sup> all stimulated two or more muscles in order to influence kinematics of gait with varying results. One practical problem of stimulating two or more muscles is the timing of the stimulation, as the proper timing may differ between muscles. Providing adequate timing is easier in one muscle and stimulating one muscle is more feasible in clinical practice. In addition, because the three mentioned studies stimulated multiple muscle groups, it is unclear what the contribution of stimulation of the individual muscle groups is on the increase of knee flexion. From a clinical point of view it is interesting if the increase of knee flexion can be achieved by stimulating only one muscle group for example the hamstrings muscle.

The second treatment option for stiff knee gait is chemodenervation of the rectus femoris. The indication for chemodenervation is normally related to the overactivity of the rectus femoris in initial swing or mid swing. This means that only patients that show this overactivity of the rectus femoris are eligible for chemodenervation. In this treatment option, a pharmacologic compound is used to paralyse a muscle or a group of muscles<sup>39</sup>. Chemodenervation of the overactive rectus femoris is thought to improve knee flexion during swing by reducing the internal knee extension moment in swing<sup>40 31</sup>.

The two methods described in the literature are motor branch blocks (MBB) and neuromuscular blocks (NMB). For the treatment of stiff knee gait, a MBB is achieved by denervation of the branch of the femoral nerve innervating the rectus femoris by injecting a local anaesthetic agent or phenol. The effect of a local anaesthetic lasts for few hours and can be used to predict the effects of longer term treatment such as with phenol or Botulinum toxin (BoNT). NMB is achieved by injecting BoNT in the rectus femoris muscle itself. BoNT denervates the muscle by blocking the release of acetylcholine at the neuromuscular junction<sup>41</sup>. However, there are some disadvantages of BoNT injections. One is the limited working time of approximately three months and a second one is the decrease in effectiveness of the BoNT injection over time due to habituation<sup>42</sup>. In addition, the effect of rectus femoris transfer chemodenervation on knee kinematics, functional outcome, and energy cost in stroke, is still unclear and results are inconsistent. The limited amount of trials that studied this treatment option<sup>35,43,44</sup> generally used small number of patients, making it difficult to generalize the results. A systematic review with the possibility of data

pooling could give insight into the effect of a chemodenervation in the rectus femoris in stroke patients.

To counteract the limited working time and decreased effectiveness of chemodenervation, a third treatment option for stiff knee gait, is to alter the function of the rectus femoris by means of a rectus femoris transfer<sup>32,45</sup>. During this surgical procedure, the distal rectus femoris tendon is transferred to the medial or lateral knee flexors to improve knee flexion during swing. The effect of the rectus femoris transfer has been scarcely studied in stroke patients<sup>46,47</sup>. As far as we know there are only two studies that evaluated the effect of rectus femoris transfer in stroke patients. These studies showed conflicting results. The studies used limited quantitative kinematic measures of gait<sup>46</sup>, no<sup>47</sup> or very limited functional outcomes<sup>46</sup> and used a retrospective design. Furthermore, the studies combined rectus femoris transfer with other surgical procedures, which make it hard to understand what the effect of the rectus femoris transfer in itself is. In addition, the study population consisted of a mix of stroke survivors and other diagnoses such as traumatic brain injury. Because of these factors, little is known about the effect of an isolated rectus femoris transfer on quantitative kinematic data of gait and functional outcomes in a group of stroke patients.

Finally, to establish abnormal rectus femoris activity, there are two options available: surface electromyography (sEMG) and the Duncan Ely test. The generally accepted gold standard is sEMG of the rectus femoris during dynamic gait analysis<sup>48</sup>. However, sEMG measurements require expensive measurement equipment and specific expertise, which limits its applicability in daily clinical practice. The second option is the Duncan Ely test<sup>49,50</sup>, which is part of a routine clinical examination of muscle tone. This test does not require any measurement equipment and is easy to perform. However, whether the Duncan Ely test is a useful and valid test to predict abnormal rectus femoris activity during swing in stroke patients is unknown. Marks et al<sup>49</sup> found promising results of the Duncan Ely test in their study in cerebral palsy patients. They showed that the Duncan Ely test has a good positive predictive value for rectus femoris dysfunction during gait. However, it is hard to translate the results of cerebral palsy to the stroke population due to differences in age and pathophysiology. As far as we know, the comparison of the Duncan Ely test to sEMG has not been made in a group of stroke survivors.

### **Objectives of this thesis.**

The general aim of this thesis is to study the effectiveness of different treatment options in stroke patients walking with a stiff knee gait and the following research questions are addressed:

1. What is the current body of evidence of the effect of chemodenervation of the rectus femoris in stroke patients walking with a stiff knee gait?
2. What is the diagnostic value of the Duncan Ely test in predicting abnormal rectus femoris activity during gait in stroke patients walking with a stiff knee gait?

3. What is the effect of functional electrical stimulation of the hamstrings in stroke patients walking with a stiff knee gait?
4. What is the effect of Botulinum toxin injection in the rectus femoris in stroke patients walking with a stiff knee gait measured in a randomized controlled trial?
5. What is the effect of a rectus femoris transfer in stroke patients walking with a stiff knee gait?

**General outline of this thesis.**

In **chapter 2**, a systematic review on the effectiveness of chemodenervation of the rectus femoris on stiff knee gait is presented. The primary aim was to determine the effect of a chemodenervation of the rectus femoris on knee kinematics during swing phase in patients walking with a stiff knee gait due to spastic paresis. The secondary aim was to determine the effect on functional outcomes and energy cost. To answer these objectives we performed a systematic review with a meta-analysis in stroke patients.

**Chapter 3** shows the results of the study where we compared the static clinically performed Duncan Ely test to the gold standard; dynamic sEMG. The aim of this study is to determine the diagnostic value of the Duncan Ely test to predict abnormal activity of the rectus femoris in stroke survivors with a stiff knee gait.

**Chapter 4** describes the results of a clinical study that focused on the influence of functional electrical stimulation of the hamstrings on knee kinematics in stroke survivors walking with a stiff knee gait.

The primary aim of this study was to explore if electrical stimulation of one muscle group (hamstring muscle) resulted in improved knee kinematics during the swing phase in chronic stroke subjects with a stiff knee gait. The secondary aim of the study was to find out which patients characteristics are related to the effect of the electrical stimulation.

**Chapter 5** describes a randomized triple blind placebo-controlled cross-over trial to determine the effect of botulinum toxin type A into the rectus femoris in stroke patients walking with a stiff knee gait.

The primary aim was to determine the effect of BoNT-A injection into the rectus femoris on knee and hip kinematics during swing. The secondary aim was to determine the effect of BoNT-A injection on functional outcome and perceived impairment.

**Chapter 6** describes the results of the rectus femoris transfer. The primary aim of this study was to evaluate the effect of an isolated rectus femoris transfer on knee and hip kinematics in stroke patients. The second aim was to evaluate the effect of an isolated rectus femoris transfer on functional outcome.

Finally, results and conclusions of the studies are summarized followed by the general discussion in **chapter 7**.







# 2

## **Effect of chemodenervation of the rectus femoris muscle in adults with a Stiff Knee Gait due to Spastic paresis: A systematic review with a meta-analysis in stroke patients.**

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## **Abstract**

### **Objective**

To determine the effect of Motor Branch Block (MBB) or Neuro Muscular Block (NMB) of the rectus femoris on knee kinematics during swing, functional outcome, and energy cost in adults with spastic paresis presenting a stiff knee gait.

### **Data sources**

Pubmed, Embase, Cinahl, and Cochrane library were searched. Studies were collected up to 26 February 2013. Reference lists were additionally scrutinized.

### **Study selection**

No restrictions were applied regarding study design. Patients were adults suffering from a central neurological disorder. Interventions had to include MBB or NMB. Outcome measures should include knee kinematics during swing phase. Study selection was independently performed by two reviewers.

### **Data extraction**

Two reviewers independently assessed methodological quality of included studies. Data on kinematics, functional outcome, and energy cost from stroke patients were extracted from the total population and when possible pooled.

### **Data synthesis**

In total nine articles were included describing twelve different studies. Knee kinematics (peak knee flexion or knee range) during swing improved significantly in all included studies. The average increase in peak knee flexion varied from 1.9 to 15.4 degrees. Data pooling of peak knee flexion in stroke patients showed a significant improvement of 7.37 degrees ( $p=0.000$ ) in the NMB studies and 9.35 degrees ( $p=0.002$ ) in the MBB studies. Data pooling of knee velocity at toe off showed a significant improvement of 53.01 degrees/sec in the NMB studies. In the MBB studies this improvement was not significant. Data pooling of knee range of motion, functional outcomes, and energy cost showed no significant difference.

### **Conclusion**

According to this review, chemodenervation of the rectus femoris shows a significant improvement on peak knee flexion during swing. The effect on functional outcomes and energy cost is still unclear.

## Introduction

Stiff Knee Gait (SKG) is characterized by a diminished knee flexion during swing<sup>25,51,52</sup> and is commonly observed in patients with spastic paresis such as cerebral palsy or following stroke, traumatic brain injury and multiple sclerosis. Clinically, a stiff knee gait can result in problems with foot clearance leading to tripping, and an increased risk of falling. The compensatory movements, such as ipsilateral hip circumduction or contralateral vaulting, performed to clear the foot can result in an increased energy expenditure.<sup>16</sup> The pathophysiology of SKG is not fully understood and several hypotheses are postulated in the literature. The role of overactivity of the rectus femoris (RF) is often cited.<sup>20,26,53-55</sup> RF overactivity is associated with an increased knee extension moment in swing and decreased knee flexion velocity at toe-off, both potentially decreasing peak knee flexion.<sup>26</sup> Other possible mechanisms cited in the literature are decreased strength of the hip flexors and ankle plantar flexors<sup>25,51</sup> leading to decreased power to propel the leg into swing<sup>20,26,28,53-55</sup> or spasticity in the vasti or soleus to decrease knee flexion velocity<sup>29</sup>. Traditional gait training techniques based on the Bobath concept have not proven to improve SKG or any other movement patterns during gait.<sup>56</sup> The other treatment options for SKG include chemodenervation of the RF or transfer of RF.<sup>20,45,57,58</sup> Functional Electrical Stimulation (FES) of the gastrocnemius or hamstrings has also been tried.<sup>59,60</sup>

Chemodenervation is a technique in which a pharmacologic compound is used to paralyse a muscle or a group of muscles.<sup>39</sup> Chemodenervation of the overactive RF is thought to improve SKG by reducing the internal knee extension moment in swing. The two methods described in the literature are neuromuscular blocks (NMB) and motor branch blocks (MBB).

For the treatment of SKG NMB is achieved by injecting Botulinum Toxin (BTX) in RF muscle itself. BTX can be either injected at one specific site or at multiple sites. BTX denervates the muscle by blocking the release of acetylcholine at the neuromuscular junction.<sup>41</sup> Motor Branch Block is achieved by denervation of the branch of femoral nerve supplying the RF by injecting local anaesthetic agent or phenol. The effect of a local anaesthetic lasts for few hours and can be used to predict the effects of longer term treatment such as with phenol or BTX.

Both methods have been frequently described in literature. However, the effect of rectus femoris chemodenervation on knee kinematics, functional outcome, and energy cost is still unclear and inconsistent. Numerous studies have been performed studying these outcomes, however, these studies generally have used small study populations making it difficult to generalise the results. Combining the results of these multiple studies would be interesting. It will enable one to reach meaningful decisions.

The purpose of this study is to systematically review the effects of chemodenervation of the RF on SKG. The primary objective of this systematic review is to determine the effect of

chemodenervation (MBB and/or NMB) of the RF on knee kinematics during swing phase in patients walking with SKG due to spastic paresis. The secondary objective is to determine whether this treatment results in an improvement in functional outcomes and energy cost of walking in these patients.

## **Methods**

### **Literature search**

A computerised literature search was conducted in Embase, PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the Cochrane Central Register of Controlled Trials (The Cochrane Library) till 26 February 2013. Additionally, the reference lists of all relevant papers were screened for potentially relevant studies missed in the literature search. Main MeSH terms were: Cerebrovascular disorders, Stroke, Brain injuries, Multiple sclerosis, Spinal cord, Hereditary spastic paraplegia, Knee, Leg, Lower extremity, Rectus femoris, Botulinum toxins, Nerve block, Organic chemicals, Gait, Walking, Kinematics, Kinetics, Range of motion, Energy metabolism, Outcome assessment, Functional outcome.

### **Selection criteria**

For inclusion in this review a study had to be published as a full text article in English, German or Dutch language journals. No restrictions were applied regarding the study design. Studies were considered for inclusion if patients were adult, had a central neurological disorder and walked with a gait pattern characterized by SKG with diminished (peak) knee flexion during the swing phase. Interventions had to include either neuromuscular blocks (NMB) or motor branch blocks (MBB). Outcome measures included at least kinematics during swing phase.

### **Selection of studies**

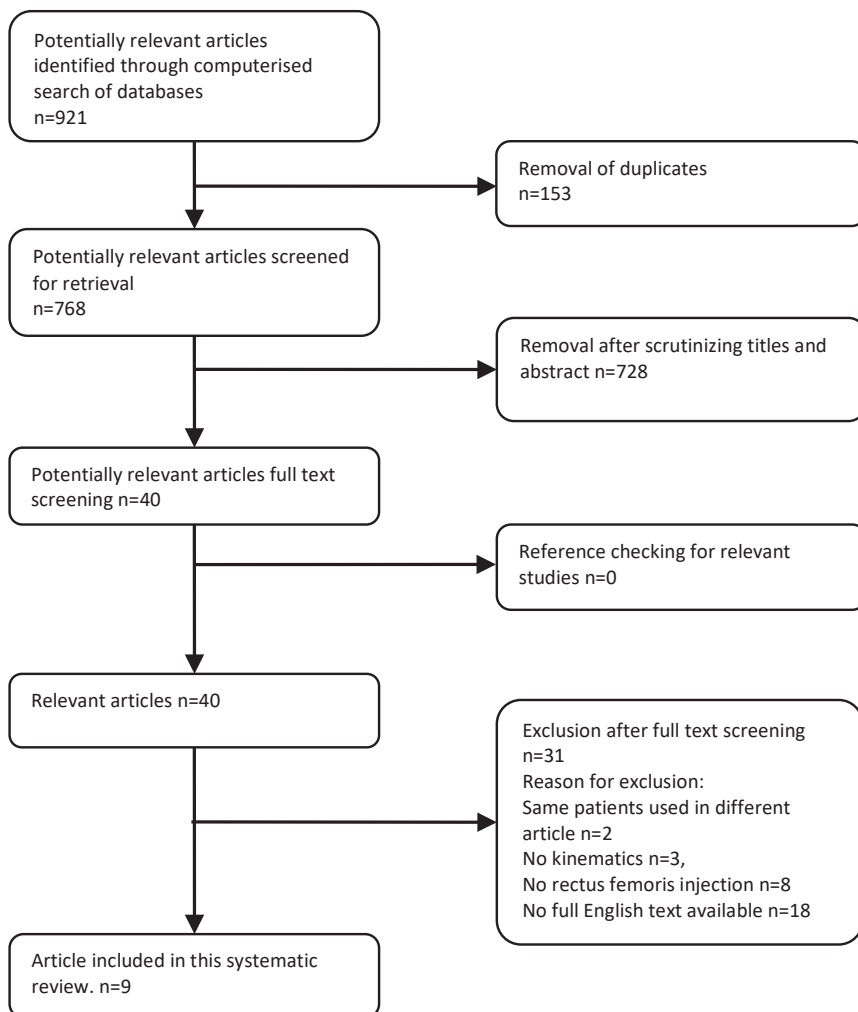
Study selection and scoring of methodological quality was performed by two independent reviewers (MT and EP) and compared for consensus. In case of disagreement between the reviewers, a third reviewer was consulted (MN) and a final decision was made.

### **Data extraction**

Data extraction was performed using a structured diagram. The content of the studies was categorised according to the description of selected articles, study characteristics, selection of patients, drug injection, adverse events, kinematics, functional outcomes and energy cost.

### Methodological quality

A method developed by Downs and Black was used to assess methodological quality of the included studies.<sup>61</sup> The Downs and Black checklist is a scale for the assessment of the methodological quality of randomized and non-randomized studies of health care interventions. The instrument consists of 27 items measuring methodological quality and is based on epidemiological principles, reviews and existing checklists for randomized studies. The checklist scores five sub-scales: reporting (10 items), internal validity which consists of bias (7 items) and confounding (6 items), external validity (3 items), and power (1 item). The maximum (Quality index) score of the checklist is 32 points. Test-retest reliability and interrater reliability (respectively  $r=0.88$  and  $r=0.75$ ) and face and content validity are good.<sup>61</sup>



**Figure 1.** Flow chart of the study selection

### Data Synthesis

Further consideration was given to investigate whether it was possible to pool data from stroke patients because majority of the study population suffered from stroke. If the included studies failed to report information needed for data pooling, we contacted the primary author to obtain the required information. When the primary author could not provide the information or when there was no response on the request, the study was excluded for data pooling. When pooling was possible then, mean difference with 95 % confidence interval, heterogeneity and confounding were calculated using Review Manager 5<sup>a</sup>. Because the statistical tests assessing heterogeneity generally have a lack of statistical power by the low number of studies combined, significance was set at a p-value of 0.10. If statistical tests showed heterogeneity, we used random effect models. In case of nonsignificant heterogeneity, we used fixed effect models. We explored confounding using a sensitivity analysis. If there was ambiguity about whether a study met the inclusion criteria, we examined the effect of including or excluding this study. Where data pooling was not possible statistical significant results are presented.

## Results

### Study Selection

Literature search using multiple databases yielded 921 citations up to 26 February 2013. Removal of duplicates left 768 articles. Scrutinizing the titles and abstracts of these articles identified 40 potential relevant studies, which were retrieved for further full text screening.<sup>23,43,44,62-98</sup> Examination of the reference lists of these articles added no study.

After applying the inclusion criteria, 31 articles were excluded. Reasons for exclusion were : same patients used before in article,<sup>73,81</sup> no kinematics<sup>63,78,92</sup> no Rectus femoris injection,<sup>62,64,66-69,79,88</sup> no full text available in English.<sup>65,70,72,74,76,77,82,83,86,87,89-91,93-96,98</sup> There was no disagreement in the selection of the remaining 9 articles<sup>23,43,44,71,75,80,84,85,97</sup> between the two reviewers. The flow diagram of study retrieval and selection is presented in figure 1.

### Description of selected articles

In total nine articles were included describing twelve different studies.<sup>23,43,44,71,75,80,84,85,97</sup> The articles of Robertson<sup>43</sup> Stoquart<sup>84</sup>, and Sung<sup>85</sup> describe two studies. Robertson<sup>43</sup> and Stoquart<sup>84</sup> examined the effect of NMB and the effect of MBB on SKG on the same population. The article of Sung<sup>85</sup> describes two MBB studies. One study examined the effect of a MBB with lidocaine injection and one study examined the effect of MBB with phenol injection. Sung also included the same patients in the two studies.

In total seven studies examined the effect of NMB<sup>43,44,71,75,80,84,97</sup> and five studies examined the effect of MBB.<sup>23,43,84,85</sup>



### Methodological quality

The twelve studies out of the nine included articles scored between 11 and 19 points out of the maximum score of 32 (Table 1).<sup>23,43,44,71,75,80,84,85,97</sup> The items with the lowest scores were external validity (use of an experimental setting or study populations not representative for the entire population), confounding (small study populations, no randomized controlled trials or longitudinal studies with follow-up measurements, no blinding possible) and power (none of the studies reported a power analysis). The highest score was for reporting (All studies scored 7 or more points out of a total of 11 points).

**Table 1.** Methodology quality

First Author	Domains Checklist for Measuring Quality						Total
	Report	External Validity	Internal Validity			Power	
			Bias	Con- founding			
Caty <sup>34</sup>	9	1	5	1	0	16	
Stoquart <sup>45</sup> NMB	9	1	5	3	0	18	
Stoquart <sup>45</sup> MBB	7	1	5	3	0	16	
Hutin <sup>40</sup>	7	0	3	1	0	11	
Tok <sup>47</sup>	10	1	6	2	0	19	
Bernuz <sup>30</sup>	8	1	5	2	0	16	
Lampire <sup>59</sup>	9	1	3	2	0	15	
Robertson <sup>42</sup> NMB	7	2	5	1	0	15	
Robertson <sup>42</sup> MBB	7	2	5	1	0	15	
Chantraine <sup>35</sup>	8	2	5	2	0	17	
Sung <sup>46</sup> lidocaine	8	0	5	1	0	14	
Sung <sup>46</sup> phenol	8	0	5	1	0	14	
Maximum score	11	3	7	6	5	32	

### Study characteristics

The nine included articles<sup>23,43,44,71,75,80,84,85,97</sup> described twelve studies (table 2 and table 3). A total of 173 patients were included in the twelve studies. Six studies included only stroke patients (total n=81).<sup>23,44,75,84,97</sup>

**Table 2.** Kinematics NMB studies

Study	N/D	Participants		Intervention		Kinematics							
		Age (y)		Dosage (u)		Peak Knee Flexion (°)		Knee Range (°)		Knee Velocity at Toe-off (°/s)			
		Mean ± SD	NA	Pre, Mean ± SD	Post, Mean ± SD	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P		
Caty <sup>34</sup>	20 ST	52.3±16.1	200	RF	NA	NA	22±19	27±16	.03*	NA	NA	NA	NA
			100	SEMI									
			200	TS									
Stoquart <sup>45</sup>	18 ST	53±15	200	RF	26±13	31±14	.001*	21±27	27±18	.004*	119.6±69.5	172.5±53.7	.005
Huth <sup>40</sup>	13 ST	41±14	200	RF	29±9	38±10	.001*	NA	NA	NA	NA	NA	NA
	1 T												
Robertson <sup>42</sup>	8 ST	40±10	200	RF	27.4±8.2	35.0±8.8	.05*	NA	NA	NA	82±63	112±75	.009
	2 TBI												
Tok <sup>47</sup>	15 ST	53.86±14.74	100–125	RF	16.81±6.53	23.93±11.60	.002*	18.09±10.21	24.92±13.90	.003*	NA	NA	NA
Bernuz <sup>30</sup>	15 ISCI	43±15	200	RF	34.7±10	38.7±10	.05*	NA	NA	NA	NA	NA	NA
Lampire <sup>59</sup>	10 ST	39.6±9.5	200	RF	27.3±7.3	34.8±7.1	.001*	NA	NA	NA	122±68.3	175.7±50.1	.001*

Abbreviations: D, diagnosis; ISCI, incomplete spinal cord injury; N, number of participants; NA, not available; ST, stroke; SEMI, semitendinosus; T, tumor; TBI, traumatic brain injury; TS, triceps surae.

\* Significant.

**Table 3.** Kinematics MBB studies

Study	N/D	Participants		Intervention		Kinematics							
		Age (y)		Dosage		Peak Knee Flexion (°)		Knee Range (°)		Knee Velocity at Toe-off (°/s)			
		Mean ± SD	NA	Pre, Mean ± SD	Post, Mean ± SD	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P		
Robertson <sup>42</sup>	8 ST	40±10	0.5mL/2%/LC	RF	27.4±8.2	38.2±10.7	.05*	NA	NA	NA	119.6±69.5	162.1±53.7	.005
	2 TBI												
Stoquart <sup>45</sup>	12 ST	51±19	2% LC	RF	28±14	31±16	.263	26±15	27±17	.632	115±56	128±65	.339
Chantraine <sup>35</sup>	6 ST	55±18	1mL/2%/LC 1mL/2%/BV	RF	38.5±15.2	40.4±14.8	.502	40.5±18.3	45.3±16.8	.04*	107.7±117.9	146.3±96.6	.04*
Sung and Bang <sup>46</sup>	18 NA	50±12.7	0.5mL/2%/LC	RF	25.7±13.7	41.1±16.2	.001*	NA	NA	NA	NA	NA	NA
(lidocaine)													
Sung and Bang <sup>46</sup>	19 NA	50±12.7	5% PS	RF	26.5±13.6	35.0±10.0	.002*	NA	NA	NA	NA	NA	NA
(phenol)													

Abbreviations: BV, bupivacaine; D, diagnosis; LC, lidocaine; NA, not available; N, number of participants; PS, phenol solution; ST, stroke; SEMI, semitendinosus; TBI, traumatic brain injury. \* Significant.

## Selection of patients

In two<sup>75,84</sup> of the seven NMB studies patient selection was based on a positive Duncan Ely test<sup>99</sup> to quantify the muscle spasticity of the RF. Robertson<sup>43</sup>, Hutin<sup>80</sup> and Lampire<sup>97</sup> selected patients based on RF activity during midswing phase measured with surface EMG. Bernuz<sup>71</sup> used a positive Duncan Ely test, a modified Tardieu scale<sup>100</sup> and 3D motion analysis, where peak knee flexion was less than 45 degrees in the swing phase as inclusion criteria. Tok<sup>44</sup> used lack of knee flexion during the swing phase as inclusion criteria. It is unclear how they defined lack of knee flexion.

In the five MBB studies, Robertson<sup>43</sup> selected patients based on RF activity during midswing phase measured with surface EMG. Chantraine<sup>23</sup> and Stoquart<sup>84</sup> used a positive Duncan Ely test to include patients. Sung<sup>85</sup> used observational gait analyses. To assess the inclusion criteria patients walked with a stiffly extended knee at swing phase and showed clinical signs of stiff legged gait, such as toe dragging.

## Drug injection

All seven NMB studies injected BTX-A (Onabotulinumtoxin A) Stoquart<sup>84</sup> Robertson<sup>43</sup> Hutin<sup>80</sup> Tok<sup>44</sup> Lampire<sup>97</sup> and Bernuz<sup>71</sup> injected only the RF muscle, whereas Caty<sup>75</sup> injected the m. semitendinosus and m. triceps surae in addition. Caty<sup>75</sup> and Stoquart<sup>84</sup> both injected total 200U BTX-A through six injections into the RF. Robertson<sup>43</sup> Lampire<sup>97</sup> and Hutin<sup>80</sup> also injected 200U BTX-A in four anatomical points into the RF belly under electrical stimulation. Tok<sup>44</sup> used 100-125U BTX-A in four points and Bernuz<sup>71</sup> used 200U BTX-A for injection in two points.

All five MBB studies<sup>23,43,84,85</sup> injected the motor branch of the RF nerve according to the technique described by Sung et al<sup>85</sup>. Sung injected 0.3 to 0.5 mL of 2% lidocaine solution in the lidocaine study and injected 5% aqueous phenol solution in the phenol study. Robertson<sup>43</sup> injected 0.3 to 0.5 mL of 2% lidocaine solution and Chantraine<sup>23</sup> used a mixture of 1 mL of 2% lidocaine and 1 mL of bupivacaine solution. Stoquart<sup>84</sup> used 1,5 ml of 2% lidocaine.

## Adverse events

Five studies reported that there were no adverse events.<sup>23,44,75,84</sup> Robertson<sup>43</sup>, Hutin<sup>80</sup> Lampire<sup>97</sup> and Bernuz<sup>71</sup> did not mention the presence or absence of adverse events. In the lidocaine study of Sung<sup>85</sup>, excessive blocking of the femoral nerve trunk occurred occasionally and buckling of the knee occurred in three of the 31 patients. The stability of the knee at stance phase usually returned within 30 minutes after the nerve block. In the phenol study of Sung two out of the 19 patients had a moderate weakness of the quadriceps caused by unwanted blocks of related motor branches of the femoral nerve. No other complications except transient pain or tenderness of the anterior thigh were caused by the phenol block.

**Primary outcome measure**

Eleven studies used peak knee flexion as outcome measurement. Only Caty<sup>75</sup> didn't measure peak knee flexion and used the range of knee flexion defined as the difference between the minimum knee flexion at the end of the stance phase and the maximum knee flexion during the swing. Stoquart<sup>84</sup>, Tok<sup>44</sup> and Chantraine<sup>23</sup> measured both peak knee flexion and range of knee motion.

Peak knee flexion during swing increased in all eleven studies (NMB & MBB), with an average varying from 1.9<sup>23</sup> to 15.4<sup>85</sup> degrees.

Six NMB studies showed a significant increase in peak knee flexion of 4.0<sup>71</sup> 5<sup>84</sup> 7.1<sup>44</sup> 7.5<sup>97</sup> 7.6<sup>43</sup> and 9<sup>80</sup> degrees. Three<sup>43,85</sup> MBB studies also showed statistically significant increase in peak knee flexion of 8.5<sup>85</sup>, 10.8<sup>43</sup>, and 15.4<sup>85</sup> degrees. Chantraine<sup>23</sup> and Stoquart<sup>84</sup> did not found a significant increase in peak knee flexion with MBB.

Tok<sup>44</sup>, Stoquart<sup>84</sup> and Caty<sup>75</sup>, found a significant increase in knee flexion range, of 6.83, 6 and 5 degrees respectively with NMB. Chantraine<sup>23</sup> found statistically significant increase in knee flexion range of 4 degrees with MBB where as Stoquart<sup>84</sup> found only 1 degree increase in knee flexion range which was not significant.

Knee velocity at toe off was measured by Robertson<sup>43</sup> Lampine<sup>97</sup> and Stoquart<sup>84</sup>. They all found a significant increase with NMB. In MBB studies, knee velocity at toe off was measured by Robertson<sup>43</sup> Chantraine<sup>23</sup> and Stoquart<sup>84</sup> where Stoquart<sup>84</sup> did not find a significant increase. Results are presented in table 2 (Kinematics NMB) and table 3 (Kinematics MBB).

**Functional outcome measures**

The included studies<sup>23,43,44,71,75,80,84,85,97</sup> reported various functional outcome measures. Results are presented in table 4 (Functional outcomes NMB) and 5 (Functional outcomes MBB).

Self Selected Walking speed (SWSS) calculated from gait analysis or tested with the 10-meter walking test (10 MWT) was reported in nine<sup>43,44,71,75,80,85,97</sup> studies. Only Hutin<sup>80</sup> Lampire<sup>97</sup> en Bernuz<sup>71</sup> reported a statistically significant increase in SSWS from 0.61 m/s (pre) to 0.74 m/s (post), from 0.57m/s (pre) to 0.70m/s (post) and from 0.56 m/s (pre) to 0.67 m/s (post), respectively.

In one study<sup>44</sup> the subjects were also asked to walk the 10 MWT as quickly as possible. Tok<sup>44</sup> reported a statistically significant improvement in maximal walking speed from 0.32 m/s to 0.43 m/s. The comfortable walking speed did not change significantly.

On the 6 minute walking test, Robertson<sup>43</sup> and Bernuz<sup>71</sup> measured no significant improvement in walking distance. However, Tok<sup>44</sup> measured a significant improvement in the 6 minute walking test from 26%. He asked the patients to walk as quick as possible.

One trial<sup>75</sup> studied the effect of walking ability using the ABILOCO<sup>101</sup> questionnaire. Functional Walking Category, Functional Ambulation Categories, the 12<sup>th</sup> item of the

**Table 4.** Functional outcomes NMB studies

Outcome Measurement	Coty <sup>34</sup>			Stoquat <sup>45</sup>			Hutin <sup>40</sup>		
	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P
	10MWT	0.63±0.29	0.66±0.30	.19	NA	NA	NA	NA	NA
GA speed	NA	NA	NA	NA	NA	NA	0.61±0.21	0.74±0.26	.001*
6MWT	NA	NA	NA	NA	NA	NA	NA	NA	NA
TUG	NA	NA	NA	NA	NA	NA	NA	NA	NA
FAC	ND	ND	NS	NA	NA	NA	NA	NA	NA
FWC	ND	ND	NS	NA	NA	NA	NA	NA	NA
ABILICO	2.2±1.9	3.2±2.1	.03*	NA	NA	NA	NA	NA	NA
SCT	NA	NA	NA	NA	NA	NA	NA	NA	NA
Energy cost	5.8±1.9	4.9±1.9	.003*	5.4±1.6	4.9±1.5	.12	NA	NA	NA

Outcome Measurement	Robertson <sup>62</sup>			Tok <sup>47</sup>			Bernuz <sup>30</sup>			Lampire <sup>59</sup>		
	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P
	10MWT	0.87±0.4	0.93±0.29	NS	0.32±0.49	0.43±0.62	.001*	NA	NA	NA	NA	NA
GA speed	0.57±0.24	0.70±0.24	NS	0.34±0.26	0.35±0.24	NS	0.61±0.21	0.74±0.26	.001	0.57±0.24	0.70±0.28	.05*
6MWT	306.7±125.2	320.3±96.5	NS	165.20±128.27	208.20±153.28	.001*	331±146	332±143	NS	NA	NA	NA
TUG	14.2±3.5	13.2±2.8	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA
FAC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FWC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ABILICO	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SCT	NA	NA	NA	NA	NA	NA	39.6±38	30.1±14	NS	NA	NA	NA
Energy cost	NA	NA	NA	5.48±1.13	4.64±1.65	.010*	NA	NA	NA	NA	NA	NA

Abbreviations: 6MWT, 6-minute walk test; FAC, functional ambulation categories; FWC, functional walking category; GA, gait analysis; NA, not available; ND, no data; NS, not significant; SCT, Stair Climbing Test; TUG, Timed Up and Go test.  
 \* Significant.

Functional Independence Measure scale and the 10-meter walking test. Only scores on the ABILOCO questionnaire changed significantly.

Only Bernuz<sup>71</sup> measured the timed stair climbing test and found a significant improvement in time by 25%.

Robertson<sup>43</sup> only measured the Timed Up and Go (TUG) and found no significant improvement.

On energy cost Tok<sup>44</sup> and Caty<sup>75</sup> measured a significant improvement in contrast to Stoquart<sup>84</sup>. Caty measured an increase in energy cost from  $5.8 \pm 1.9$  to  $4.9 \pm 1.9$  J kg<sup>-1</sup> m<sup>-1</sup> ( $p=0.03$ ) and Tok<sup>44</sup> from  $5.47 \pm 1.13$  to  $4.64 \pm 1.56$  J kg<sup>-1</sup> m<sup>-1</sup>. ( $p=0.010$ )

### Data pooling

The possibility of pooling the data of stroke patients only was examined. Six<sup>23,44,75,84,97</sup> of the twelve selected studies included only stroke patients. Robertson<sup>43</sup>, Sung<sup>85</sup> and Hutin<sup>80</sup> included also patients with other diagnoses. Bernuz<sup>71</sup> included only incomplete spinal cord injury patients. Therefore, the primary authors were contacted to obtain data of stroke patients only. These data were provided, which allowed data pooling including these results:

All seven NMB studies<sup>43,44,71,75,80,84,97</sup> injected BTX-A in the m. rectus femoris. Because Caty<sup>75</sup> injected in all patients additional muscles next to the m. rectus femoris, this study was excluded for data pooling.

Data pooling in NMB showed a significant improvement of 7.37 degrees (( $P=0.000$ ), (95% CI (4.11-10.62 degrees)) in peak knee flexion.

Four<sup>23,43,84,85</sup> of the five MBB studies injected a lidocaine solution. Sung<sup>85</sup> also injected Phenol solution. For data pooling we excluded the study of Sung<sup>85</sup> using the Phenol solution. Data pooling in MBB showed a significant improvement of 9.35 degrees (( $P=0.002$ ), (95% CI 3.49-15.21 degrees)) in peak knee flexion.

Data pooling of knee flexion velocity at toe off showed a significant improvement of 53.01 (( $P=0.001$ ), 95% CI 20.91- 85.12)) degrees/sec in NMB. In MBB this improvement was not significant.

Data pooling of knee flexion range, SSWS, and energy cost showed no significant changes in both, the NMB and MBB studies.

Results are presented in figure 2 (Forest plots NMB) and figure 3 (Forest plots MBB).

## Discussion

In this systematic review a total of twelve <sup>23,43,44,71,75,80,84,85,97</sup> studies were included that described the effect of chemodenervation of the RF in stiff knee gait in adults with spastic paresis and specifically in stroke patients.

Peak knee flexion or knee flexion range increased significantly in all studies individually. However, after pooling the data for stroke patients, knee flexion range showed no significant improvement in both NMB and MMB. On the other hand, on peak knee flexion treatment with a neuromuscular blocking agent BTX-A showed an significant increase of 7.37 degrees and blocking the motor branch of the femoral nerve with an anaesthetic improved peak knee flexion significantly by 9.35 degrees. Also knee flexion velocity at toe off showed a significant improvement of 53.01 degrees/sec in NMB whereas, in MBB this improvement was not significant.

Although peak knee flexion improved in all studies it did not reach normal values. The poor to moderate positive effects could be explained by the fact that SKG is often a multifactorial problem. There is strong evidence that a decrease in peak knee flexion is also caused by decreased strength of the ankle plantar flexors<sup>25,51</sup> and hip flexors<sup>20,26,28,53-55</sup>. Given activity of multiple muscles may contribute to SKG, injection of BTX into multiple muscles could be considered. There are studies that use dynamic simulations to estimate muscle forces during the gait cycle.<sup>29,102</sup> The results from these studies confirm that the gastrocnemius and iliopsoas are important muscles that accelerate the knee into flexion during pre-swing. Increased forces in vasti, rectus femoris, and soleus were found to decrease knee velocity at toe off. These findings corroborate the results of the study of Sung<sup>85</sup>. They found that patients with sufficient hip flexor strength showed more favorable results than those with hip flexor weakness. Also, when prolonged activity of the rectus femoris coincided with activity of the vastus muscles, the effects of chemodenervation on knee flexion was less in swing phase. Stoquart performed subsequential data analysis to check whether there was a relationship between SKG severity and treatment effect. They found that in patients with severe SKG (<10°), the treatment effect was lower than in individuals with relative mild SKG. Based on this finding we tried to determine whether this trend was also seen in the data of the other included studies. Unfortunately, this was not possible due to lack of individual data.

Gait speed was one of the most consistent functional outcome to evaluate the effects of chemodenervation on ambulation ability in the studies included in this review.

Self selected walking speed (SSWS) was assessed by the 10 meter walking test (10MWT) or instrumented gait analysis and improved statistically significant after NMB in three studies<sup>71,80,97</sup>. However, data pooling of SSWS showed no significant improvement.

Although walking speed is an important functional outcome measure that relates to walking ability<sup>103,104</sup> foot clearance might be a more appropriate outcome measure in SKG because decrease in knee flexion relates to an increased risk of stumbles and falls. Therefore, activities that appeal to footclearance, such as obstacle avoiding, and measures that assess fall and stumble incidents should be included in future research.

Data pooling in NMB showed a decrease of 0.67 (CI -0.03-1.36) J. kg<sup>-1</sup>.m<sup>-1</sup> in energy cost which was almost significant. This is approximately 12.4 % decrease. Existing literature does

not provide concrete information about clinically relevant changes in energy cost. However, literature<sup>105</sup> suggest, that a change in energy cost is clinical meaningful when they meet or exceed 10%.

These results suggest that the detected moderate increase in peak knee flexion in this review may result only in a modest increase in gait speed, but the results may have an important clinical impact on the energy efficiency of walking. Two mechanisms could be responsible for this phenomenon. Firstly, the knee extensor torque decreases after paralyzing the RF muscle and as such decreases the eccentric work phase K3<sup>106</sup>. This suggestion was supported by the clinical experiments of Stoquart<sup>84</sup> and the dynamic simulation studies of Fox<sup>107</sup>. Additionally, the findings of Nene<sup>108</sup> also showed that the level of RF activity highly correlates ( $r=0.9968$ ) with knee extension torque in a linear relationship. Another explanation of a decrease in net energy cost is that improving knee flexion and consequently foot clearance, decreases the energy-inefficient compensatory movements, i.e. the necessity of lifting the center of the body mass with the healthy leg.<sup>109</sup>

To reflect on the results of this review in the context of the alternative treatment options, we compared the effects of chemodenervation on SKG to that of existing literature concerning RF transfer or release, FES and physical exercises. However, comparison is difficult because this literature is scarce and diverse in methodology. Namdari<sup>110</sup> studied the effects of a combination of rectus femoris transfer and fractional lengthening of the vastii in adults with stroke and traumatic brain injury. Measured with observational evaluation of ambulation, the knee flexion during swing increased from 8 degrees pre operatively (range 0-15) to 33 degrees postoperatively (range 20-50). The literature on RF transfer or release is much more abundant in Cerebral Palsy (CP) than in stroke. Moreover, the results in CP cannot be easily transposed to adults. The results of trials in CP are variable.<sup>107</sup> The majority of studies describe an average improvement in knee flexion by 7 to 10 degrees, in some exceptional studies improvement ranged between 12 and 26 degrees and in some no significant differences was seen. The results suggest that surgical approach leads to a large improvement in knee flexion compared to injection of chemodenervation. A possible explanation could be that the RF is not fully paralyzed as a knee-extensor by NMB or MBB. Consequently, the knee extension moment is preserved to some extent. In addition, a surgical transfer of the distal part of the rectus preserves some of the muscle's hip flexion moment, which adds to the induction of knee flexion<sup>107</sup>.

FES of the hamstrings to improve SKG showed similar outcomes as chemodenervation. Tenniglo<sup>111</sup> found an increase of 8.7 degrees in peak knee flexion in 16 chronic stroke patients stimulating the hamstrings. Mann and Burrige<sup>59,60</sup> stimulated the calf and/or hamstrings and mentioned gait improvements but didn't measure peak knee flexion. Kesar<sup>112</sup> stimulated the plantar flexors and dorsalflexors and found no significant improvement in peak knee flexion.



Lennon<sup>56</sup> found no significant improvement in peak knee flexion after physiotherapy based on the Bobath concept in adults with stroke.

An alternative treatment option for SKG could be femoral selective neurotomy. Wang<sup>113</sup> found a significant improvement in peak knee flexion of 14.5 degrees in 15 CP patients after femoral selective neurotomy measured with goniometer.

The included article of Sung<sup>85</sup> describes two MBB studies on the same patient's population. One study examined the effect of a MBB with lidocaine injection and one study examined the effect of MBB with phenol injection. Both studies report a significant improvement of peak knee flexion. It seems that there is no difference on peak knee flexion in a different pharmacologic MBB compound.

Based on the included studies, a few guidelines for future research could be stated. First future research should use more uniform outcome measures and use a more precise description of SKG. Second, future studies should focus on patient characteristics for inclusion. It seems that patients who had EMG overactivity of the RF without EMG activity of the vastus medialis or lateralis are the best candidates for inclusion. Three studies, Robertson<sup>43</sup> Lampire<sup>97</sup> and Hutin<sup>80</sup> based their inclusion on RF activity measured with surface EMG. The results of these studies showed a slightly higher increase in peak knee flexion (range 7.5<sup>0</sup>-11<sup>0</sup>) compared to the studies<sup>23,71,84</sup> that based their inclusion on the Duncan Ely test (range 1.9<sup>0</sup>-5.0<sup>0</sup>). Precise definitions used for positive electrical EMG activity or a positive Duncan Ely test are not explicitly stated in these studies.

**Table 5.** Functional outcomes MBB studies

Outcome Measurement	Robertson et al <sup>62</sup>			Stoquart et al <sup>65</sup>			Chantraine et al <sup>65</sup>			Sung and Bang <sup>66</sup> Lidocaine			Sung and Bang <sup>66</sup> Phenol		
	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P	Pre, Mean ± SD	Post, Mean ± SD	P
10MWT	0.87±0.4	0.92±0.28	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GA speed	0.57±0.24	0.64±0.30	NS	NA	NA	NA	NA	NA	NA	0.53±0.23	0.57±0.22	NS	0.52±0.23	0.61±0.22	NS
6MWT	306.7±125	322.0±97.1	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TUG	14.2±3.5	17.0±6.3	NS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Energy cost	NA	NA	NA	5.2±1.6	4.5±1.8	.112	5.5±1.5	5.2±1.7	NS	NA	NA	NA	NA	NA	NA

Abbreviations: 6MWT, 6-minute walk test; GA, gait analysis; NA, not applicable; NS, not significant; TUG, Timed Up and Go test.

### Study limitations

The number of included studies is low. For data pooling of knee range of motion, knee angular velocity at toe off, SSWS, and energy cost, results of only two or three studies could be pooled. Data pooling for energy cost almost reached statistical significance ( $P=0.06$ ). The limited number of studies may have led to reduced statistical power, making it harder to find significant differences. The fact that statistically significant differences were only found for peak knee flexion during swing, does not imply that there is no influence of BTX-A or NMB on the other outcome measures. Statistical power may have been insufficient to validate such an effect.

The methodology quality of included studies was low with scores ranging between 11 and 19 points out of a maximum score of 32 (table 1). The items with the lowest scores were external validity, confounding and power. It is known that these factors are often limited in observational research<sup>114</sup>. Because the size and characteristics of the source population from which the sample was extracted were poorly described, the results of this meta-analysis and review are difficult to generalize.

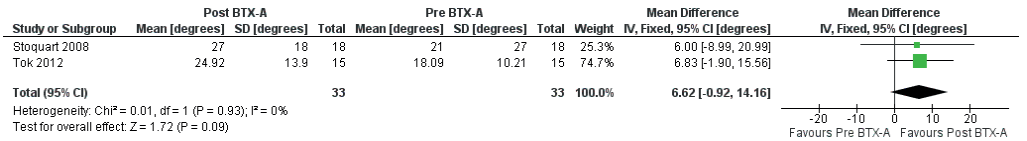
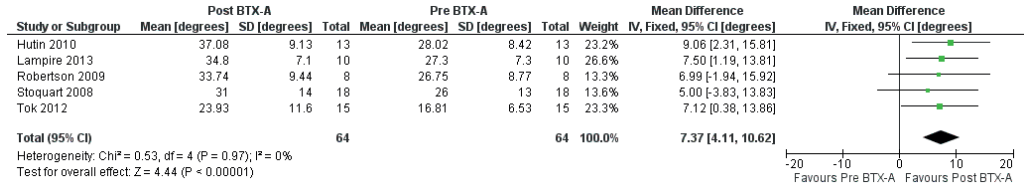
### Conclusion

In NMB as well as in MBB the rectus femoris muscle, data pooling of peaked knee flexion showed a significant improvement of respectively 7.39 degrees and 9.35 degrees. However, data pooling of knee range of motion, functional outcome and energy cost showed no significant difference. Based on the results it can be concluded that chemodenervation of the rectus femoris results in an improvement of peak knee flexion in stroke patients presenting a stiff knee gait. The effect on functional outcome and energy cost is still unclear.

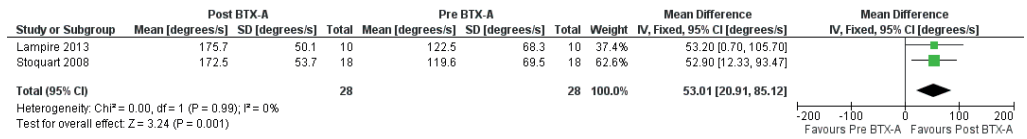
Finally, future research should use more uniform outcome measures and should focus on patient characteristics for inclusion. In addition, the pathophysiologic principles underlying stiff knee gait should be further elucidated. This will allow further tailoring of treatment programs, which may improve indication settings for different treatment options. This, in turn, could lead to better outcomes for treating SKG.

**Figure 2.** NMB Forest plots

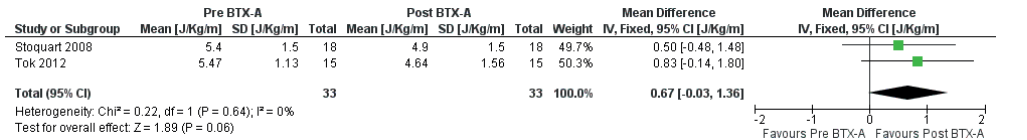
Forest plot: NMB Peak knee flexion



Forest plot: NMB Knee flexion velocity at toe off



Forest plot: NMB Energy cost



Forest plot: NMB SSWs

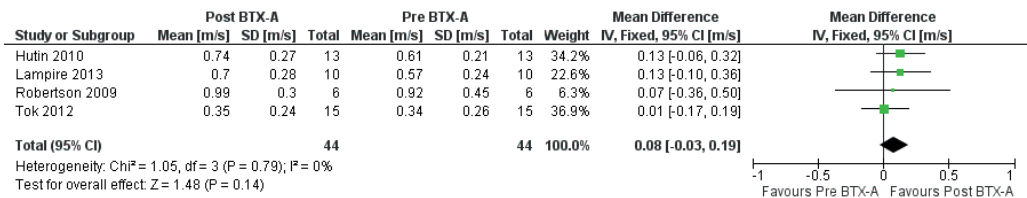
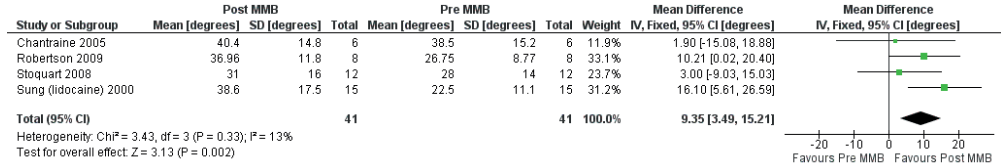
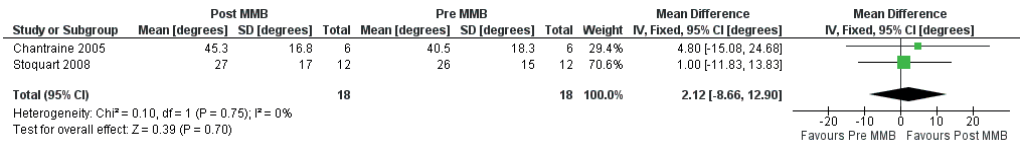


Figure 3. MBB Forest plots

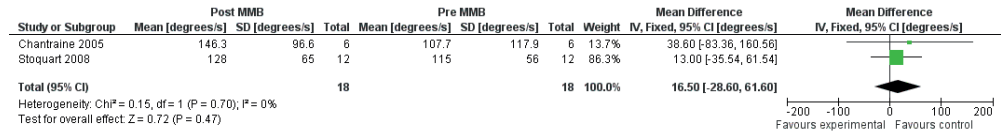
Forest plot: MBB Peak knee flexion



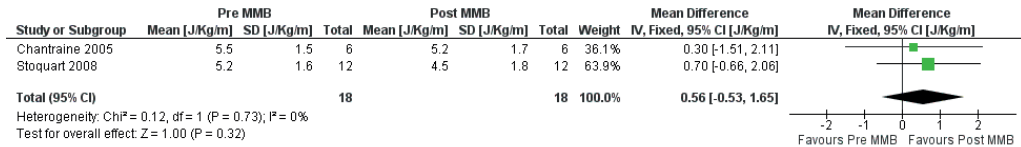
Forest plot: MBB Knee flexion range



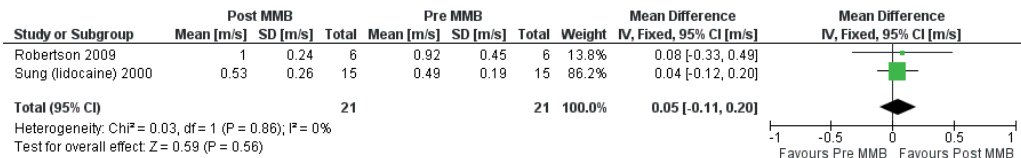
Forest plot: MBB Knee flexion velocity at toe off



Forest plot: MBB Energy cost



Forest plot: MBB SSWS



2



# 3

## **Does the Duncan Ely test predict abnormal activity of the rectus femoris in stroke survivors with a stiff knee gait?**

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Picture 1 is added.

## Abstract

**Objective:** To determine the diagnostic value of the Duncan Ely test in predicting abnormal rectus femoris activity during gait in stroke survivors walking with a stiff knee gait.

**Design:** Cross-sectional diagnostic study.

**Subjects:** A total of 95 patients with chronic stroke.

**Methods:** During physical examination, the Duncan Ely test was performed and scored. Surface electromyography of rectus femoris was then recorded during dynamic gait. To determine the diagnostic value, the results of the Duncan Ely test and surface electromyography recordings (gold standard) were compared.

**Results:** The Duncan Ely had a sensitivity of 73%, a specificity of 29%, a positive predictive value of 60% and a negative predictive value of 42%. The area under the curve was 0.488 (CI 0.355- 0.621,  $p= 0.862$ ) and showing that the Duncan Ely test is not better than random guessing.

**Conclusions:** The Duncan Ely test has no predictive value for determining abnormal activity of the rectus femoris during gait. Using this test can lead to the incorrect identification of abnormal rectus femoris activity, which might hamper the selection of optimal treatment options. We recommend stopping use of the Duncan Ely test to predict rectus femoris overactivity during swing, and instead use surface electromyography.

### Lay Abstract

After stroke, some patients have difficulty bending their knee when they swing their leg forwards. This can be the result of the rectus femoris muscle being too active. It is important to know whether this is the case. If the rectus femoris is too active, we can select a treatment option that aims to reduce its activity. Healthcare professionals often use the Duncan Ely test, to test for overactivity of the rectus femoris. However, it is not known whether this test is reliable. This study therefore compared the Duncan Ely test with a measurement in which the activity of the rectus femoris was recorded during walking. No correlation was found between the score of the Duncan Ely test and the activity of the rectus femoris during walking. We conclude that healthcare professionals should no longer use the Duncan Ely test to assess overactivity of the rectus femoris, but should replace it with surface electromyography.



## Introduction

Stiff knee gait (SKG) is commonly observed in individuals with spastic paresis as a result of an upper motor neuron lesion such as cerebral palsy, multiple sclerosis, traumatic brain injury, or stroke. SKG is characterized by a diminished knee flexion during swing and can result in problems with foot clearance. Although the exact mechanisms remain unclear and seem to be multifactorial, abnormal activity of the rectus femoris during swing phase is a frequently mentioned cause of SKG <sup>26,29,54,55</sup>.

Different treatment options for SKG <sup>115</sup> are used in clinical care, and mainly focus on influencing the abnormal activity of, or the force produced by, the rectus femoris. These options include chemodenervation of the rectus femoris <sup>35,116</sup> and a rectus femoris transfer <sup>36,37</sup>. Chemodenervation is a technique in which a pharmacologic compound such as botulinum toxin is used to paralyze a muscle or a group of muscles <sup>39</sup>. The indication for chemodenervation or rectus femoris transfer treatment is often based on abnormal activity of the rectus femoris in pre-swing or swing phase of the gait cycle.

In clinical practice, there are two options available for establishing abnormal rectus femoris activity: surface electromyography (sEMG) and the Duncan Ely test. The generally accepted gold standard is sEMG of the rectus femoris during dynamic gait analysis <sup>48</sup>. However, sEMG measurements require expensive measurement equipment and specific expertise, which limits its applicability in daily clinical practice. The second option is the Duncan Ely test <sup>49,50</sup>, which is part of a routine clinical examination of muscle tone. This test (see picture 1) is performed with the patient lying in a prone position and the examiner passively flexing the knee rapidly. This clinical test does not require any measurement equipment and is easy to perform making it suitable for daily clinical practice. However, whether the Duncan Ely test is a useful test to predict abnormal rectus femoris activity during the swing phase of gait is dependent on how the outcomes of this test relate to the golden standard. Using a test with a limited diagnostic value can lead to the incorrect selection of patients and treatment options for SKG. To the best of our knowledge, comparison of the Duncan Ely test with sEMG has not been performed in a group of stroke survivors.

The aim of this study is therefore to determine the diagnostic value of the Duncan Ely test to assess how accurately the test can predict abnormal rectus femoris activity during gait in stroke survivors with a SKG. In this light, this study can also contribute to the discussion whether a clinical test to establish abnormal activity or spasticity performed on the bench in a static (relaxed) position can actually provide information about how muscles act in dynamic situations.



**Picture 1.** The Duncan Ely test

## Methods

### Design and participants

Participants were recruited from Roessingh, Centre for Rehabilitation in Enschede, The Netherlands. Inclusion criteria were: chronic stroke survivors (at least 6 months post stroke), age over 18 years, able to walk independently with or without walking aids, diminished peak knee flexion in swing ( $>45^\circ$ )<sup>52</sup> as established by video observation and a written informed consent.

Exclusion criteria were: botulinum toxin injection in the rectus femoris in the five months prior to inclusion in the study, rectus femoris transfer surgery, length of the rectus femoris  $<65^\circ$ , presence of joint range of motion (ROM) limitation which impedes walking or other neurological problems than stroke. The study was designed as a cross-sectional trial with a single measurement and is a part of the randomized controlled trial in which the efficacy of a botulinum toxin injection into the rectus femoris was investigated (TRIAL NL2052 (NTR2169), and is approved by the Medical ethics committee (MEC Twente).

### Procedure

During physical examination, the length of the rectus femoris was measured. This is the normal length test of the rectus femoris in which we checked for a fixed contracture of the rectus. The patient was lying in a prone position and the examiner passively flexed the knee slowly until hip flexion appeared. The knee joint was flexed until hip flexion appeared and

the knee angle at this moment was measured with a goniometer. After this, the Duncan Ely test was performed twice in a standardized manner<sup>49,50</sup>. While the patient was lying in a prone position in a relaxed state, the examiner passively flexed the knee fast (we used the speed similar to the limb falling under gravity) over the total length of the rectus femoris. The test was considered positive if the examiner perceived resistance (perceived resistance) and/or the patient flexed the ipsilateral hip (occurrence of hip flexion)<sup>49,50</sup>. The perceived resistance was scored using the modified Ashworth scale (MAS). The occurrence of hip flexion was visually inspected and manually checked by the examiner. The lowest measured score of the MAS was noted in case of doubt, which is in line with the recommendation of Fleuren et al.<sup>117</sup>. The test was positive if the score on the MAS was  $\geq 1$  and/or hip flexion occurred. It was scored negative when no increase in muscle tone was felt and hip flexion did not occur. Two well-trained examiners with substantial experience in physical assessments evaluated all participants prior to the gait analysis to ensure that they were blinded for the results of the sEMG evaluation.

### **Gait analysis**

To obtain EMG of the rectus femoris during walking, participants completed four walking trials on a 10-meter walkway at comfortable walking speed. During these walking trials, sEMG of the rectus femoris and vastus lateralis of the affected leg was measured. The gait pattern and sEMG were synchronously recorded using the Flamenco system (TMSi, Oldenzaal, The Netherlands), using two cameras (Basler scout high resolution scA1300-32gc GigE camera, 50 frame per seconds, Ahrensburg, Germany) in the sagittal and the frontal plane.

Participants were allowed to walk with an ankle foot orthosis or walking aid in case they used these in their daily live. The first 2 and last 2 strides of the 10-meter walkway were discarded for sEMG analysis to exclude variations in gait speed caused by initiating and terminating gait.

### **EMG analysis**

The electrodes (Kendall ECG H93SG, 42 mm x 24 mm Covidien Mansfield USA) were placed on the rectus femoris and vastus lateralis according to the SENIAM recommendations<sup>118</sup>. SEMG was recorded with the Mobita sEMG device (TMSi, Oldenzaal, The Netherlands), with a bandwidth of 0-400 Hz and a 24-bit resolution. SEMG was recorded with a frequency of 1,000 Hz and band-pass filtered at 20-400 Hz. The noise level of this system was determined to be 10  $\mu\text{V}$  which was subtracted from the band-pass filtered signal. Subsequently, the sEMG signals were full-wave rectified and filtered with a second-order Butterworth 10 Hz low-pass filter with phase correction in order to create the sEMG linear envelope for each gait phase.

### **Detection of abnormal activity of the rectus femoris**

A custom-made computerized algorithm was used to detect abnormal activity of the rectus femoris and to discriminate it from crosstalk activity of the vastus intermedius. The algorithm is based on the normal sEMG pattern of the rectus femoris and vastus lateralis<sup>54</sup>. It compares the area under the curve (AUC) of the Root-Mean-Square value (RMS) of the rectus femoris and vastus lateralis muscle activity. Rectus femoris activity was labelled abnormal when activity was seen in the second part of initial swing and/or in midswing. In case the AUC of the RMS in initial swing and/or midswing of the vastus lateralis was equal or higher compared to the rectus femoris activity, the sEMG signal obtained over the rectus femoris was considered to be the result of cross-talk from the vastus intermedius<sup>119</sup>.

A stride could be scored as normal activity of the rectus, abnormal rectus femoris activity or crosstalk activity. For each patient a sample of ten strides was randomly selected from the four trials, and scored according to the predefined categories. Of the 10 strides the dominating type of rectus femoris activation allocated the patient in 1 of the 3 categories. In case there was no clear dominating pattern, the patient was scored as undefined.

### **Statistical analysis**

To determine the diagnostic value of the Duncan Ely, sensitivity, specificity, positive and negative predictive value were calculated. This was done separately for the perceived resistance and for the occurrence of ipsilateral hip flexion. The Receiver operator characteristic (ROC) curve and the area under the curve (AUC), which relates the outcome of the sEMG measurement and the Duncan Ely test, were calculated using IBM SPSS Statistics version 19.0 for Windows (IBM Inc. Chicago, USA).

## **Results**

### **Participants**

A total of 95 stroke survivors participated in this study. For patient characteristics, see table I. One patient was excluded from the study because no sEMG was recorded due to technical problems.

**Table I.** Patients' characteristics

Characteristics	
Number of participants, <i>n</i>	94
Affected side (left/right)	45/49
Time after stroke, years, mean (SD) [Range]	6.9 (5.9) [2–21]
Men/women	65/29
Age, years, mean (SD)	57.0 (12.6)
Use of ankle-foot orthosis (yes/no)	36/58
Use of assistive device (yes/no)	34/60

SD: standard deviation.

### Results categorization of sEMG activity rectus femoris

Based on the sEMG signal, 31 participants were categorized as having normal rectus femoris activity and 45 participants as having abnormal rectus femoris activity. Twelve participants were categorized as cross-talk activity and 6 participants as undefined. Because the individuals in the last 2 groups could not be categorized as having normal or abnormal rectus femoris activity, these 18 participants were not included in results of the analysis.

### Results test characteristics of the Duncan Ely test: perceived resistance.

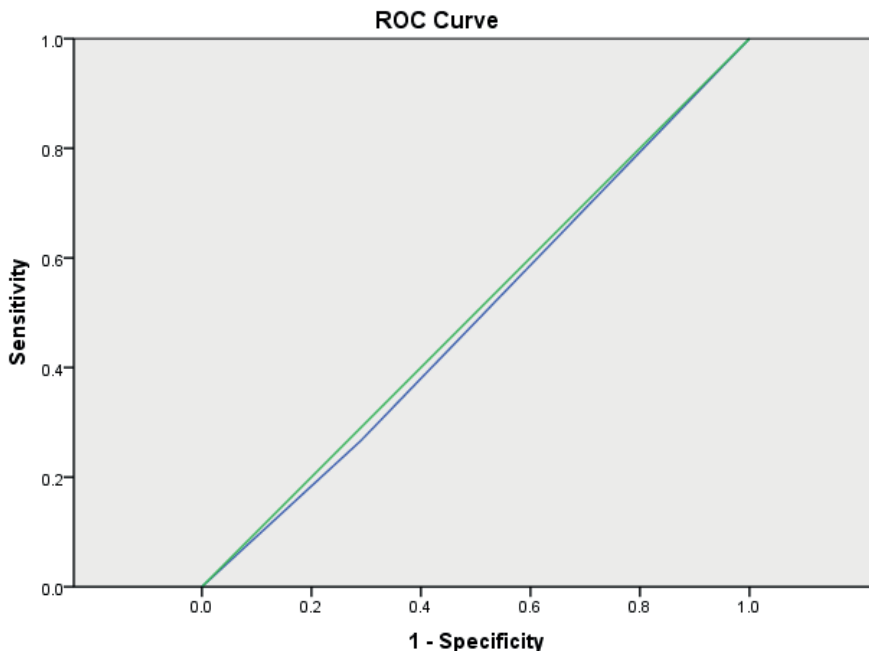
Based on the Duncan Ely test, 70 participants scored positive on the perceived resistance and 24 scored negative. As stated before, based on sEMG results, 76 individuals could be classified as having normal or abnormal activity. These 76 individuals were included in the analysis. The results for perceived resistance are presented in Table II.

**Table II.** Perceived resistance during the DuncanEly test

	sEMG abnormal	sEMG normal	
Duncan-Ely $\geq 1$ (perceived resistance)	33 (true positives)	22 (false positives)	Positive predictive value: 60% (33/55)
Duncan-Ely =0 (perceived resistance)	12 (false negatives)	9 (true negatives)	Negative predictive value: 42% (9/21)
	Sensitivity: 73% (33/45)	Specificity: 29% (9/31)	76

sEMG: surface electromyography.

The ROC curve is shown in figure 1. The area under the curve is 0.488 (p= 0.862 CI 0.355-0.621).



**Figure 1.** Receiver operating characteristics (ROC) curve for perceived resistance during the Duncan-Ely test. Green diagonal reference line: indicates a worthless test. Blue: measured line.

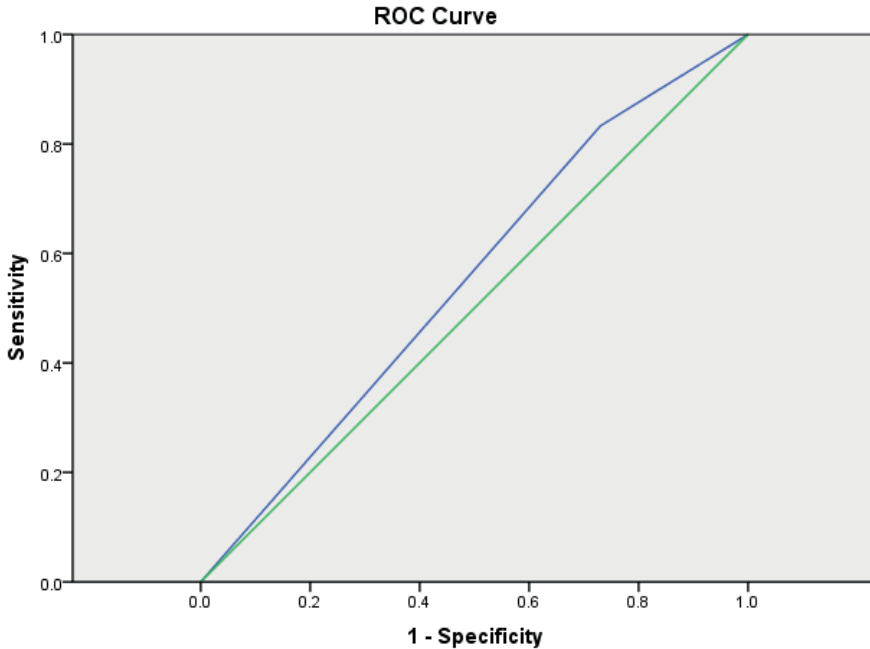
**Results test characteristics of the Duncan Ely test: occurrence of hip flexion.**

During the execution of the Duncan Ely test, there were 18 participants in which hip flexion occurred and 68 participants in whom no hip flexion occurred. From 8 participants, the absence or presence of hip flexion during the Duncan Ely test was not written down. These 8 participants were not included in the calculation. Of the remaining 86 participants, 68 participants could be classified as having normal or abnormal rectus femoris overactivity based on sEMG. These 68 participants were included in the analysis. The results for the occurrence of hip flexion are displayed in Table III. The results of the ROC curve are shown in Figure 2. The AUC is 0.551, p=0.480 (CI 0.408-0.695).

**Table III.** Occurrence of hip flexion during the DuncanEly test

	sEMG abnormal	sEMG normal	
Duncan-Ely ≥ 1 (Perceived resistance)	7 (true positives)	7 (false positives)	Positive predictive value: 50% (7/14)
Duncan-Ely = 0 (Perceived resistance)	35 (false negatives)	19 (true negatives)	Negative predictive value: 35% (19/54)
	Sensitivity: 16% (7/42)	Specificity: 37% (7/26)	68

sEMG: surface electromyography.



Diagonal segments are produced by ties.

**Figure 2.** Receiver operating characteristics (ROC) curve for occurrence of hip flexion during the Duncan-Ely test. Green diagonal reference line: indicates a worthless test. Blue: measured line.

## Discussion

This study investigated the diagnostic value of the Duncan Ely test for predicting abnormal activity of the rectus femoris during gait of stroke survivors with SKG. Test characteristics were calculated to investigate whether abnormal sEMG-activity of the rectus femoris during swing phase (gold standard) corresponds with a positive score on the Duncan Ely test (diagnostic test). For perceived resistance during the Duncan Ely test, this study showed a positive predictive value of 60.0% and a sensitivity of 73.3%. Looking at the occurrence of hip flexion during the Duncan Ely test, the positive predictive value and sensitivity are considerably lower at respectively 50.0% and 16.7%. Based on the calculated tables it can be concluded that the Duncan Ely test has no value in predicting abnormal muscle activity of rectus femoris during the swing phase of stroke survivors walking with SKG. This is also reflected in the ROC curve which showed no relation ( $AUC= 0.488$ ;  $p=0.480$ ) between perceived resistance during the Duncan Ely test and abnormal sEMG- of the rectus femoris. There was also no relation ( $AUC= 0.551$ ;  $p= 0.480$ ) between the measurements of only the

occurrence of hip flexion and the sEMG measurements. The AUC showed that the Duncan Ely test is no better than random guessing.

The limited relation between the Duncan Ely test and the sEMG analysis might be explained by several factors. During the execution of the Duncan Ely test, both the rectus femoris and the vastus intermedius, vastus lateralis and vastus medialis are stretched. Therefore, the Duncan Ely test might not only test the velocity-dependent activity of the rectus femoris but might also assess the velocity-dependent activity of these other muscles. It might therefore be hard to distinguish between the rectus femoris and vastus intermedius, vastus lateralis and vastus medialis during the Duncan Ely test.

That other muscles might be involved in a positive Duncan Ely has been reported before by Perry et al.<sup>120</sup>. They concluded that the Duncan Ely test is not a specific indicator for the rectus femoris tightness or spasticity. In addition to an electromyographic response in the rectus femoris, the test can also provoke an electromyographic response in the iliacus in subjects with cerebral palsy. The fact that up to 3 muscles could be involved in a positive test might imply that the test is not able to distinguish between velocity-dependent activity of the rectus femoris, vastus intermedius, vastus lateralis and vastus medialis and iliacus. This could have reflected on all studied outcome parameters and might contribute to the limited relation between the Duncan Ely test and the sEMG of the rectus femoris. Furthermore, the fact that other muscles cause a positive Duncan Ely test could be one of the reasons that after a chemodenervation of the rectus femoris or rectus femoris release, the Duncan Ely test is still positive in some participants<sup>23,35,121-123</sup>. Future research could focus on these points by investigating whether the relation between the Duncan Ely test and overactivity of any of the knee extensors as measured by sEMG is more sound.

Another explanation for the limited relation between the sEMG and the Duncan Ely test could be the fact that the score of the Duncan Ely test is based on a subjective evaluation by the examiner. The score on the perceived resistance and the occurrence of hip flexion could be dependent on which examiner performs the test and interprets the results differently. Furthermore the occurrence of hip flexion is difficult to observe and rating is not standardized. In addition, the angular velocity with which the Duncan Ely test should be performed is not standardized nor controlled. This could influence the score on the Duncan Ely test because it aims to measure the velocity-dependent response to passive moment. In case the angular velocity is higher, one might hypothesize that the response is also larger. Based on the findings of Lee et al.<sup>124</sup> we tried to standardize the angular velocity in a speed similar or faster to the speed of the limb falling under gravity. Although we tried to standardize the angular velocity, speed it is not controlled and can be different between examiners and patients potentially leading to different scores in similar cases.

Furthermore, there may be a discrepancy between the knee angular velocity and knee range of motion during walking and the knee angular velocity and knee range of motion applied during the Duncan Ely test<sup>125</sup>. In case the knee angular velocity and range of motion



during the Duncan Ely test is much higher than the knee angular velocity during walking, the velocity-dependent resistance of the rectus femoris during the Duncan Ely test will also be higher. This discrepancy between the knee angular velocity executed on the bench and the knee angular velocity during functional walking can contribute to the reported differences between the results of the Duncan Ely test and the results of the sEMG.

Besides these apparent shortcomings of the Duncan Ely test itself, it is also disputable whether a clinical test to establish overactivity or spasticity performed on the bench in a static (relaxed) position can provide information about how muscles act in dynamic situations. In other words, it is debatable to which degree the results of a passive measurement of an impairment relates to the dynamic functional activity such as walking<sup>126-128</sup>. There are more studies supporting this notion. Dietz and Sinkjaer<sup>129</sup> suggest that there is a disparity between clinical assessment findings and how spasticity manifests during walking. In addition to the discussion about static versus dynamic test situations, there is also an influence of posture on the static test conditions. Yelnik et al.<sup>130</sup> and Perry et al.<sup>131</sup> reported that the spastic response varies greatly according to the position of sitting or standing. This is also the case when comparing the activity patterns of knee extensors and flexors during sitting and lying in different patient populations<sup>132-134</sup>. Additionally, the study of Lamontagne et al.<sup>135</sup> showed that spasticity at rest only weakly predicts spasticity during the stance phase of gait, which emphasizes the need for a locomotor-specific measure of spasticity. Finally, Nonnekes et al.<sup>136</sup> mentioned that the presence or absence of spasticity observed during clinical examination often does not translate to muscle activity or overactivity observed by instrumented analysis of the gait, and suggested that sEMG is necessary to detect or confirm muscular overactivity during gait.

The findings that the Duncan Ely test has no diagnostic value for predicting overactivity of the rectus femoris in stroke survivors walking with SKG has implications for clinical care as well as scientific research. In both fields, abnormal activity of the rectus femoris is usually quantified using the Duncan Ely test. Because of its limited diagnostic value, this test can lead to the selection of incorrect treatment options for SKG. Furthermore, using the Duncan Ely test to establish rectus femoris activity might lead to the false identification of individuals with and without rectus femoris activity during walking. This, in turn, could lead to heterogeneous study population which might have contributed to the variable results that have been published about the effect of treating abnormal rectus femoris activity<sup>23,35,116,137-140</sup>.

This study had some limitations. First, some assumptions were made in determining abnormal activity based on the sEMG. The algorithm contained assumptions that can give room for discussion. One example of this is the noise level value. To test the robustness of these assumptions, additional analyses were performed in which the noise level was changed to 8 and 12  $\mu\text{V}$ . Varying the noise level did not change the conclusions of this study. Furthermore, 18 participants were excluded from the analysis, due to crosstalk activity or

undefined sEMG. Exclusion of these individuals could have influenced the current results. We therefore performed a sensitivity analysis based to investigate whether our conclusion would change if we had included these 18 participants. This sensitivity analysis did not change the conclusion. When all 18 patient were included and categorized as normal activity rectus femoris sEMG, the AUC of perceived resistance was 0.511 ( $p=0.856$ ). When all 18 patients were included and categorized as abnormal activity rectus femoris, the AUC of perceived resistance was 0.474 ( $p=0.682$ ).

Future research could investigate whether the findings of this study can be replicated when the signals from the rectus femoris are obtained using fine-wire EMG. Compared to sEMG, fine-wire is not susceptible for crosstalk activity from the vastus intermedius, and is therefore more precise.

Furthermore, this study raises additional information concerning the diagnostic performance of clinical tests for spasticity of other muscles which relate test results in a static position to the muscle activity in a dynamic functional activity such as walking. This might also be true for other clinical tests, which could be subject for future research.

## Conclusion

In conclusion, this study showed that the Duncan Ely test has no diagnostic value for predicting abnormal activity of the rectus femoris in stroke survivors with SKG. Factors that may contribute to this conclusion are that the score on the Duncan Ely test is a subject assessment, that a static test is used to assess a problem occurring in dynamic situations and that the Duncan Ely test might assess other knee extensors and hip flexors. We recommend stopping use of the Duncan Ely test for this purpose, but instead using sEMG. Furthermore, this study confirms the notion that it is dispu whether a clinical test that aims to establish overactivity or spasticity performed on the bench in a static position can provide information about how muscles act in dynamic situations.

## Acknowledgement

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## Declaration of Conflicting Interests:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors have no conflict of interest to declare.





# 4

## **Influence of functional electrical stimulation of the hamstrings on knee kinematics in stroke survivors walking with stiff knee gait.**

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Picture 1 is added.

## Abstract

**Objective:** To explore whether functional electrical stimulation of the hamstrings results in improved knee kinematics in chronic stroke survivors walking with a stiff knee gait.

**Design:** Quasi-experimental.

**Subjects:** Sixteen adult chronic stroke survivors.

**Methods:** Survivors received functional electrical stimulation of the hamstrings, 3 times a week for 1 h during a period of 5 weeks. 3D kinematics was calculated before the training period and after 5 weeks of training. Knee kinematics of walking without stimulation before the training period was compared with walking with stimulation after 5 weeks of training. (intervention effect). In addition, knee kinematics of walking without stimulation before the training period was compared with walking without stimulation after the training period (therapeutic effect).

**Results:** The intervention effect showed a significant increase, of mean  $8.7^\circ$  (standard deviation (SD) 8.3,  $p = 0.001$ ), in peak knee flexion. The therapeutic effect showed a significant increase in peak knee flexion, of mean  $3.1^\circ$  (SD 4.7,  $p = 0.021$ ).

**Conclusion:** The results of this exploratory study shows an increase in knee kinematics in swing after functional electrical stimulation of the hamstrings in stroke survivors walking with a stiff knee gait. The largest improvement in peak knee flexion in swing was seen when participants walked with hamstring stimulation. Participants with low neurological impairment responded better to hamstring stimulation, and there are indications that the effect of hamstring stimulation can be predicted during a single session. The effect of functional electrical stimulation is comparable to that of more invasive treatment options, such as botulinum toxin or soft-tissue surgery. This makes functional electrical stimulation a feasible treatment option for daily clinical practice.

### Lay Abstract

This exploratory study examined the effect of functional electrical stimulation of the hamstrings on knee kinematics and walking speed in 16 chronic stroke survivors walking with a stiff knee gait. Participants were measured before and after 5 weeks of training with functional electrical stimulation. There was an increase in peak knee flexion in the swing phase after the training period, while walking with functional electrical stimulation. Participants with low neurological impairment responded better to hamstring stimulation, and there are indications that the effect of hamstring stimulation can be predicted during a single session. The effect of functional electrical stimulation is comparable to that of more invasive treatment options, such as botulinum toxin or soft-tissue surgery. Functional electrical stimulation is therefore a feasible treatment option for daily clinical practice.

## Introduction

Stiff knee gait is an abnormal movement pattern commonly observed in stroke survivors. It is characterized by a reduced peak knee flexion (PKF) during swing phase. The limited knee flexion may cause toe dragging or energy-inefficient compensatory movements<sup>52</sup> compromising the stability of gait and increasing the risk of falling<sup>15</sup>. The pathophysiology of stiff knee gait is only partly understood and several hypotheses are postulated in the literature. The role of overactivity of the rectus femoris during swing phase is often cited<sup>26,45,55</sup>. Other possible causes of stiff knee gait are increased forces generated by the vasti,<sup>29</sup> decreased hip flexion moments<sup>28</sup> and decreased ankle plantar flexion moments<sup>25</sup>. However, the exact mechanisms remain unclear and seem to be multifactorial.

Different treatment options for stiff knee gait are available that are aimed at influencing the overactivity of the rectus femoris. These options include chemodenervation of the rectus femoris<sup>35</sup> and rectus femoris transfer<sup>36,37</sup>. The indication for chemodenervation or RF transfer treatment is related to the over activity of the rectus femoris in pre-swing or swing. This means that only those patients that show this over activity are eligible for this type of treatment. Electrical stimulation of the calf and/or hamstring muscles<sup>33,34</sup> is a treatment option that might be suitable for all patients, irrespective of the cause of stiff knee gait as it might directly assist in achieving sufficient knee flexion. Studies on the effect of electrical stimulation of the calf or hamstrings on the hemiplegic gait pattern are, however, scarce and most of the studies stimulated two or more muscle groups in order to influence kinematics of gait.

One practical problem of stimulating two or more muscles is the timing of the stimulation, as the proper timing of muscle contraction may differ between muscles. Providing adequate timing is easier when stimulating only one muscle, which makes it more feasible in clinical practice. From a clinical point of view, it is therefore interesting to investigate whether knee flexion during swing can be improved by stimulating only one muscle group.

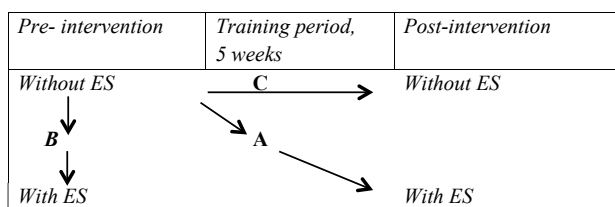
The primary aim of the present study was to explore whether five weeks of functional electrical stimulation of the hamstrings resulted in improved knee kinematics during the swing phase in chronic stroke subjects with a stiff knee gait. The study compared: (i) walking without electrical stimulation pre-intervention with walking with electrical stimulation post-intervention (intervention effect). The secondary aims were to compare: (ii) walking without electrical stimulation pre-intervention with walking without electrical stimulation post-intervention. (therapeutic effect) and (iii) walking without stimulation pre-intervention with walking with stimulation pre-intervention (immediate effect).

Furthermore, based on clinically experience, we explore: (iv) the relation between the immediate effect and the intervention effect. Finally, based on the findings of Haldon and Anderson<sup>141</sup> who found a positive relation between walking speed and knee kinematics, we aimed to explore: (v) the influence of walking speed on the intervention effect of stimulation.

## Methods

### Study design

The study was designed as an exploratory prospective quasi-experimental study (Fig 1). It was approved by the local Medical Ethical Committee (MEC Twente).



**Fig. 1.** Study design. A: intervention effect (post-intervention with electrical stimulation (ES) minus pre-intervention without ES). B: immediate effect (pre-intervention with ES minus pre-intervention without ES). C: therapeutic effect (post-intervention without ES minus pre-intervention without ES).

### Study population

A convenience sample of adult chronic stroke survivors (>6months after stroke) were recruited for participation at Roessingh Centre for Rehabilitation (RCR), Enschede, the Netherlands. Inclusion was based on: visible diminished knee flexion during the swing phase, ability to walk without physical support, ability to complete a 3.5-h assessment, and ability to understand and follow verbal instructions. Exclusion criteria were: a pacemaker, metal implants in the paretic leg, or orthopaedic problems or progressive diseases influencing the walking pattern. Participants were allowed to continue their regular treatment during the study and received oral and written information about the study before they decided to participate.

### Intervention

Patients were treated with electrical stimulation for 1 h, 3 times a week, for a period of 5 weeks (15 h in total). Therapy was provided by a senior physical therapist with longstanding experience (over 20 years) in the use of electrical stimulation in the stroke population. Each session consisted of walking with electrical stimulation of the hamstrings of the paretic leg. Participants walked at a comfortable speed indoors at the physical therapy department and were allowed to stop or rest when necessary. The Odstock 2-channel footswitch controlled stimulator system (Odstock Medical Limited, Salisbury, UK) was used for stimulation. Self-adhesive skin surface electrodes, with a size of 50 × 100 mm (CefarComplex Medical, Lund, Sweden) were placed on the mediolateral aspect of the hamstrings<sup>142</sup>. A footswitch was used to trigger the stimulation between heel off and toe off. The indifferent electrode was placed approximately 5 cm above the knee crease and the active electrode was placed approximately 10 cm above the indifferent electrode. During an initial, pre-intervention



session the location of the foot switch, the locations for electrode placement and stimulation settings (amplitude, pulse duration) were determined for maximum optimization of the walking pattern. These locations remained the same during the 15 sessions. The pulse duration varied between 0.125 and 0.475 s. The stimulation frequency was 40 Hz.



**Picture 1.** Hamstrings stimulation

### **Experimental protocol**

All participants were tested pre- and post-intervention, both during walking without and with stimulation. During the pre-intervention session, anthropometric data were collected. Participants were instructed to walk at their natural, comfortable speed. During both evaluations and training period, participants used the same walking aids, orthoses and shoes.

### **Participant characteristics**

The Rivermead Mobility Index <sup>143</sup>, Functional Ambulation Category <sup>144</sup>, Motricity index <sup>145</sup> and the Duncan Ely test <sup>49</sup> were administered only at the pre-intervention assessment to determine participants' characteristics. Furthermore, the use of an ankle foot orthosis

(AFO) and walking aids were recorded. In addition, adverse events during the experiment, such as blisters, skin problems or intolerance of the stimulation, were recorded.

### **Kinematics**

To determine knee kinematics and preferred walking speed, an infrared opto-electronic 3D-motion analysis system (VICON MX + 6 MX13 cameras, frame rate 100 Hz; Vicon Motion Systems, Oxford, UK) was used. Participants walked a 10-m walkway. A standard marker-placement (Plug in Gait model) was used and one person made all the marker placements. To normalize data to the gait cycle, initial contact and toe off events were detected. A minimum of 10 strides were analysed and averaged for each participant to determine PKF during swing, knee range of motion (minimum stance phase vs maximum swing phase) and walking speed.

### **Statistical analysis**

All variables showed sufficient closeness to a normal distribution, as determined visually by a senior statistician. To identify the effect of ES on knee kinematics and walking speed, data for the 3 walking conditions were compared: (i) the intervention effect (pre-intervention without ES vs post-intervention with ES); (ii) the therapeutic effect (pre-intervention without ES vs post-intervention without ES); and (iii) the immediate effect (pre-intervention without ES vs pre-intervention with ES). Data were analysed with paired samples t-test. (iv) To predict the intervention effect in one try-out session (immediate effect) the correlation between knee kinematics of the intervention effect and those of the immediate effect were calculated using Pearson's correlation. (v) To explore the influence of walking speed on the effect of stimulation the correlation between knee kinematics of the intervention effect and the intervention effect for walking speed were calculated using Pearson's correlation.

Participant characteristics and outcome measures were described with descriptive statistics using mean and standard deviation (SD). All statistical analyses were performed using SPSS 19.0 for Windows. A  $p \leq 0.05$  was considered as statistically significant. A correlation above 0.7 was considered relevant.

## **Results**

### **Participants**

A total of 16 chronic stroke survivors were included in the study (Table I). All participants attended all therapy sessions and there were no dropouts. Eight patients walked with an

AFO, 5 patients walked with a cane, and 1 patient walked using a quad cane. No adverse events were reported.

**Table I.** Participant characteristics

Participants (dropouts), <i>n</i>	16 (0)
Age, years, mean (SD)	57.6 (10.3)
Sex (male/female), <i>n</i>	14/2
Time after stroke, years, mean (SD)	5.8 (5.4)
Paretic side (left/right), <i>n</i>	7/9
Use of walking aids, walking with/without, <i>n</i>	6/10
Use of ankle foot orthosis, walking with/without, <i>n</i>	8/8
Duncan Ely, median, (IQR)	1 (1–2)
Functional Ambulation Categories, median, (IQR)	5 (4–5)
Rivermead Mobility Index, (0–15), mean (SD)	12.2 (0.9)
Motricity Index lower extremity, (0–99), mean (SD)	64.7 (17.8)

SD: standard deviation; IQR: interquartile range.

### **Kinematics and walking speed**

The kinematic parameters analysed for the different testing conditions are shown in Table II. The kinematic parameters and walking speed of the intervention effect, therapeutic effect and immediate effect are shown in Table II.

### **Correlations**

The calculated correlations are shown in Table III.

**Table II.** Knee kinematics and walking speed

Outcome measure	Pre-intervention		Post-intervention		Difference effect		Immediate effect Mean (SD)
	Without ES Mean (SD)	With ES Mean (SD)	Without ES Mean (SD)	With ES Mean (SD)	Intervention effect Mean (SD)	Therapeutic effect Mean (SD)	
Peak knee flexion (°)	29.1 (9.0)	34.6 (12.1)	32.2 (11.6)	37.9 (13.4)	8.7 (8.3) <i>p</i> = 0.001*	3.1 (4.7) <i>p</i> = 0.021*	5.5 (7.0) <i>p</i> = 0.007*
Knee range total cycle (°)	27.7 (8.0)	33.2 (10.4)	30.2 (9.6)	35.9 (10.7)	8.2 (7.7) <i>p</i> = 0.001*	(CI 4.3; 13.2) 2.5 (4.0) <i>p</i> = 0.027*	(CI 1.7; 9.2) 5.5 (6.5) <i>p</i> = 0.004*
Walking speed (m/s)	0.86 (0.22)	0.95 (0.24)	0.91 (0.21)	0.97 (0.23)	(CI 4.0; 12.2) 0.11 (0.10) <i>p</i> = 0.000*	(CI 0.3; 8.9) 0.05 (0.06) <i>p</i> = 0.005*	(CI 2.0; 8.9) 0.09 (0.09) <i>p</i> = 0.001*
					(CI 0.06; 0.17)	(CI 0.02; 0.08)	(CI 0.04; 0.14)

\*Denotes a statistically significant difference between the conditions. *p* ≤ 0.05. (Paired sample *t*-test).  
SD: standard deviation; ES: electrical stimulation; CI: confidence interval.

**Table III.** Correlations

Outcome	Intervention effect peak knee flexion	Intervention effect knee range of motion
Intervention effect walking speed	R = 0.12, $p = 0.650$	R = 0.09, $p = 0.741$
Immediate effect peak knee flexion	R = 0.75, $p = 0.001^*$	R = 0.74, $p = 0.001^*$

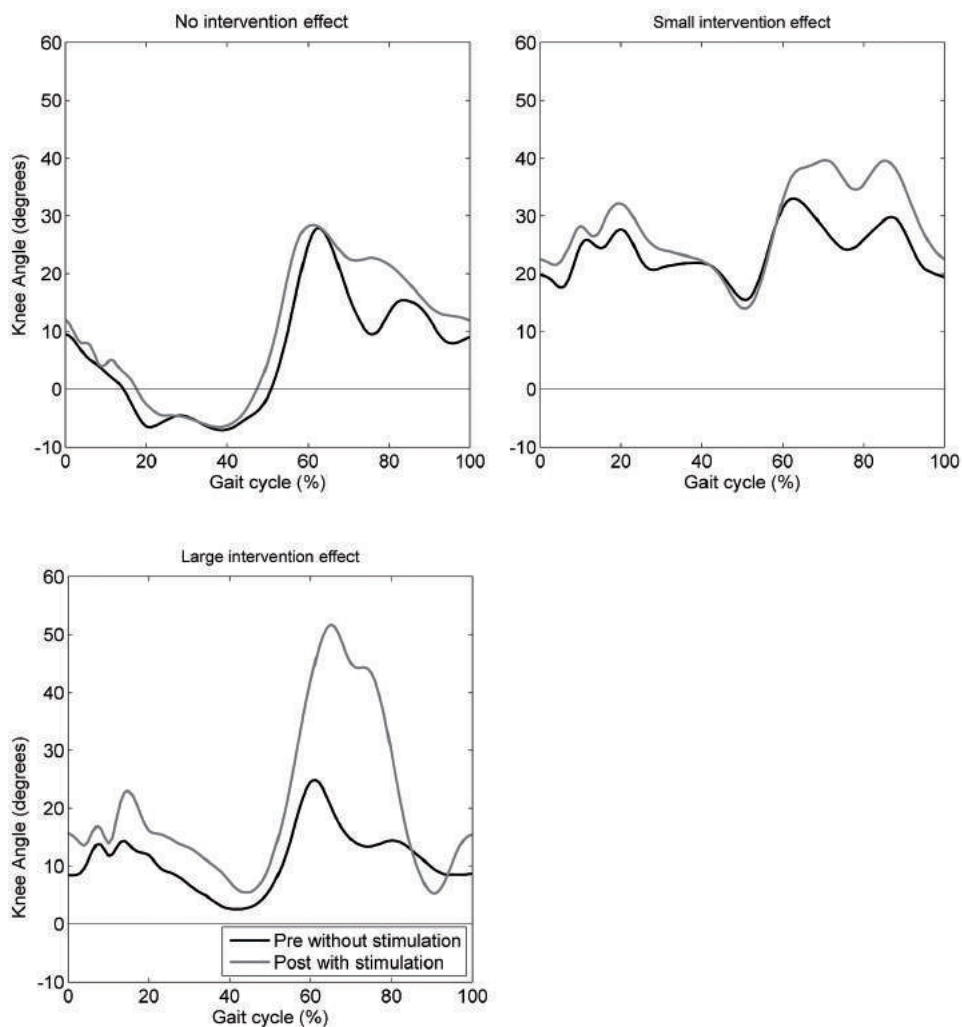
\*Denotes a statistically significant difference between the conditions.  $p \leq 0.05$ .

## Discussion

The results showed that walking with stimulation of the hamstrings after 5 weeks of training resulted in a statistically significant increase in PKF and knee range of motion in chronic stroke survivors with a stiff knee gait. In addition, a statistically significant therapeutic and immediate effect was found for PKF and knee range of motion. Self-selected walking speed increased statistically significantly with hamstring stimulation (intervention effect). It is not known what the clinically meaningful difference in PKF is for treatment options for stiff knee gait. Therefore, it is debatable whether the statistically significant increase of 3° as a therapeutic effect is clinically meaningful for the patient. The intervention effect of hamstring stimulation is considerably larger (8.7°). Thus, hamstring stimulation might be regarded more as an assistive device than a therapeutic device, as the effect of functional continuous stimulation (comparison of pre with stimulation and post with stimulation) is much larger than when it is used only as a training device (comparison of pre without stimulation and post without stimulation). Although this study found a positive result for hamstring stimulation at the group level, there was a strong heterogeneity in effect at the individual level (see Fig. 2 for the exemplary data for 3 individuals). In other words, there were participants in whom a large intervention effect was seen and there were participants in whom no or only a small intervention effect was seen. The 4 participants with the largest response showed an improvement of more than 16° in PKF during swing. From a clinical point of view, insight into the participant characteristics that distinguish this subpopulation from the overall study population is of interest. All 4 large responders walked without an AFO or walking aid, had a high score on the Motricity Index (> 69) of the lower extremity, and had a low spasticity score of the rectus femoris measured with the Duncan Ely Test (score = 1). Therefore, responders with the largest improvement appeared to have low neurological impairment and were able to adapt their walking pattern to the electrical stimulation. Following this line of thought, patients with severe neurological impairments may have limited ability to adapt their walking pattern to incorporate the hamstring stimulation.

A strong statistically significant correlation was found between the knee kinematics of the immediate effect and the knee kinematics of the intervention effect. Participants with a

large immediate response also showed a large response after 5 weeks of training and for participants in whom the immediate response was low, the response after 5 weeks of training was also low. Clinically this might be a crucial issue. It means that the effect of functional electrical stimulation of the hamstrings at the individual level can be predicted with a high probability during a single session.



**Fig. 2.** Heterogeneity in intervention effect.

A statistically significant increase in walking speed was found, which may have contributed to an increase in knee kinematics <sup>141</sup>, reducing the true effect of hamstrings stimulation. However, a non-significant correlation between the change in walking speed and the knee

kinematics (PKF and knee range of motion) was found. Furthermore, Heldel et al <sup>146</sup> showed that, in healthy subjects, an increase in walking speed of 0.9–1.0 m/s, which is the magnitude of the differences that we found, led to an increase in PKF of 1–2°. Based on this, it can be concluded that positive influence of the increased walking speed on knee kinematics is negligible in our study, and that the described differences are the result of the electrical stimulation. In addition, it is debatable whether the significant improvement in walking speed, of 0.11 m/s from mean 0.86 (SD 0.22) to 0.97 (SD 0.23) m/s (intervention effect), was clinically meaningful for the patients, as there is no consensus on the magnitude of the minimal clinical important difference. Tilson et al <sup>147</sup> concluded that a meaningful improvement of comfortable walking speed in subacute stroke patients is >0.16m/s whereas Perera et al <sup>148</sup> stated that a change of 0.1 m/s in walking speed was a significant clinical difference.

To our knowledge, this is the first study to examine the effect of stimulating only one muscle (hamstring), instead of more muscles, on knee kinematics during the swing phase of gait for the treatment of stiff knee gait. The results of this study can therefore only be compared with the results of studies that stimulated 2 or more muscles. Kesar et al <sup>33</sup> stimulated the dorsal and plantar flexors of the ankle, but found no significant improvement in PKF. Mann et al <sup>34</sup> investigated the effect of stimulation of hamstring muscles in addition to common peroneal nerve stimulation. Of the 6 participants that were stimulated, one participant showed a substantial improvement in knee flexion and 3 showed a general improvement (not specified) in knee flexion response. Mann <sup>34</sup> did not mention PKF or knee range of motion. Daly et al <sup>38</sup> used intramuscular electrodes to stimulate 8 lower limb muscles, including the hamstrings, for gait training in combination with a 3-month treatment protocol, consisting of weight-supported-treadmill training, strength and coordination training and overground training in chronic stroke. They found a significant improvement in PKF of 10.0° ( $p = 0.02$ ) during walking without stimulation in the group who also received functional neuromuscular stimulation, in comparison with the group without neuromuscular stimulation treatment ( $\text{PKF} \pm 1.4^\circ$ ,  $p = 0.84$ ). This significant therapeutic increase in PKF of 10° is larger than the significant therapeutic increase of mean 3.1° (SD 4.7,  $p = 0.021$ ) in our study. Although our study and the study of Daly <sup>38</sup> are difficult to compare, a possible explanation for the larger increase in PKF in the study of Daly could be the difference in training intensity. In literature, other treatment options for stiff knee gait have been investigated. A systematic review performed by Tenniglo et al. <sup>116</sup> reported that chemodenervation of the rectus femoris resulted in a significant pooled improvement of 7.4° in PKF in stroke patients with a stiff knee gait. However, no significant difference in knee flexion range of motion was reported in this review. Namdari et al. <sup>46</sup> examined the effect of rectus femoris transfer in combination with fractional lengthening of the vastii in adults with stroke and found an increased knee flexion during swing, changing from 8° preoperatively (range 0°-15°) to 33° postoperatively (range 20°-50°). Lennon et al <sup>149</sup> found

no improvement in PKF after physiotherapy based on the Bobath concept in adults with stroke.

Overall, it seems that the intervention effect of hamstring stimulation on knee kinematics is comparable or slightly better compared to the other treatment options for stiff knee gait. However, comparison between studies is difficult, because literature about the treatment of stiff knee gait is scarce and very diverse in methodology. In addition, inclusion criteria were different and the diversity in reasons resulting in a stiff knee gait may have affected the results.

### **Study limitations and future research.**

limitation of the present study was the lack of a control group. Furthermore, both participants and assessors were not blinded in the present study. Despite the general increase in PKF and knee range of motion, not all participants in the present study responded equally to hamstring stimulation. The multiple reasons mentioned for stiff knee gait, such as overactivity of the rectus femoris in the swing phase (3–5) or a lack of push off from the gastrocnemius moments<sup>22,25</sup>, may have influenced the effect of hamstring stimulation. In addition, generalization of the present study results to the broader stroke population is difficult, because of the relatively small study population. Future research with more participants (control group, randomization, blinding) should deepen our understanding about the aetiology of stiff knee gait and evaluate how interventions can influence the causative factors of stiff knee gait .

## **Conclusion**

This exploratory study shows an increase in knee kinematics in the swing phase after functional electrical stimulation of the hamstrings in stroke survivors walking with a stiff knee gait.

The largest improvement in peak knee flexion in the swing phase is seen when participants walked with the hamstring stimulation. Participants with low neurological impairment responded better to hamstring stimulation and there are indications that the effect of hamstring stimulation can be predicted during a single session.

The effect of functional electrical stimulation is comparable to that of more invasive treatment options, such as botulinum toxin (BTX) or soft-tissue surgery. Functional electrical stimulation is therefore a feasible treatment option for daily clinical practice.

### **Acknowledgements**

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**Conflict of interest**

The authors have no conflicts of interest to declare.



# 5

## **The effect of Botulinum Toxin Type A injection in the rectus femoris in stroke patients walking with a stiff knee gait: A randomized controlled trial.**

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<https://doi.org/10.1177/15459683231189712>  
Added Picture 1.

## **Abstract**

### **Background**

Overactivity of the rectus femoris is often cited as a main cause for stiff knee gait. Botulinum toxin (BoNT) can be used to reduce this overactivity. Inconsistent results for the effect of BoNT injections were found in literature which can possibly be explained by the study design as these were uncontrolled or non-randomized studies.

### **Objective**

To conduct a randomized controlled trial (RCT) to investigate the effect of botulinum toxin type A (BoNT-A) injections in the rectus femoris on gait kinematics and functional outcome in adult stroke patients.

### **Methods**

Twenty-six participants were included in this triple-blind cross-over RCT. The intervention consisted of an injection with BoNT-A. Placebo is an injection with saline. Besides knee and hip kinematics, functional outcomes were measured.

### **Results**

Comparison of the effect of BoNT-A injection to placebo injection showed a significant increase in peak knee flexion and knee range of motion of 6.7° and 4.8° respectively. There was no difference in hip kinematics. In functional outcomes, only the 6 Minute Walking Test showed a significant increase of 18.3 meter.

### **Conclusions**

BoNT-A injections in the rectus femoris is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics. To study the effect on functional outcome more research is necessary with different functional outcome measures that can capture the effect in kinematics. It is important to use kinematic measurements to demonstrate effects in quality of movement that are not captured by commonly used functional outcome measurements post stroke.

Clinical trial registration: <https://trialssearch.who.int/Trial2.aspx?TrialID=NTR2169>

## Introduction

Stiff knee gait (SKG) is characterized by a diminished knee flexion during the swing phase of gait and frequently affects patients with an upper motor neuron lesion (e.g. stroke or traumatic brain injury). The lack of knee flexion can lead to foot clearance problems, increase the risk of tripping and falling and restrict the patients in their daily live activities<sup>15,52</sup>. Several mechanisms that can cause SKG are described in literature. Some authors attribute stiff knee to overactivity of the vastii muscles of the quadriceps<sup>29,150</sup>, others to weak hip flexors<sup>151</sup>, altered foot-ankle mechanisms (lack of push off)<sup>151</sup>, overactivity of the rectus femoris<sup>26,55,108,152,153</sup> or decreased knee flexion velocity at toe-off in pre-swing<sup>154</sup>. The discussion about etiology is still ongoing, but overactivity of the rectus femoris is assumed to be the overarching cause.

Several treatment options for SKG are used in clinical care, mainly aimed at influencing the abnormal activity or force production of the rectus femoris. These include injections with botulinum toxin (BoNT) in the rectus femoris<sup>35,116</sup> and/or a rectus femoris transfer<sup>36,37</sup>.

While the efficacy of BoNT injections to reduce abnormal activity or (spasticity) has been reported in literature<sup>155</sup>, inconsistent results for BoNT injections were found in the effect on kinematics and functional outcomes in stroke patients walking with a SKG. Robertson et al.<sup>43</sup> and Hutin et al.<sup>80</sup> found increases in peak knee flexion of 8° and 9°, respectively. In contrast, Stoquart et al.<sup>35</sup> and Caty et al.<sup>75</sup> found an increase of only 5°. In addition, inconsistent results were found in walking speed. Hutin et al.<sup>80</sup>, Lampiere et al.<sup>97</sup> and Berenus et al. al<sup>71</sup>. reported a significant increase in self-selected walking speed calculated from the 10 meter walking test (10 MWT), while Tok et al.<sup>44</sup> and Robertson et al.<sup>43</sup> found no differences. Variable outcomes were also found on the 6 minutes walking test (6 MWT). Robertson et al.<sup>43</sup> and Bernuz et al.<sup>71</sup> measured no significant improvement in covered distance during the 6 MWT while Tok et al.<sup>44</sup> found a significant improvement. Finally, energy expenditure decreased significantly in the studies of Tok et al.<sup>44</sup> and Caty et al.<sup>75</sup> while Stoquart et al.<sup>35</sup> found no significant results for energy expenditure.

The variability of results reported in these studies can possibly be explained by the study design. Since all studies reported in literature so far are uncontrolled or nonrandomized studies, a potential placebo effect was not considered which could have biased the results. Only the study by Tok et al<sup>44</sup> used a placebo group, but this study lacks randomization and did not use a double-blind design which may cause additional bias in the results.

Furthermore, it is unclear if the effect of BoNT injection of the rectus femoris for reducing SKG also leads to significant improvements in functional outcomes, such as walking speed and walking distance, energy cost as well as patients self-reported quality of gait. Therefore, the primary objective was to evaluate the effect of BoNT-A injection on knee and hip kinematics during swing. The secondary objective was to investigate if the effect of BoNT-A

injection to reduce SKG also leads to improvements in functional outcomes and patients self-reported quality of gait.

To rule out bias by confounding factors such as blinding in the current trial, we performed a randomized triple blind placebo-controlled cross-over trial to examine the efficacy of BoNT type A injection into the rectus femoris on SKG in a group of stroke patients.

Based on the literature, we expect an increase in knee kinematics as well as improved scores on functional outcome measures.

## Methods

### Participants

Participants were recruited from 2013-2019 Roessingh, Center for Rehabilitation (Enschede, the Netherlands). Inclusion criteria were stroke survivors (at least 6 months post stroke), age over 18 years, activity of the rectus femoris in second part of initial swing and/or mid swing. This was determined by measuring muscle activity using sEMG of the rectus femoris and vastus lateralis simultaneously to differentiate between true activity and cross-talk<sup>108,152</sup>. Subjects were able to walk independently with or without walking aids and had diminished peak knee flexion in swing (<50°)<sup>52</sup> as established by video observation and willingness to provide written informed consent.

Exclusion criteria were: Chemodenervation of the rectus femoris prior to the study, co-activation of the vastii in initial- or midswing, length of the rectus femoris <65° (measured with the slow Duncan Ely test), presence of a reduced joint range of motion impeding walking or other neurological problems. During participation in the study, participants were allowed to continue regular treatment. However, treatments focused on improvement of knee flexion were not allowed.

### Study design

This study was conducted as a triple-blind randomized controlled trial (RCT) with a cross-over design. The participants, the physician performing the BoNT-A and placebo injections and the researchers involved in post injection measurements were all blinded for group allocation. The study was approved by the local medical ethical research committee (MERC Enschede). The study was registered in the Netherlands Trial Register (NTR) with the unique identifier:NTR2169. Clinical trial registration:

<https://trialsearch.who.int/Trial2.aspx?TrialID=NTR2169>

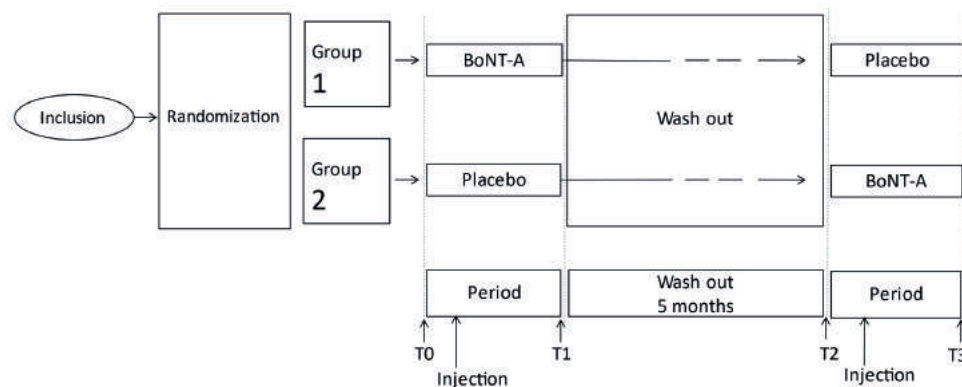
A computerized randomization into 2 groups was done in blocks of 4 participants to ensure similar group size. Group 1 first received a BoNT-A injection followed by a wash out period of 5 months, which was followed by the placebo injection; group 2 first received the placebo

injection followed by a wash out period of 5 months which was followed by the BoNT-A injection. A wash-out period was implemented to exclude a carry-over effect of the BoNT-A injections <sup>156</sup>. An overview of the study design is presented in figure 1.

### Study protocol

Data were collected before and after the BoNT-A and placebo injection. This resulted in 4 measurement moments, T0, T1, T2, and T3 as can be seen in figure 1. Pre injection measurements (T0 and T2) were done 1 week before the injection, for optimal peak effect of the BoNT-A injection, post injection measurements (T1 and T3) were done 4 to 6 weeks after the injection. Data collection consisted of 3D kinematics, determination of energy expenditure during walking and the execution of functional outcome measures and assessment of the perceived level of impairment. The data of one measurement moment (e.g. T0) were collected in 1 day. The randomization key was released when all data were fully analysed.

**Figure 1.** Study design RCT.



Abbreviation: RCT, randomized controlled trial.

### Study drug intervention

Interventions consisted of injecting BoNT-A or a placebo into the rectus femoris.

A total amount of 200U BoNT-A (Botulinum Toxin Type A, Allergan) was injected in the rectus femoris, at six points (six injections of 33U) according to the method of Stoquart et al.<sup>35</sup> For the placebo a saline (NaCl 0.9 %) solution was injected using the same procedure as the BoNT-A injection. All injections were performed by one experienced physician (A.N.) with the aid of intramuscular electrical stimulation (0-5 mAmp) for optimal needle placement of the injection.

### **Gait analysis**

To determine 3D kinematics, an infrared opto-electronic 3D-motion analysis system (VICON MX + 8 MX13 cameras, frame rate 100 Hz; Vicon Motion Systems, Oxford, UK) was used with a standard marker placement (lower-limb Plug-in-Gait model VICON Oxford UK <sup>157</sup>). Initial contact was detected as the first point at which weight is detected on the force plate (20 Newton). Toe-off was detected as the first point at which the ground reaction force was not detected. During gait analysis participants walked on a 10-meter walkway at least 20 times with sufficient rest periods. For data analysis, a minimum of 10 strides were analyzed. Outcome measures were calculated for each gait cycle and averaged the outcomes measures afterwards. Participants walked at their natural comfortable speed and used the same walking aids, orthoses and shoes during all data collection.



**Picture 1.** BoNT injection

### **Kinematic outcome measures**

Kinematics of knee and hip are calculated with an inhouse MATLAB based software. Peak knee flexion and peak hip flexion were defined as the maximum amount of flexion in swing. The range of motion of knee and hip was calculated as the difference between maximum extension in stance and maximum flexion in swing. Knee flexion angular velocity at toe off was calculated with a five points calculation.

### **Energy expenditure**

After the gait analysis session, energy expenditure was measured during the 6 minutes walking test (6 MWT) using the Cosmed K4 b2 system (Cosmed, Rome, IT). Participants



completed the 6 MWT at a self-selected, comfortable speed on a circular track of 75 m. Patients were notified of the elapsed time every minute and were allowed to rest in case they were not able to walk any further. Patients were not allowed to talk during the 6 MWT. Assistive devices and necessary orthoses were allowed during walking but remained identical during the entire study.

To determine steady state during the 6 MWT, a moving window (of two minutes) was shifted over the measurement from two minutes after the start of the 6 MWT.<sup>158,159</sup> This was done for five time blocks: 2-4 min; 2.5-4.5 min; 3-5 min; 3.5-5.5 min; and 4-6 min.

To check for steady state, O<sub>2</sub> rate and Respiratory Exchange Ratio (ration between VCO<sub>2</sub> and VO<sub>2</sub>) were averaged over these time blocks and were checked whether they stayed within the borders of variance of 20%<sup>160</sup>. Furthermore, the respiratory exchange RER was checked whether it was below 1 as this is the threshold between aerobic and anaerobic activity. For every individual patient, the five time blocks were checked for the steady state conditions and RER score. The time block for which the stated conditions were met for most patients was used in the analysis. The energy cost was computed by dividing O<sub>2</sub> rate by the walking speed (m/s) which was computed by dividing the covered distance on the 6 MWT by 360 seconds.

### Functional outcome measures

Each participant completed the 6 MWT, Timed Up and Go Test, 10 m walk test, the Motricity Index and the Rivermead Mobility Index. The Medical Research Council (MRC) score was used to assess the strength of the hip flexors and knee extensors. The Duncan-Ely Test was assessed to obtain information about the spasticity of the rectus femoris. The Visual Analogue Scale (VAS) (range 0-10)<sup>161</sup> and a Borg CR10 score (range 0-10)<sup>162</sup> were used to determine the subjective value of the experienced stiff knee gait during walking. A lower value of the VAS and Borg means less experienced stiff knee gait during walking. Finally, the Stroke Impact Scale (SIS)<sup>163</sup> was used to determine the level of participation of the subjects.

Gait analysis, functional tests, energy expenditure and the analysis of the complete data set, were carried out by the same person (MT).

### Statistical analysis

Due to the design of the study as a randomised controlled blind cross-over trial, carry-over and period effects for each variable must be excluded before treatment effects can be analysed. Testing for carry-over effects was done using an unpaired t-test for the sum of the variables at T<sub>0</sub> and T<sub>2</sub>. Testing for period effects was done by an unpaired t-test for the difference between BoNT-A and placebo injection at T<sub>1</sub> and T<sub>3</sub>.

Before statistical tests were chosen, the normal distribution of the data was checked. This was done using the Shapiro-Wilk test and a visual inspection of histograms.

In case data were normally distributed, we used the paired or independent samples t-test. For variables that were not normally distributed, a Wilcoxon Signed Rank test or Mann Whitney U test was used.

For statistical analysis we use IBM SPSS statistics 19.0 for Windows (IBM Inc. Chicago, IL, USA).

### Power analysis

A power analysis showed a sample size of 23 patients to achieve 91% power to detect a mean differences of 5 with an estimated standard deviation of 7.3. (two-sided paired z-test,  $\alpha=0.05$ ). Inclusion of 26 patients allowing a 10 % dropout.

## Results

In all, 26 patients were included in the study. One patient dropped out due to family problems. Data from this participant was not included in the analysis. All remaining 25 participants completed the study. No side-effects of the BoNT-A injections were reported. In contrast, two patients reported a small side-effect after receiving placebo. One patient reported headache for a short period on the day of the injection. The other person reported headache one day after the injection. Participant characteristics are shown in table 1.

### Statistical check for carry over effect or period effect

The Motricity index Total score lower extremity was the only test that showed a carry-over effect. Therefore, we only used data from T0 and T1 in the statistical analysis. There was no significant difference (independent t-test) for the Motricity Total score.

For all other variables, all four data points were used and checked with the paired t-test.

**Table 1.** Participants Characteristics.

Characteristics	value (n = 25)
Participants/dropouts	25/1
Age in years (mean)	57.4 (SD 12.7) range 27.7-83.2
Sex male/female	19/6
Time after stroke years (mean)	8.2 (SD 5.6) range 2-26
Paretic side left right	15/10
Ischemia/hemorrhage	17/8
Use of stick with/without	5/16
Use of ankle foot orthosis with/without	9/16
Use of stick and ankle foot orthosis	6/16
Functional ambulation categories (mean)	4.6 (SD 0.4) range 4-5

Abbreviation: SD, standard deviation.

**Kinematics**

All results are displayed in table 2 (affected side). The between group analysis, comparison of the effect of the BoNT-A injection to the effect of the placebo injection, showed a significant difference of 6.7° in peak knee flexion in favour of the BoNT-A injection. Knee range of motion and knee angular flexion velocity at toe off showed a significant difference of 4.8° and 24.9 °/s, respectively. The Cohen's d effect size for peak knee flexion is 0.63 (medium to large effect). For Knee range of motion and knee angular velocity at toe-off is the Cohen's d effect size respectively 0.41 and 0.31 (medium effect).

No significant differences were found for the peak hip flexion and hip range of motion and walking speed.

**Functional outcome measurements**

All results are displayed in Table 3. Between group analysis showed a significant difference of 18.3 meter on the 6 MWT and a significant decrease of 0.7 points on spasticity score of the Duncan Ely test in favour of the BoNT-A injection.

No significant differences were demonstrated in the other functional outcomes. (See table 3 and 4).

**Table 2.** Kinematic Outcomes.

Outcome measure (N = 25)	BoNT-A			Placebo			Comparing mean difference pre-post BoNT-A vs mean difference pre-post Placebo
	Pre injection value mean (SD)	Post injection value mean (SD)	Difference pre-post injection effect mean (SD)	Pre injection mean (SD)	Post injection mean (SD)	Difference pre-post injection mean (SD)	
Peak knee flexion (°)	35.9 (11.8)	43.2 (11.9)	7.3 (6.4) P = .000* CI (4.62 to 9.98)	38.7 (11.3)	39.3 (10.4)	0.5 (5.6) P = .605 CI (-1.75 to 2.94)	6.7 (8.8) P = .001* CI (3.1 to 10.3)
Knee range of motion (°)	33.3 (11.6)	38.0 (13.6)	4.7 (5.6) P = .000* CI (2.37 to 7.03)	34.5 (10.5)	34.4 (11.6)	-0.07 (4.3) P = .932 CI (-1.88 to 1.73)	4.8 (6.9) P = .002* CI (1.9 to 7.6)
Knee flexion angular velocity at toe-off (°/s)	109.3 (106)	142 (97)	32.9 (51.6) P = .004* CI (11.5 to 54.1)	111.8 (85.7)	119.8 (89.6)	7.9 (34.9) P = .265 CI (-6.6 to 22.4)	24.9 (51.7) P = .024* CI (3.5 to 46.2)
Peak hip flexion (°)	34.2 (8.8)	35.8 (7.6)	1.6 (6.0) P = .192 CI (-0.8 to 4.0)	37.1 (7.0)	36.7 (7.4)	-0.4 (4.3) P = .686 CI (-2.1 to 1.4)	1.9 (7.7) P = .219 CI (-1.2 to 5.1)
Hip range of motion (°)	36.6 (8.3)	37.2 (8.6)	0.6 (2.3) P = .201 CI (-0.3 to 1.5)	36.8 (7.2)	36.4	-0.4 (2.8) P = .522 CI (-1.5 to 0.8)	0.9 (3.1) P = .133 CI (-0.3 to 2.2)
Walking speed (m/s)	0.90 (0.21)	0.95 (0.23)	0.04 (0.08) P = .019* CI (0.008 to 0.08)	0.90 (0.22)	0.92 (0.25)	0.02 (0.09) P = .182 CI (-0.01 to 0.06)	0.01 (0.10) P = .375 CI (-0.02 to 0.06)

Paired t-test.

Abbreviations: SD, standard deviation; CI, confidence interval; BoNT-A, botulinum toxin type A.

\*Statistic significant.

**Table 3.** Functional Outcomes.

Outcome measure n=25	BoNT-A		Placebo		Comparing mean difference pre-post: BoNT-A vs mean difference pre-post: Placebo
	Pre injection value mean (SD)	Post injection value mean (SD)	Pre injection mean (SD)	Post injection mean (SD)	
6 MWT (m)	327.9 (80.3)	342.1 (79.4)	340.0 (75.1)	335.8 (82.0)	-4.2 (21.4) P=.336 CI (-13.0 to 4.6)
10 MWT (sec)	9.9 (2.5)	9.9 (2.8)	9.9 (2.3)	9.7 (2.6)	-0.12 (0.75) P=.778 CI (-0.35 to 0.46)
Timed up and go (s) (mean of 3 test)	12.1 (3.4)	11.9 (3.4)	12.1 (3.3)	11.9 (3.1)	-0.30 (1.24) P=.504 CI (-0.29 to 0.58)
Duncan Ely (Ashworth score 0 or ≥1)	1.4 (0.8)	0.5 (0.6)	1.3 (1.1)	1.1 (1.1)	-0.2 (0.7) P=.170 CI (-0.5 to 0.1)
Motricity index score hip (min max (0-33))	20.8 (6.7)	19.6 (6.3)	20.3 (6.2)	20.9 (6.2)	0.6 (4.6) P=.470 CI (-1.2 to 2.6)
Mobility index score knee (min max, 0-33)	22.6 (5.8)	23.0 (5.9)	20.1 (6.2)	22.7 (5.4)	2.6 (5.4) P=.025* CI (0.3 to 4.8)
Mobility index score ankle (min-max, 0-33)	20.1 (8.8)	19.3 (8.0)	17.6 (8.7)	17.9 (9.1)	0.3 (3.6) P=.663 CI (-1.1 to 1.8)
MRC hip flexion (range 0-5)	3.9 (0.5)	4.0 (0.6)	3.8 (0.6)	4.0 (0.6)	0.2 (0.5) P=.161 CI (-0.36 to 0.12)
MRC knee extension (range 0-5)	4.2 (0.5)	4.2 (0.6)	4.2 (0.5)	4.2 (0.5)	0.04 (0.6) P=.770 CI (-0.23 to 0.31)
VAS Subjective value of experienced SKG (min max 0-10)	5.1 (2.6)	3.6 (2.4)	5.0 (3.0)	4.3 (2.9)	-0.7 (1.7) P=.053 CI (-1.5 to 0.01)
Borg score subjective value of experienced SKG (min max 0-10)	3.7 (2.3)	2.5 (2.3)	3.8 (2.6)	2.9 (2.3)	-0.8 (1.9) P=.033* CI (-1.6 to -0.1)
FAC score (range 0-5)	4.6 (0.5)	4.8 (0.3)	4.6 (0.5)	4.7 (0.5)	0.1 (0.3) P=.161 CI (-0.03 to 0.19)
Rivermead Mobility Index (range 0-15)	12.9 (1.3)	13.1 (90.7)	13.4 (0.7)	13.2 (0.9)	-0.2 (0.6) P=.134 CI (-0.5 to 0.1)
					0.7 (3.1) P=.259 CI (-2.0 to 0.5)
					0.4 (3.2) P=.563 CI (-1.7 to 0.9)
					0.0 (0.4) P=1.0 CI (-0.16 to 0.16)
					-0.4 (0.2) P=.038* CI (0.0 to 0.8)

Paired t-test.

Abbreviations: SD, standard deviation; 6 MWT, 6 minutes walking test; 10 MWT, 10 meter walking test; CI, confidence interval; BoNT-A, botulinum toxin type A; MRC, Medical Research Council; VAS, Visual Analogue Scale; SKG, stiff knee gait; FAC, functional ambulation categories.

\*Statistic significant.

### Energy expenditure

The results of the energy expenditure are displayed in Table 5. The energy expenditure measurements only started after the METC approval of an amendment for measurements with the Cosmed device during the 6 MWT. Consequently, only the last 16 included patients were measured with Cosmed. Two patients didn't reach the steady state and the RER value  $< 1$  with the Cosmed measurement. The results of these patients were not included in the results. Comparison of the effect of the BoNT-A injection to that of the placebo injection did not show a significant difference.

## Discussion

In this RCT we investigated the effect of BoNT-A injections in the rectus femoris of stroke patients walking with a stiff knee gait. The results of this RCT confirms findings on knee kinematics found in uncontrolled studies. We found in this RCT a significant difference in peak knee flexion ( $6.7^\circ$ ) which is in line with the  $7.37^\circ$  increase that was found in the systematic review by Tenniglo et al.<sup>116</sup> that pooled the data of stroke patients in uncontrolled studies. The reported significant difference in knee range of motion of  $4.8^\circ$  is in line with the significant increase of  $6^\circ$  that was reported by Stoquart et al.<sup>35</sup> and the significant increase of  $6.83^\circ$  reported by Tok et al.<sup>44</sup>.

The significant difference in knee angular velocity at toe off  $24.9^\circ/s$  however is less than the  $53.01^\circ/s$  found in the systematic review<sup>116</sup>. The reason for this difference in outcome remains unclear. Possible differences in the determination of knee angular velocity may have played a part.

Our result showed that there is no decrease in hip kinematics which is in accordance with other studies<sup>43,80</sup>. This is an important clinical outcome, because the rectus femoris, being a biarticular muscle, not only stretches the knee but also flexes the hip.<sup>54,152</sup> BoNT decreases the function of the rectus femoris, meaning that it decreases knee extension and possibly also hip flexion. This in turn, can increase foot clearance problems which can be a reason for caution in BoNT treatment. Our study, however, does not confirm this risk as results show no adverse effects in hip flexion during walking.

Against our hypothesis, we found that reduction in SKG did not lead to significant improvements in walking speed, energy cost nor scores on the different questionnaires of self-report such as SIS, Rivermead Mobility Index, VAS score and Borg sore. Also, measurements of selectivity or strength with the Motricity Index or MRC score did not change. Obviously, effects of BoNT-A to reduce SKG does not lead to significant changes in walking speed, energy cost, strength or patient self-reported outcomes.

We found only a significant difference in walking distance on the 6 MWT, in line with a few uncontrolled studies<sup>44,71,80,97</sup> in this field. However, it should be noted, that found

significant difference in walking distance was only 18.3 meter and with that not clinically meaningful from the perspective of the patient. For achieving improvements beyond the minimal clinical difference (MCD) on the 6 MWT, Tang et al<sup>164</sup> found a MCD of 34.4 meter on the 6 MWT for patients after stroke. Fulk<sup>165</sup> et al (2018) found a MCD varying between 44 and 74 meter (classified for different walking speeds) on the 6 MWT in post- stroke.

The question is why found improvements in kinematics reflecting SGK and reductions in muscle tone<sup>166</sup> do not generalize to significant improvements in functional outcomes such as walking speed, energy cost and self-reported outcome. One explanation might be that the effects are too small to impact these functional outcomes. Alternatively, one may also argue the lack of responsiveness of most used functional outcome measures because they reflect different underlying constructs, acknowledging that quality of movement is not captured by these functional outcomes and self-reported outcome.

The current study emphasizes the importance of using kinematic metrics such as peak knee flexion, knee range of motion, next to functional outcomes, in recovery trials to capture these changes. This latter finding is in line with the recommendations seen in the upper extremity in the second Stroke and Recovery and Rehabilitation Round table task force (SRRR)<sup>167</sup> and support the need for global SRRR consensus on balance and mobility outcomes including biomechanics.

The inclusion of rectus femoris overactivity is based on EMG measurement and not, as in some studies<sup>23,35,75</sup>, based on the Duncan Ely test. In a recent study<sup>168</sup> we showed that the Duncan Ely test has no predictive value for determining abnormal activity of the rectus femoris during gait in patients after stroke. We therefore recommend not to use the Duncan Ely test to predict abnormal rectus femoris activity during swing, and instead use EMG. That the Duncan Ely test has no predictive value for determining abnormal activity of the rectus femoris may be a reason for a weaker effect on knee kinematics<sup>23,75</sup> in the studies that based their inclusion on the Duncan Ely test instead of EMG<sup>43,80</sup>.

Table 4. Stroke Impact Scale.

Outcome measure SIS	BoNT-A			Placebo			Comparing mean difference pre-post BoNT vs mean difference pre-post Placebo
	Pre injection mean (SD)	Post injection mean (SD)	Difference pre-post injection mean (SD)	Pre injection mean (SD)	Post injection mean (SD)	Difference pre-post injection mean (SD)	
1 Strength	11.6 (3.8)	12.5 (4.0)	0.9 (2.5) P=.098 CI (-0.17 to 1.93)	12.0 (4.2)	11.6 (4.5)	-0.4 (3.7) P=.562 CI (-1.9 to 1.1)	1.4 (3.8) P=.095 CI (-0.2 to 2.9)
2 Memory	36.9 (4.3)	36.9 (4.9)	0.04 (2.2) P=.930 CI (-0.9 to 0.9)	36.3 (5.9)	35.0 (9.4)	-1.3 (7.6) P=.394 CI (-4.4 to 1.8)	1.4 (7.3) P=.360 CI (-1.6 to 4.4)
3 Emotion	31.7 (3.8)	32.1 (1.8)	0.4 (3.1) P=.535 CI (-0.9 to 1.7)	31.9 (2.4)	31.5 (6.9)	-0.4 P=.773 CI (-3.2 to 2.4)	-0.8 (7.4) P=.593 CI (-2.2 to 3.8)
4 Communication	32.0 (4.1)	32.6 (3.7)	0.6 (1.9) P=.139 CI (-0.2 to 1.4)	31.8 (4.6)	31.2 (7.5)	-0.6 (6.2) P=.613 CI (-3.2 to 1.9)	1.2 (5.8) P=.278 CI (-1.1 to 3.5)
5 Activities of daily living	52.6 (6.8)	52.4 (8.2)	-0.1 (3.3) P=.858 CI (-1.5 to 1.3)	51.8 (8.0)	50.0 (13.3)	-1.3 (12.0) P=.600 CI (-6.2 to 3.7)	1.2 (12.6) P=.649 CI (-4.0 to 6.4)
6 Mobility	43.8 (5.3)	45.6 (3.9)	1.8 (2.8) P=.003* CI (0.6 to 3.0)	44.4 (5.3)	43.6 (10.2)	-0.8 (9.9) P=.676 CI (-4.9 to 3.3)	-2.7 (9.9) P=.190 CI (-1.4 to 6.8)
7 Hand function	14.7 (7.4)	15.6 (7.7)	0.8 (6.6) P=.550 CI (-1.9 to 3.5)	14.6 (8.0)	14.0 (8.7)	-0.6 (3.6) P=.389 CI (-2.1 to 0.8)	1.4 (7.0) P=.320 CI (-1.5 to 4.4)
8 Participation	37.6 (8.4)	36.6 (7.7)	-1.0 (5.0) P=.383 CI (-3.3 to 1.3)	35.7 (8.9)	37.1 (11.8)	1.4 (10.1) P=.505 CI (-2.8 to 5.5)	2.4 (13.0) P=.370 CI (-7.6 to 3.0)
9 Composite physical	61.2 (19.2)	62.1 (17.6)	0.9 (10.6) P=.668 CI (-3.5 to 5.3)	57.7 (22.6)	59.8 (21.7)	2.1 (23.1) P=.656 CI (-7.4 to 11.6)	1.2 (26.5) P=.823 CI (-12.1 to 9.7)
Total	323.0 (46.1)	323.5 (36.1)	0.5 (28.0) P=.932 CI (-11.1 to 12.1)	316.5 (50.0)	310.4 (81.7)	-6.1 (78.1) P=.700 CI (-38.3 to 26.1)	6.6 (79.8) P=.685 CI (-26.4 to 39.5)

Paired t-test.

Abbreviations: BoNT-A, botulinum toxin type A; SD, standard deviation; CI, confidence interval.

\*Statistic significant.

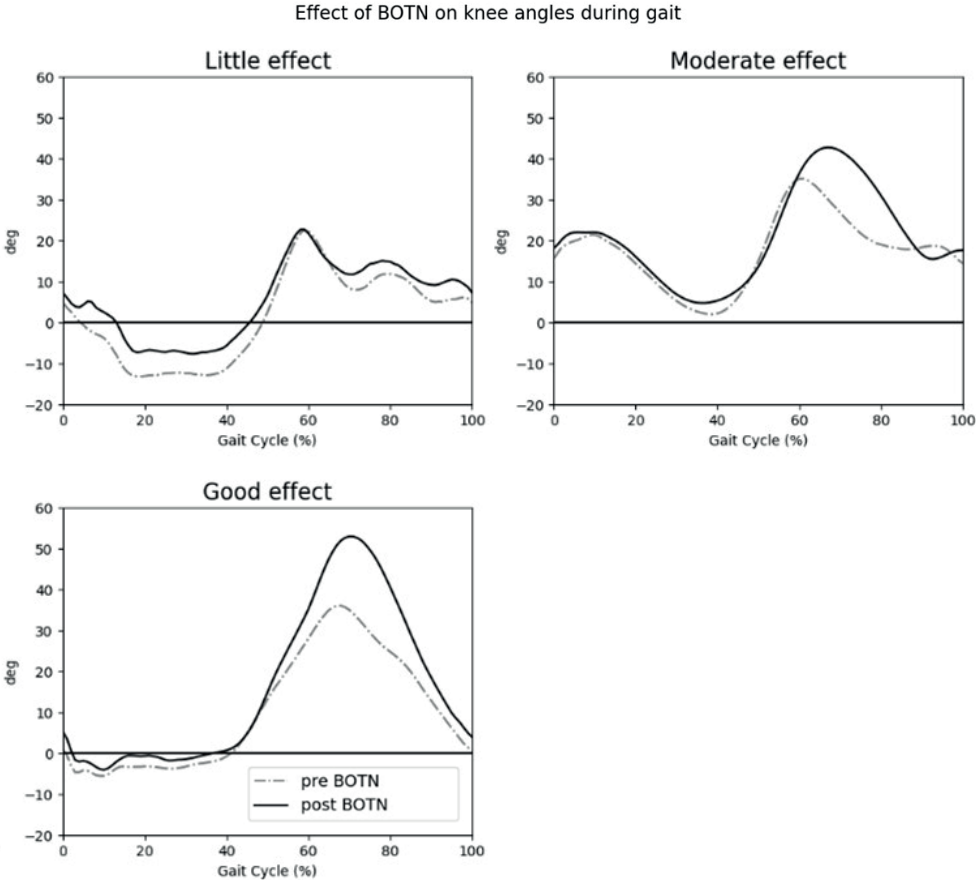


**Table 5. Energy Expenditure.**

Outcome measure energy expenditure (N = 14)	BoNT-A		Placebo		Comparing mean difference pre-post BoNT-A vs mean difference pre-post Placebo
	Pre injection value mean (SD)	Post injection value mean (SD)	Pre injection mean (SD)	Post injection mean (SD)	
Energy cost (ml/kg/m)	0.305 (0.070)	0.293 (0.066)	0.287 (0.051)	0.295 (0.066)	0.009 (0.037)
O <sub>2</sub> rate (ml/kg/min)	15.61 (3.45)	15.85 (3.17)	15.90 (3.64)	15.74 (2.62)	-0.162 (1.59)

Paired t-test.

Abbreviations: BoNT-A, botulinum toxin type A; SD, standard deviation; CI, confidence interval.



**Figure 2.** Treatment effect varied from little effect to a good effect.

Furthermore, regarding patient inclusion, it is unclear whether there is a relation between specific patient characteristics and treatment effect. This is of importance because we saw that the treatment effect varied from little effect to a good effect. Typical examples of these different treatment effects are graphically displayed in figure 2. One may hypothesize that individuals with higher levels of selectivity, for instance, respond differently to a BoNT injection when compared to individuals with lower levels of selectivity. Whether relations between patient characteristics and treatment effect exist, and more importantly which patient characteristics are of influence, could be a topic for future research.

### Strengths and limitations

The major strengths of the study are the fact that this trial was designed as a triple-blinded cross-over RCT and that we based our inclusion criteria on sEMG which led to an objective and verifiable inclusion of participants with abnormal activity of the rectus femoris.

Another strength of the study was that we chose a primary outcome measure that reflects normalization of the gait pattern which is in line with the anticipated effect of BoNT.

A limitation of the study are the used functional outcome measures as they may not be sensitive or specific enough to measure difference on functional measure abilities after BoNT in the rectus femoris. Furthermore, we did not study the effect of BoNT-A injection in the rectus femoris on functioning in everyday life but focused on performance in a lab environment instead.

Finally, we did not measure the effect of BoNT-A of the rectus femoris on foot clearance problems like stumbling, tripping or falling in the current trial. Reducing foot clearance problems is an often made remarkable comment of patients after the injection. Reason for the reduced foot clearance problems can be that the increase in knee kinematics normally give an increase in foot /ankle lift from the ground. This can reduce the functional foot clearance problems like stumbling or tripping. However, with the current outcome measures we were not able to assess foot clearance. Patients also mentioned improvements of functional abilities like gait initiation, getting in and out of the car, obstacle avoiding, automatically walk and turning. Unfortunately, all these items are not covered by the functional outcomes of mobility or questionnaires that are available for use in stroke survivors. It is important to use kinematic measurements to demonstrate effects in quality of movement that are not captured by commonly used functional outcome measurements post stroke.

### Conclusions

This triple blind RCT showed that knee kinematics significantly improve after BoNT-A injection in the rectus femoris. For functional outcomes, the distance walked over the 6 MWT was significantly increased. Other functional outcomes didn't improve. BoNT-A injections in the rectus femoris is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics. To study the effect on functional outcome more research is necessary with different functional outcome measures that can capture the effect in kinematics. This study emphasizes that it is important to use kinematic measurements to demonstrate effects in quality of movement that, otherwise, are not captured by commonly used functional outcome measurements post stroke.

**Authors' Note**

All authors have read and approved the submitted original research article. No part of this work has been published.

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**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.





# 6

## **The effect of rectus femoris transfer on kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait.**

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Revision manuscript submitted in Gait and Posture.  
Added Picture 1

## **Abstract**

### **Title**

The effect of rectus femoris transfer on kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait.

### **Background**

Stiff knee gait is characterized by a reduced peak knee flexion during swing. Overactivity of the rectus femoris is often cited as a main cause for stiff knee gait. Little is known about the effect of an isolated rectus femoris transfer treatment on kinematic and functional outcomes in a group of stroke survivors.

### **Objective**

To perform an experimental study to evaluate the effect of an isolated rectus femoris transfer on knee and hip kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait.

### **Method**

In this experimental study, 10 stroke survivors were included. During the surgical procedure, the distal rectus femoris tendon of the affected side was transferred to the medial knee flexors to improve knee flexion during swing. Knee and hip kinematics and a variety of functional outcomes were measured within 3 weeks before surgery and between 6 and 7 months after the surgery.

### **Results**

We found a statistically significant improvements in peak knee flexion during swing and knee range of motion of respectively  $10.6^\circ$  (sd 4.7,  $p=0.000$ ) and  $10.5^\circ$  (sd 6.2,  $p=0.001$ ) post-surgery, respectively. Hip kinematics showed no significant differences.

In addition, we found statistically significant improvements on the 6-minute walk test (42.5, sd 36.7,  $p=0.008$ ), 10-meter walk test (1.26, sd 1.4,  $p=0.030$ ), Timed up-and-go test (1.34, sd 1.18,  $p=0.009$ ), L-test (2.97 sd 2.85,  $p=0.014$ ) and on a subjective BORG scoring of foot clearance (1.8, sd 0.6,  $p=0.006$ ). No significant differences were found on other measured functional outcomes.

### **Conclusions**

Rectus femoris transfer is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics and a selection of functional outcomes. There are no detrimental side effects on hip kinematics.



## Introduction

Stiff knee gait is often observed in patients with upper motor neuron lesions such as stroke or cerebral palsy and was first described by Sutherland and Davids in 1993<sup>52</sup>. It is characterized by diminished and delayed peak knee flexion in swing and can lead to foot clearance problems, such as tripping, falling and energy-inefficient compensatory movements. Several factors contribute to stiff knee gait, but overactivity of the rectus femoris is considered as an important cause<sup>20,26,30,45,54</sup>. Several treatment options are available such as electrical stimulation of the hamstrings<sup>115</sup>, botulinum toxin in the rectus femoris or rectus femoris transfer. Botulinum toxin (BoNT) injection in the rectus femoris has shown to be an effective treatment option to improve peak knee flexion in swing in stroke<sup>35,43,44,116</sup>. Despite the positive effects of BoNT injections, there are some drawbacks. First, the duration of action is limited to approximately three months and secondly, decrease in effectiveness of the BoNT injection over time might be seen due to habituation<sup>42,169</sup>. To counteract these drawbacks, a permanent treatment option is the rectus femoris transfer<sup>32,45</sup>. During this surgical procedure, the distal rectus femoris tendon is transferred to the medial or lateral knee flexors to improve knee flexion during swing.

To our knowledge, there are only two studies evaluating the effect of rectus femoris transfer in stroke patients with promising but conflicting results. Namdari et al<sup>46</sup> found a non-significant increase on knee flexion of 25° while Vermeiren et al<sup>47</sup> found a significant increase on peak knee flexion of 19.9°. However, the studies have very limited qualitative measures of gait<sup>46</sup> and no<sup>47</sup> or very limited functional outcomes<sup>46</sup>. Furthermore, the previously conducted studies have a retrospective design and combined rectus transfer with other surgical procedures. These other surgical procedures included fractional lengthening of the vastus muscles<sup>46</sup> or lengthening of the gastrocnemius aponeurosis or Achilles tendon<sup>47</sup> which hinders the evaluation of the effect of the rectus femoris transfer alone. In addition, the study population consisted of a mix of stroke survivors with other diagnoses such as traumatic brain injury. Thus, little is known about the effect of an isolated rectus femoris transfer on knee and hip kinematics during gait and functional outcomes in a group of stroke survivors.

Therefore we performed an experimental study with two aims. The first aim was to evaluate the effect of an isolated rectus femoris transfer on kinematics of the knee and hip in stroke patients. The second aim was to evaluate the effect of rectus femoris transfer on functional outcomes.

## Methods

Participants were recruited between 2015 and 2020 from Roessingh, Center for Rehabilitation (Enschede, the Netherlands).

The inclusion criteria were: stroke survivors (at least 6 months post stroke), age over 18 years, able to walk independently with or without walking aids, a diminished peak knee flexion in swing ( $<50^\circ$ )<sup>52</sup> (as established by video observation) accompanied by muscle activity of the rectus femoris in the second part of initial swing and/or mid swing and willingness to provide written informed consent. The muscle activity of the rectus femoris was determined through surface Electromyography (sEMG) of the rectus femoris and vastus lateralis simultaneously to differentiate between true activity and cross-talk<sup>108,152</sup>. sEMG has been reviewed through visualisation of the signal, by an independent clinical expert in sEMG analysis (rehabilitation physician). Initial swing and midswing were determined as % of the gait cycle. Inclusion was checked by positive results of a BoNT injection in the rectus femoris using pre- and post motion analysis.

Exclusion criteria were: co-activation of the vastii in the second part of initial swing and/or midswing, presence of a reduced passive joint range of motion impeding walking or other neurological problems. During the study, participants were allowed to continue regular treatment. However, other treatments focused on the improvement of knee flexion were not allowed.

This study was conducted as an experimental study with a prospective design with pre- and post-intervention measurements. The study was approved by the local medical ethical research committee (MERC Enschede) and is registered in the Netherlands Trial Register (NTR 5129). Clinical trial registration: <https://trialssearch.who.int/Trial2.aspx?TrialID=NTR5129>.

Pre-surgery measurements were performed within 3 weeks before the transfer. Post-surgery measurements were performed between 6 and 7 months after the rectus femoris transfer. Collected data included 3D joint kinematics, determination of energy expenditure during the 6 minute walking test and functional outcomes. All data were collected on the same day. All data were analysed after the end of the study.

### Gait analysis

To determine 3D joint kinematics, an infrared opto-electronic 3D-motion analysis system (VICON MX + 8 MX13 cameras, frame rate 100 Hz; Vicon Motion Systems, Oxford, UK) was used with a standard marker placement<sup>157</sup> (lower-limb Plug-in-Gait model with knee alignment device). During gait analysis participants walked on a 10-meter walkway. Initial contact and toe off events were detected by using the ground reaction force of the force

plate. Outcome measures were calculated for each gait cycle and outcome measures were averaged afterwards. A minimum of 10 strides were analyzed for the data analysis. Participants walked at comfortable speed and used the same walking aids, orthoses and shoes during all data collection.

### **Kinematic outcome measures**

Sagittal kinematics of knee and hip were calculated with an inhouse MATLAB based software. Peak knee flexion and peak hip flexion were defined as the maximum amount of flexion during swing phase. Knee and hip range of motion was calculated as the difference between maximum extension in stance phase and maximum flexion in swing phase. Knee angular flexion velocity at toe off was calculated with a five point based calculation.



**Picture 1.** Surgical procedure

### **Energy expenditure**

After the gait analysis session, energy expenditure was measured using the Cosmed Kb2 system (Cosmed, Rome, IT) during the 6 minute walking test (6MWT) at a self-selected, comfortable speed on a circular track of 75 m. To determine steady state, a moving window of two minutes was shifted over the measurement<sup>158,159</sup>. This was done for five time blocks: 2-4 min; 2.5-4.5 min; 3-5 min; 3.5-5.5 min; and 4-6 min. To check for steady state, O<sub>2</sub> rate and Respiratory Exchange Ratio (RER) (ratio between VCO<sub>2</sub> and VO<sub>2</sub>) were averaged over these time blocks and were checked whether they stayed within the borders of variance of

20%<sup>160</sup>. Furthermore, the respiratory exchange (RER) was checked whether it was below 1 as this is the threshold between aerobic and anaerobic activity. For every individual patient, the five time blocks were checked for the steady state conditions and RER score. The time block for which the stated conditions were met for most patients was used in the analysis. The energy cost was computed by dividing O<sub>2</sub> rate by the walking speed (m/s) which, in turn, was computed by dividing the covered distance on the 6MWT by 360 seconds.

### **Functional outcomes**

Each participant completed the 6MWT<sup>170</sup>, Timed Up and Go Test (TUG)<sup>171</sup>, 10 meter walk test (10MWT)<sup>103</sup>, L- test<sup>172</sup>, Timed up stair test<sup>173</sup>, the Motricity Index (MI)<sup>174</sup>, Functional Ambulation Categories (FAC)<sup>175</sup> and the Rivermead Mobility Index (RMI)<sup>176</sup>. The Medical Research Council (MRC)<sup>177</sup> score was used to assess the strength of the hip flexors and knee extensors. Foot-clearance problems were evaluated with a 4 points BORG score of the subjective experienced self-rated number of tripping/stumbles a day. A score of 0 indicated zero tripping/stumbles, a score of 1 indicated 1 to 15, a score of 2 indicated 16 to 30 and a score of 3 indicated more than 30 tripping/stumbles a day. Finally, the Stroke Impact Scale (SIS)<sup>163</sup> was used to determine the level of participation of the subjects.

### **Surgical procedure**

The distal rectus femoris tendon of the affected side was separated from the vastii and was released from its insertion at the patella. The tendon was moved to the dorsal side of the leg and pulled around the medial hamstring. Afterwards the tendon was sutured with a vycyl 1.0 suture to itself. See picture 1.

### **Post operative protocol**

The first 10 days after surgery were used for wound healing. Weight bearing (with splint) was allowed from the first day after surgery onwards. If the pain allowed, patients were stimulated to exercise the knee without weight. Patients were able to walk without restrictions 6 weeks postoperatively.

### **Statistical analysis**

Normality testing for data distribution was performed using the Shapiro-Wilk test and visual inspection of histograms. Depending on the outcomes, a paired T-test or the Wilcoxon Signed Rank test was used ( $\alpha=0.05$ , two-sided testing).

For statistical analysis we used IBM SPSS statistics 19.0 for Windows (IBM Inc. Chicago, IL, USA).

### Power analysis.

An a-priori power analysis was difficult to perform due to the absence of effect sizes for an isolated rectus femoris transfer in stroke survivors. Therefore we decided to use an arbitrary convenience sample of 10 individuals for this exploratory trial.

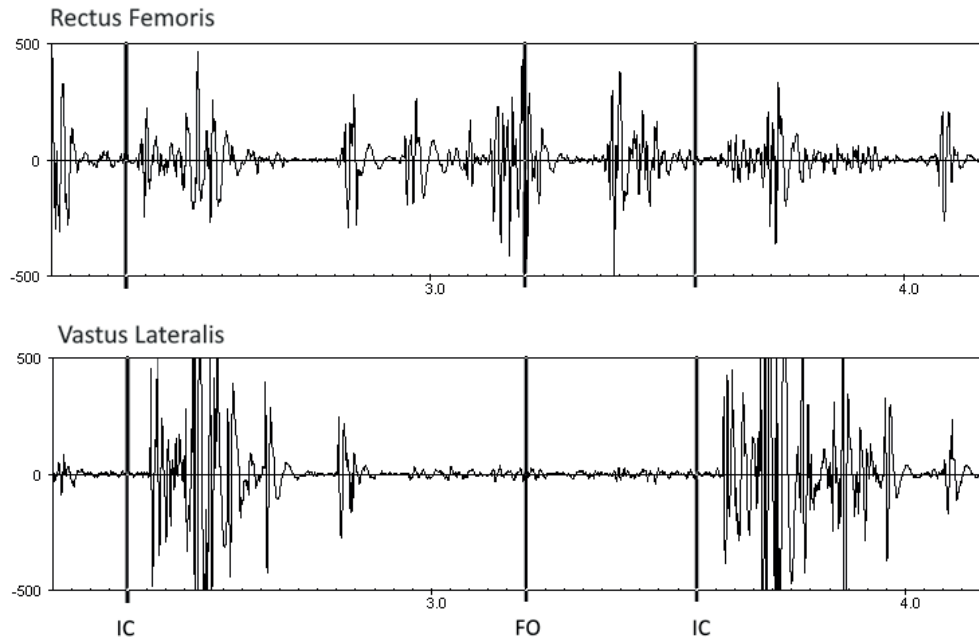


Figure 1. sEMG signals of the rectus femoris and vastus.

IC= Initial contact

FO = Foot off

## Results

Ten patients were included in the study. One patient dropped out due to the COVID-19 infection before the surgery. Data from this patient were not included in the analysis. The remaining 9 patients completed the study. Event adverse effects: One patient mentioned knee pain the first 5 days after surgery which was treated with non-steroidal anti-inflammatory drugs. One patient had a superficial wound infection for a week. There were no side effects mentioned by the patients as knee instability or buckling of the knee during the stance phase. All patients were guided by a physical therapist during the first 2-3 weeks after the surgery. No physical therapy was prescribed after these 2-3 weeks. No specific gait training was given in all 9 patients after surgery and afterwards. All surgical procedures were performed by a senior orthopedic surgeon (EZ).

Gait analysis, functional tests, energy expenditure and the analysis of the complete data set, were carried out by the same researcher (MT). Patient characteristics are shown in table 1.

**Table 1.** Patient Characteristics. FAC= Functional Ambulation Categories, SD : standard deviation.

Characteristics	
Participants /dropouts	10/1
Age in years, mean (SD)	48.4 (12.8)
Sex male / female	5/4
Paretic side left/right	6/3
Use of stick with/ without	2/7
Use of ankle foot orthosis with/ without	5/4
FAC, mean (sd)	4.2 (0.4)

### Kinematic outcome measures

Peak knee flexion during swing showed a mean significant increase of 10.6° (4.7 sd, p=0.000) and knee range of motion showed a significant increase in of 10.5° (6.2 sd, p=0.001) post-surgery. Knee flexion angular velocity at toe off and hip kinematics showed no significant differences. The results are shown in table 2.

**Table 2.** Kinematic outcomes.

Outcome measure (VICON)	Rectus Femoris Transfer		
	Pre Transfer mean value (SD) (range)	Post Transfer mean value (SD) (range)	Mean difference pre- post Transfer (SD)
Peak knee flexion in swing (degrees)	34.0 (11.8) (18.4 to 49.1)	44.7 (14.7) (27.4 to 67.3)	10.6 (4.7) P=0.000* CI (7.01 to 14.23) #
Knee range of motion (degrees)	32.7 (14.4) (10.5 to 59.1)	43.3 (18.7) (11.7 to 77.5)	10.5 (6.2) P=0.001* CI (5.78 to 15.41) #
Knee flexion angular velocity at toe-off (degrees/s)	81.6 (96.6) (-88.1 to 316.2)	127.3 (138.4) (-110 to 336.1)	45.6 (65.7) P=0.071 CI (-4.87 to 96.16) #
Peak hip flexion in swing (degrees)	39.9 (6.4) (30.9 to 51.8)	40.5 (5.9) (27.2 to 48.4)	0.5 (4.3) P=0.696 CI (- 2.73 to 3.89) #
Hip range of motion (degrees)	38.2 (6.8) (28.5 to 50.8)	40.5 (8.3) (27.9 to 53.4)	2.3 (3.9) P=0.101 CI (- 0.66 to 5.34) #
Walking speed (m/sec)	0.90 (0.21) (0.5 to 1.2)	1.00 (0.23) (0.6 to 1.3)	0.09 (0.15) P=0.093 CI (-0.02 to 0.22) #

SD= standard deviation, CI= confidence interval, \*= statistically significant, #=Paired student t test.

**Functional outcomes**

All functional walking performance tests showed a significant improvement. The walking distance on the 6MWT increased with 42.5 (36.7 sd,  $p=0.008$ ) meters and the time to complete the 10MWT, the TUG and the L-test decreased with 1.26 (1.4 sd,  $p=0.030$ ), 1.34 (1.2 sd,  $p=0.009$ ) and 2.97 (2.9 sd,  $p=0.014$ ) seconds, respectively. All patient mentioned that foot-clearance problems, as indicated by the number of tripping /stumbles, almost disappeared, and that walking was more automatically without thinking not to trip. (see table 3).

No significant differences were found on the Timed up stair test, MRC, MI, RMI, and the FAC. The SIS scores showed also no differences on the total score as well on the domain score. Results are shown in table 3.

**Table 3.** Functional outcomes.

Outcome measure	Rectus Femoris Transfer		
	Pre Transfer mean value (SD) (range)	Post Transfer mean value (SD) (range)	Mean difference pre- post Transfer (SD)
6 MWT (meter)	325.3 (80.2) (220 to 437)	367.8 (66.9) (242 to 455)	42.5 (36.7) P=0.008* CI (14.3 to 70.7) #
10 MWT (sec)	10.0 (1.8) (6.9 to 12.4)	8.8 (2.1) (6.5 to 12.7)	-1.26 (1.4) P=0.030 CI (-2.36 to -0.15) #
TUG (Sec, mean of 3 test)	12.1 (2.6) (8.4 to 17.2)	10.8 (2.3) (8.2 to 16.2)	-1.34 (1.18) P=0.009* CI (-2.25 to -0.43) #
L test (Sec, mean of 3 test)	26.25 (4.1) (21.4 to 34.6)	23.3 (5.0) (19.1 to 35.4)	-2.97 (2.85) P=0.014* CI (-5.16 to -0.77) #
Timed up stair test (Sec, mean of 3 test)	12.0 (4.6) (7.4 to 20.5)	11.8 (5.3) (7.0 to 21.7)	-0.23 (0.83) P=0.428 CI (-0.86 to 0.40) #
MI Total lower extremity (min-max, 0-100)	63.2 (12.6) (42 to 77)	65.2 (11.8) (44 to 75)	2.0 ( 15.9) P=0.673 ##
MI Hip (min max 0-33)	23.7 (2.6) (19 to 25)	25.0 (0.0) (25 to 25)	1.3 (2.6) P=0.157 ##
MI Knee (min max, 0-33)	24.3 (2.0) (14 to 33)	24.0 (5.1) (19 to 25)	0.3 (4.8) P=0.655 ##
MI Ankle (min-max, 0-33)	15.6 (9.0) (0 to 25)	14.9 (11.6) (0 to 25)	0.7 (11.3) P=0.892 ##
MRC Hip flexion (Range 0-5)	3.9 (0.3) (3 to 4)	4.0 (0.0) (4 to 4)	0.1 (0.3) P=0.317 ##
MRC Knee extension (Range 0-5)	4.4 (0.5) (4 to 5)	4.3 (0.5) (4 to 5)	0.1 (0.3) P=0.317 ##
Foot clearance BORG score, (Range 0-3)	2.0 (0.8) (4 to 5)	0.1 (0,3) (4 to 5)	-1.8 (0.6) P=0.006 * ##
FAC score (Range 0-5)	4.2 (0.4) (1 to 3)	4.2 (0.4) (0 to 1)	0.0 (0.5) P=1.0 ##
RMI (Range 0-15)	13.8 (0.6) (13 to 15)	13.9 (0.7) (12 to 15)	0.1 (0.6) P=0.564 ##
SIS (Total score)	318.9 (56.9) (229 to 384)	323.3 (58.1) (223 to 397)	4.4 (18.8) P=0.498 (CI -10.0 to 18.9) #

SD= standard deviation, CI= confidence interval, \*= statistic significant, . # =Paired student t test. ## =Wilcoxon signed rank test, 6MWT= 6 minute walk test, 10MWT=10 meter walk test, TUG=Timed Up and Go Test, MI=Motricity Index, MRC=Medical Research Council, FAC=Functional Ambulation Categories, RMI=Rivermead Mobility Index, SIS=Stroke Impact Scale.



### Energy expenditure

Due to technical problems with the cosmed equipment, data of only 7 participants are available. All 7 patients reached the established criteria of steady state and the RER value < 1 with the cosmed measurement. There was no significant change in energy cost and O2 rate when comparing the pre- and post-measurement. See table 4.

**Table 4.** Energy expenditure.

Outcome measure	Rectus Femoris Transfer		
	Pre transfer mean value (SD) (range)	Post transfer mean value (SD) (range)	Mean difference pre- post Transfer (SD)
Energy cost (ml/kg/m)	0.307 (0.04) (0.244 to 0.395)	0.301 (0.04) (0.249 to 0.372)	-0.005 (0.02) P=0.585 (CI -0.03 to 0.02) #
O2 Rate (ml/kg /min)	16.5 (2.8) (11.8 to 20.6)	17.4 (3.3) (12.3 to 21.0)	0.8 (1.3) P=0.121 (CI -0.3 to 2.0) #

SD= standard deviation, CI= confidence interval, \*= statistic significant. # =Paired student t test.

### Discussion

In this experimental study we investigated the effect of a rectus femoris transfer in stroke survivors walking with a stiff knee gait. The results showed a significant improvement in knee kinematics and functional outcomes. We found a significant increase of peak knee flexion during swing of 10.6° (4.7 sd, p=0.000) and a significant increase of knee range of motion 10.5° (6.2 sd, p=0.001) after surgery. In addition, we found significant improvements on the 6MWT, 10MWT, Timed up-and-go Test, the L test and the self-reported number of tripping/stumbles a day.

To the best of our knowledge, there are no other prospective studies that investigated the effect of the rectus femoris transfer in stroke survivors. This makes the comparison of our results to the existing body of knowledge difficult. We are aware of two retrospective studies in which the rectus femoris transfer was combined with other procedures in a more heterogenous group with diverse neurological disorders. Namdari et al<sup>46</sup> studied the effect of rectus femoris transfer combined with a fractional lengthening of the vastii in a group of adult stroke and brain injury patients. They reported a non-significant increase of knee flexion from 8° to 33°. Vermeiren et al<sup>47</sup> found a significant increase of 19.9° on peak knee flexion during swing and the significant increase of 20.7° in knee range of motion. They combined rectus femoris transfer with lengthening of the gastrocnemius or lengthening of the Achilles tendon in a group of 10 stroke survivors and brain injury patients. There is

abundant literature on the effect of the rectus femoris transfer in cerebral palsy were it is often part of single-event multi-level surgery. Most studies in cerebral palsy report an increase between 7°-11° in peak knee flexion<sup>32,57,178-181</sup>. Some studies report an increase between 12° and 26° in peak knee flexion<sup>30,139,182</sup>. There are also studies in cerebral palsy that reported no significant improvement<sup>183-185</sup> or even a decrease in peak knee flexion<sup>186,187</sup>. However, it is hard to translate these results in cerebral palsy to the stroke survivor population due to differences in age and the pathophysiology of stroke and cerebral palsy.

When comparing the results of the rectus transfer to the results of BoNT injection, we see that the significant increase of 10.6° peak knee flexion in our study is clearly more than the pooled significant increase of 7.4° peak knee flexion after BoNT injection found in the systematic review of Tenniglo et al<sup>116</sup>. It is also more than the significant increase of 6.7° after a BoNT injection in the rectus femoris in a randomized controlled in stroke patients<sup>188</sup>. The results of this study may suggest that rectus femoris transfer compared to BoNT injection of the rectus femoris, has a better effect on knee kinematics. A possible reason for this larger effect may be that the rectus is converted from a knee extensor to a knee flexor as originally intended by Perry et al<sup>45</sup> which is also shown by a study on cadavers<sup>40</sup>.

Since the rectus femoris is a biarticular muscle which also provides hip flexion, it is important to know if the rectus femoris transfer might lead to unwanted side effects on hip flexion kinematics. We found no changes in hip flexion kinematics as a result of the rectus femoris transfer which is in line with the study of Vermeiren et al<sup>47</sup>. In addition, this was also not reported by the numerous publications that studied the effect of a BoNT injection in the rectus femoris<sup>43,80</sup>. Finally, the study of Hemo et al<sup>139</sup> in which the effect of an isolated rectus femoris transfer in cerebral palsy was studied, did not find any influence on hip kinematics. Our results, together with previous findings, seems to indicate that there is no detrimental side effect of the rectus femoris transfer on hip kinematics.

On functional outcomes, we found significant improvements on the scores of the 6MWT, 10 MWT, Timed up-and-go test, L-test and self-perceived foot clearance. The significant improvement of 42,5 (36.7 sd) meter on the 6MWT can be assumed clinically relevant for the patient and is higher than the minimum clinically important difference of 34.4 meter that was reported by Tang et al<sup>164</sup>.

Reduction of perceived foot clearance problems such as tripping or stumbling is an important treatment goal in this group of patients. We found significant decrease in self-perceived foot clearance problems. All patients reported a reduction in tripping from an average of 15 to 30, to almost zero incidents per day and reported that walking is more automatically without thinking not to trip. All patients were satisfied with their clinical and functional outcomes, which is in accordance with the study of Namdari et al<sup>46</sup>. Drefus et al<sup>180</sup>

and Thawrani et al<sup>189</sup> also mentioned fewer foot clearance problems such as less tripping in their study in cerebral palsy. The reasons for the improvements in foot clearance could be attributed to the increase in knee flexion which normally gives an increase in foot/ankle lift from the ground. This can reduce the functional foot clearance problems like stumbling or tripping. Whether this link exists, should be studied in future research.

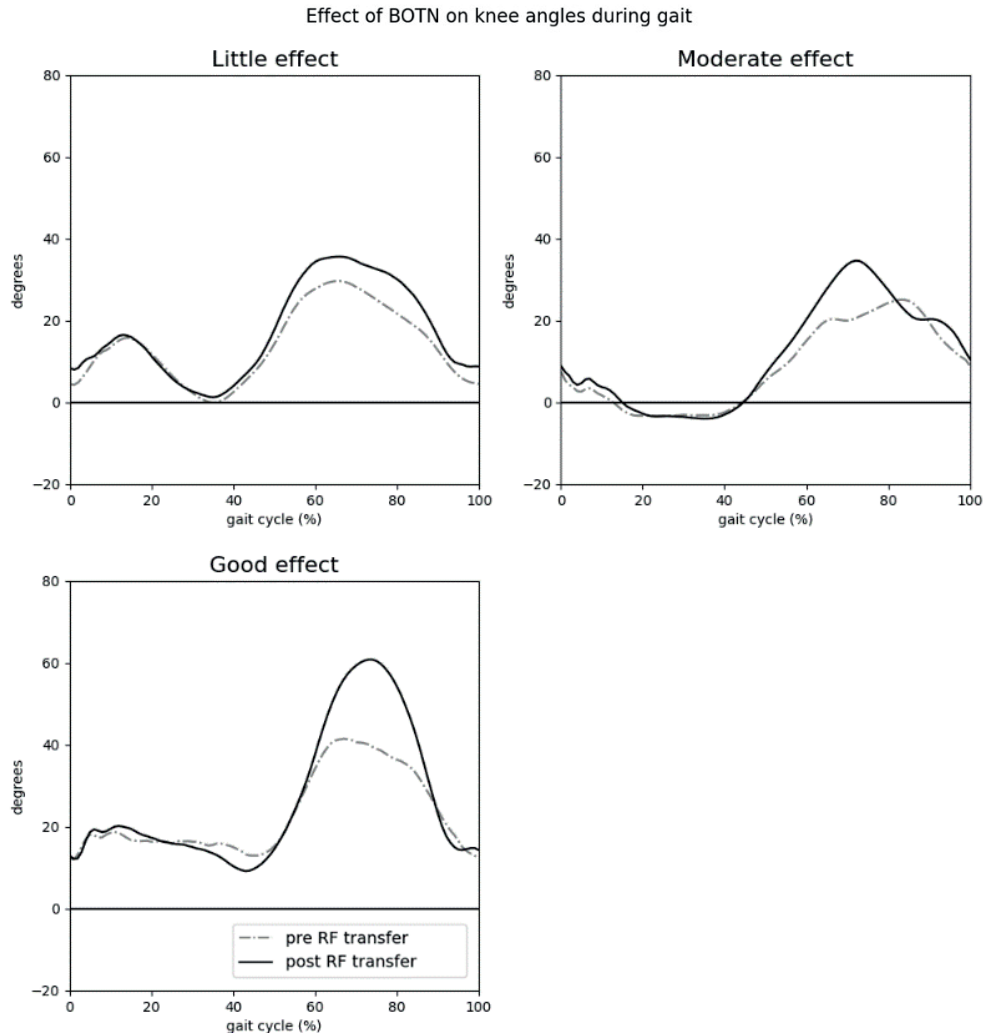


Figure 2. Effect of rectus femoris transfer on knee kinematics

Our positive findings on knee kinematics did not translate to all selected functional outcomes. We found no significant differences on more general functional outcome measures such as the FAC, RMI, MI, MRC and SIS scores. This partial discrepancy between

the knee kinematics and the functional outcomes may be explained by methodological issues. For example, the used functional outcome measures may not be sensitive or specific enough to measure difference on functional abilities after rectus femoris transfer. The SIS and RMI assess more global function whereas the rectus femoris transfer has a more local effect. This local effect may have had a limited effect on overall functioning because other mobility related issues were still present after the rectus femoris transfer. Future research can focus on developing new functional outcomes or questionnaires for establishing the potential effect of interventions aimed at treating stiff knee gait. For example, we measured foot clearance problems like tripping and stumbling with a subjective BORG questionnaire and not with an objective measurement. New objective functional measurements in everyday life are necessary to confirm the improvement in foot clearance. New specific measurements should therefore also focus on other functional walking tasks like turning or obstacle avoidance.

Since little research has been done on rectus femoris transfer in stroke patients and determinants for success are not yet exactly known (See figure 2), we advise to establish the role of rectus femoris in stiff knee gait with a reversible BoNT injection if a rectus femoris transfer is considered.

Furthermore, our criterium for overactivity of the rectus femoris is related to prolonged activity in initial and midswing. However, as the function of the rectus femoris, in normal gait, is to prevent excessive knee flexion during initial swing, one may speculate that all rectus femoris activity has no function in patients walking with a stiff knee gait because this excessive knee flexion is, per definition, absent. This could indicate that the inclusion for a treatment option on influencing overactivity of the rectus femoris can be expanded to not only abnormal activity in initial and midswing but also to normal rectus activity in preswing and initial swing. This line of thought could be investigated in future research.

Future research can also focus on the different methods of surgery to influencing the muscle activity of the rectus femoris tightening.

### **Strengths and weakness of the study.**

A major strength of the study is the prospective study design which is, as far as we know, the first on evaluation of a rectus femoris transfer in a group of stroke survivors. Furthermore, the use of both kinematic variables and functional outcomes and the evaluation of a solitary rectus femoris transfer without other surgical procedures provided results of the selective effect of this procedure in a precise manner.

A limitation of the study is our small sample size and the uncontrolled study design. This could have introduced bias in the study and our study may have been underpowered for finding an effect on several of the studied outcome parameters. Furthermore, several of the used functional outcomes may not be specific or sensitive enough to quantify an effect of

the rectus femoris transfer. We also used the BORG scale to quantify tripping/stumbling, although the validity of this questionnaire was not tested.

## **Conclusion**

This experimental study showed a significantly increase in knee kinematics with no detrimental side effects on hip kinematics after a rectus femoris transfer surgery. On functional outcomes, we found functional improvements on gait parameters. The 6MWT, 10 MWT, TUG, L-test and self-perceived foot clearance all improve significantly. Rectus transfer surgery is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics and a variety of functional outcomes. More research is necessary to confirm our findings.

## **Acknowledgments**

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The authors declare that there are no conflicts of interest.

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# 7

## General Discussion

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*“Super super superrrr.... Thanks, the result is huge, from 70 meters to 15 km walking without looking down when walking, I would do it again in a second”.*

---

This is the quote from the same person mentioned in the introduction.

It expresses a personal experience after a rectus femoris transfer for a patient walking with a stiff knee gait.

The general aim of this thesis was to study the effectiveness of different treatment options in stroke patients walking with a stiff knee gait.

In this last chapter of the thesis, the main findings of the individual chapters are given and discussed. First a systematic review gave insight in the studied effect of chemodenervation of the rectus femoris. After that, determination of rectus femoris overactivity using the Duncan Ely is discussed. Subsequently, the three studied treatment options are chronologically discussed in relation to each other and in relation to previous work. Next, the strengths and weaknesses of the performed research are discussed. Finally, the implication for clinical practice and future research are presented.

### **Systematic review**

While the efficacy of Botulinum toxin (BoNT) injections to reduce abnormal activity (spasticity) has been reported in literature<sup>155</sup>, inconsistent results were found for kinematics and functional outcomes in stroke patients walking with a SKG. The systematic review (chapter 2) gave insight in the effect of chemodenervation of the rectus femoris on knee kinematics, functional outcomes and energy cost. Results showed that knee kinematics (peak knee flexion and/or knee range of motion (ROM)) improved significantly in all 12 included studies. Data pooling of included studies investigating neuromuscular or motor branch block indicated a significant improvement in peak knee flexion of 7.39° and 9.35°, respectively. Data pooling of knee ROM, functional outcomes and energy cost showed no significant differences. Moreover, the systematic review showed that the available literature consists only of uncontrolled studies with low methodological quality which could have influenced the results of the individual studies. The systematic review also revealed that two different methods were used to detect overactivity of the rectus femoris, being surface electromyography (sEMG) and the Duncan Ely test.

### **Determine rectus femoris overactivity.**

The question is whether we can use the clinical Duncan Ely test to predict overactivity of the rectus femoris during walking. In chapter 3 we compared the clinical Duncan Ely test with



the gold standard, sEMG, to determine overactivity of the rectus femoris. This study showed that the Duncan Ely test has no diagnostic value for predicting abnormal activity of the rectus femoris in stroke survivors with stiff knee gait. The study confirms the notion that it is disputable whether a clinical test that aims to establish overactivity or spasticity performed in a static position can provide information about how muscles act in dynamic situations. We recommend to stop using the Duncan Ely test for this purpose and use sEMG instead.

The Duncan Ely study showed that the test has no value for determining abnormal activity of the rectus femoris during gait in stroke survivors and that using this test can lead to incorrect identification of abnormal rectus femoris activity in this patient group. This conclusion was adopted in another study<sup>190</sup> on stiff knee gait where the Duncan Ely test was assessed in clinical routine but not used as an inclusion criteria for the study for measuring rectus femoris muscle activity.

Our criterium for overactivity of the rectus femoris is related to prolonged activity in initial and midswing. However, as the function of the rectus femoris, in normal gait, is to prevent excessive knee flexion during initial swing, one may speculate that all rectus femoris activity in stroke survivors has no function because in stroke survivors walking with a stiff knee gait this excessive knee flexion is, per definition, absent. This could indicate that the inclusion for a BoNT injection in the rectus femoris can be expanded to not only abnormal activity in initial and midswing but also to normal rectus activity in preswing and initial swing. This line of thought could be investigated in future research.

### **Hamstrings stimulation**

In chapter 4 we found that electrical stimulation of the hamstrings, gives an improvement of 8.7° in peak knee flexion when comparing walking without electrical stimulation at inclusion to walking with electrical stimulation after 5 weeks of training. (Intervention effect).

The results also showed an increase of 3.1° in peak knee flexion comparing walking without electrical stimulation at inclusion to walking without electrical stimulation after 5 weeks of training. (Therapeutic effect).

Furthermore, walking speed showed a significant increase of 0.11 m/s as intervention effect and 0.05m/s as therapeutic effect.

Looking at the results in more detail, we see that the good responders to electrical stimulation seem to be patients with low neurological impairments and that the effect of electrical stimulation of the hamstrings on knee kinematics can be predicted within one session.

While we found positive results on knee kinematics and walking speed when using the electrical stimulation, the working mechanism is not fully clear. Hypothetic reasons for the

working principle of hamstrings stimulation could be that the stimulation of knee flexors in swing biomechanically assists with knee flexion. Other reasons can be that the electrical stimulation stimulates a withdrawal reflex which gives knee flexion or the stimulation works as a sensory reminder to flex the knee during walking. However, the exact workings principle remain unclear and can be a topic for future research.

### **Chemodenervation**

One of the treatment options for stiff knee gait is a chemodenervation of the rectus femoris by means of a BoNT injection. Our systematic review (chapter 2) showed that the available literature about chemodenervation of the rectus femoris, consists of only uncontrolled studies with average to low methodological quality which could have influenced the results of the individual studies.

To address these methodological issues, we conducted a triple-blind randomized controlled trial (RCT) to explore the effect of BoNT injection into the rectus femoris on stiff knee gait.

Because chapter 3 showed that the Duncan Ely test has no diagnostic value for predicting abnormal activity of the rectus femoris we based our inclusion on sEMG and not on a positive score on the Duncan Ely test. We believe that this has led to a more precise inclusion of individuals that potentially could benefit from the BoNT injection. This seems to be confirmed by the fact that studies, looking at the effect of BoNT in the rectus femoris, that base their inclusion on the Duncan Ely test generally show a weaker effect on knee kinematics<sup>23,75</sup> when compared to studies that based their inclusion on EMG<sup>43,80</sup>.

The results of the RCT study (chapter 5) showed that BoNT injections in the rectus femoris is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics. It showed no detrimental effects on hip kinematics and no statistically significant and/or clinical important differences on the measured functional outcomes such as the 6 minute walking test, timed up and go test, 10 meter walking test, Stroke Impact Scale (SIS) or Rivermead mobility index.

When looking at the results of the functional outcomes in more detail, several reasons for not showing an improvement on functional outcomes are available.

One explanation might be that the effects are too small to impact these functional outcomes. Secondly, the used functional outcome measures may not have been able to capture the increase in knee kinematics possible due to a lack of responsiveness.

Despite the fact that we found no functional improvements with the used functional outcome measures, patients were enthusiastic about the effect of the BoNT injections. They mentioned improvements in functional abilities, in foot clearance like no more tripping or stumbling or improvements in gait initiation, getting in and out of the car, obstacle avoidance and automatically walk and turn. A subjective experience of a lighter leg was also

mentioned. All of these items were not captured by the functional outcome measures of mobility or questionnaires that we used. Furthermore, we did not collect these data in a standardized way, making it anecdotal evidence at best.

This raises the question of whether this treatment option should be part of the toolbox used in rehabilitation if there are no differences on the used functional outcomes.

We believe that it is a valuable treatment option to improve knee kinematics. To study the effect on functional outcomes, more research is necessary with other functional outcome measures that may be able to capture the effect of the BoNT injection. These include, for example, the measurement of foot clearance or tripping in daily live activities using inertial sensors.

Another outcome of interest is the change in gait adaptability in individuals after stroke after a BoNT injection in the rectus femoris.

### **Rectus femoris transfer**

One of the disadvantages of BoNT injection of the rectus femoris is that injections need to be placed periodically and that the treatment effect reduces over time. To counteract these disadvantages, a rectus femoris transfer may be a viable treatment option. In Chapter 6 we studied the effect of a rectus femoris transfer on knee kinematics and functional outcome in adult stroke patients with a stiff knee gait. The results showed a statistically significant increase of 10.6° in peak knee flexion and 10.4° in knee range of motion. On functional outcomes, we found statistically significant improvements on the 6 MWT, 10-meter walk test, Timed up-and-go test, L-test and on the subjective BORG scoring of foot clearance.

The increase of 10.6° in peak knee flexion is higher than the 6.7° increase in peak knee flexion we found in the BoNT study. Reasons for this larger effect may be that the rectus femoris is converted from a knee extensor to a knee flexor as originally mentioned by Perry et al<sup>45</sup> which is also confirmed by a study on cadavers<sup>40</sup>.

A reason for the larger effect of the rectus femoris transfer comparing to the BoNT injection can also be a selection bias because the patient selected for the rectus femoris transfer were preselected based on the effect of BoNT injection on knee kinematics and patients' subjective experiences. Since rectus femoris transfer is an irreversible treatment option one should be certain of the role of rectus femoris overactivity in stiff knee gait. Therefore, all 9 participants in the rectus femoris transfer study received a BoNT injection before the rectus transfer.

Comparing the functional outcomes of the rectus femoris transfer to the BoNT injection we see a significant increase on the 6 MWT, 10-meter walk test, Timed up-and-go test, L-test and on a subjective BORG scoring of foot clearance after rectus femoris transfer. After the

BoNT injection, there was only a statistically significant increase on the 6 MWT. One of the reasons for this difference can be that the higher increase in peak knee flexion of 10.6° after the rectus femoris transfer is large enough to be captured by the used functional outcomes measurements.

Before the start of the BoNT study we did not know that most of the improvements patients mentioned are on functional abilities not captured by often-used functional outcomes measurements (eg foot clearance, gait initiation getting in and out the car). For the rectus femoris transfer study, we therefore added a self-reported BORG-score for foot clearance. This questionnaire showed a statistically significant change after the rectus femoris transfer. However this questionnaire is not validated for this specific purpose. Future research may focus on validating the self-reported BORG-score for foot clearance in stroke patients. It can also focus on measuring foot clearance in the gait lab and during activities of daily living.

As was the case for the BoNT injection, one may once again question whether the rectus femoris transfer should be part of the treatment toolbox used during rehabilitation care. We believe that this is the case. The rectus femoris study showed an improvement in knee kinematics and on a selection of functional outcomes, making it a valuable treatment option. Future research could focus on functional outcomes that focus on more complex activities of daily living.

### **Linking patients characteristics to effect of the three treatment options**

Finding patients characteristics that can be linked to the effect of the treatment options is of importance because for all three treatment options we saw that the effect ranged from little effect to a good effect in. Based on our studies and results, it is unclear whether there is a relation between specific patient characteristics and the treatment effect. One of the reasons for the variability in effect can be the underlying mechanisms involving the pathophysiology of stiff knee gait. It could be related to a lack of push of power at the end of the stance phase<sup>22,25-27</sup> or insufficient hip pull off power at to off<sup>28,29</sup> or increased forces generated by the vasti<sup>29</sup>. For the hamstrings stimulation it seems that the patients with mild neurological impairments may have a good reaction on the stimulation. One may hypothesize that individuals with mild neurological impairments respond differently to a BoNT injection or rectus femoris transfer compared to patients with severe neurological impairments.

We did not investigate the relation between patients characteristics (eg the different underlying mechanisms of stiff knee gait) and the effect of the treatment options also because of the low patient numbers. Whether relations between patient characteristics and treatment effect exist, which patient characteristics are of influence, could be a topic for future research with more patients and in a standardised research.

### **Comparing the three treatments**

All three treatment options were well tolerated by stroke survivors. Comparing the three treatment options on knee kinematics and functional outcome, rectus femoris transfer showed the highest rates of improvement in knee kinematics with statistically significant and clinically relevant changes on functional outcomes. In this respect, the comparison showed a preference for the rectus femoris transfer.

When looking at the indication setting for the three treatment options, we see that electrical stimulation of the hamstring muscles might be suitable for all patients, irrespective of the cause of stiff knee gait. This means that this treatment option can potentially be used for a larger group of patients.

Despite the positive results in peak knee flexion and the fact that hamstring stimulation is relative cheap, easy to perform and the effect on knee kinematics can be predicted within one session, it is rarely used in clinical practice due to practical problems. These problems include repeated donning and doffing, skin irritation or displacement of the electrode after sitting down. In addition, the reimbursement of the electrostimulation devices is still an issue that barriers implementation in clinical practice. If these practical problems can be solved, hamstring stimulation can be a valuable and practical treatment option for stiff knee gait.

Regarding the BoNT injection and rectus femoris transfer we see the indication setting is related to overactivity of the rectus femoris during pre-swing or swing. This means that only patients with overactivity of the rectus femoris are eligible for the latter treatment options.

The practical problems mentioned with hamstring stimulation are not present by the BoNT injection and rectus femoris transfer. However, it requires repeated injections or a surgery and not everyone will be able or want to go through the injection/surgical route.

Furthermore, one may hypothesize that the rectus femoris transfer is one-time treatment and its effect will last longer than hamstrings stimulation and a BoNT injection. In addition, for the different treatment choice, patients preference plays also an important role.

### **Strengths and Limitations of the thesis**

A major strength is that the research questions were based on questions that originated from clinical practice and the results are useful for daily clinical practice.

Another strength of the thesis is that we used kinematic outcomes and functional outcomes that are relevant for clinical practice. Furthermore we used a measurement protocol with the same core set of kinematic in the different treatment studies and

functional outcomes in the BoNT and rectus femoris study. This offers the possibility to compare the effect of the different treatment options.

We included a homogeneous group of chronic stroke patients with a functional ambulation score of 4 or more. This means that the results can be transposed to this selected group of stroke patients. On the other hand this is also a limitation, as we do not know what the efficacy of the studied treatment options are for (sub-)acute stroke survivors and/or stroke survivors with lower functional ambulation category scores.

In addition, all three treatments were isolated interventions and not multilevel treatments. This provided insight into the selective effect of the treatment in a precise manner.

One of the limitations is the selection of the used functional outcomes. The selection of functional outcome measures were done with care and those selected are widely used and/or recommended <sup>191</sup> in studies with stroke patients. During and after the performed studies, it appeared that the found kinematic improvements did not always translate to improvements on functional outcomes.

This raises the question of whether the measurement tools used are the right measurement tools to capture the changes. Especially as the patients themselves were enthusiastic about the effect of the BoNT injections and rectus femoris transfer and reported many (anecdotal) effects such as fewer stumbles and trips. In this context, it is important to mention that we were not able to directly assess foot-clearance, which could have objectively captured the important changes in stumbling and tripping.

In the BoNT study and rectus femoris transfer study, we focused on rectus femoris overactivity as the main cause of stiff knee gait. We are aware of the fact that there are more reasons for stiff knee gait and therefore other possible treatment options exist. Possible other reasons for stiff knee gait are activity of the vastii, a lack of pull off by the hip flexors or a lack of push off by the ankle plantar flexors. Previous research <sup>192,193</sup> studied electrical stimulation of the gastrocnemius to increase knee flexion. In this study, no effects were found. To support hip flexion, the Hip Flexion Assisted Device (HFAD) and EXO Band are possible treatments to improve hip flexion and stiff knee gait.

Another limitation is the limited sample size in the three treatment studies. However, an a-priori power calculation for the BoNT study indicated a sample size of 26 patients which has been reached in this study. An a-priori power analysis for the hamstrings study and rectus femoris study was difficult to perform due to the absence of effect sizes in existing literature. Therefore we decided to use an arbitrary convenience sample (of respectively 20 and 10 individuals) for these studies.

Furthermore the exploratory study design of the hamstrings study and rectus femoris transfer study is a limitation. It was not possible to blind the subjects and researchers for the treatment option which introduced a potential risk of bias.

Finally we did not take patients' subjective experiences into account in the various studies. Along the process however we experienced the importance of these patients' subjective experiences for clinical decision making, for example to repeat the BoNT injection.

### **Implications for clinical practice**

In this thesis, we studied the effects of three different treatment options for stiff knee gait. The posed research questions came directly from clinical practice and the research design (with exception of the RCT) was strongly related to clinical practice. The results of the thesis can therefore be directly applied in clinical practice. All three treatment options are currently used in the clinical setting as a regular treatment option, However, in clinical practice, hamstring stimulation is only used occasionally. Hamstrings stimulation has the advantage that within one intake session it is clear what the effect can be. Despite the occasional use of hamstrings stimulation, this treatment option is commercialized by BioNess in the L300-Go where hamstrings stimulation can be combined with stimulation of knee extension. Future research can focus on solving the practical problems of hamstrings stimulation (eg skin irritation, electrode displacement), to make it a more feasible and clinically used treatment option.

One should realize that the outcome of a static test to assess overactivity (spasticity) of a muscle might not be representative for the overactivity or spasticity during a dynamic task as walking. Our Duncan Ely study contributes to the ongoing discussion on what to do with other clinical static muscle tests of spasticity. The main question whether a static muscle test can predict overactivity or spasticity of this muscle during a dynamic task is unknown and should be further elaborated upon in future research.

This thesis showed that there is no detrimental side effect on hip kinematics after a BoNT study and the rectus femoris transfer. In clinical practice, decrease of hipflexion can be a reason for caution for a BoNT injection. Based on the results of this thesis, this caution seems not warranted.

### **Important Clinical Message**

We recommend stopping use of the Duncan-Ely test to predict rectus femoris overactivity during swing, and instead use surface electromyography.

Hamstring stimulation is a valuable treatment option for stroke patients to improve knee kinematics. The effect can be predicted within one session.

BoNT injection in the rectus femoris is a valuable treatment option for stroke patients to improve knee kinematics. This treatment option seems viable for a large number of stroke patients with abnormal activity of the rectus.

To study the effect of the BoNT injection, measuring knee kinematics is recommended. To study the effect on functional outcomes, more research is necessary with different functional outcome measures that may be able to capture the effect of the BoNT injection.

Rectus femoris transfer is a valuable treatment option for stroke patients to improve knee kinematics and a selection of functional outcome. It can be a next irreversible step after the BoNT injection to counteract drawbacks as the limited working time or habituation of the BoNT injection.

If a rectus femoris transfer is considered, we recommend to also establish the role of rectus femoris overactivity in stiff knee gait with a BoNT injection.

### **Future research**

An often made remark by patients after the BoNT injection or rectus femoris transfer is an improvement in functional outcome such as tripping and stumbling. The reasons for these improvements in foot clearance could be caused by the increase in knee flexion. Whether this relation exists, should be studied in future research. However, with the current outcome measures we were not able to directly assess foot clearance. Future research should focus on directly measuring foot clearance with, for example, inertial sensors. Future research can also focus on developing questionnaires regarding the mentioned functional outcomes by patients like tripping or stumbling, improvements in gait initiation, getting in and out of the car, subjective experience of a lighter leg, obstacle avoiding, automatically walk and turn.



Looking at the mentioned experience of patients to repeat the BoNT injection, we notice that there is sometimes a discrepancy between patients subjective experiences and the improvement in knee kinematics. This can be a topic for future research.

This thesis showed that the effect of the three treatment ranged from little effect to good effect. For clinical practice it is important to be able to select the patients that will have good treatment effects. Therefore, future research may focus on the relation between patients characteristics and the prediction of these treatment effects. In this light future research may also focus on the underlying mechanisms involving the pathophysiology of stiff knee gait as a lack of push of power or insufficient hip pull off power. It may also focus on the role of the vastii in stiff knee gait and the possible effects of a chemodenervation of these muscles.

Future research can focus on the comparison between the BoNT injections and rectus femoris transfer on individual patient level and can focus on possible reasons for the larger effect of the rectus femoris transfer.

Furthermore, future research could focus on long-term effects and cost effectiveness of hamstrings stimulation, BoNT injections and the rectus femoris transfer to treat stiff knee gait.

Zijn in this thesis we focused on three treatment options for stiff knee gait. Future research can also focus on new treatment options. For example an external motorized knee flexion device, a hip flexion device or ankle plantair flexion device.



**References**

**Summary**

**Samenvatting**

**Dankwoord**

**About the author**

**Journal publications**

**Progress Range**

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## Summary

Stroke is a disorder of the central nervous system of vascular origin being either ischemic (80%) or hemorrhagic (20 %) with a large variety in the clinical presentation depending on the stroke characteristics as location and severity and age of the patient. The functional consequences are often a combination of cognitive, emotional, sensory and motor impairments will lead to limitations in daily life. An important goal in stroke rehabilitation is regaining the ability to walk again.

In stroke patients one major problem with walking is the ease of foot clearing the floor in swing. These so called foot clearance problems can be caused by a decrease or diminished knee flexion in swing. This so called stiff knee gait or stiff legged gait is one of the most commonly observed gait disorders and affects approximately 60 % of the stroke patients with gait disorders.

The pathophysiology of stiff knee gait is only partly understood and several hypotheses involving the ankle, hip or knee joints are postulated in the literature. Although the exact mechanisms of stiff knee gait remains unclear and seem to be multifactorial, abnormal activity of the rectus femoris during swing is a frequently mentioned cause of stiff knee gait.

There are two options available for the assessment of abnormal rectus femoris activity: surface electromyography (sEMG) and the Duncan Ely test. The generally accepted gold standard is sEMG of the rectus femoris during dynamic gait analysis. The second option is the Duncan Ely test, which is part of a routine clinical examination of muscle tone. However, whether the Duncan Ely test is a useful test in stroke patients to predict abnormal rectus femoris activity during swing is unknown. In literature there are different treatment options aimed at reducing stiff knee gait described, including electrical stimulation of the calf and/or hamstring muscles, chemodenervation of the rectus femoris, and rectus femoris transfer. Although, these three treatment options are mostly used in scarce research studies with other diagnose groups, they are not often used in clinical daily practice in stroke patients.

Important questions like what is the solitaire effect of functional electrical stimulation of the hamstrings in stroke patients is unanswered.

Regarding the chemodenervation of the rectus femoris: in literature there are a few articles present that studied the effect of Botulinum toxin (BoTN) injection in the rectus femoris in stroke patients. These studies showed conflicting results. A systemic review can give more insight in the effect of a chemodenervation injection in the rectus femoris. Most of the chemodenervation studies are uncontrolled studies. This makes a randomized controlled trial to the effect of a chemodenervation injection in the rectus femoris without bias desirable.

Regarding the next step after a BoNT injection, the rectus femoris transfer, there is need for a clear answer on the effect of this treatment option.

As presented in **chapter 1**, the general aim of this thesis was to study the effectiveness of different treatment options in stroke patients walking with a stiff knee gait.

The focus of this thesis will be on the following questions:

1. What is the current body of evidence of the effect of chemodenervation of the rectus femoris in stroke patients walking with a stiff knee gait?
2. What is the diagnostic value of the Duncan Ely test in predicting abnormal rectus femoris activity during gait in stroke patients walking with a stiff knee gait?
3. What is the effect of functional electrical stimulation of the hamstrings in stroke patients walking with a stiff knee gait?
4. What is the effect of Botulinum toxin injection in the rectus femoris in stroke patients walking with a stiff knee gait measured in a randomized controlled trial?
5. What is the effect of a rectus femoris transfer in stroke patients walking with a stiff knee gait?

In **chapter 2** the results of a systematic review to determine the effect of Motor Branch Block (MBB) or NeuroMuscular Block (NMB) of the rectus femoris on knee kinematics and functional outcome are presented.

A total of nine articles were included describing 12 studies. Knee kinematics (peak knee flexion or knee range) during swing improved significantly in all the included studies.

Furthermore, a pooled data analysis in stroke patients showed a significant improvement in peak knee flexion after a MBB and after a NMB. The effect on functional outcomes and energy cost remains unclear.

When intervening on the rectus femoris as part of the treatment of stiff knee gait, it is important that this muscle shows abnormal or overactivity during the swing phase. In **chapter 3** we compared the outcomes of the gold standard assessment, which is sEMG during dynamic gait analysis, to the outcomes of the Duncan Ely test. We included 95 stroke survivors walking with a stiff knee gait. The results showed that the Duncan Ely test is not better than random guessing to predict rectus femoris overactivity. Possible reasons for the low correlation is the fact that, the Duncan Ely test is a subjective assessment, the Duncan Ely test might also test other knee extensors and hip flexors and/or that the static Duncan Ely test has a limited relation to a problem occurring during a dynamic situation.

We therefore recommended stop using the Duncan Ely test to predict rectus femoris overactivity and use sEMG obtained during walking.



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In **chapter 4** the effects of functional electrical stimulation of the hamstrings on knee kinematics in 16 patients are presented. Positive effects on knee kinematics were found after five weeks, three times per week for one hour of training with hamstrings stimulation. Instrumented gait analysis were performed before and after the five weeks of training. Walking with electrical stimulation after 5 weeks of training showed an increase in peak knee flexion of 8.7° compared to walking without electrical stimulation at the start of the 5 weeks of training (intervention effect). Walking without electrical stimulation before the 5 weeks training compared to walking without electrical stimulation after 5 weeks of training (therapeutic effect) showed an increase of 3.1° in peak knee flexion.

Furthermore, it seems that patient with low neurological impairment respond better to hamstrings stimulation, and that the intervention effect of hamstrings stimulation can be predicted within one try out session.

The systemic review showed also that all studies reported in literature so far are uncontrolled or nonrandomized studies or do not have a (triple) blind design which could have biased the results. In **chapter 5** the results of our triple blind randomized controlled trail are presented. In this study, we included 26 stroke patients who received a (BoNT) injection and a placebo injection in the rectus femoris. 3D gait analysis and functional outcome measures and energy cost of walking were collected before and after the injections. The wash-out period was five months. The results showed that a BoNT injections in the rectus femoris gives a significant increase of peak knee flexion and knee range of motion of 6.7° and 4.8° respectively compared to the placebo treatment. Hip kinematics did not show any changes. On functional outcomes, we only found a significant improvement in the 6 minute walking test (6 MWT) of 18.3 meter which does not exceed the minimal clinically important difference of 34.4 meter.

The results showed the BoNT injection is a valuable clinical treatment option to improve knee kinematics for stroke patients walking with a stiff knee gait. The results also showed that the changes in knee kinematics are not captured by de common used functional outcomes such as walking speed, energy cost or self-reported questionnaires. This could indicate the need for different functional outcome measures that can capture the effects in knee kinematics. Based on patient experience, there are indications that foot clearance can be an important functional outcome.

To counteract the drawbacks from a BoNT treatment, such as a limited effect time and habituation, a permanent treatment option to alter the function of the rectus femoris is the rectus femoris transfer. In **chapter 6** we presented the results of our study on the effect of a rectus femoris transfer on knee and hip kinematics, functional outcome measures, self-reported questionnaires, and a BORG questionnaire that focused on foot clearance. Ten patients were included. During the surgical procedure, the distal rectus femoris tendon was



transferred to the medial knee flexors to improve knee flexion during swing. The results showed a significant increase in peak knee flexion and knee range of motion of 10.6° and 10.5° respectively, with no changes in hip kinematics. Furthermore, we found statistically significant improvements on the 6 MWT, 10 meter walk test (10 MWT), Timed up-and-go test, L-test and on the BORG questionnaire of foot clearance. The significant change on the 6 MWT of 42.5 meter is clinically relevant for the patient. The significant difference on the 10 MWT, Timed up-and-go and L-test are 1.26 sec, 1.34 sec and 2.97 sec respectively. The results showed that rectus femoris transfer surgery is a valuable treatment option for stroke patients walking with a stiff knee gait to improve knee kinematics and several functional outcome measures.

Finally, the thesis concludes with a general discussion in **chapter 7** In this chapter the main findings are summarized and discussed together with strengths and limitations of the studies. Emphasis is given on the implications and recommendations for clinical practice.

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## Samenvatting

Een Cerebro Vasculair Accident (CVA) is een aandoening van het centrale zenuwstelsel van vasculaire oorsprong die ofwel ischemisch (80%) of hemorragisch (20%) is met een grote variëteit in het klinisch beeld afhankelijk van de kenmerken van de CVA zoals locatie, ernst en leeftijd van de patiënt. De functionele gevolgen zijn vaak een combinatie van cognitieve, emotionele, sensorische en motorische beperkingen die leiden tot beperkingen in het dagelijks leven. Een belangrijk doel van revalidatie na een CVA is om weer te kunnen lopen. Het gemakkelijk kunnen doorzwaaien van het aangedane been tijdens de zwaafase van het lopen is vaak een groot probleem met als risico struikelen of vallen. Deze zogenaamde foot clearance problemen kunnen worden veroorzaakt door een verminderde kniebuiging tijdens het zwaaien. Deze stiff knee gait is een van de meest voorkomende loopstoornissen en komt voor bij ongeveer 60% van de CVA met loopstoornissen.

De pathofysiologie van stiff knee gait wordt slechts gedeeltelijk begrepen en in de literatuur worden verschillende hypothesen genoemd waarbij de enkel-, heup- of kniegewrichten betrokken zijn. Hoewel de exacte oorzaak van een stiff knee gait niet geheel duidelijk is, lijkt de oorzaak multifactorieel. Een veelvuldig genoemde oorzaak van stiff knee gait is een abnormale activiteit van de rectus femoris tijdens de zwaafase.

Er zijn twee opties beschikbaar voor de beoordeling van de abnormale activiteit van de rectus femoris: oppervlakte elektromyografie (sEMG) en de Duncan Ely test. De algemeen geaccepteerde gouden standaard is sEMG van de rectus femoris tijdens dynamische ganganalyse. De tweede optie is de Duncan Ely test, welke deel uitmaakt van een routinematig klinisch onderzoek naar spiertonus. Het is echter niet bekend of de Duncan Ely test een bruikbare test is bij CVA patiënten om abnormale activiteit van de rectus femoris tijdens de zwaafase te voorspellen.

In de literatuur worden verschillende behandelopties beschreven om het lopen met een stiff knee gait te verminderen, zoals bijvoorbeeld elektrostimulatie van de kuitspieren en/of hamstrings, chemodenervatie van de rectus femoris en een rectus femoris transfer. Deze behandelopties zijn niet uitgebreid onderzocht bij mensen die een CVA hebben gehad. Belangrijke vragen zoals wat het effect is van functionele elektrostimulatie van alleen de hamstrings bij CVA patiënten zijn niet beantwoord.

Wat betreft chemodenervatie van de rectus femoris zijn in de literatuur enkele artikelen te vinden die het effect van Botuline toxine (BoTN) injectie in de rectus femoris bij CVA patiënten hebben onderzocht. Echter, deze studies laten tegenstrijdige resultaten zien. Een systemische review kan meer inzicht geven in het effect van een chemodenervatie injectie in de rectus femoris. De meeste chemodenervatie studies zijn ongecontroleerde studies. Dit maakt een gerandomiseerd gecontroleerd onderzoek naar het effect van een chemodenervatie injectie in de rectus femoris zonder bias wenselijk.

Een volgende stap na een BoNT injectie is de rectus femoris transfer. Bij deze behandeloptie is er behoefte aan een duidelijk antwoord op de vraag wat het effect van de rectus femoris transfer is.

Zoals gepresenteerd in **hoofdstuk 1**, was het algemene doel van dit proefschrift om de effectiviteit van verschillende behandelopties te bestuderen bij CVA patiënten welke lopen met een stiff knee gait.

De focus van dit proefschrift ligt op de volgende vragen:

1. Wat is het huidige bewijs voor het effect van chemodenervatie van de rectus femoris bij patiënten met een CVA welke lopen met een stiff knee gait?
2. Wat is de diagnostische waarde van de Duncan Ely test in het voorspellen van abnormale rectus femoris activiteit bij CVA patiënten welke lopen met een stiff knee gait?
3. Wat is het effect van functionele elektrostimulatie van de hamstrings bij CVA patiënten welke lopen met een stiff knee gait?
4. Wat is het effect van botuline toxine injectie in de rectus femoris bij CVA patiënten welke lopen met een stiff knee gait, gemeten in een gerandomiseerde gecontroleerde trial?
5. Wat is het effect van rectus femoris transfer bij CVA patiënten welke lopen met een stiff knee gait?

In **hoofdstuk 2** zijn de resultaten gepresenteerd van een systematische review naar het effect van Motor Branch Block (MBB) of NeuroMuscular Block (NMB) van de rectus femoris op knie kinematica en functionele uitkomsten.

In totaal werden negen artikelen geïnccludeerd die 12 studies beschreven. De knie kinematica (piek knieflexie of knie range of motion) tijdens de zwaai verbeterde significant in alle geïnccludeerde onderzoeken. Een gepoolde data-analyse bij CVA patiënten toonde een significante verbetering in piek knieflexie na een MBB en na een NMB aan. Het effect op functionele uitkomsten en energiekosten blijft onduidelijk.

Indien er wordt ingegrepen op de rectus femoris als onderdeel van de behandeling van stiff knee gait, is het belangrijk dat deze spier abnormale of overactiviteit vertoont tijdens de zwaai fase. In **hoofdstuk 3** vergeleken we de uitkomsten van de gouden standaard, sEMG tijdens dynamische loopanalyse, met de uitkomsten van de Duncan Ely test. We includeerden 95 CVA patiënten die liepen met een stiff knee gait. De resultaten toonden aan dat de Duncan Ely test niet beter is dan het willekeurig raden om rectus femoris overactiviteit te voorspellen. Mogelijke redenen voor de lage correlatie is het feit dat de Duncan Ely test een subjectieve beoordeling is, dat de Duncan Ely test ook andere kniestrekkers en heupflexoren

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kan testen en/of dat de statische Duncan Ely test een beperkte relatie heeft met een probleem dat optreedt tijdens een dynamische situatie.

We raden daarom aan om de Duncan Ely test niet meer te gebruiken om rectus femoris overactiviteit te voorspellen maar gebruik te maken van sEMG tijdens het lopen.

In **hoofdstuk 4** zijn de effecten van functionele elektrostimulatie van de hamstrings op de knie kinematica bij 16 patiënten gepresenteerd. Positieve effecten op de knie kinematica werden gevonden na vijf weken, drie keer per week gedurende een uur trainen met hamstring stimulatie. Geïstrumenteerde loopanalyses werden voor en na de vijf weken training uitgevoerd. Lopen met elektrostimulatie na de 5 weken training liet een toename van  $8,7^\circ$  in piek knieflexie zien. Dit vergeleken met lopen zonder elektrostimulatie aan het begin van de 5 weken training (interventie effect). Lopen zonder elektrostimulatie na de 5 weken training liet een toename van  $3,1^\circ$  in piek knieflexie zien. Dit vergeleken met lopen zonder elektrostimulatie vóór de 5 weken durende training (therapeutisch effect). Verder lijkt het erop dat CVA patiënten met een milde neurologische beperking beter reageren op hamstring stimulatie en dat het interventie effect van hamstring stimulatie binnen één oefensessie kan worden voorspeld.

De systemische review toonde ook aan dat alle tot nu toe in de literatuur gerapporteerde studies ongecontroleerde of niet-gerandomiseerde studies zijn zonder (drievoudige) blinding, waardoor de resultaten vertekend kunnen zijn. In **hoofdstuk 5** zijn de resultaten van onze drievoudige geblindeerde, gerandomiseerd en gecontroleerde studie gepresenteerd. In deze studie includeerden we 26 CVA patiënten welke een (BoNT) injectie en een placebo injectie in de rectus femoris kregen. Voor en na de injecties werden geïstrumenteerde loopanalyses, functionele uitkomstmaten en zuurstofverbruik van het lopen verzameld. De wash-out periode was vijf maanden. De resultaten toonden aan dat een BoNT-injectie in de rectus femoris een significante toename van de piek knieflexie en knie range of motion van respectievelijk  $6,7^\circ$  en  $4,8^\circ$  geeft. Dit in vergelijking met de placebobehandeling. De heup kinematica vertoonde geen veranderingen. Wat betreft de functionele uitkomsten vonden we alleen een significante verbetering in de 6 minuten looptest (6 MWT) van 18,3 meter, wat niet hoger is dan het minimaal klinisch belangrijk verschil van 34,4 meter.

De resultaten toonden aan dat de BoNT injectie een waardevolle klinische behandeloptie is om de knie kinematica te verbeteren bij CVA patiënten welke lopen met een stiff knee gait. De resultaten toonden ook aan dat de veranderingen in de knie kinematica niet overeenkomen met veel gebruikte functionele uitkomsten zoals loopsnelheid, zuurstofverbruik of vragenlijsten. Dit zou kunnen wijzen op de behoefte aan andere functionele uitkomstmaten die de effecten in de knie kinematica kunnen vastleggen. Op

basis van patiëntervaringen zijn er aanwijzingen dat foot clearance een belangrijke functionele uitkomst kan zijn.

Om de nadelen van een BoNT behandeling tegen te gaan, zoals een beperkte werkingstijd en gewenning, is de rectus femoris transfer een permanente behandeloptie om de functie van de rectus femoris te veranderen. In **hoofdstuk 6** presenteerden we de resultaten van ons onderzoek naar het effect van een rectus femoris transfer op knie- en heup kinematica, functionele uitkomstmaten, vragenlijsten en een BORG-vragenlijst die zich richtte op foot clearance. Tien patiënten werden geïnccludeerd. Tijdens de chirurgische ingreep werd de distale rectus femoris pees verplaatst naar de mediale kniebuigers om de knieflexie tijdens de zwaai te verbeteren. De resultaten toonden een significante toename in piek knieflexie en knie range of motion aan van respectievelijk 10,6° en 10,5°, zonder veranderingen in heupkinematica. Verder vonden we statistisch significante verbeteringen op de 6 MWT, 10 meter looptest (10 MWT), Timed up-and-go test, L-test en op de BORG vragenlijst van foot clearance. De significante verandering op de 6 MWT van 42,5 meter is klinisch relevant voor de patiënt. Het significante verschil op de 10 MWT, Timed up-and-go en L-test is respectievelijk 1,26 sec, 1,34 sec en 2,97 sec. De resultaten toonden aan dat rectus femoris transfer chirurgie een waardevolle behandeloptie is voor CVA patiënten welke lopen met een stiff knee gait om de knie kinematica en verschillende functionele uitkomstmaten te verbeteren.

Tot slot wordt het proefschrift afgesloten met een algemene discussie in **hoofdstuk 7**. In dit hoofdstuk worden de belangrijkste bevindingen samengevat en besproken, samen met de sterke punten en beperkingen van de onderzoeken. De nadruk ligt op de implicaties en aanbevelingen voor de klinische praktijk.

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## Dankwoord

Nou, na 138 3D patiëntmetingen, het plaatsen van 1436 EMG-electroden, het plaatsen van 2484 Vicon markers, het afnemen van 2580 functionele testen, meer dan 60.000 Vicon markers muisklikken in het NEXUS 3D programma te hebben geplaatst en de resultaten te hebben opgeschreven in 5 artikelen, kan ik zeggen, het promotie traject is af. Het was een prachtige, leerzame, mooie, leuke reis waarvan ik niet gedacht had deze ooit te kunnen en mogen maken. Af en toe was het fietsen tegen de wind in, maar vaak voelde het alsof ik de wind in de rug had. Het gevoel van wind in de rug hebben komt natuurlijk ook door de vele collega's welke mij op een of andere manier hebben geholpen met het onderzoek. Zonder een groot aantal van deze mensen was dit promotie traject niet over de finish lijn gekomen. Graag wil ik iedereen hiervoor dan ook heel erg graag danken.

Allereerst alle patiënten welke deelnamen aan het onderzoek, hartelijk dank voor jullie tijd en bereidheid om te participeren in het onderzoek. Zonder jullie was het onderzoek niet tot stand gekomen. Het doet me goed, dat voor een groot aantal van jullie, deelname aan het onderzoek ook een duidelijke praktische meerwaarde heeft opgeleverd. Allen hartelijk dank voor deelname aan het onderzoek.

Jaap, het werken op RRD is lang geleden, rond 1996, voor mij begonnen als kamergenoot van je, voor 2 uurtjes in de week vanuit de afdeling fysiotherapie, samen als fysiotherapeut. Na het afnemen van veel long vragenlijsten zei je: "daar moet je een artikel van schrijven!!" En van het één komt het ander. Jij hoogleraar en ik nu (bijna) doctor. Alhoewel we nooit een echte begindatum hebben gehad van het promotieonderzoek vielen lang geleden in Salisbury (Odstock) ooit de woorden "promotie Martin" bij je. Ik had geen flauw idee wat het inhield maar stond wel open voor een uitdaging. En dan is het heel bijzonder dat je jaren later, rond 2013 je eigen promotie traject kunt uitstippelen, van het begin tot het einde, van idee naar stimulatie, van patiënt naar operatie. Ik vat het traject nu heel kort samen, maar zonder jouw Jaap, zonder je enthousiasme, relaxte, nuchtere en mooie kijk op patiënten en problemen, was het mij niet gelukt. Je leerde me in het begin letterlijk "de poot stijf te houden" of je eigen idee te volgen. Je gaf me de vrijheid om mijn eigen gang te gaan, met mijn eigen keuzes, mijn eigen opzet en mijn eigen richting te bepalen in het onderzoek. Dit is iets wat ik als zeer prettig heb ervaren. Dank voor het vertrouwen hierin. Je bijzondere kennis van wetenschap in combinatie met patiënten, zijn onmisbaar geweest in dit proefschrift en bij de verschillende presentaties. Het gemak waarmee jij een bruggetje kunt slaan tussen wetenschap en patiënten is bijzonder groot. Na een gesprek met je bij de koffiehoeke of een werkoverleg, kreeg ik altijd energie of ideeën van je. Ik heb genoten van de vele samen gevolgde congressen, denk hierbij aan Londen, Wenen, Toronto, Sevilla en Kaapstad. Je humoristische, nuchtere uitspraken zijn een genot om aan te horen. Promotor

Jaap, dank voor alle jaren samenwerking en ik hoop dat we nog veel van je kennis gebruik kunnen en mogen maken.

Erik, je kwam op RRD werken en ik zou je stagebegeleider worden. Kijk, dat zou leuk geweest zijn. Ik denk dat na twee maanden de rollen omgedraaid waren en ik bij jouw stage had gelopen. Zonder jou kennis, inzicht en hulp was dit proefschrift mij nooit gelukt. Ik heb ontzettend veel van je geleerd. Langzaam maar zeker is mijn Twengels iets richting het Engels gegaan. Hoe je Margret Thatcher uitspreekt zal ik niet vergeten. In artikelen kun je haarfijn de vinger op de zere plek leggen en inzicht geven in wat ik bedoel of wil schrijven. Zonder jouw hulp, als het "Orakel van Gaanderen", was mijn finishlijn zeker niet gehaald. De vele samen gevolgde congressen (veelal met Corrie), waar je als deskundig reisleader met culinaire hoogstandjes optrad, waren een genot om te bezoeken. (bv een appelstrudel met vanillesoße in Oostenrijk of een noedelsoep in Tokio (Ichiran). Co-promotor Erik, hartelijk dank voor alles, je hulp, je kennis, je humor, je persoon, je opbouwende kritiek en je luisterend oor als gesprekspartner en de wijze waarop we samen werken. Ik kijk uit naar de komende jaren.

Erik en Jaap, ik heb geen stellingen bij het proefschrift maar er zou er ongetwijfeld één bij staan in de trant van ... "Het is de functie van de begeleiders om alle "jus" uit een artikel te halen". Erik en Jaap, hartelijk dank voor het sterker maken van de artikelen en voor de mooie uren begeleiding en coaching.

Hans, als mede promotor ben je vanaf de start bij mijn promotie betrokken geweest. Met je mooie open houding maar ook met een zeer scherpe klinische blik als revalidatiearts, was de feedback op de artikelen zeer waardevol. Met je humoristische en veelal hilarische opmerkingen (het leek soms wel of we bij Vandaag Inside zaten) bij een voortgangsoverleg konden we zeer open maar ook zeer serieus discussiëren. Hartelijk dank hiervoor.

Ik wil ook alle leden van de promotiecommissie bedanken voor hun kostbare tijd om mijn proefschrift te beoordelen en in de oppositie plaats te nemen. Peter, Gabriëlle, Noël, Han en Marc, hartelijk dank hiervoor.

Leendert, hoe vaak ben ik wel niet je kamer binnen gelopen. Ehm..... Leendert, heb je even, er gaat iets mis met de meting, er gaat is mis met de analysis, er gaat iets mis met de data, Leendert..., ergens moet er een fout in de berekening zitten. Je zou er moe van worden. Hartelijk dank voor al de tijd die je vrijmaakte om mij te helpen, en dat is nogal wat. Dank voor de mooie samenwerking in alle verschillende studies, met name de Duncan Ely studie, het samen stagiaires begeleiden, en de gesprekken waarbij altijd wel weer een idee (lees

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werk) uit voort kwam. Leendert zonder jouw hulp en tijd was dit proefschrift zeker niet tot stand gekomen. Ik hoop dat we de aankomende jaren nog veel mogen samenwerken.

Anand, met je bijzondere kennis over de musculus rectus femoris ben je een van de grondleggers geweest van dit project. Je hebt mij wegwijs gemaakt in de gangbeeld analyses en de stiff knee gait problematiek. Zonder jouw inzet bv bij het beoordelen van EMG signalen en het verrichten van alle injecties bij het botuline onderzoek, was dit proefschrift niet tot stand gekomen. Anand, hartelijk dank voor de leuke congressen, je inhoudelijke en kritisch blik (vaak in het mooie Engels) en de ondersteuning op belangrijke momenten.

Mijn dank gaat ook uit naar wijlen Gerrit Zilvold, onze gezamenlijke belangstelling voor elektrostimulatie heeft de start mogelijk gemaakt voor het promotie traject. Dank voor de goede gesprekken en het bijzonder leuke uitstapje in Frankrijk. Jan Feijen, dank voor je deskundig inzicht, je kennis en je waardevolle kritische blik en m.b.t. het project. Gerrit en Jan, samen hebben jullie een zeer grote faciliterende rol gespeeld in het Stiff Knee Gait project. Mede namens alle patiënten hartelijk dank.

Corien (of Corrie, roommate), eindelijk, na al die jaren, het is dan zover. Het zit erop. Nu valt er niet meer “wat te zeuren” bv over onze gelijktijdige, zeer lange, leuke promotietrajecten. Het samen werken aan bv het BALANS project met CVA patiënten lijkt wel prehistorie. Je open, nuchtere, kritische houding kan ik zeer waarderen, zowel in werk- als in privé situaties. Dank voor al die geweldig mooie en humoristische maar ook bijzondere momenten (orkaan Japan) tijdens de vele verre, leerzame congressen. Het samen met Erik zingen van een geweldig duet (in onze ogen dan) in een karaoke bar, was volgens jou toch niet echt ons ding. “Jullie hebben andere kwaliteiten”. Nee, mijn kwaliteiten liggen dan meer in even “een Tennigloo’tje” te doen, om een kopje koffie te bestellen na een lange wandeltocht. Het zal even wennen worden met een volgend congres als jullie er eventueel niet bij zijn. Een muntje opgooien in de zin van “throw up a coin” zal ik niet meer doen. Corrie, ik hoop nog vele jaren met je samen te werken, is het niet tijdens metingen dan wel onder de noemer RDC, hartelijk dank voor alles.

Ruth (Hey Roethie....). Dit keer niet als collega fysiotherapie, maar als paranimf sta je naast me. Het is altijd een genot om samen met je de gangbeeld analyses te draaien. Samen vullen we elkaar goed aan om er een leuke ontspannen meting van te maken. De vele computer technisch storingen zijn een peulenschil voor ons.. (leuk he.... gangbeeld), althans, we proberen er samen achter te komen waarom het mis gaat. Ruth, dank voor alle leuke gesprekken en overleggen. Ik kijk uit naar mogelijk 2028, je weet wel waarom.

Corien en Ruth, het doet me goed dat jullie mijn paranimfen zijn.



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je. Job en Marjolein, dank voor de ondersteuning in de statistiek. De studenten Camiel, Arthur, Ingrid, Anke, Karin, Jennifer, Amy, Ilona, Maaïke, Daan, Laura, Mirjam, Alley, Carmen, Tom en Daniel, dank voor jullie bijdrage aan mijn promotie traject.

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"Als je wat wilt, moet je actie ondernemen" (Martin Tenniglo)

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## About the author

Martin Tenniglo was born in Oldenzaal the Netherlands on January 27th, 1964. After finishing secondary school from Thij College in Oldenzaal, he started studying Physical therapy at the University of Applied Sciences in Enschede, the Netherlands. After his graduation with an article about lung patients in the summer of 1989, Martin started working as a physiotherapist in several primary care practices in the Netherlands and Germany. In 1990 he started working as a Physical therapist at Roessingh Centre for Rehabilitation Enschede. In his work as a Physical therapist he has always shown interested in research with patients. After attending various scientific education courses in addition to his work as Physical therapist, he started working at Roessingh Research and Development (RRD) in 1996. He was involved in different projects; Medical Psychological Questionnaire for CARA project, Implantable Peroneal nerve Stimulator project, Split Tibialis Anterior Tendon Transfer project, BALANS project, Electrical Stimulation Upper Extremities project; Handmaster project, Automove trial project, Electrical stimulation Calf muscle project. This laid the foundation for his PhD-project "Stiff Knee Gait" at RRD and the University of Twente, under supervision of Jaap Buurke, Erik Prinsen and Hans Rietman. His PhD project, focussed on the effectiveness of different treatment options in stroke patients walking with a stiff knee gait. The results of this research are presented in this thesis.

Currently, Martin still works on his "Stiff Knee Gait" project that aims to develop further treatment options for stiff knee gait. Amongst others, he works on the developing of a knee flexion device and on the investigation of the effect of a chemodenervation in the vastii and rectus femoris. He combines this with his work as Physical therapist at RCR, as a gait specialist in Roessingh Diagnostic Centre and as a specialist in electrical stimulation.

Furthermore, Martin is involved in the gait analysis courses organized by RRD.

## Journal publications

**Tenniglo MJB**, J.H. Buurke, A.V.C.M. Zeegers, J.F.M. Fleuren, J.S. Rietman, E.C. Prinsen. The effect of rectus femoris transfer on kinematics and functional outcomes in adult stroke patients walking with a stiff knee gait. Revision manuscript submitted in *Gait and Posture*. Okt 2023.

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