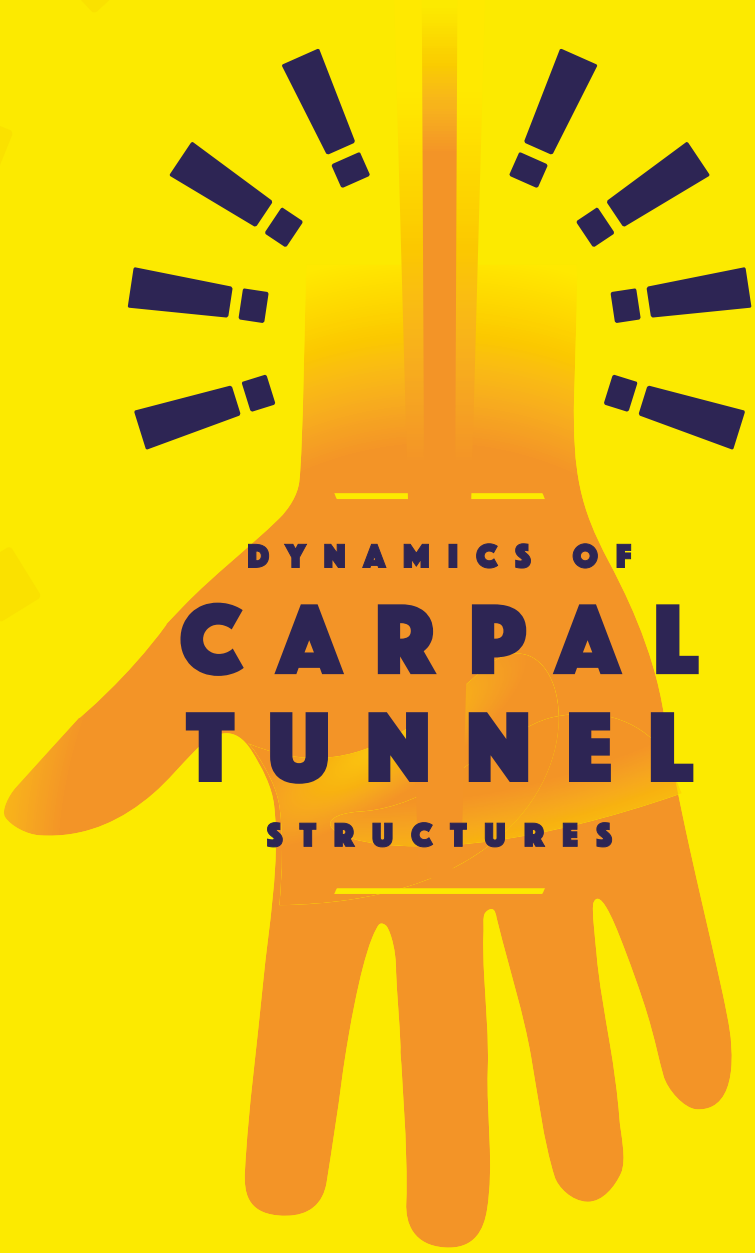

# DYNAMICS OF CARPAL TUNNEL STRUCTURES

## ITS ASSESSMENT AND ROLE IN UNDERSTANDING CARPAL TUNNEL SYNDROME ETIOLOGY

ANIKA FILIUS

# DYNAMICS OF CARPAL TUNNEL STRUCTURES

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The studies described in this thesis were performed at:
- The departments of Plastic Surgery, Rehabilitation Medicine and Neurology, Erasmus MC, Rotterdam, the Netherlands.
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# DYNAMICS OF CARPAL TUNNEL STRUCTURES

## ITS ASSESSMENT AND ROLE IN UNDERSTANDING CARPAL TUNNEL SYNDROME ETIOLOGY

# DYNAMICA VAN CARPALE TUNNEL STRUCTUREN

## ANALYSE HIERVAN EN HUN ROL IN DE ETIOLOGIE VAN HET CARPALE TUNNEL SYNDROOM

**Proefschrift**

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

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en volgens besluit van het College voor Promoties.

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# 1

# INTRODUCTION

## GENERAL OVERVIEW OF CTS

Carpal tunnel syndrome (CTS) is caused by compression of the median nerve in the carpal tunnel (Figure 1). Compression of the median nerve in the carpal tunnel is characterized by pain, numbness and paraesthesia in the first three digits and the radial side of the fourth digit, diminished range of motion of the thumb and weakness of the thenar muscles (Figure 2).[1-4]

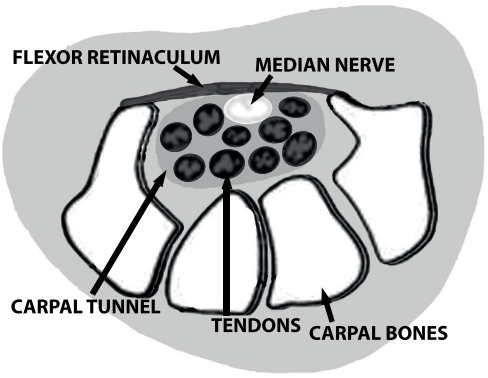


**Figure 1** Systematic representation of the carpal tunnel.

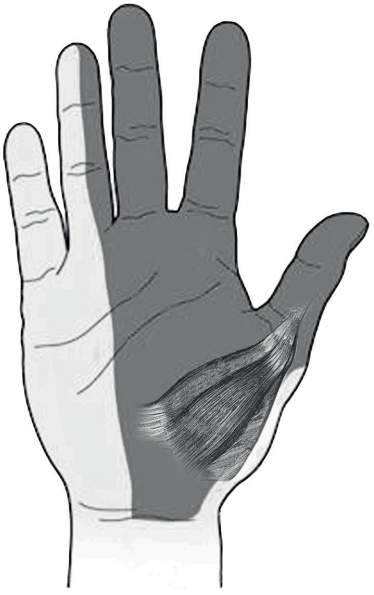

**Figure 2** Symptomatology of CTS; numbness and pain in the first three digits and the radial side of the fourth digit, and hypotrophy of the thenar muscles.

With a prevalence of 4.9%, CTS is the most common compression neuropathy and it can cause significant impairment of the hand function.[5,6] Due to the high prevalence and incidence,[7] CTS causes a significant socio-economic burden. The most commonly reported compensation claim for damage of work-related disorders is CTS,[8] and together with hearing loss, CTS accounts for more absence days of work than any other disease in the United States.[9]

These data illustrate that CTS has a major impact on society, unfortunately the exact pathophysiology is often unknown and, in addition, there is no golden standard for diagnosing CTS. This makes it difficult to develop preventive measures and decide for appropriate treatment. The aim of this thesis is to gain more knowledge about the pathophysiology of CTS and investigate if ultrasound is a potent tool to diagnose CTS.

## HISTORY AND DEFINITION OF CTS

At the end of the 19th century the first descriptions on median nerve compression symptomatology were published and various hypotheses were suggested to explain the pathophysiology.[10-12] Putnam advocated that altered blood supply caused damage to the small nerve ends and recommended therapies like galvanic current, phosphorus, strychnine, potassium bromide and cannabis.[11] Others thought that CTS was caused by compression of the brachial plexus at the level of the thoracic outlet and advised surgical resection of the cervical rib as a treatment for CTS.[13] Halfway the 20th century, Brain et al. were the first to publish an accurate definition of CTS.[14] They concluded that the tingling and paraesthesia in the first three digits and hypotrophy of the thenar muscles were caused by median nerve compression in the wrist.

## PATHOPHYSIOLOGY OF CTS

Compression of the median nerve is the result of an underlying conflict between the container size (the carpal tunnel) and the volume of its contents (the median nerve, the flexor tendons and surrounding tissue) causing the pressure to rise in the carpal tunnel. In a few cases the onset of CTS can be explained based on a clear cause-effect relation. For example, a ganglion or aberrant muscles in the carpal tunnel can increase the volume of the carpal tunnel, and wrist fractures may alter the anatomy of the carpal tunnel and thereby reduce the carpal tunnel volume.[15-17] In other CTS patients, underlying systemic diseases can affect the volume of the carpal tunnel contents through different mechanisms.[18,19] Diabetes, for example, is thought to increase the volume of the median nerve by increasing collagen deposition in the nerve and decreased elasticity may further cause nerve irritation.[20,21] Hypothyroidism can cause myxedema, which directly increases carpal tunnel pressure.[22] Pregnancy leads to increased fluid retention that could cause a direct increase in carpal tunnel pressure as well.[23] And in patients with rheumatoid arthritis tenosynovitis is thought to increase the volume of the carpal tunnel contents.[24] However, in the majority of cases the pathophysiology of CTS is unknown. This type of CTS is also known as idiopathic CTS. In these cases, vibration and repetitive motion are considered significant contributing factors to CTS.[25,26] Repeated mechanical stress due to tendon motion causes micro-damage of the tissue surrounding the flexor tendons and nerve within the carpal tunnel.[27-29] This tissue is also known as the subsynovial connective tissue (SSCT) (Figure 3 and 4). In damaged SSCT the small interconnecting fibres are replaced by thicker parallel fibrous bundles.[30-32] Fibrotic SSCT ruptures at smaller strains during tendon excursion.[33] The failure of SSCT at smaller tendon excursions ensures a vicious cycle.[34,35]

### *The SSCT*

The SSCT is the tissue surrounding the nerve and the tendons within the carpal tunnel (Figure 3).

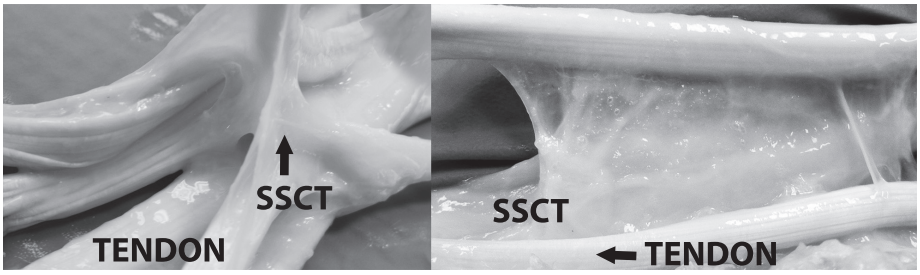


**Figure 3** Human cadaver flexor tendons and SSCT.

The SSCT consists of multiple fibrous layers with interconnecting collagenous fibres that facilitates tendon motion by sliding layer-by-layer smoothly and separately whereby the deep layers close to the tendon move first after which the more superficial layers follow. This prevents direct abrasion between the median nerve and moving flexor tendons (Figure 4).

Damage to the SSCT can cause median nerve irritation in various ways. Due to damage, the SSCT's function to prevent abrasion between the median nerve and moving flexor tendons will get impaired,[27,36] which can result in irritation of the median nerve. Next, oedema, thickening of the SSCT,[37] increased absorption capabilities of the SSCT,[38] and impaired movement of interstitial fluid within the carpal tunnel as a result of the SSCT healing and repair process can increase carpal tunnel pressure,[39] which can cause nerve compression and thereby irritate the median nerve as well.

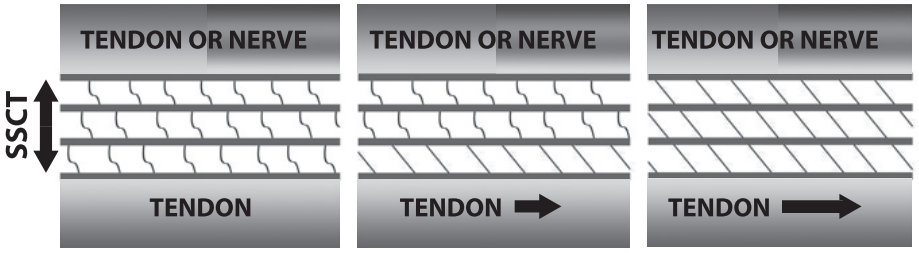


**Figure 4** A simplified model of the function of SSCT during tendon motion. When tendons are in relaxed state, the SSCT fibers are loosely connected. As the tendon moves, the SSCT stretches layer-by-layer.

## DIAGNOSIS OF CTS

Due to the incomplete understanding of the pathophysiology of CTS, its diagnosis is presently based on evaluation of symptoms through clinical assessment, supported by nerve conduction studies (NCS). NCS can help to confirm the diagnosis and exclude other pathologies.[40] Modern NCS methods achieve a high sensitivity and specificity in clinical populations.[41] However, the sensitivity of NCS is low when compared with clinical diagnosis. Approximately 25% of patients with evident CTS symptoms have a negative NCS test result.[42] It should be noted, however, that all such studies are hampered by the fact that clinical diagnosis is clearly not infallible either.

A number of recent studies have shown that imaging of the median nerve can provide important diagnostic information. These studies used computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound.[43-47] In particular the area measurement of the median nerve was found to be a promising diagnostic measurement with sensitivities ranging from 65 to 97% and specificities ranging from 73 to 98%.[48] The advantage of using imaging modalities is that abnormalities in the carpal tunnel can be visualized and that the imaging modalities may help to predict the effect of treatment.[15-17,49]

Ultrasound is an increasingly used imaging modality to confirm the clinical diagnosis of CTS.[50,51] Ultrasound has several advantages compared to other imaging modalities, including its low cost and capability of detecting underlying pathology. Furthermore, ultrasound is often already used in staging associated disorders (e.g., rheumatoid arthritis).[52-55] Lastly, it is more suitable than MRI and CT to investigate dynamics of structures within the carpal tunnel in relation to wrist and hand movement since it is capable of real-time imaging.

## TREATMENT OF CTS

There are surgical and non-surgical therapies for CTS. The therapy of preference depends on several factors. In mild cases, non-surgical treatment is initiated and consists mainly of splinting of the wrist and corticosteroid injections. However, the evidence on splint use during the night compared to no treatment is limited.[56] Effectiveness of corticoid injections was proven to be effective in approximately 77% of the patients.[57] Moreover, its effect may be temporarily and no more than 2 to 3 injections maximum are recommended.[2] When non-surgical treatment fails, or in case of severe CTS, surgery is generally indicated. Decompression through an open or endoscopic carpal tunnel release is effective in about 65 to 75% of the patients.[1,58] Similar effectiveness has been established for endoscopic and open surgical techniques.[59]

## OUTLINE OF THIS THESIS

This thesis consists of two parts. Part I focuses on biomechanical and dynamical behaviour of the SSCT and the relation between (high-velocity) tendon gliding and SSCT damage. Part II focuses on possible changes in dynamics of the median nerve, flexor tendons, and SSCT in CTS patients using ultrasound and the potential of ultrasound as diagnostic tool is investigated (Figure 5).

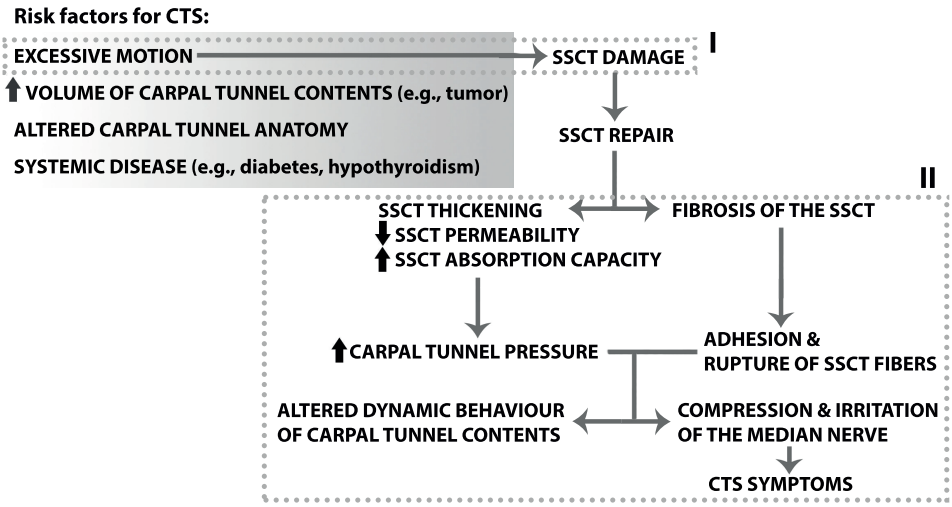


**Figure 5** Outline of this thesis. Excessive motion is a risk factor for CTS. Excessive motions are high-velocity and highly repetitive motions.[60-63] In part I we investigate the effect of (high-velocity) tendon excursion on biomechanical and dynamical behaviour of the SSCT and on generating SSCT damage, which is thought to play a key role in the pathogenesis of CTS.[27] Damaged SSCT needs to be repaired. During the repair process damaged SSCT is replaced by thickened fibrotic SSCT, which impairs movement of interstitial fluid within the carpal tunnel and leads to increased absorption capabilities of the SSCT.[37-39] This can all generate increased carpal tunnel pressure and thereby compress the median nerve. In addition, the fibrotic SSCT may cause adherence of the median nerve to other structures and thereby irritating the median nerve or it may lead to complete disconnection of the SSCT and the adjacent median nerve and flexor tendon.[27,64,65] The increased carpal tunnel pressure and adhesions or disconnection of the SSCT with adjacent tissues may affect dynamical behaviour of the flexor tendons, median nerve and SSCT in the carpal tunnel. Studying the dynamics of carpal tunnel contents is therefore valuable for getting a better understanding of CTS and may make ultrasound a valuable diagnostic test (part II).

### *Part I. A possible link between hand motions and CTS onset*

Phalen already reported during the 1960s on CTS symptoms being aggravated by repeated and forceful hand and wrist motions.[66] However, it was not until the 1980s that the relation between hand and wrist motion and the incidence of CTS was more extensively investigated.[67] Since then various epidemiological studies have investigated

exposure-response relations and the occurrence of CTS mainly in the working population and conveyed that repetitiveness and hand vibration were related to a higher incidence of CTS.[60-63,68,69]

Higher tendon excursion velocity may increase the amount of SSCT damage and affect SSCT displacement. Cadaver studies have shown that fibrils of the SSCT can rupture during excursions within the physiological range of motion at low-velocity tendon excursions.[29,70] High-velocity tendon motion could lead to higher strain rates of the SSCT, and higher strain rates can decrease failure strain in tissues having a viscoelastic respons,[71] as SSCT is thought to posses. In addition, faster strain rates lead to increased stiffness in viscoelastic materials.[72-74] Therefore, the SSCT may be more prone to damage at higher tendon excursion velocities.

In **chapter 2** we evaluate an experiment in human cadaver hands hypothesizing that the SSCT damage threshold is lowered by higher tendon excursion velocities. In **chapter 3** we investigate in depth the effect of tendon excursion (velocity) in human cadaver hands and try to delineate the different components involved in gliding resistance, with special attention for gliding resistance caused by the SSCT. In **chapter 4** we investigate in vivo directly and indirectly the effect of tendon excursion velocity on respectively the median nerve and SSCT displacement in both healthy subjects and CTS patients. These investigations contribute to a better understanding of carpal tunnel content dynamics and the onset of CTS in relation to (high-velocity) tendon excursion.

### *Part II. Evaluation of dynamical changes of the carpal tunnel contents in CTS patients using ultrasound*

Non-invasive high frequency ultrasound imaging is a highly suitable tool to objectively measure dynamical behaviour of the median nerve, flexor tendons and SSCT in the carpal tunnel. The rationale behind investigating dynamical behaviour of these structures is that this may be affected by changes in the volume of the carpal tunnel contents, increased pressure within the carpal tunnel, changed carpal tunnel shape and fibrosis of the SSCT.[34,75] In addition, carpal tunnel release affects displacement of the SSCT and the main effect of carpal tunnel release is considered to be a decreased carpal tunnel pressure.[76-83] Thus, if a decrease of carpal tunnel pressure affects dynamics of the structures within the carpal tunnel, an increase of pressure is likely to affect dynamics as well.

High-resolution ultrasound allows precise imaging and is a suitable tool to investigate carpal tunnel dynamics in vivo, though the image quality and therefore the interpretation of the images are rater-dependent.[84] Therefore, before investigating dynamical behaviour of the carpal tunnel structures using ultrasound, we investigated the reliability of the ultrasound-based measurements. A small number of studies have investigated the reliability of ultrasound measurements at the level of the wrist in the transverse plane.[85-87] However, these studies have focused on the median nerve, investigated solely the reliability of static

measurements, and/or did not examine interrater and intrarater reliability (Table 1). Also, the reliability of longitudinal displacement measurements has scarcely been investigated. Therefore, we conducted studies to investigate the intrarater, interrater and re-test reliability of dynamic ultrasound measurements at the wrist level (**chapter 5 and 8**).

We also aimed to reveal the dynamical behaviour of carpal tunnel contents. As from today much is unknown about the median nerve, flexor tendons and SSCT dynamics in the carpal tunnel of neither healthy subjects nor CTS patients.[34,88-91] Measuring shape and displacement of the nerve, tendons and SSCT in healthy subjects and CTS patients may provide useful information about possible dynamical changes in CTS patients. In **chapter 5, 6 and 7** we investigate the deformation and mobility of the median nerve and flexor tendons in the cross-sectional plane during different hand and wrist motions. In **chapter 8** the carpal tunnels of healthy subjects and CTS patients were imaged in both the transverse as well as the longitudinal plane. The most useful parameters for diagnosing CTS are defined based on these different views into the carpal tunnel.

Summarizing, the aim of this thesis is (part I) to extend the knowledge about biomechanical and dynamical behaviour of the SSCT during (high-velocity) tendon gliding, and (part II) to establish potential changes in dynamics of the carpal tunnel contents of CTS patients using ultrasound, and to investigate if ultrasound could be a reliable and valuable tool to diagnose CTS.

| **Parameter** | **Intrarater reliability** (ICC) | **Interrater reliability** (ICC) | **Test-retest reliability** (ICC) |
|---|---|---|---|
| Area | - | * (0.87), † (0.81) | ‡ (>0.75) |
| Circularity | - | - | ‡ (>0.75) |
| Perimeter | - | - | ‡ (>0.75) |
| Displacement | - | - | ‡ (>0.75) |

**Table 1** Reported reliability results of previous ultrasound studies of median nerve measurements in the carpal tunnel. The reliability values are shown in parentheses.
* Wong et al.
† Moran et al.
‡ Doesburg et al.
Abbreviations: ICC; intraclass correlation coefficient.

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# 2

## THE EFFECT OF LOW- AND HIGH-VELOCITY TENDON EXCURSION ON THE MECHANICAL PROPERTIES OF HUMAN CADAVER SUBSYNOVIAL CONNECTIVE TISSUE

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## ABSTRACT

Fibrosis of the subsynovial connective tissue (SSCT) in the carpal tunnel is the most common histological finding in carpal tunnel syndrome (CTS). Fibrosis may result from damaged SSCT. Previous studies found that with low-velocity tendon excursion (2 mm/s), tendon excursion can irreversibly damage the SSCT. We investigated the effect of high-velocity tendon excursion in the generation of SSCT damage. Nine human cadaver wrists were used. Three repeated cycles of ramp-stretch testing were performed simulating 40%, 60%, 90% and 120% of the physiological excursion of the middle finger flexor digitorum superficialis tendon with an excursion velocity of 60 mm/s. Energy and force were calculated and normalized by values obtained in the first cycle for each excursion level. Data was compared with low-velocity tendon excursion data. For high-velocity tendon excursions, a significant drop in the excursion energy ratio was first observed at an excursion level of 60% of the physiological excursion ($P<0.024$) and that for low-velocity excursions was first observed at 90% of the physiological excursion ($P<0.038$). Furthermore, the energy ratio was lower at 60% of the physiological excursion for high-velocity tendon excursion ($P\leq0.039$). Increasing tendon excursion velocity lowers the SSCT damage threshold. This finding may be relevant for understanding the pathogenesis of SSCT fibrosis, such as that accompanying CTS, and the onset of CTS in relation to occupational factors.

## INTRODUCTION

Carpal tunnel syndrome (CTS) is a commonly diagnosed compression neuropathy of the median nerve. It is estimated to have a prevalence of 3 to 5% and has a great economic impact.[1,2] CTS causes numbness and paresthesias on the radial side of the hand and, in severe cases, weakness of the thenar muscles.[3] The exact aetiology of carpal tunnel is unknown in most cases. One hypothesis is that overuse from forceful, repetitive hand motions causes cumulative trauma to structures within the carpal tunnel. Epidemiological studies showed that highly repetitive work is related to an increased risk for CTS.[4-7] In vivo studies found biomechanical alterations of the tissues within the carpal tunnel in CTS patients.[8,9]

The carpal tunnel contains the median nerve, nine flexor tendons and the subsynovial connective tissue (SSCT) that envelops the nerve and tendons. The SSCT is a multi-layered fibrous structure with interconnecting collagenous fibres that facilitates tendon motion and functions as a cushion to protect vascular and nerve systems from injury.[10-12] The SSCT serves as a sliding unit moving layer-by-layer smoothly and separately to prevent direct abrasion between the median nerve and tendons and reduces friction during tendon motion (Figure 1).[10] Cadaveric and histological studies showed that the SSCT can be injured during tendon motion,[13-15] and fibrosis of the SSCT, which is thought to be the result of SSCT damage, is one of the most common findings in CTS patients.[16-18]

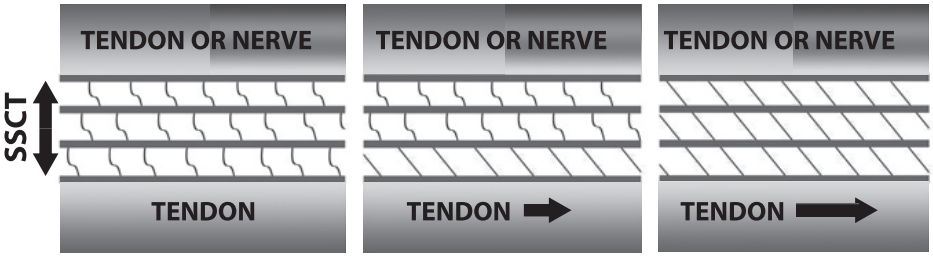


**Figure 1** A simplified model of the function of SSCT during tendon motion. When tendons are in relaxed state, the SSCT fibres are loosely connected. As a tendon moves, the SSCT stretches layer-by-layer, thereby reducing friction between an adjacent tendon or the median nerve.

Hand motions are a result of coordinated displacements of various tendons at various velocities. High-velocity tendon excursion causes less relative SSCT motion compared to low-velocity tendon excursion.[13] This may predispose the SSCT to shear injury when performing repetitive tasks.[13] Tendon excursion, even within the normal range of motion, can cause irreversible damage to the SSCT.[14,15] These experiments were performed using a tendon excursion velocity of 2 mm/s, resembling low speed physiological tendon excursions.[4,19] However, since CTS is related to highly repetitive tasks and hand vibration, we were interested in the effect of high-velocity tendon excursion (60 mm/s) on the SSCT damage threshold.

The primary aim of this study was to evaluate the effect of tendon excursion velocity in generating irreversible damage of the SSCT by investigating changes in the SSCT mechanical response caused by high-velocity and low-velocity tendon excursion using a human cadaver model. We hypothesized that the threshold of SSCT shear damage at high-velocity tendon excursion would be lower than that with low-velocity tendon excursion.

## MATERIALS AND METHODS

### *Specimen preparation and setup*

Specimens were obtained from our Institutional Anatomical Bequest Program, with approval of the Biospecimen Committee and the Institutional Review Board. Nine human cadaver forearms were prepared for high-velocity tendon excursion testing. The sample size was determined by a power calculation. A previous study of low-velocity tendon excursion (2 mm/s) had reported a maximum standard deviation of 0.11 for the energy ratios at various tendon excursions.[15] Assuming similar variability in our data, a sample size of nine specimens would provide 80% power to detect a difference of 0.15 between energy ratios of low-velocity and high-velocity tendon excursions ($\alpha = 0.05$, $\beta = 0.20$). Cadaver specimens were screened for a documented medical history of CTS or wrist fractures. Specimens obtained included four males and five females with a mean age of 77 years (range 58 to 92 years). No significant difference was found for cadaver specimen gender between studies ($P=0.335$); a significant difference was found for cadaver age ($P=0.036$).

The experimental set up has been described previously.[15] Briefly, the wrist was mounted in a neutral position onto a custom test device (Figure 2). The index, long and little finger were held in extension by fixing the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints with K-wires. The flexor digitorum superficialis tendon of the index, middle and ring fingers (FDS2-4) and the flexor digitorum profundus tendon of the middle finger (FDP3) were exposed proximal to the carpal tunnel, and 50 g weights were connected proximally to each of them to maintain tension.

To measure the physiological excursion of the FDS3 tendon, the FDS2, FDS3 and FDS4 tendons were marked with a suture at the level of the proximal edge of the transverse carpal ligament while all fingers were extended. Next, the middle finger was flexed. The distance between the suture marker of the FDS3 tendon and the suture markers of the FDS2 and FDS4 tendons at full middle finger flexion represented the physiological FDS3 tendon excursion, and was measured with a digital calliper (SC-6, Mitutoyo, Kanagawa, Japan). After physiological excursion was measured, the middle finger was fixed as well with a K-wire in extended position. Then, the FDS3 tendon was exposed distal to the carpal tunnel and sharply transected at the metacarpophalangeal joint level. The distal end of the FDS3 tendon within the carpal tunnel was connected to a 50 g weight while the proximal end of the FDS3 tendon was connected to a 25N load cell (MDB-5, Transducer

Techniques, Temecula, CA, USA). A stepper motor-driven actuator controlled the velocity and displacement of the movement for each cycle and a laser displacement sensor (LK-081, Keyence, Elmwood Park, NJ, USA) was used to record carriage displacement. The maximum steady-state velocity was set at 60 mm/s with an acceleration time set between 80 and 100 msec. Force and displacement data were recorded at 1000 Hz. The actuator pulled the tendon proximally to simulate flexion and then reversed with the tendon moving distally by the dead weight to simulate extension. Testing was conducted at room temperature, and specimens were kept moist with a saline drip for the duration of testing.

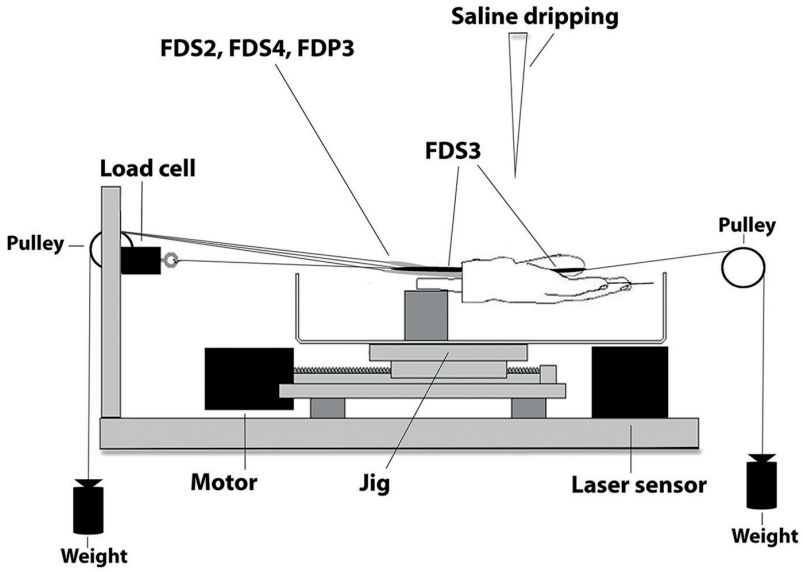


**Figure 2** Experimental set up.

### *Cyclic excursion test*

Sequentially repeated excursions were applied at magnitudes of 40%, 60%, 90%, and 120% of the physiological excursion of the FDS3 tendon. For excursion magnitudes of 40% through 90%, an initial excursion to the target amplitude at target velocity was executed followed by an immediate return to the neutral position, where the tissues were allowed to relax for 15 minutes. A second, identical loading cycle followed. Afterwards, the process was repeated with the next highest excursion level (Figure 3). Once the 120% physiological excursion level was reached, a third, final excursion to 120% was executed. For all other levels, the first cycle of the subsequent excursion level was also treated as a "third" cycle for analysis.

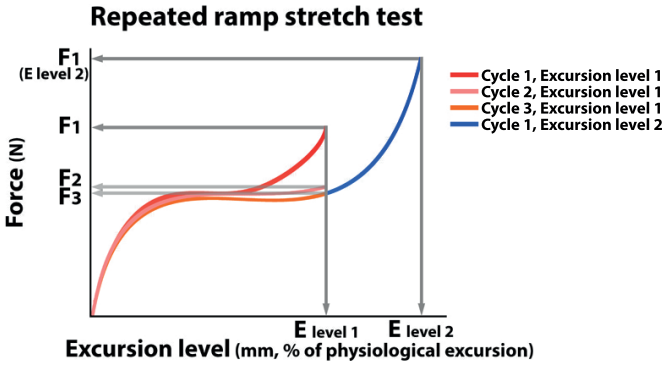


**Figure 3** Example of a repeated ramp-stretch test at one excursion level. Three cycles are performed at each excursion level. The excursion levels were respectively 40%, 60%, 90% and 120% of the physiological excursion of the FDS3 tendon. The first cycle of the following excursion level was also considered to be the third cycle of the previous excursion level by recording the data at two points; the point where the final excursion of the third cycle of the previous excursion level was reached and again at the final excursion of the first cycle of the next excursion level.

### *Data analysis*

Damage to the SSCT was apparent when a loss of energy was observed upon comparing the two cycles of each excursion level. The excursion resistance energy (E) was defined as the area under the force curve and the peak force (F) was defined as the highest force observed during testing (Figure 3). Ratios for E and F between the first and second cycles, as well as between the first and third cycle, whereby the third cycle was as well the first cycle of the next excursion, were calculated for each excursion level. A custom MATLAB program (Mathworks, Natick, MA, USA) was developed to analyse the force-excursion data and to calculate all ratios. The damage threshold was defined when a significant difference was observed between two different excursion levels, whereby the E ratio at the first excursion level indicated that no damage had been done (95% confidence interval included an E ratio of 1) and the E ratio at the next excursion level did indicate damage (95% confidence interval did not include an E ratio of 1). The damage threshold and the energy and force ratios for testing conducted at 60 mm/s were compared with the data generated using a low-velocity tendon excursion of 2 mm/s, previously published.[15]

Results were analysed using a repeated measure ANOVA to examine differences between the ratios of each parameter for each excursion magnitude. The defined damage threshold was compared with that of the low-velocity tendon excursion data.[15] In addition, a one-way ANOVA was used to compare high-velocity tendon excursion data with low-velocity tendon excursion data. P-values ≤0.05 were considered significant. The statistical analysis was done with Statistical Package for Social Science software (SPSS version 17.0, Chicago, IL, USA).

## RESULTS

### *High-velocity tendon excursion*

Detailed results are displayed in Table 1. No significant difference was found when comparing E2/E1 ratio to E3/E1 ratio or when comparing F2/F1 ratio to F3/F1 ratio for any excursion level (P≥0.066). The lack of difference between the different ratios of the same excursion levels confirmed that substantially all the viscoelastic recovery had been taken place.[15]

The E2/E1 ratios at 60%, 90% and 120% of the physiological excursion of the FDS3 tendon were significantly lower than that at 40% (P≤0.023). The E2/E1 ratios at 90% and 120% of the physiological excursion were also significantly lower than that at 60% (P≤0.009). There was no significant difference in E2/E1 ratios between 90% and 120% of the physiological excursion (Figure 4).

| | Percentage of the physiological excursion | | | |
|---|---|---|---|---|
| | 40% | 60% | 90% | 120% |
| **Energy ratios** | | | | |
| E2/E1 | 1.00 (±0.06) | 0.93 (±0.04) | 0.86 (±0.06) | 0.83 (±0.05) |
| E3/E1 | 1.07 (±0.08) | 0.96 (±0.06) | 0.87 (±0.07) | 0.80 (±0.05) |
| **Force ratios** | | | | |
| E2/E1 | 1.00 (±0.05) | 0.91 (±0.05) | 0.77 (±0.09) | 0.72 (±0.07) |
| E3/E1 | 1.09 (±0.08) | 0.94 (±0.06) | 0.78 (±0.11) | 0.67 (±0.08) |

**Table 1** Mean energy and force ratios with standard deviation (± SD) for different excursion levels.

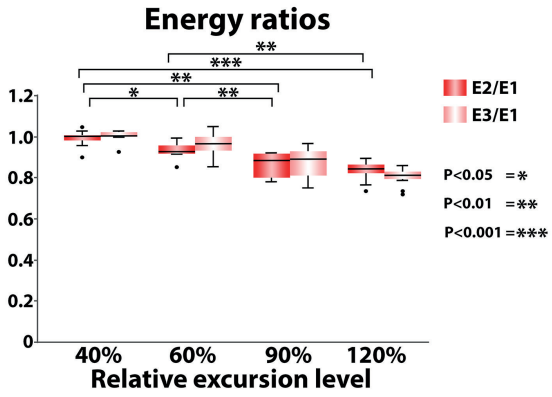


**Figure 4** Displayed are the E1/E2 ratios and E1/E3 ratios at different excursion levels. Note the significant differences between the ratios of all different excursion levels except for the ratios at 90% excursion versus 120% excursion.

The F2/F1 ratios at 60%, 90%, and 120% of the physiological excursion of the FDS3 tendon were significantly lower than that at 40% (P≤0.009). The F2/F1 ratios at 90% and 120% of the physiological excursion were also significantly lower compared to that at 60% (P≤0.002). There was no significant difference between F2/F1 ratios at 90% and 120% of the physiological excursion.

### *High-velocity (60 mm/s) versus low-velocity (2 mm/s) tendon excursion*

When comparing the high-velocity tendon excursion results with those obtained at low-velocity,[15] resistance energy was observed to be substantially greater at all excursion levels (P≤0.031) (Figure 5). More force was needed for high-velocity tendon excursion solely at 40% and 60% of the physiological excursion, as well as at 90% when removing one outlier (P<0.001).

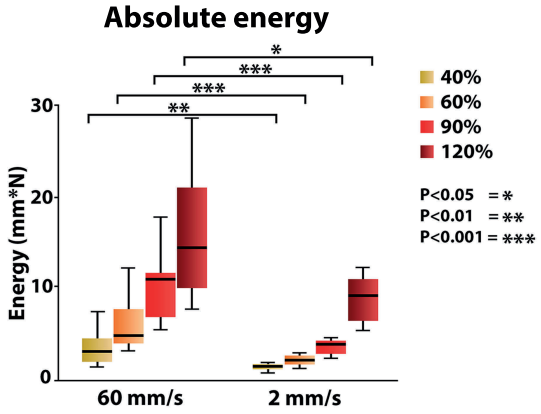


**Figure 5** Absolute energy needed for different excursion levels at high-velocity (60 mm/s) and low-velocity (2 mm/s) tendon excursions. High-velocity tendon excursion required more energy at most excursion levels. Low-velocity tendon excursion data previously published by Vanhees et al.[15]

We found a significant drop of the energy ratio between 40% and 60% of the physiological excursion (Figure 4). At low-velocity tendon excursions, no significant drop was found between the energy ratios at this level but, rather, was delayed until 90% of the physiological excursion.[15] Furthermore, a lower energy ratio was found for high-velocity tendon excursions at 60% of the physiological excursion (P≤0.039) (Figure 6). At 120% of the physiological excursion, the high-velocity tendon excursion showed a higher energy ratio compared to the low-velocity tendon excursions at the same level (P≤0.035).[15] Force ratios at 90% and 120% of the physiological excursion were lower at high-velocity testing compared to the low-velocity testing (P≤0.005).[15]

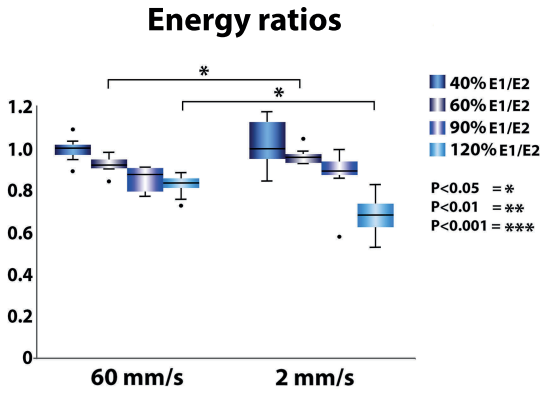


**Figure 6** Displayed are the E1/E2 ratios for different relative excursion levels at high-velocity (60 mm/s) and low-velocity (2 mm/s) tendon excursions. Low-velocity tendon excursion data previously published by Vanhees et al.[15]

## DISCUSSION

The SSCT is a multi-layered collagenous structure that envelops each individual flexor tendon and the median nerve within the carpal tunnel. The tendon motion stretches the layer of the SSCT that is most close to the tendon, and then sequentially stretches layer-by-layer until all interconnecting fibres between the layers are successfully engaged. The tissue may be stretched to the point that the tensile strength of some of the interconnecting fibres is exceeded causing them to rupture. The SSCT is thought to be viscoelastic like most biological tissues (e.g., tendon, ligaments, muscle).[20] Abundant evidence exists to show that stiffness increases in viscoelastic tissues in response to increasing strain rate.[21-26] With loading at faster strain rates, less time is available for fluid to displace, which limits deformation and leads to increased stiffness.[22,23,27] In addition, higher strain rates decrease failure strain, suggesting an embrittlement of the material.[25] Being such a material, SSCT should stiffen and be more prone to damage at higher velocities. Our results support both these phenomena in the SSCT.

When comparing low-velocity tendon excursion data as reported by Vanhees et al. with high-velocity tendon excursion test results of this study, a significant drop in energy and force ratios occurred earlier in the physiological range of tendon motion at high-velocity tendon excursion, and more force and energy were needed for high-velocity tendon excursions.[15] A significant drop in energy and force ratios was observed at a smaller physiological tendon excursion for high-velocity tendon excursions. Stiffening results in diminished stretching capabilities of the interconnecting fibers. Yoshii et al. found decreased SSCT stretching at high-velocity tendon excursions as well.[13] Secondly, peak forces and resistance energy were found to be 1.7 up to 4.2 times greater in specimens tested at higher velocities, with the exception of peak force measurements at 120% excursion, a direct result of the viscoelastic stiffening.

High-velocity tendon excursions seem to advance the damage threshold. Previous studies have suggested that damage to the SSCT occurs within the physiological range of tendon excursion.[14,15] Low-velocity tendon excursion results showed that the damage initiated approximately around 90% of the physiological excursion.[15] In this study, tendon excursions were considerably faster. Using this velocity of tendon excursion, the onset of the drop in energy and force ratios occurred earlier, approximately at 60% of the physiological tendon excursion. This tendon excursion velocity simulated fast tendon motion during common tasks, either during single motions or in the performance of repetitive tasks.[4] We did not attempt to simulate the damage associated with handling vibrating tools, such as drills, which generate vibrations at a frequency of 35 to 150 Hz,[28] or chain saws, which have a frequency range up to 500 Hz and, in undampened mode, produce displacements of 300-400 microns.[29]

Incomplete relaxation of materials with viscoelastic properties can influence energy and force measurements. We found no differences between ratios of energy or force comparing the ratio of the second cycle versus the first cycle and the third cycle versus the first cycle. Furthermore, the relaxation state forces at the start of each ramp-stretch test cycle were all comparable within the same cadaver hand. This suggests that there was sufficient relaxation time between test cycles and that loss of energy and force can be attributed to damage of the SSCT.[15]

After 90% of the physiological excursion of the FDS3 tendon, the drop in energy ratio declined. We performed repeated ramp-stretch test cycles whereby stepwise damage was initiated by increasing the relative tendon excursion stepwise. The damage done was irreversible. The number of fibres, which can be damaged, is finite. Progressively larger excursions will damage fibres that may have been stretched but were undamaged by the previous excursions. If more fibres are damaged at the next highest excursion level, the energy ratio will drop. Eventually, however, more fibres will have been damaged in all previous cycles than can be damaged in a single cycle, even to the point that all fibres have been destroyed. At this point the ratio will theoretically increase to a value of 1, and no further damage can be done. The shape of the energy ratio curve may therefore provide additional information about the amount of fibres damaged.

This study has several limitations. First, the properties of the SSCT within the cadaver model may be different compared to the in vivo carpal tunnel (e.g., changes in carpal tunnel pressure, no repairing capabilities). Changes between properties in vivo and the cadaver model need to be taken into account when interpreting the results. However, since conclusions were based on ratios rather than absolute data, we believe that the results found are likely to be applicable to the in vivo situation. Second, no distinction was made between the different components of the resistance load present in the carpal tunnel complex (e.g., friction). Friction has been postulated to play a role when a tendon is pulled through the carpal tunnel.[15] We observed a higher-magnitude toe region in the force-

displacement response generated with the high-velocity tendon excursions,[15,30] although no quantitative comparisons were made. This is consistent with classical models of viscoelastic material behaviour of the friction and thereby velocity dependent. Higher velocities are accompanied by relative higher friction forces of viscoelastic materials. Contact friction is unaffected by damage and remains constant regardless the excursion level. Since energy is an accumulated measure and peak force measurements are instantaneous, energy ratios may be particularly sensitive to changes in the resistance distributed between different mechanisms, namely SSCT stretching and friction. This may explain as well why the ratio of energy declines less rapidly than the force ratios, particularly at high-velocity tendon excursions. Third, the data of high-velocity tendon excursions was compared with low-velocity tendon excursion data of a previous study.[15] Although the two cadaver specimen groups were comparable for gender, the average ages of the specimens were different. However, since the increase of incidence of CTS is found to initiate around the age of 40,[31,32] possible anatomical changes that may affect the pathogenesis of CTS are likely to occur around this age and not later. Therefore the difference of the average age of the wrist specimens (77 years in this study compared to 60 years in the study of Vanhees et al.) was thought to be insignificant.[15] In addition, the protocol and equipment were similar, therefore the studies were assumed to be comparable. Finally, we would have preferred to study the damage thresholds at the two different tendon excursion velocities within the same hand, to minimize any form of bias. However, whether done concurrently or sequentially, this was not possible. Since we were testing for a damage threshold (and assumed we reached it following the protocol for one velocity), we would no longer have a pristine specimen in which we could test reliably the properties and thresholds for a subsequent velocity.

In conclusion, increasing tendon excursion velocity lowers the threshold of the SSCT damage. This finding may have relevance in understanding the pathogenesis of conditions associated with SSCT fibrosis, such as CTS, and their relation to occupational factors.

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# 3

# DELINEATION OF THE MECHANISMS OF TENDON GLIDING RESISTANCE WITHIN THE CARPAL TUNNEL

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## ABSTRACT

Forceful, high-velocity and repetitive manual hand tasks have been identified to contribute to the onset of carpal tunnel syndrome (CTS). Little is known about the components contributing to tendon gliding resistance in the carpal tunnel. The purpose of this study was to identify these different components. Four pairs of human cadaver hands were used. Tendon gliding resistance was measured under different conditions; with and without intact subsynovial connective tissue (SSCT), at 2 mm/s and 60 mm/s tendon excursion velocity, and with and without relaxation time before a tendon excursion. Force, energy and stiffness were calculated. SSCT stretching was found to play a substantial role. Higher tendon excursion velocities resulted in increased gliding resistance force and energy that could be contributed to the SSCT and SSCT stiffening was observed. Poroelastic properties of the tendon, and possibly SSCT, played a role as well since relaxation time significantly increased gliding resistance force and energy (all $p<0.01$) and the difference for energy and force between high-velocity and low-velocity tendon excursions increased with relaxation time ($p=0.01$ and $p<0.01$). Lastly, without relaxation time no difference in force and energy was found ($p=0.06$ and $p=0.60$), suggestive for contact friction. With increased carpal tunnel pressure, as in CTS, increased gliding resistance is observed. Increased gliding resistance can come from changes in any of the above-mentioned components due to fibrozation and damage of the SSCT.

## INTRODUCTION

Forceful, high-velocity and repetitive manual hand tasks have been identified to contribute to the onset of carpal tunnel syndrome (CTS),[1-3] a commonly diagnosed neuropathy of the median nerve (MN). These motions are related to high tendon gliding resistance (GR).[4-6] Various studies have been performed analysing various hand and wrist motions that resulted in high tendon GR.[4,5,7,8]

Little is known about the components contributing to the tendon GR. Filius et al. and Vanhees et al. observed the tendon GR curve to have an initial "toe" followed by a plateau and an ascending response.[5,9] The "toe" with the plateau reflected what has been observed in isolated flexor tendon gliding experiments in the zone A2-pulley area, whereby it was suggested that this behaviour was the result of contact friction between tissues.[10,11] The ascending response of the tendon GR curve was hypothesized to be the result of stretching of the subsynovial connective tissue (SSCT), a multi-layered structure surrounding the flexor tendons and MN within the carpal tunnel that is thought to reduce friction between these structures and provide resistance to tendon motion.[12,13] Lastly, the poroelastic properties of the tendon, and possibly a similar poroelastic response in the SSCT, may also play a role in GR.[14-16] Many biological tissues are infused with an ionic interstitial fluid that may interact with the deformation of biological tissues, a phenomenon known as poroelasticity.[17]

To date, just the total tendon GR within the carpal tunnel has been evaluated and solely hypothesizes are made about the delineation of the components contributing to the GR. Fortunately, observations of the structural composition of the carpal tunnel through histology have been reported and recognition of similar mechanical behaviour to that of flexor tendon gliding provides clues to the separate mechanisms that may play a role.[13,18]

The purpose of this study was to develop an experimental set up that sequentially isolates the resistance components and thereby identifies the components of tendon GR within the carpal tunnel. The approach to separating the resistance components will be based on differences in mechanical response expected from changes in structural integrity, tendon excursion velocity, and relaxation time allowed between excursions. These findings will allow us to better interpret cadaver studies about tendon GR and relate results of previous cadaver studies to the in vivo condition, which in turn may lead to more a complete understanding of digit motion and it's role in the pathophysiology of CTS.

## MATERIALS AND METHODS

The GR measured during tendon excursion is hypothesized to be the result of SSCT deformation, tendon deformation and contact friction between the flexor tendon and surrounding tissues (Figure 1 and equation 1). [15,19-23]

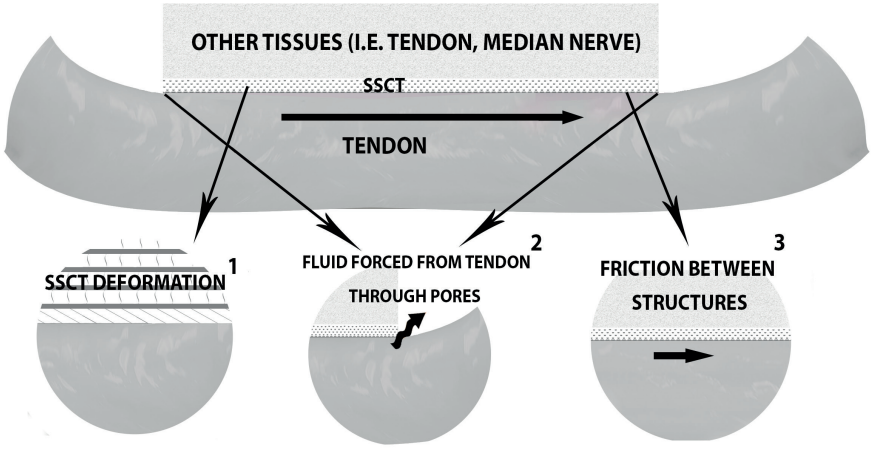


**Figure 1** The different components thought to play a role in GR: 1) SSCT deformation, 2) tendon deformation and 3) residual contact friction.

$$F_{\text{total gliding resistance}} = F_{\text{SSCT deformation}} + F_{\text{tendon deformation}} + F_{\text{contact friction}} \quad \text{Eq. 1}$$

The SSCT contribution to the GR is expected to result from SSCT stretching as previously has been observed with electron microscopy.[13,18] The tendon and possibly the SSCT, possess poroelastic properties that have a time-dependent effect on tendon biomechanics and may therefore have an effect on GR.[24,25] Lastly, contact friction is thought to play a role in GR, as has been observed with tendon gliding at the A2-pulley level.[10,16]

Four pairs of human cadaver hands were used. Two pairs of hands were from males and 2 pairs of hands were from females. The mean age of the cadaver specimens was 74 years (range 57 to 83 years). Specimens were obtained from the Mayo Clinic Institutional Anatomical Bequest Program with Biospecimens Committee and had Institutional Research Board approval. The cadaver specimens were screened for a medical history of CTS, upper extremity surgery, and fractures of the upper extremity.

### *Specimen preparation*

The cadaver specimens were thawed approximately 10 hours before testing at 5°C. The cadaver hands were prepared as previously described.[5,9] Briefly, the wrist was mounted onto a jig, with the wrist fixed in the neutral position and all fingers fixed with a K-wire in an extended position, except the middle finger. After determining the physiologic excursion of the flexor digitorum superficialis tendon of the middle finger (FDS3), the middle finger was fixed as well in a fully extended position. The FDS3 tendon was exposed distal to the carpal tunnel and sharply transected at the metacarpophalangeal joint level. The distal end of the FDS3 tendon was connected to a 50 gr weight while the proximal end was connected to a 25-N load cell (MDB-5, Transducer Techniques, Temecula, CA, USA) (Figure 2).

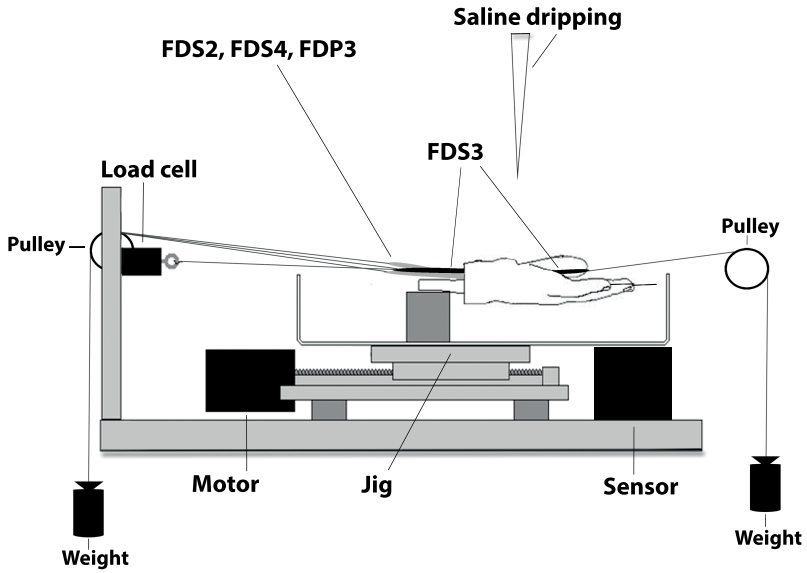


**Figure 2** Experimental set up.

### *Mechanical testing*

A stepper motor-driven test actuator controlled the velocity and displacement of the movement for each cycle. Displacement of the stage was monitored with a potentiometer sensor (TR 75, Novotechnik U.S., Southborough, MA, USA). Force and displacement data were recorded at a sample rate of 100 Hz for low-velocity tendon excursion (2 mm/s) and 1000 Hz for high-velocity tendon excursion (60 mm/s). The FDS3 tendon was preconditioned by repeating 3 tendon excursions to 5 mm at 2 mm/s. GR was evaluated over a FDS3 tendon excursion of 55 mm, which was enough to ensure that the 95% confidence interval of the physiological excursion of the FDS3 tendon was included in the excursion and an

additional 5 mm for deceleration. Where applicable, tissue was allowed to relax for 15 minutes, which is an adequate period of time for tissue to relax to equilibrium.[5,9] The specimens were kept at room temperature (20°C) and were moistened throughout testing with a sterile saline drip. A flow-chart of the experiment conditions is shown in Figure 3.

For each condition, the general force-displacement curve was grossly described. GR forces (F) and energy (E) at 100% of the physiological excursion of the FDS3 tendon were calculated for each tendon excursion. The stiffness (S) at 100% of the physiological excursion for intact SSCT conditions was also calculated, which was the slope of the linear region at 100% of the physiological excursion.[9]

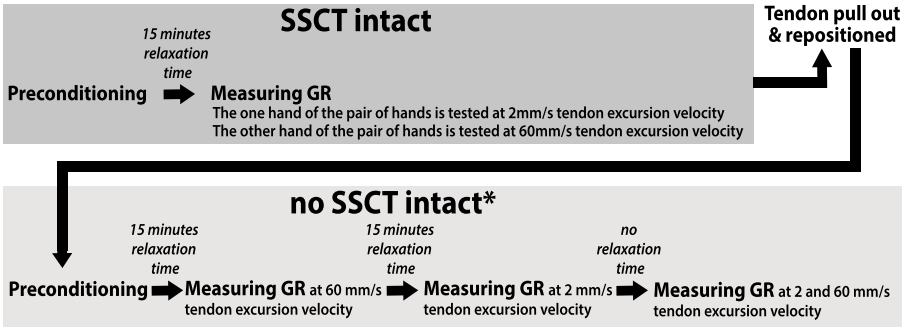


**Figure 3** Flow diagram of the mechanical testing protocol. *The order of testing (i.e., 2mm/s or 60mm/s and with or without relaxation time) was done in a random order.

### *Analysing the contribution of the SSCT*

To test the contribution of the SSCT to GR, the total GR with and without intact SSCT was compared. Four hands were tested with an excursion velocity of 2 mm/s and the contralateral hands of the 4 pairs of hands were tested at 60 mm/s. First the tendon GR was measured with the SSCT intact. Hereafter, the FDS3 tendon was completely pulled out, severing all SSCT connections, repositioned in the carpal tunnel, and then the tendon GR was measured again. Before each pull, the tissue was allowed to relax for 15 minutes regardless whether or not the SSCT was intact. By subtracting the GR data with intact SSCT from GR data without intact SSCT the SSCT contribution to tendon GR was isolated.

In addition, to analyse the presumed viscoelastic properties of the SSCT, the effect of tendon excursion velocity was tested based on the SSCT GR data. If SSCT is a viscoelastic material as hypothesized, the GR force, energy and stiffness at 100% of the physiological excursion are expected to be higher at the 60 mm/s tendon excursion velocity compared to 2 mm/s tendon excursion velocity. We used the Wilcoxon signed rank test to compare both groups. A p-value of $<0.05$ was considered significant.

Lastly, we evaluated the contribution of SSCT to the total GR by calculating the portion of the SSCT contribution to the total GR at 25%, 50%, 75% and 100% of the physiological excursion of the FDS3 tendon.

### *Analysing the contribution of tendon deformation*

The contribution of tendon deformation, hypothesized to be a poroelastic effect, was evaluated next. After complete pull out and repositioned of the FDS3 tendon, all hands were tested at 2 mm/s and 60 mm/s tendon excursion velocities and with and without relaxation time in-between pulls, these different test conditions were tested at random. A poroelastic response, if present as the model supposes, was expected to cause a higher GR force and energy for excursions with relaxation time compared to those without.[16,23,24] Further evidence would be provided if these differences were amplified with higher tendon excursion velocities. Excursions under these different test conditions were compared using the paired t-test. A p-value of $<0.05$ was considered significant.

### *Analysing the contribution of contact friction*

Allowing no relaxation time in-between pulls was expected to nullify the poroelastic effect, and the contribution of the contact friction could be confirmed and evaluated. If contact friction effect were present, it was expected to result in a measurable, non-zero GR, and that this value would not be sensitive to the excursion velocity. Excursions not preceded by relaxation time at different excursion velocities were compared using the paired t-test as described earlier. A p-value of $<0.05$ was considered significant. All statistical analysis was done with Statistical Package for Social Science software (SPSS version 17.0, Chicago, IL, USA).

## RESULTS

The mean physiological excursion of the FDS3 tendon was 18.4 mm (range 16.4-21.3 mm).

### *SSCT contribution*

The SSCT GR curve was a monotonically ascending curve increasing with excursion at both low-velocity and high-velocity tendon excursions. At the high-velocity tendon excursions, mean GR forces, energy and SSCT stiffness were considerably higher than those observed at the low-velocity tendon excursions, although the difference was not significant ($p=0.07$, $p=0.07$ and $p=0.14$, respectively) (Table 1).

At the beginning of the FDS3 tendon excursion, SSCT stretching contributed for 40 to 75% to the total GR and at the end of the physiological excursion of the FDS3 tendon the SSCT stretching contributed up to almost a 100% (Figure 4).

| Motion Type | Force (mN) | Energy (μJ) | Stiffness (mN/mm) |
|---|---|---|---|
| Slow | 720 (577-1084) | 3667 (2542-4607) | 144 (72-219) |
| Fast | 1444 (852-2643) | 6324 (4656-16907) | 215 (164-519) |

**Table 1** The median SSCT GR force, energy, and stiffness with range at 100% of the FDS3 tendon physiological excursion in the 4 pairs of cadaver hands.

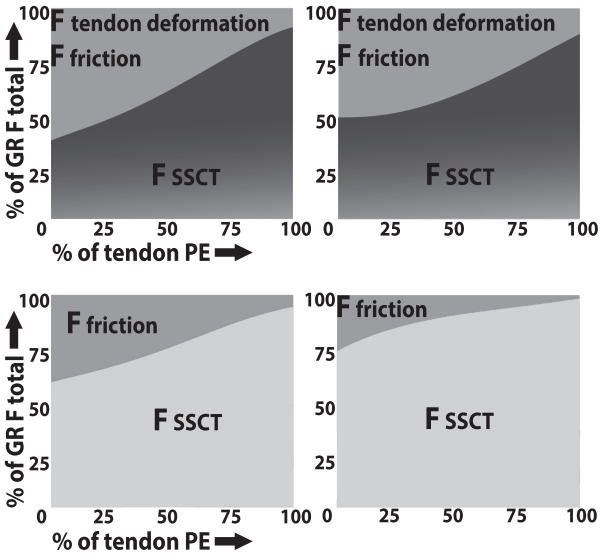


**Figure 4** F SSCT deformation and F contact friction with and without F tendon deformation as portion of GR F total.Represented are the data; **A**. with excursion velocity 2 mm/s with relaxation time. **B**. with excursion velocity 60 mm/s with relaxation time. **C**. with excursion velocity 2 mm/s without relaxation time. **D**. with excursion velocity 60 mm/s without relaxation time. Abbreviations: GR; gliding resistance, F; force, PE; physiological excursion.

### *Poroelastic properties of the tendon*

When comparing GR with and without relaxation time, there was a significant difference for GR force and energy between these groups at both low- and high-velocity tendon excursion ($p<0.01$ and $p<0.01$) (Table 2). The difference in GR force and energy between pulls with and without relaxation time was amplified at the higher tendon excursion velocity compared to the low-velocity tendon excursion ($p=0.01$ and $p<0.01$).

### *Contact friction contribution*

The contact friction was 48 mN at low-velocity tendon excursion and 55 mN at high-velocity tendon excursion. Without relaxation time the GR force and energy at high- and low-velocity tendon excursion were not different ($p=0.06$ and $p=0.60$) (Table 2).

| Motion Type | Force (mN) | Energy (μJ) | Force (mN) | Energy (μJ) |
|---|---|---|---|---|
| | With relaxation time | | Without relaxation time | |
| **Slow** | 69<br>SD 25 | 1328<br>SD 472 | 48<br>SD 16 | 752<br>SD 276 |
| **Fast** | 279<br>SD 146 | 4356<br>SD 346 | 55<br>SD 16 | 772<br>SD 220 |

**Table 2** Mean GR force and energy with standard deviation (SD) at different test conditions in 8 cadaver hands.

## DISCUSSION

Elevated carpal tunnel pressure, a predominant feature of CTS, is associated with increased GR and high-velocity repetitive hand and wrist motions.[4,5,7,26] GR is the result of moving tendons. Therefore a good understanding about GR is important. Although various studies have evaluated the GR and frictional work of the flexor tendon in the carpal tunnel during various motions and hand-wrist positions, the delineation of the different mechanisms involved in GR has not been elucidated. The results of this study indicate that SSCT stretching, poroelastic properties of the flexor tendon, and possibly SSCT, and contact friction with surrounding tissues all contributed to the GR.

An increase of GR force and energy and a trend of increased stiffness due to SSCT stretching was seen at larger excursions and higher tendon excursion velocities. Although previous studies have speculated the ascending part of the GR curve was an isolated result of SSCT stretching, we have confirmed this hypothesis.[5,18,27] The SSCT demonstrates characteristics corresponding to viscoelastic material characteristics, proving that SSCT is a viscoelastic tissue.[20-22,28] In an ex vivo experiment with SSCT of CTS patients increased stiffening of the SSCT was found as well, and this led to SSCT embrittlement.[27] If the same mechanism applies for the SSCT at high-velocity tendon excursion, then this may explain why high-velocity tendon excursion is a risk factor for CTS.

After disruption of all SSCT fibres connected with the FDS3 tendon, we found a static GR curve after an initial toe region. The height of this curve depended on relaxation time and tendon excursion velocity. An increase in GR was observed when allowing relaxation time in-between pulls and increasing tendon excursion velocity amplified this effect. This response of tissue to these different test conditions is typical for poroelastic materials.[16,29] Without relaxation time between tendon excursion cycles, there was still GR, which was not velocity depended. We believe this believe is the result of contact friction with surrounding tissues. This is also found in other flexor tendon excursion experiments without SSCT involvement.[10,11] Whether the absolute GR is equal to that found for intrasynovial flexor digitorum profundus tendon GR through the A2-pulley is unknown since different loads were used which makes the results not fully comparable.[10,30]

This study has several limitations. First, we have not analysed if relaxation time influences GR when SSCT is intact. Previous studies have shown that SSCT can be damaged within the range of physiological tendon excursion and allowing no relaxation time in-between pulls would not allow viscoelastic recovery of the stretched SSCT.[5,9] Therefore the source (e.g., damage or poroelastic effects) for possible differences found for GR with SSCT intact with or without relaxation time could not be attributed. Secondly, cadaver hands were moistened with sterile saline. Although saline is a standard means of attempting to simulate physiological conditions for testing tendons, it has shown that it can be absorbed more actively compared to normal internal fluids.[9,23] Therefore, the moistening may have led to a non-physiological increase of GR. Lastly, the sample size to compare the SSCT data at different tendon excursion velocities was too small to show significant differences between groups for some measurements. However, since our purpose was merely to demonstrate prove for assumptions made in previously published studies and since for all paired cadaver hands similar trends were seen, we do think it is possible to draw conclusions based on our results.

Although various studies reported about the GR in the carpal tunnel, none investigated the contributions of the different components to the total GR. In this study we identified the different components of GR based on differences in mechanical response under different test conditions. SSCT stretching, poroelasticity of the tendons, and friction contact with surrounding tissues all appeared to contribute to the total tendon GR. With increased carpal tunnel pressure, as in CTS, increased gliding resistance is observed. Increased gliding resistance can come from changes in any of the GR components due to fibrozation and damage of the SSCT.

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# 4

## THE EFFECT OF TENDON EXCURSION VELOCITY ON LONGITUDINAL MEDIAN NERVE DISPLACEMENT: DIFFERENCES BETWEEN CARPAL TUNNEL SYNDROME PATIENTS AND CONTROLS

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## ABSTRACT

The subsynovial connective tissue (SSCT) is a viscoelastic structure connecting the median nerve (MN) and the flexor tendons in the carpal tunnel. Increased strain rates increase stiffness in viscoelastic tissues, and thereby its capacity to transfer shear load. As a result, tendon excursion velocity may impact the MN displacement. In carpal tunnel syndrome (CTS) the SSCT is fibrotic and can be ruptured, which may affect MN motion as well. In this study, ultrasonography was performed on 14 wrists of healthy controls and 25 wrists of CTS patients during controlled finger motions performed at 3 different velocities. Longitudinal MN and tendon excursion were assessed using a custom speckle tracking algorithm and compared across the 3 different velocities. In general, MN displacement increased with increasing tendon excursion velocity ($p \leq 0.031$). CTS patients exhibited significantly less MN motion than controls ($p \leq 0.002$). These findings are consistent with the current knowledge of SSCT mechanics in CTS, in which in some patients the fibrotic SSCT appears to have ruptured from the tendon surface.

## INTRODUCTION

Motion of the median nerve (MN) has found to be different in patients with carpal tunnel syndrome (CTS).[1,2] One plausible explanation for this is that the subsynovial connective tissue (SSCT) between the MN and tendons becomes severely damaged and ruptures, which leads to disconnection between the SSCT and tendon or SSCT and the MN.[3] The SSCT is a multi-layered structure with interconnecting collagenous fibres that envelops the MN and tendons.[4-6] Stretching of the interconnecting fibres between the layers and successive engagement of each consecutive layer allows the SSCT to serve as a friction-reducing unit between tendons and between tendon and the MN when tendons are in motion (Figure 1). Ettema et al. showed through cadaveric study, subsequently confirmed clinically, that the SSCT of CTS patients falls into at least two distinctly different categories, either tightly adhering to the tendon or becoming completely disconnected from the tendon.[3]

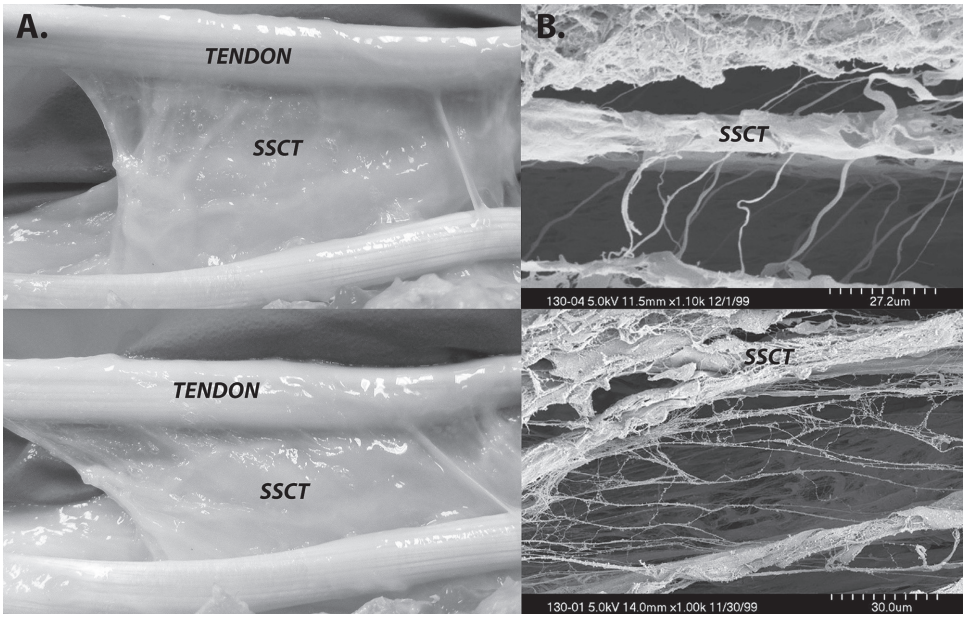


**Figure 1 A-B** Shown is a macroscopic (**A**) and electron microscopic (**B**) image of the SSCT between tendons. Normally, the SSCT is a flimsy structure that envelops the structures within the carpal tunnel. The SSCT consists of layers with interconnecting fibres. These interconnecting fibres are also connected to the tendon, stretching the interconnecting fibres between consecutive layers when the tendon moves. *Copyright for figure 1B is granted (Plast Reconstr Surg. 2006 Nov; 118(6): 1413-22).*

As a soft connective tissue, SSCT is thought to possess viscoelastic properties.[7] Abundant evidence exists demonstrating that increased strain rates increases stiffness and reduces deformation at failure in viscoelastic tissues.[8-14] Filius et al. showed that peak forces and

resistance energy of tendon excursion in the carpal tunnel were greater in specimens tested at higher velocities, most probably a direct result of viscoelastic stiffening of the SSCT.[15] If SSCT stiffness, and thereby its capacity to transfer shear load, increases as a result of higher strain rates, MN displacement should increase at higher tendon excursion velocities, since the MN is a relatively loose structure within the carpal tunnel and the nerve cannot move actively.

In CTS patients, fibrotic changes of the SSCT have been observed.[16-18] Fibrotic SSCT is stiffer and ruptures at smaller strains during tendon excursion.[19] This combination of increased stiffness and failure at smaller tendon excursions could be a major contributor in a vicious cycle of initial SSCT injury, resulting fibrosis, decreased elasticity, further sensitivity to injury, and more fibrosis.[3,20] Indeed, some authors have postulated that such a vicious cycle may be the root cause of CTS.[3,21-23] This effect might be even more pronounced during higher velocity tendon excursions.[15]

Much of our knowledge of SSCT mechanical behaviour has come through cadaveric experiments. While useful, there are a number of limitations in these experiments that necessitate study in live subjects to identify similar response to confirm these models. In this study we investigated the effect of increasing tendon excursion velocity on the resulting MN displacement in both CTS patients and healthy controls. Secondly, we investigated whether or not tendon excursions change in CTS patients.

## METHODS

### *Subjects*

Fourteen healthy controls and 18 CTS patients were selected for this study. Seven patients had bilateral CTS, so subsequently 25 CTS hands were analysed in this study. CTS was confirmed based on clinical examination and nerve conduction study results.[24,25] Subjects were excluded from this study if they had a medical history of upper extremity surgery or fractures of the wrist or hand or disorders of the musculoskeletal system. All procedures were reviewed and approved by our Institutional Review Board.

### *Ultrasound assessment and analysis*

Subjects were seated with the arm positioned on an adjacent table. The arm was positioned such that the forearm was supinated, the elbow flexed to 60 degrees, and the wrist was in the neutral position. Subjects were asked to flex their fingers from full extension until the tip of their fingers touched the palm of the hand. They were asked to perform this motion over time periods of 8, 4 and 2 seconds (defined, respectively as low-, medium-, and high-velocity tendon excursion). High frequency ultrasound scans of the MN, the flexor digitorum superficialis tendon of the middle finger (FDS3) and the flexor digitorum profundus tendon

of the middle finger (FDP3) were made using a Philips iU33 ultrasound machine (Philips Electronics, Best, The Netherlands) with a 7-15 MHz linear array transducer. The full range of frequencies was used, depending on the depth of the structure. The transducer was placed at the distal wrist crease at the level of the inlet of the carpal tunnel defined as the proximal border of the pisiforme bone (Figure 2). After the structure of interest (i.e., the MN, FDS3 or FDP3) was clearly visualized, there was zoomed in on the structure using the "zoom" function. The ultrasound imaging settings were set at maximum frame rate and lossless imaging formats were used.

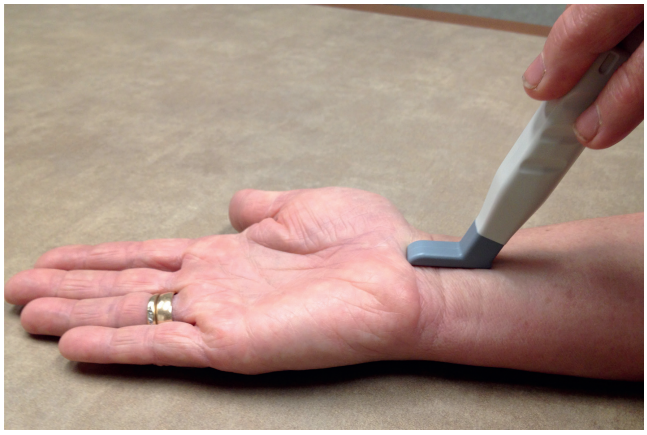

**Figure 2** Placement of the probe on the wrist when making ultrasound scans of the median nerve and flexor tendons of the middle finger at the carpal tunnel.

Data processing to calculate longitudinal displacement of the aforementioned structures has been described previously by Korstanje et al.[1,26] In brief, ultrasound images were imported into the program OsiriX (version 4.1.2 64-bits, http://osirix-viewer.com), rotated if needed and exported as uncompressed audio-video interleave (AVI) files. The uncompressed AVI's were imported into Matlab (Version 2011a, The MathWork Inc., Natick, MA, USA) and analysed with an in-house developed and validated speckle tracking algorithm (Figure 3).[27]

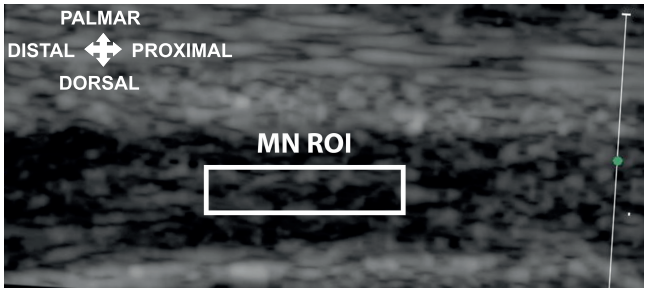


**Figure 3** Representative example of a longitudinal plane ultrasound scan of the median nerve (MN) with placement of the region of interest (ROI).

Absolute displacements of the MN, FDS3 tendon and FDP3 tendon were calculated. The FDS3 and FDP3 tendon displacements were calculated for solely the low velocity. Relative MN displacements were characterized by normalizing absolute MN displacement with the FDS3 tendon displacement. Defining MN motion relative to FDS3 tendon displacement in this way was done because the FDS3 tendon is the tendon closest to the nerve and assumed to have the greatest influence on MN motion.[28] Relative tendon excursion was defined as the ratio of the FDP3 tendon displacement to FDS3 tendon displacement.

### *Statistical analysis*

Differences between the controls and CTS patients for group characteristics, absolute displacement of the MN and tendons as well as the MN/FDS3 and FDS3/FDP3 ratios were analysed using the unpaired t-test and the chi-square test. Repeated measures ANOVA was used to evaluate differences in relative MN displacement at different tendon excursion velocity levels within the two groups. P-values of 0.05 or less were considered significant. The statistical analysis was done with Statistical Package for Social Science software (SPSS version 17.0, Chicago, IL, USA).

## RESULTS

Twenty-five hands of 18 CTS patients were imaged, as were 14 hands of 14 healthy controls. No significant differences where found for age, gender or body mass index between the two groups (Table 1).

| | Patients (N=18) | Controls (N=14) | P-value |
|---|---|---|---|
| **Age** | 50 (SD 12) | 42 (SD 12) | 0.066 |
| **Gender (male)** | 44% | 36% | 0.618 |
| **BMI** | 32 (SD 7) | 30 (SD 13) | 0.503 |

**Table 1** Study group characteristics.
Abbreviations: SD; standard deviation, BMI; body mass index.

Patients had significantly less absolute and relative MN motion regardless of the tendon excursion velocity, respectively $p \leq 0.002$ and $p < 0.001$ (Table 2). The largest difference in relative MN motion was observed at high-velocity tendon excursion. No significant differences between patients and controls were found for either absolute FDS3 or FDP3 tendon displacement. However, the FDP3/FDS3 ratio for CTS patients was significantly smaller than that for controls ($p=0.001$).

| | CTS hands (N=25) | Control hands (N=14) | P-value |
|---|---|---|---|
| **Absolute MN displacement (cm) at** | | | |
| *Low*-velocity tendon excursion | 0.18 (SD 0.10) | 0.21 (SD 0.07) | <0.001 |
| *Medium*-velocity tendon excursion | 0.21 (SD 0.12) | 0.33 (SD 0.10) | 0.002 |
| *High*-velocity tendon excursion | 0.23 (SD 0.12) | 0.40 (SD 0.11) | <0.001 |
| **Absolute tendon displacement (cm) at** | | | |
| FDS3 tendon excursion | 1.88 (SD 0.48) | 1.56 (SD 0.52) | 0.064 |
| FDP3 tendon excursion | 2.73 (SD 0.49) | 2.82 (SD 0.51) | 0.608 |
| **Relative MN displacement at** | | | |
| *Low*-velocity tendon excursion | 0.10 (SD 0.06) | 0.22 (SD 0.07) | <0.001 |
| *Medium*-velocity tendon excursion | 0.12 (SD 0.07) | 0.23 (SD 0.07) | <0.001 |
| *High*-velocity tendon excursion | 0.13 (SD 0.08) | 0.28 (SD 0.11) | <0.001 |
| **FDP3/FDS3 excursion ratio** | 1.53 (SD 0.40) | 1.95 (SD 0.44) | 0.005 |

**Table 2** Mean absolute and relative displacement with standard deviation of the MN, FDS3 tendon and FDP3 tendon at different tendon excursion velocities.
Abbreviations: cm; centimetre, SD; standard deviation, MN; median nerve, FDP3; flexor digitorum profundus tendon of the middle finger, FDS3; flexor digitorum superficialis tendon of the middle finger.

In the control group, there was a significant difference in the relative MN displacement between slow-velocity tendon excursion and medium- and high-velocity tendon excursions (p=0.005 and p=0.001). In the CTS patient group solely a difference in MN displacement was seen between low- and high-velocity tendon excursion (p=0.012) (Figure 4).

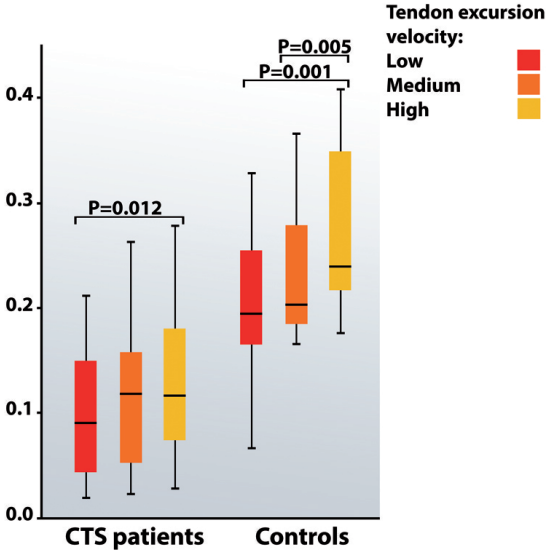


**Figure 4** Relative MN displacements at different tendon excursion velocity levels for CTS patients and controls. Significant differences exist for relative MN motion between the different tendon excursion velocity levels for CTS patients and controls.

## DISCUSSION

In this study we investigated the effect of tendon excursion velocity on MN displacement in CTS patients and healthy controls. We found that in the healthy control group there was more MN displacement compared to the CTS group, and a trend of increased MN displacement at higher tendon excursion velocities was found. This trend, however less obvious, was also observed in the CTS patient group.

Increased tendon excursion velocities resulted in increased MN displacement. The SSCT is a multi-layered structure that interconnects structures within the carpal tunnel. The MN is a structure that moves only passively, by traction either of its attachments or due to contact friction with adjacent tissues, presumably driven by loads of moving tendons that are transmitted through the SSCT.[6,29] High-velocity tendon excursions require more force to overcome sliding resistance compared to low velocity tendon excursions in healthy subjects.[15] A plausible explanation is that this is a result of the viscoelasticity of the SSCT, with the SSCT becoming stiffer at higher velocities. A stiffer SSCT will resist stretching more and will move more closely associated with the driving tendon and taking along the MN. This was indeed observed in our study.

The relative MN displacement was not as strongly affected by different velocities of tendon excursion in the CTS patient group compared to the controls. Moreover, the average relative MN displacement in the CTS patient group was well below that observed in the control group, as noted by others as well.[1,2] This may suggest that in this patient population the SSCT between the MN and FDS3 tendon was at least partly disrupted. We made the assumption that any observed MN motion would be a result of SSCT action, and that if MN velocity and excursion matched that of the adjacent tendon, the most probable explanation was a fibrotic SSCT binding the nerve and tendon together, similar to what has been shown with regard to the SSCT and the flexor digitorum superficialis (FDS) tendon by Ettema et al.[3] Their study showed a non-normal distribution of SSCT motion. Hereby varying degrees of adherence of the SSCT and FDS tendon were found, ranging from tight adherence and linked motion in some CTS patients, to a complete failure of the SSCT-FDS tendon connection in other CTS patients, with no correlation between the movement of one structure and another. This latter phenomenon, we saw especially in our low excursion nerves, but to some extent in all the CTS nerves. This finding suggests that, unlike the SSCT around the FDS tendon, which is often adherent in CTS,[3] with regard to the MN, the SSCT between it and the underlying tendons tend to fail, so that the nerve and tendons are less closely associated. This may result in more fixation of the nerve to the overlying flexor retinaculum, resulting in less dorsal-palmar nerve mobility, a phenomenon observed by others.[30,31]

In this study there was a trend of increased FDS3 tendon excursion. Comparable to the current study, Hough et al. and Doesburg et al. also observed a trend of increased

FDS tendon excursion, although not significant.[2,32] Korstanje et al. found significantly more FDS3 excursion and less FDP3 excursion in CTS patients.[1] Their rationale for this finding was that fibrotic SSCT tissue causes adhesions between the FDS and flexor digitorum profundus (FDP) tendon of corresponding fingers, causing the FDS tendon to be more adherent to the FDP tendon, thereby increasing FDS tendon excursion and restricting FDP tendon excursion.[31] More hands were included into that study and the wrists within the same CTS patient were compared, which will affect the statistical power. To our knowledge finger motion in CTS patients has not been investigated and therefore it is unknown if this motion path is altered. We find the possibility of changes in FDP3/FDS3 synergy in CTS patients intriguing and would find it an interesting topic for further investigation.

Our study has several limitations. First, we measured MN motion and not the SSCT motion. Measuring the SSCT would be relevant, because it is an important component of the carpal tunnel and implicated in the aetiology of CTS. However, obtaining consistent and reliable SSCT displacement measurements is difficult, because the SSCT is a very thin structure (<1 mm), at the limit of resolution of our ultrasound method, especially at high-velocity tendon excursions. High-velocity tendon excursions associated with more vigorous movements are likely to cause more transverse displacement and more speckle pattern changes per frame. Currently very-high frequency ultrasound machines (i.e., VisualSonics Vevo 2100) are developed with increased quality of imaging and storage capacity. In the future usage of these machines in vivo may increase the accuracy of the measurements of SSCT motion. In addition, more experience and further development of analysing methods taking into account the layered properties of SSCT may also lead to more accurate measurements. For now, our rationale to focus on the MN is that CTS is ultimately a disorder of the MN. Moreover, in this study we made the assumption that any observed MN motion would be a result of SSCT action, as described above. Therefore MN motion was considered to be a good alternative to measuring SSCT motion directly, although this could be a matter of debate based on findings of this study. A second limitation is that we have not investigated factors that could also play a role in affecting the MN motion, such as the size of the MN, which is altered in patients with CTS.[33,34] Third, tendon excursion was only measured at one speed and was assumed constant. Yoshii et al. showed that for the same motion tendon excursion remained constant regardless different tendon velocities.[35] Therefore, we believe that this is a reasonable assumption, but if excursions were different at different velocities, this will have affected the results. Lastly, we did not take into consideration the difference between dominant versus non-dominant hand or right versus left hand. Few is know about possible biomechanical differences for hand dominance in vivo. Filius et al. did not find difference in transverse plane tendon and nerve motion between the two hands of one individual.[28] However, the effect on hand dominance and tendon and nerve motion in the longitudinal plane is unknown.

In summary, ultrasonography in living subjects confirms that MN displacement increases with increasing tendon excursion velocity. Less MN displacement is found in CTS patients overall and there is a diminished effect of tendon excursion velocity on the MN displacement. This could be caused by a disruption of the SSCT between the MN and nearby tendons, an observation consistent with other studies of CTS patients. These findings may have clinical utility. Whether individual variations in the sonographic findings of CTS patients might have therapeutic or prognostic implications is unknown, but could be studied.

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# 5

# DYNAMIC SONOGRAPHIC MEASUREMENTS AT THE CARPAL TUNNEL INLET: RELIABILITY AND REFERENCE VALUES IN HEALTHY WRISTS

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## ABSTRACT

Reliability and reference values are not well established for most dynamic sonographic measurements of the median nerve and flexor tendons that may be used for diagnosing carpal tunnel syndrome (CTS). Wrists of 20 healthy participants were imaged using ultrasound. Cines of the carpal tunnel inlet were acquired during hand motion. Based on shape and displacement measurements, intrarater and interrater reliability and reference values were calculated. Intraclass correlation coefficients (ICC) for measurements of the median nerve and most flexor tendons were ≥0.51 for shape parameters and ≥0.71 for displacement parameters. During hand motion the median nerve flattened with ulnar movement, tendons became more circular, and flexor tendons of corresponding fingers moved towards each other. Shape and displacement measurements of the median nerve and most flexor tendons had reliability results ranging from moderate to excellent. The reference values may be useful for the diagnosis of CTS.

## INTRODUCTION

Ultrasound is an increasingly used modality for detecting abnormalities at the carpal tunnel. Different studies have shown that in carpal tunnel syndrome (CTS) the cross sectional area (CSA) of the median nerve increases.[1] Recent studies have suggested that ultrasound may not only be valuable for detecting changes in the CSA of the median nerve, but also for measuring changes in shape and displacement of the nerve and tendons during flexion and extension movements of the fingers.[2,3] These sonographic measurements may be valuable for diagnosing CTS.[4-7]

The rationale for measuring shape and displacement can be found in the observed non-inflammatory fibrosis and thickening of the connective tissue in the carpal tunnel.[8] It is suggested that the non-inflammatory fibrosis of connective tissue plays an important role in the development of CTS.[9-13] Moreover, changes in the properties of the connective tissue might be the first pathophysiological step in the development of CTS.[14] Changes in connective tissue properties may alter movement of the nerve and tendons and thus affect the median nerve.[15-18] Consequently, measuring changes in shape and displacement of the nerve and flexor tendons just proximal to the carpal tunnel inlet may provide information about possible changes in CTS patients.

Nonetheless, the sonographic image quality and thus the interpretation of the sonographic images varies between raters.[19] While some studies have reported on the dynamic changes of the nerve and tendons in transverse sonographic images,[2,3] to our knowledge, no study has been conducted to examine the reliability of these measurements within 1 rater or between raters.

To answer these questions, we assessed the reliability of measuring shape (area, circularity and perimeter) and displacement (endpoint displacement and path displacement) of the median nerve and the tendons in both wrists of healthy participants using ultrasound. In addition, if measurements were reliable, we report the reference values of shape and displacement parameters for different hand postures.

## MATERIALS AND METHODS

### *Participants*

We recruited 20 asymptomatic participants (10 men and 10 women), with a mean age of 28 years (range 21 to 72 years) and without any history of wrist pathology or upper extremity surgery (e.g., history of traumatic injuries to the hand or forearm, carpal tunnel release, trigger finger). The local medical ethics committee approved this study, and informed consent was obtained from all participants.

### *Sonographic recordings and measurement protocol*

We acquired cines at the carpal tunnel inlet using the Philips iU22 ultrasound system (Philips Electronics, Eindhoven, The Netherlands) and the L12-5 linear array transducer with a frequency band ranging from 5 to 12MHz. The full range of frequencies was used, depending on the depth of the tissue. The following settings were used: all image enhancers on (Xres, SonoCT, and AGC) with exception of persistence, which was turned off to minimize blurring during tendon and nerve displacement. Power output was maximized for full penetration, and the pulse repetition frequency was set at high. The frame rate was fixed at 73Hz, and image resolution was 0.083 mm/pixel. A physician with experience in musculoskeletal sonography of the upper extremity made the cines.

Participants were seated with the arm positioned on a table. The elbow was flexed approximately 120°, and the wrist was extended. The transducer was placed at the distal flexion wrist crease to image the proximal carpal tunnel inlet, which was identified by the pisiform bone and the scaphoid tubercle. Due to the relatively high attenuation rate of bone compared to soft tissue, we visualized just proximal to the pisiform bone and scaphoid tubercle to achieve a more clear view of the nerve and tendons. The median nerve was identified by the hypoechoic fascicular structure surrounded by a hyperechoic nerve sheath, and the tendons were identified by their hyperechoic fibrillar structure. After identification of the median nerve, we identified the flexor digitorum superficialis (FDS) and the flexor digitorum profundus (FDP) tendons of the index finger and middle finger. The tendons of the ring finger and little finger were excluded from identification. These tendons were poorly visible due to different angulation between transducer and tendons compared to that of the median nerve, which was our main focus. Since tendon visualization strongly depends on the angle of insonation, slightly different angles result in a diminished view of the tendon. This change of echogenicity of the tendon due to change of angulation of the tendon with respect to the transducer is called anisotropy.

### *Motion protocol*

We made a 10 second cine of the right and left wrists. Starting from full extension of all fingers (Figure 1A), participants were asked to fully flex all fingers (Figure 1B) within 5 seconds without force. After flexion, participants were asked to maintain this finger position for 2 seconds followed by a forceful grip for 3 seconds (Figure 1C).[20] Participants were not allowed to flex their wrists during finger motions. An assistant researcher checked to be certain that participants followed the protocol. The examination time was approximately 5 to 10 minutes per wrist.

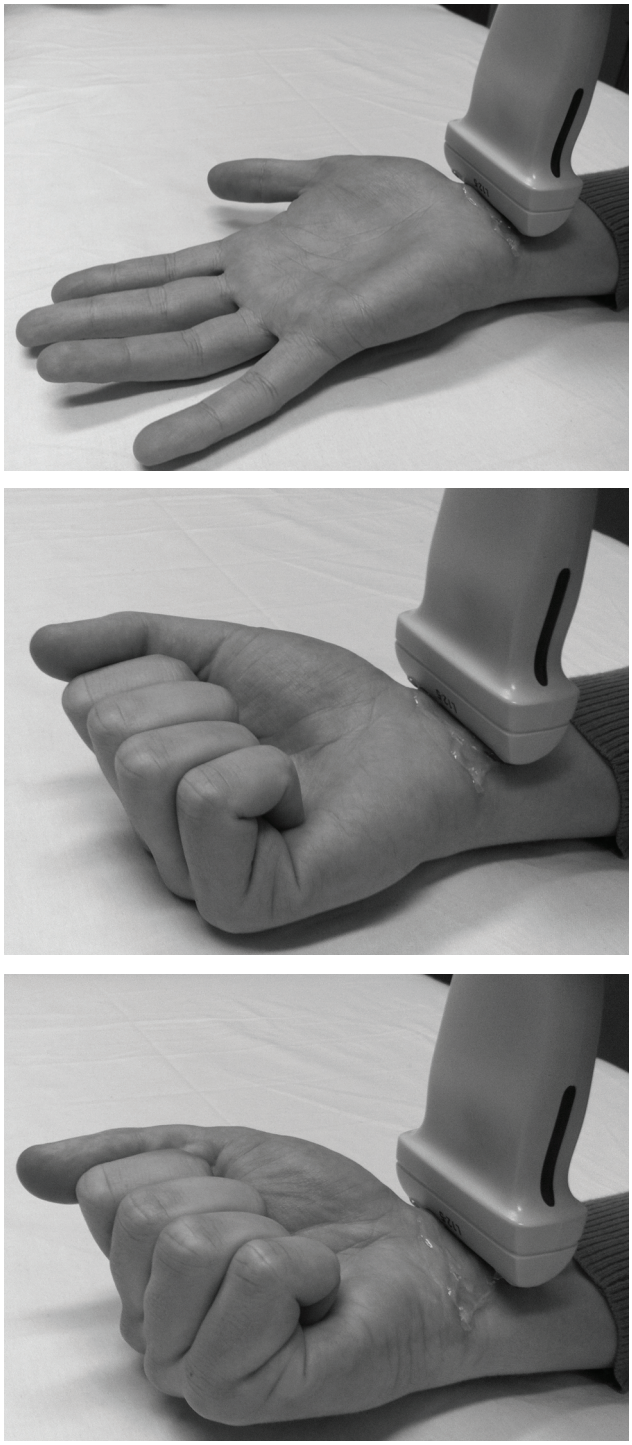

**Figure 1A-C** The different hand postures of the motion protocol; extension of all fingers (**A**), flexion of all fingers (**B**), and flexion with forceful grip (**C**).

### *Image processing*

For analysis we used an in-house developed image processing software package based on Matlab (7.10 R2010a; The MathWorks, Inc., Natick, MA, USA). To identify the different structures and to calculate shape and displacement parameters, we placed polygons manually on the outside border of the median nerve and the 4 flexor tendons in the frames of the audio video interleave (AVI) (Figure 2). All consecutive frames were analysed similarly with a frame interval of 40 frames. This way, we placed polygons on 11 images during the flexion movement of the fingers.

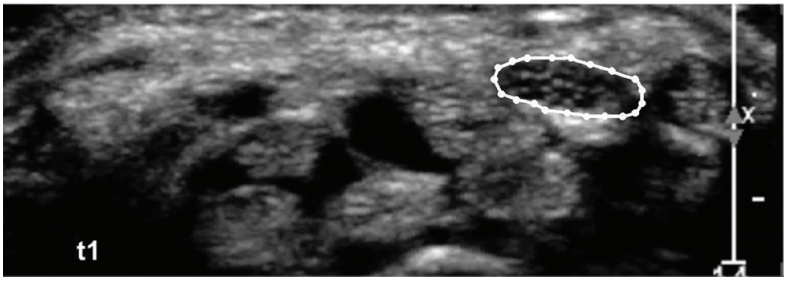


**Figure 2** A transverse sonographic image at the carpal tunnel inlet of the right wrist of a healthy person during extension of all fingers. A manually placed polygon on the outside border of the median nerve is displayed. These polygons were also placed manually around the median nerve and flexor tendons in the different frames of the cines.

### *Shape and displacement parameters*

From the polygons in the AVI files, the following outcome measures were calculated: area, perimeter, circularity, centre of mass (CoM), and the transverse endpoint displacement and path displacement of the median nerve and tendons. The shape parameters values were calculated for all fingers at extension (frame 1), flexion (frame 6), and during forceful grip. Area was calculated based on the number of pixels within the polygon. Perimeter was calculated as the total length of the line segments of the polygon. Circularity was defined as:

$$circularity = 4\pi \cdot \frac{area}{perimeter^2} \qquad \text{Eq. 1}$$

A circularity of 1 indicates a perfect circle, while a circularity smaller than 1 indicates a deviation from a circle, such as a more ellipsoid or a more irregular shape.

Displacement calculations were based on the displacement of the CoM between different frames relative to the CoM of the FDP tendon of the middle finger. The CoM was defined as the gravitational point of the polygon in terms of a x-coordinate (radial-ulnar axis) and y-coordinate (palmar-dorsal axis). Two displacement parameters were calculated; the endpoint displacement and the path displacement.

To calculate endpoint displacement, the displacement was calculated as the difference of CoM coordinates between the frames of the 3 hand postures. N is the frame at the start point and p is the frame at the endpoint, and x and y are the corresponding coordinates of the CoM. For path displacement we compared the displacement between extension of all fingers (frame 1) and flexion of all fingers (frame 6) and extension of all fingers (frame 1) to forceful grip (maximum displacement frame). The endpoint displacement vector between frame n and frame p was defined as:

$$\bar{d}_{endpoint,n,p} = \sqrt{(x_p - x_n)^2 + (y_p - y_n)^2} \quad \text{Eq. 2}$$

To calculate path displacement, the displacements between all consecutive frames were used (frames 1 to 11) and the $\Delta x_p$ in Eq. 2 was substituted by $x_{n-1,}$ and all separate vectors were summated:

$$\bar{d}_{path,n} = \sum_{1}^{n-1} \sqrt{(x_{n-1} - x_n)^2 + (y_{n-1} - y_n)^2} \quad \text{Eq. 3}$$

Since the path displacement includes displacements across all frames, the path displacement is by definition larger than the endpoint displacement.

### *Statistical analysis*

To determine intrarater reliability the first rater analysed the AVI files of the right wrist of 10 participants twice in a randomized order with an interval of at least 1 day. To determine the interrater reliability, a second rater analysed the same AVI files for the right wrist of the same 10 participants, again in a randomized order and blinded to the results of the first rater. The first rater was a physician with experience in performing musculoskeletal ultrasound. The second rater was a junior researcher who had participated in more musculoskeletal sonographic research. From these data, we calculated both the intra- and the interrater reliability of the intraclass correlation coefficients (ICC) using a two-way random effect model with single measure and absolute agreement. We classified our results according to the classification of Fleiss.[21]

We calculated the reference values for all shape and displacement parameters, except if the intrarater or interrater ICC was lower than 0.4. Moreover, if 1 or more shape parameters had an intrarater or interrater ICC under 0.4, all shape parameters of the structure were not reported. A repeated measure ANOVA with 2 within factors (hand posture and side) was used to determine significant differences between the reference values of the different parameters of the 3 different hand postures and between the left and right hands. *Post hoc* tests with Bonferroni correction were used to evaluate differences between hand postures. A p-value of less than 0.05 was deemed significant. The statistical analysis was made with the Statistical Package for Social Science software version 17.0 (SPSS, Chicago, IL, USA).

## RESULTS

### *Intrarater reliability*

Overall there was a moderate to excellent intrarater reliability (ICC≥0.64) for area, circularity, and perimeter of the median nerve and all tendons. The reliability of CoM and displacement of the median nerve and tendons were excellent (ICC≥0.82), except for the ICC of the endpoint displacement of the ring finger FDP (ICC=0.65) and the middle finger FDP (ICC=0.24) (Table 1).

| Intrarater reliability | MN | FDS2 | FDP2 | FDS3 | FDP3 |
|---|---|---|---|---|---|
| | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) |
| **Area** | **0.75** (0.28-0.93) | **0.87** (0.56-0.97) | **0.72** (0.15-0.93) | **0.64** (0.04-0.90) | **0.77** (0.28-0.94) |
| **Circularity** | **0.77** (0.36-0.94) | **0.94** (0.80-0.99) | **0.86** (0.55-0.96) | **0.89** (0.62-0.97) | **0.71** (0.23-0.92) |
| **Perimeter** | **0.87** (0.54-0.97) | **0.80** (0.31-0.95) | **0.71** (0.21-0.2) | **0.97** (0.89-0.99) | **0.78** (0.33-0.94) |
| **Centre of Mass x-coordinate** | **0.98** (0.64-0.97) | **0.96** (0.85-0.99) | **0.99** (0.98-1.00) | **0.97** (0.94-0.99) | **0.89** (0.57-0.98) |
| **Centre of Mass y-coordinate** | **0.99** (0.94-1.00) | **0.89** (0.64-0.97) | **0.99** (0.97-1.00) | **0.99** (0.94-1.00) | **0.97** (0.84-0.99) |
| **Endpoint displacement** | **0.91** (0.69-0.98) | **0.85** (0.42-0.97) | **0.65** (0.00-0.93) | **0.82** (0.34-0.96) | **0.24** (-0.21-0.79) |
| **Path displacement** | **0.96** (0.85-0.99) | **0.99** (0.96-1.00) | **0.92** (0.72-0.98) | **0.94** (0.79-0.98) | **0.95** (0.82-0.99) |

**Table 1** Intrarater reliability. The intrarater ICCs with 95% CI for the measurements of different parameters of the MN, FDS2, FDP2, FDS3 and the FDP3.
Abbreviations: MN; median nerve, FDS2; flexor digitorum superficialis tendon of the index finger, FDP2; flexor digitorum profundus tendon of the index finger, FDS3; flexor digitorum superficialis tendon of the middle finger, FDP3; flexor digitorum profundus tendon of the middle finger, ICC; intraclass correlation coefficient, CI; confidence interval.

### *Interrater reliability*

Overall there was a moderate to excellent intrarater reliability (ICC≥0.51) for area, circularity and perimeter of the median nerve and the FDS and FDP of the index finger and the FDS of the middle finger. Most of the ICCs of the shape parameters of the middle finger FDP were poor (ICC≤0.41) and therefore excluded from further analysis. Overall, the reliability of CoM and displacement of the median nerve and tendons was excellent (ICC≥0.86), except for the ICC of the endpoint displacement of the middle finger FDP (ICC=0.71) (Table 2).

| Interrater reliability | MN | FDS2 | FDP2 | FDS3 | FDP3 |
|---|---|---|---|---|---|
| | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) |
| **Area** | **0.75** (0.29-0.93) | **0.64** (0.05-0.90) | **0.65** (0.12-0.90) | **0.51** (-0.18-0.86) | **0.26** (-0.44-0.75) |
| **Circularity** | **0.58** (-0.08-0.88) | **0.84** (0.49-0.96) | **0.90** (0.48-0.98) | **0.83** (0.47-0.96) | **-0.17** (-0.82-0.52) |
| **Perimeter** | **0.83** (0.48-0.95) | **0.94** (0.79-0.99) | **0.85** (0.54-0.96) | **0.88** (0.60-0.97) | **0.41** (-0.30-0.82) |
| **Centre of Mass x-coordinate** | **0.94** (0.79-0.99) | **0.90** (0.65-0.97) | **0.86** (0.52-0.97) | **0.92** (0.73-0.98) | **0.95** (0.77-0.99) |
| **Centre of Mass y-coordinate** | **1.00** (0.98-1.00) | **0.99** (0.95-1.00) | **1.00** (0.99-1.00) | **0.97** (0.73-0.99) | **0.95** (0.77-0.99) |
| **Endpoint displacement** | **0.96** (0.83-0.99) | **0.87** (0.55-0.97) | **0.86** (0.27-098) | **0.71** (0.14-0.93) | **0.97** (0.36-1.00) |
| **Path displacement** | **0.98** (0.90-.99) | **0.99** (0.95-1.00) | **0.89** (0.61-0.97) | **0.98** (0.93-1.00) | **0.92** (0.73-0.98) |

**Table 2** - Interrater reliability. The interrater ICCs with 95% CI for the measurements of different parameters of the MN, FDS2, FDP2, FDS3 and the FDP3.
Abbreviations: MN; median nerve, FDS2; flexor digitorum superficialis tendon of the index finger, FDP2; flexor digitorum profundus tendon of the index finger, FDS3; flexor digitorum superficialis tendon of the middle finger, FDP3; flexor digitorum profundus tendon of the middle finger, ICC; intraclass correlation coefficient, CI; confidence interval.

### *Shape reference values*

The largest differences were seen between extension and flexion of all fingers using forceful grip. The circularity decreased by 12% for the median nerve ($P<0.05$), indicating a less-circular nerve, while the perimeter increased by 6% ($P<0.05$). The tendons showed an opposite trend; the tendons became on average 36% more circular while the perimeter decreased by 11% on average. This pattern was supported by significant differences ($P<0.05$) in all tendons, except by the change in perimeter of the index finger FDP and middle finger FDS (Table 3) (Figure 3).

### *Displacement reference values*

The largest displacement was observed in the median nerve; the path displacement from extension to flexion using a forceful grip was 218% larger ($P<0.001$) than the path displacement from extension to flexion of all fingers. The endpoint displacement of the median nerve from extension to flexion using a forceful grip was 190% ($P<0.001$) larger than the endpoint displacement from extension to flexion. Except for the endpoint displacement of the FDS3, all tendons showed, on average, an increase of 99% in path displacement ($P<0.001$) and an increase of 40% in endpoint displacement ($P\leq0.012$), from extension to flexion using a forceful grip compared to extension to flexion of all fingers (Table 4).

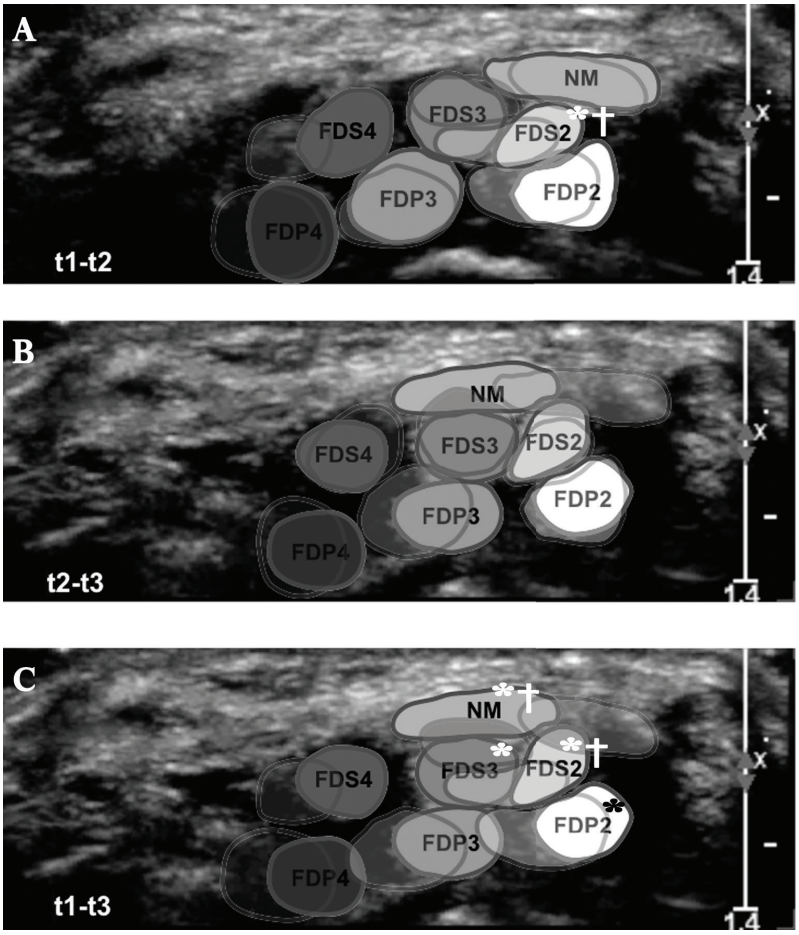


**Figure 3A-C** Illustration of the median nerve (MN) and the flexor digitorum superficialis (FDS) tendons of the index (FDS2), middle (FDS3), and ring finger (FDS4) and the flexor digitorum profundus (FDP) tendons of index (FDP2), middle (FDP3), and ring finger (FDP4) of 1 participant during the different hand postures. The shape and position of the nerve and flexor tendons during the initial hand posture are displayed in a transparent colour, and the shape and position of the nerve and tendons during the final hand postures are displayed in an opaque colour. **A**. The initial hand posture is extension of all fingers, and the final hand posture is flexion of all fingers. **B**. Full flexion of the fingers is compared to forceful grip. **C**. Full extension of the fingers is compared with the hand in a forceful grip. Based on the manually placed polygons on the outside border of each structure in different frames selected by the examiner, area, circularity and perimeter were calculated as described in Methods. Significant changes between the different hand postures for circularity are marked with *, and significant changes for perimeter are marked with †. There were no significant changes in area between the different hand postures.

| Structure | Area in mm² mean (SD) | | | Circularity mean (SD) | | | Perimeter in mm mean (SD) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Extension | Flexion | Force-ful grip | Extension | Flexion | Force-ful grip | Extension | Flexion | Force-ful grip |
| MN | **9.99** (2.47) | **9.74** (2.91) | **9.96** (2.86) | **0.57** (0.11) | **0.52** (0.08) | **0.50*** (0.13) | **15.00** (2.25) | **15.16** (2.19) | **15.90*** (2.81) |
| FDS2 | **9.20** (2.20) | **9.60** (1.96) | **9.16** (1.91) | **0.53** (0.15) | **0.68*** (0.13) | **0.76*** (0.11) | **15.00** (2.14) | **13.42*** (1.98) | **12.34*** (1.65) |
| FDP2 | **11.65** (2.92) | **12.42** (1.93) | **11.89** (2.09) | **0.62** (0.12) | **0.73** (0.12) | **0.74*** (0.11) | **15.31** (2.01) | **14.67** (1.44) | **14.31** (1.69) |
| FDS3 | **10.63** (2.63) | **11.55** (3.02) | **12.29** (3.08) | **0.60** (0.14) | **0.76** (0.15) | **0.88*** (0.16) | **15.27** (2.48) | **14.48** (1.97) | **14.33** (1.87) |

**Table 3** Shape reference values of the median nerve and flexor tendons. Shown are the reference values of the MN, FDS2, FDP2 and the FDS3 in healthy persons (N=20, 40 wrists) with SD during 3 hand postures: extension of all fingers, flexion of all fingers, and forceful grip. No significant difference was found for area, circularity and perimeter between the left and right hand for the MN and tendons, except for circularity of the FDS2. Averages of left and right hand are therefore not shown. Significant differences ($P<0.05$) between the reference values of extension and flexion of all fingers and between extension and flexion with forceful grip are indicated with an asterisk (*).
Abbreviations: SD; standard deviation, MN; median nerve, FDS2; flexor digitorum superficialis tendon of the index finger, FDP2; flexor digitorum profundus tendon of the index finger, FDS3; flexor digitorum superficialis tendon of the middle finger.

| Structure | Path displacement in mm mean (SD) | | | Endpoint displacement in mm mean (SD) | | |
|---|---|---|---|---|---|---|
| | Extension → flexion | Extension → forceful grip | P-value | Extension → flexion | Extension → forceful grip | P-value |
| **MN** | **3.95** (1.95) | **8.63** (3.29) | <0.001 | **2.59** (2.19) | **4.91** (3.07) | <0.001 |
| **FDS2** | **3.04** (1.14) | **6.14** (2.27) | <0.001 | **1.40** (1.13) | **1.97** (1.37) | 0.009 |
| **FDP2** | **3.24** (1.20) | **6.30** (2.32) | <0.001 | **1.56** (1.32) | **2.09** (1.81) | 0.012 |
| **FDS3** | **3.77** (1.67) | **7.63** (2.84) | <0.001 | **2.49** (1.74) | **2.50** (2.07) | 0.976 |

**Table 4** Displacement reference values of the median nerve and flexor tendons. Shown are the displacement reference values of the MN, FDS2, FDP2 and the FDS3 in healthy persons (N=20, 40 wrists) with SD. No significant difference was found between the left and right hand for the MN and the flexor tendons, except for the right FDS3, which had a significantly lower endpoint displacement. However, this significance disappeared when a single outlier was excluded. Therefore, we averaged all displacement reference values of the left and right hands. The first column shows the displacement values of the structure from extension to flexion of all fingers and the second column from extension to forceful grip. The path displacement was significantly larger ($P$<0.001) than the endpoint displacement for the median nerve and the flexor tendons.
Abbreviations: SD; standard deviation, MN; median nerve, FDS2; flexor digitorum superficialis tendon of the index finger, FDP2; flexor digitorum profundus tendon of the index finger, FDS3; flexor digitorum superficialis tendon of the middle finger.

On average, from extension to forceful grip the major displacement direction of the median nerve was in ulnar direction, and each FDS moved toward its corresponding FDP (Figure 3). While the average direction of both path displacement and endpoint displacement was in the ulnar direction (Figure 4), a large variety in directions was found between subjects. We found that the median nerve had a radial direction of displacement in 15 (38%) wrists. This number decreased to 4 wrists (10%) when going to forceful grip.

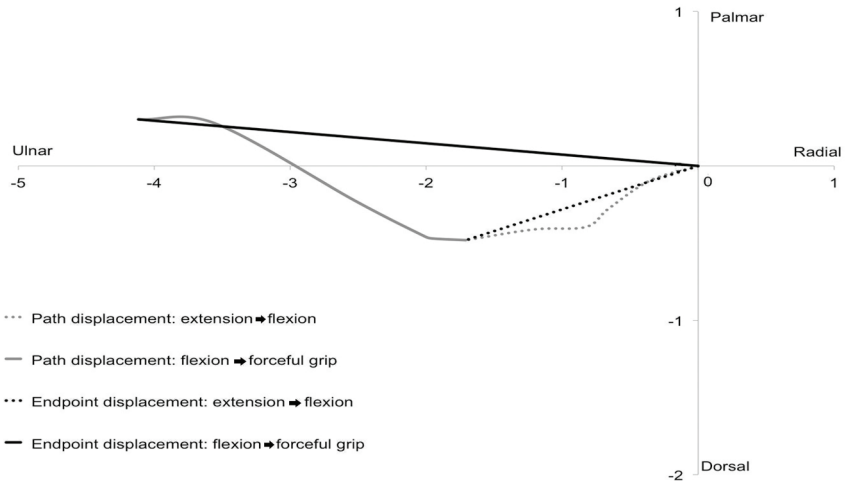


**Figure 4** Representation of the median nerve direction vector of displacement (mm) relative to the center of mass (CoM) of the flexor digitorum profundus tendon of the middle finger (FDP3).

## DISCUSSION

Insight into reliability of sonographic measurements can be helpful when deciding which measurements can be investigated as a potential test for diagnosing CTS. We found that measurements of shape of the median nerve, FDS and FDP for the index finger, and the FDS of the middle finger, and the displacement parameters of the median nerve and all flexor tendons measured had a moderate to excellent reliability. Based on the reliability analysis, we established reference values of shape and displacement parameters during the 3 different hand postures. The largest changes in shape and displacement were observed between extension to flexion using a forceful grip. For the median nerve and different tendons, the total path displacement could be up to 3 times larger than the displacement between the start point and end point, indicating that the structures do not move in a straight line.

Although high-resolution ultrasound allows precise imaging, image quality and therefore the interpretation of the images is rater dependent.[19] While previous studies focused on the reliability of measuring cross sectional area,[6,22] in this study we evaluated the intrarater and interrater reliability of dynamic sonographic recordings of the median nerve and tendons at the carpal tunnel inlet. We reported exact ICC-values of all nerve and tendon parameters so that researchers can choose their own cut-off values. Most other ultrasound studies reported solely their lowest ICC values or calculated only a single ICC.[3,6,22] When reporting reference values, we used the cut-off value of ICC>0.40 to decide if reference values would be reported. This is according to the classification of Fleiss who stated that an ICC<0.40 represents poor reliability, an ICC of 0.40-0.75 represents fair to good reliability, and above 0.75 represents excellent reliability.[21] The same classification has been used in other recent studies.[23,24]

Since the carpal tunnel is a narrow space, possible alterations or impaired movement of structures in the carpal tunnel due to non-inflammatory fibrosis of the connective tissue will change relative movement of structures. Some studies have used a device to fixate the wrist and the transducer to calculate absolute displacement.[2,3] In our experience, it is difficult to exclude all motion of the hand in relation to the transducer during dynamic conditions, even when using a fixating device. In addition, using a fixating device for making measurements will extend the duration of the examination, and such a device is not available in most hospitals. Therefore, using a reference point (e.g., ulnar artery, radial artery, scaphoid tubercle, tendon) is more convenient to use and a feasible method for measuring displacement.[20,25] When the aim is to correct for external movement there is no difference in normalizing to a stationary reference point or a moving reference point. In this study the FDP of the middle finger was used as a reference point. This tendon could be located reliably throughout the motion. It was located near the median nerve, and therefore it can serve as a suitable reference point, even in larger wrists.

Displacements and changes in shape parameters were larger when the fingers were fully flexed with a forceful grip as compared to the flexed fingers without force. If thickening and

fibrosis of connective tissue may alter the ability of the nerve and tendons to move in the carpal tunnel,[14,26] this condition may be more suitable for detecting differences between patients and controls. In addition, adding this condition may be valuable, since forceful gripping is part of the movements made in everyday life activities and because CTS is often associated with labor involving higher forces.[27] Since displacements were the largest during force production, the chances of detecting a signal are more reliable.

Compared to other studies, we found that our intrarater ICCs were comparable with the reported ICCs of Doesburg et al..[3] This study reported that the test-retest ICCs for shape parameters of the nerve and tendons was >0.75. Unfortunately, no detailed data were given regarding the calculated ICC, therefore no exact comparison can be made. The interrater ICCs of the area of the median nerve were slightly lower than reported by Wong et al. and Moran et al. (ICC>0.81).[6,22] Reliability of the other parameters calculated in this study, to our knowledge, has not been reported previously.

Our study is subject to a number of limitations. First, we focused only on the carpal tunnel inlet, since more distal parts were not accessible with the transducer during the full movement. Especially during flexion with forceful grip, the palm of the hand deforms, making full skin contact difficult. At the more proximal location, skin contact was maintained without pressure by placing the transducer manually and using large quantities of sonographic gel. In addition, more proximal ultrasound measurements are more reliable compared to measurements of the distal carpal tunnel.[19,22] Second, it should be noted that we included healthy subjects and not CTS patients. We expect the difference in the image quality between healthy subjects and patients will be small. In patients, the median nerve can often be easily visualized and therefore be readily identified due to its enlargement and its more hypoechoic appearance.[1] Considering the tendons, no sonographic alterations have been found in CTS patients, therefore no difference in reliability measurements is expected. However, future studies should indicate whether the reliability of sonographic measurements is similar in CTS patients. The last limitation is that we calculated the ICC over a limited set of wrists, and to calculate the interrater reliability we used 2 raters. Although values for most parameters and structures were high (ICC>0.75), in small datasets, 1 aberrant measurement might have a relatively great effect on the ICC. However, there is a clear overall tendency of all measurements to have sufficient reliability.

In conclusion, shape measurements showed fair to excellent intrarater and interrater reliability, and excellent intrarater and interrater reliability was found for displacement measurements of the median nerve and most flexor tendons at the carpal tunnel. Displacements and shape changes are most prominent when moving all fingers from full extension to flexion with a forceful grip. While this study evaluates healthy subjects and therefore reliability needs to be verified in patients, the reported values and the effect of different hand postures on structures in the carpal tunnel can be used for evaluating possible changes in the displacement and shape of the median nerve and tendons in CTS patients and patients with tendon pathology.

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# 6

# TRANSVERSE ULTRASOUND ASSESSMENT OF MEDIAN NERVE DEFORMATION AND DISPLACEMENT IN THE HUMAN CARPAL TUNNEL DURING WRISTS MOVEMENTS

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## ABSTRACT

The symptoms of carpal tunnel syndrome, a compression neuropathy of the median nerve at the wrist, are aggravated by wrist motion, but the effect of these motions on median nerve motion is unknown. In order to better understand the biomechanics of the abnormal nerve, it is first necessary to understand normal nerve movement. The purpose of this study was to evaluate the deformation and displacement of the normal median nerve at the proximal carpal tunnel level on transverse ultrasound images during different wrist movements, in order to have a baseline for comparison with movements of the abnormal nerve. Dynamic ultrasound images were obtained in both wrists of 10 asymptomatic volunteers during wrist maximal flexion, extension and ulnar deviation with finger extension or flexion. In order to simplify the analysis, the initial and final shape and position of the median nerve were measured and analysed. The circularity of the median nerve was significantly increased and the aspect ratio of the minimal enclosing rectangle and perimeter were significantly decreased in the final image compared to that in the first image during wrist flexion with finger extension and with finger flexion and wrist ulnar deviation with finger extension ($p<0.01$). There were significant differences in median nerve displacement vector between finger flexion, wrist flexion with finger extension and wrist ulnar deviation with finger extension (all $p<0.001$). The mean amplitudes of the median nerve motion in wrist flexion with finger extension (2.36±0.79 normalized units), wrist flexion with finger flexion (2.46±0.84 NU) and wrist ulnar deviation with finger extension (2.86±0.51 NU) were higher than those in finger flexion (0.82±0.33 NU), wrist extension with finger extension (0.77±0.46 NU) and wrist extension with finger flexion (0.81±0.58 NU) ($p<0.001$). In the normal carpal tunnel, wrist flexion and ulnar deviation could induce significant transverse displacement and deformation of the median nerve.

## INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome, with a prevalence of 3.7% in the general US population.[1] One plausible mechanism of CTS is median nerve impingement by one or more of the nine digital flexor tendons in the carpal tunnel. During finger or wrist movement, the median nerve stretches passively, under traction from finger motion, where the nerve attaches distally, as well as both longitudinally and transversely in response to the motion of the surrounding tendons, which move actively in the carpal tunnel. Longitudinal sliding of the median nerve in the carpal tunnel has been observed both in vitro and in vivo.[2-7] Wright et al. showed in a cadaver study that motion of the wrist and fingers could induce substantial excursion of the median nerve at the wrist. With wrist motion, the mean total median nerve excursion was 5.6 mm (4.31.95± mm in extension and 1.25±0.81 mm in flexion).[4] Using motion techniques which aimed to let the median nerve slide through the carpal tunnel while minimizing the strain, longitudinal excursions of up to 12.4 mm were observed.[3] In contrast, in patients with CTS the longitudinal gliding of the median nerve at the wrist is decreased compared to normal subjects.[6]

However, while these studies provide valuable information about the proximal-distal movement of median nerve in the carpal tunnel, the tunnel is a three dimensional structure. Studying the transverse plane movement of the median nerve in the carpal tunnel is also important, and has gained increasing attention in recent years. On transverse section, both radial-ulnar and palmar-dorsal movement of the median nerve occurs in response to wrist or even single digit motion.[8-11] As with longitudinal motion, the transverse movement of the median nerve in response to finger movement is reduced in patients with CTS compared to normal subjects.[8]

In contrast to studies on the transverse movement of the median nerve associated with finger movement, only a few studies have addressed the transverse movement of the median nerve associated with wrist movement. The most common manoeuvre, however, to provoke the symptoms of CTS, the Phalen test, is wrist flexion without any finger motion.[12] In addition, strong pinch or grip associated with wrist flexion is considered to be a risk factor for CTS.[13,14] Up to date, little is known about the kinematics of the median nerve during these movements.

Several studies have used magnetic resonance imaging (MRI) to measure the displacement or deformation of the median nerve at some specific wrist positions.[15-18] Yet MRI has limitations in demonstrating the dynamic movement of the median nerve during wrist movement. High frequency ultrasound has become an important musculoskeletal imaging modality due to its portability, low cost, ease of use, comfort for the patient, high resolution, and capacity for dynamic imaging. While several ultrasound studies have been performed to observe the mobility of the median nerve on the transverse section, their

data were obtained either semi-quantitatively or at specific wrists positions, as opposed to imaging the nerve dynamically as the wrist moved.[19,20]

In previous studies of nerve position in the carpal tunnel, static images were obtained at various wrist positions. Such studies do not allow the analysis of the dynamic effect of tendon motion or its impact on nerve motion. In this study, therefore, we analysed dynamic ultrasound images in order to evaluate the deformation and displacement of the median nerve in vivo. We hypothesized that certain wrist motions might result in significant deformation and/or displacement of the median nerve in the carpal tunnel.

## MATERIALS AND METHODS

This study protocol was approved by our Institutional Review Board. Ten asymptomatic volunteers (four males and six females), with a mean age of 39.1± 9.8 years, were recruited. Individuals were excluded if they had the following conditions: body mass index (BMI) greater than 30, cervical radiculopathy, rheumatoid arthritis, osteoarthritis, degenerative joint disease in the hand or wrist, flexor tendinitis in the hand or wrist, gout, kidney failure on haemodialysis, sarcoidosis, peripheral nerve disease, amyloidosis, or fractures to the hand or wrist. Written informed consent was obtained from all participants.

### *Ultrasound examination*

Each subject was imaged while sitting with the shoulder in neutral position and the forearm supinated. The forearm of the subject was put on a custom-made table with the wrist in the neutral position. An ultrasound scanner (Acuson Sequoia C512, Siemens Medical Solutions, Malvern, PA, USA) was used, equipped with a linear array transducer (15L8; frequency: 8-14MHz). The depth of the ultrasound image was adjusted to 25-30 mm according the thickness of the examined hand. The ultrasound examinations were performed by a radiologist with more than 5 years' experience in musculoskeletal ultrasound. The image acquisition frame rate was set at 70Hz with minimal image compression. Both hands of each subject were imaged.

To study the transverse movement of the median nerve in the carpal tunnel, dynamic cross-sectional images of the carpal tunnel were obtained by placing the transducer at the proximal carpal tunnel (Figure 1). The proximal carpal tunnel was defined as the area between the pisiform and the scaphoid tubercle; these two landmarks are easily palpable in all hands. The transducer was maintained perpendicular to the median nerve in order to get clear images and to avoid anisotropic artefact. To keep the transducer stable during finger or wrist motion, a custom-made transducer-fixing device was fastened at the subjects' palm. For minimization of compression of the tissue in the carpal tunnel, the transducer was applied to the skin without additional pressure. To measure the wrist angle during wrist movement, a goniometer (CXT102, Crossbow Technology Inc., Milpitas, CA,

USA) was fixed on the back of hand. The wrist angles were collected simultaneously with the ultrasound images.

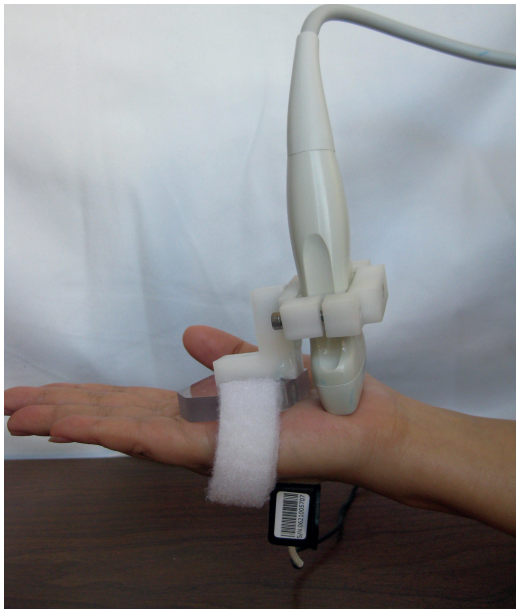

**Figure 1** Ultrasound examination setup. The transducer was placed at the proximal carpal tunnel. A custom-made transducer-fixing device was fastened at the subjects' palm to keep the transducer stable during finger or wrist motion. A goniometer was fixed on the back of hand to measure the wrist angle during wrist movement.

Dynamic ultrasound images were obtained during the following finger and wrist movements:

1. Finger flexion, defined as the wrist held in the neutral position while all four fingers and the thumb moved from full finger extension to maximal flexion to make a fist;
2. Wrist flexion with finger extension, defined as wrist motion from the neutral position to maximal flexion while all fingers were held in full extension;
3. Wrist flexion with finger flexion, defined as wrist motion from the neutral position to maximal flexion while all fingers were flexed to form a fist;
4. Wrist extension with finger extension, defined as wrist motion from the neutral position to maximal extension while all fingers were held in full extension;
5. Wrist extension with finger flexion, defined as wrist motion from the neutral position to maximal extension while all fingers were flexed to form a fist;
6. Wrist ulnar deviation with finger extension, defined as wrist motion from the neutral position to maximal ulnar deviation while the fingers were held in full extension.

The subjects were asked to move in synchrony with a metronome, beating at 40 pulses per minute (0.67 Hz), thus requiring 1.5 s to complete the finger or wrist movements. Each movement was repeated 3 times, and the clip in which the median nerve was observed most clearly was chosen for final analysis. Before data collection, the participants practiced the assigned motion 2 to 3 times with the examiner.

### *Image analysis*

All images were evaluated using Analyze 11.0 software (Mayo Clinic, Rochester, MN, USA). After the initial and final frames of the motion were selected and reviewed, the median nerve was outlined manually using a continuous boundary trace just within the echogenic boundary of the nerve.[21] Area, perimeter, circularity and aspect ratio of a minimum-enclosing rectangle (MER) of the median nerve were calculated automatically. Circularity was defined as:

$$circularity = 4\pi \cdot \frac{area}{perimeter^2} \quad \text{Eq. 1}$$

If the circularity is 1, the outlined polygon resembles a perfect circle; less than 1 indicates a deviation of a circle (e.g., oval or irregular shaped polygon). The MER was determined as the smallest possible enclosing rectangle to the median nerve. The aspect ratio of the MER was defined as the ratio of the major axis divided by the minor axis of this rectangle.[8] The position of the nerve was defined as the centroid coordinates of the median nerve in the first and final images of each motion sequence. The displacement in ulnar-radial (*x*) and palmar-dorsal directions (*y*) was calculated by comparing the initial and final centroid positions. The amplitude of median nerve displacement during each movement was calculated as:

$$displacement = \sqrt{x^2 + y^2} \quad \text{Eq. 2}$$

To analyse motion direction the palmar and ulnar directions were defined as positive and the radial and dorsal directions were defined as negative.

### *Normalization of measurements*

The measurements of area, perimeter and displacement of the median nerve were normalized to hand length, defined as the distance from the tip of the middle finger to the midline of the distal wrist crease when the forearm and hand were supinated on a table.[22] Normalized results were presented as normalized units (NU) in which 1 NU= 1% of the normalized length. Thus, if the hand length was 100 mm and the actual measurement of interest (e.g., nerve motion) was 3 mm, the measurement would be expressed as 3 NU, i.e., 3% of the hand length. Area was also normalized by dividing by hand length, and so is also represented in NU. The mean hand length was 179.25 ± 10.20 mm. Thus, one normalized unit (NU) was roughly 1.79± 0.10 mm.

### *Reliability of median nerve measurements*

To assess intra-observer agreement, one examiner re-analysed the ultrasound data for the dominant hand in each subject. The interval of the two analyses was at least 3 months. Area, perimeter, aspect ratio of the MER, circularity on the first image and final image and the displacement amplitude of the median nerve were measured with the same Analyze 11.0 software. To assess inter-observer agreement, two examiners analysed the same ultrasound data for wrist flexion with finger extension of the dominant hand in each subject. Area, perimeter, aspect ratio of the MER, circularity on the first image and final image and displacement amplitude of median nerve were measured with the same Analyze 11.0 software.

### *Data analysis*

Analysis JMP 9.0 (SAS Institute, Cary, North Carolina, USA) was used for the paired t-test and the one-way ANOVA, custom Matlab (MathWorks Inc., Natick, MA, USA) was used for the bivariate statistics and Statistical Package for Social Science software version 12.0 (SPSS, Chicago, IL, USA) was used for the intraclass correlation coefficients (ICC). All results are expressed as mean ± standard deviation. A paired t-test was used to analyse the difference of median nerve parameters between the dominant and non-dominant hands and the one-way ANOVA between the different wrist movements. The difference of the median nerve displacement vector between different movements was analysed using the bivariate Mardia's two-sample test and the Mardia-Watson-Wheeler non-parametric test.[23] The mean vector (in polar coordinates) was used to represent the sample centre. The standard ellipse, representative of sample variation, and Hotelling's confidence ellipse parameters ($\alpha = 0.05$) were calculated for each motion to describe sample variation. P-values of less than 0.05 were considered statistically significant. Intra- and inter-observer agreements were examined using ICC and their 95% confidence intervals.[24]

## RESULTS

### *The maximal wrist angles with different wrist movements*

There was no significant difference in the maximal wrist angle between the dominant and non-dominant hands during any of the movements ($p>0.05$). Thus, we used the mean value of all 20 wrists to do the comparison between the different wrist movements. There was no difference in the maximal wrist angle between wrist flexion with finger extension and wrist flexion with finger flexion or between wrist extension with finger extension and wrist extension with finger flexion ($p>0.05$).

### *Measurements of the dominant versus non-dominant hand*

There was no difference in the area, perimeter, circularity, aspect ratio of the MER or displacement of the median nerve between the dominant and non-dominant hands for any movement ($p$>0.05). Thus, we used the mean value of all 20 wrists to do the comparison between the different wrist movements.

### *The deformation of the median nerve during finger and wrist movements*

The area, perimeter, circularity and aspect ratio of the MER of the median nerve for the first and final images of the various wrist movements are shown in Table 1. Significant differences between the first and last images were found for area, perimeter, circularity and aspect ratio of the MER of the median nerve during various movements.

| | Normalized area (NU) | Normalized perimeter (NU) | Aspect ratio | Circularity |
|---|---|---|---|---|
| **Finger flexion** | | | | |
| First image | 5.27 (±0.73) | 8.51 (±1.02) | 3.11 (±0.68) | 0.52 (±0.10) |
| Final image | 5.25 (±0.82) | 8.23 (±0.83) | 2.79 (±0.57) | 0.55 (±0.09) |
| **Wrist flexion with finger extension** | | | | |
| First image | 4.74 (±0.92) | 7.97 (±1.51) | 2.78 (±0.54) | 0.55 (±0.13) |
| Final image | 5.12 (±0.96)* | 6.91 (±0.80)** | 1.80 (±0.64)** | 0.76 (±0.08)** |
| **Wrist flexion with finger flexion** | | | | |
| First image | 4.79 (±0.76) | 7.84 (±1.10) | 2.71 (±0.49) | 0.57 (±0.13) |
| Final image | 4.55 (±0.61) | 6.27 (±0.52)** | 1.88 (±0.61)** | 0.81 (±0.05)** |
| **Wrist extension with finger extension** | | | | |
| First image | 5.12 (±0.71) | 8.55 (±0.98) | 3.42 (±0.65) | 0.50 (±0.10) |
| Final image | 5.49 (±1.03) | 8.32 (±1.07) | 2.88 (±0.46)** | 0.56 (±0.07)* |
| **Wrist extension with finger flexion** | | | | |
| First image | 5.08 (±0.48) | 8.21 (±0.81) | 3.19 (±0.69) | 0.55 (±0.08) |
| Final image | 5.10 (±0.81) | 8.08 (±0.93) | 2.19 (±0.73) | 0.55 (±0.07) |
| **Wrist ulnar deviation** | | | | |
| First image | 5.20 (±0.63) | 8.31 (±0.97) | 2.73 (±0.52) | 0.54 (±0.10) |
| Final image | 5.17 (±0.96) | 7.34 (±0.98)** | 1.82 (±0.55)** | 0.68 (±0.12)** |

**Table 1** The median nerve deformation parameters for different finger and wrist movements. Abbreviations: NU; normalized units.
* p<0.05
** p<0.01

There was a significant difference found for the median nerve area solely for wrist flexion with finger extension. The circularity of the median nerve was significantly increased and the aspect ratio of the MER and perimeter were significantly decreased in the final image compared to that in the first image during wrist flexion with finger extension, wrist flexion with finger flexion and wrist ulnar deviation with finger extension ($p<0.01$) (Figure 2-4). The circularity of the median nerve was significantly increased and the aspect ratio of the MER decreased in the final image compared to the first image during wrist extension with finger extension ($p<0.05$). There was no significant difference found for any of these parameters between the first and final images for finger flexion or wrist extension with finger flexion ($p>0.05$).

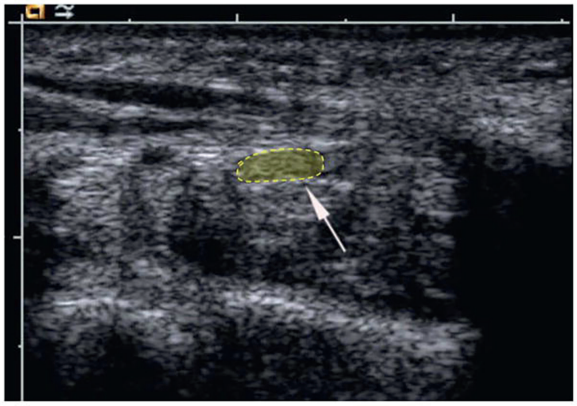

**Figure 2** The location of median nerve at the beginning of wrist flexion with finger extension: the median nerve (arrow) is located at the palmar midline position of the carpal tunnel.

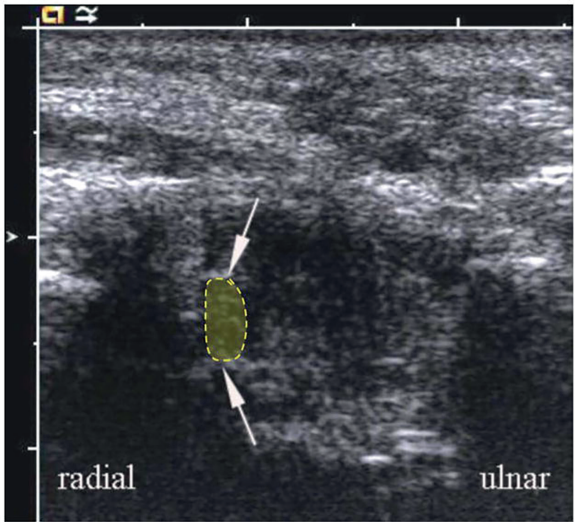


**Figure 3** The location of median nerve at the end of wrist flexion with finger extension: the median nerve (arrows) was located dorsally in the carpal tunnel.

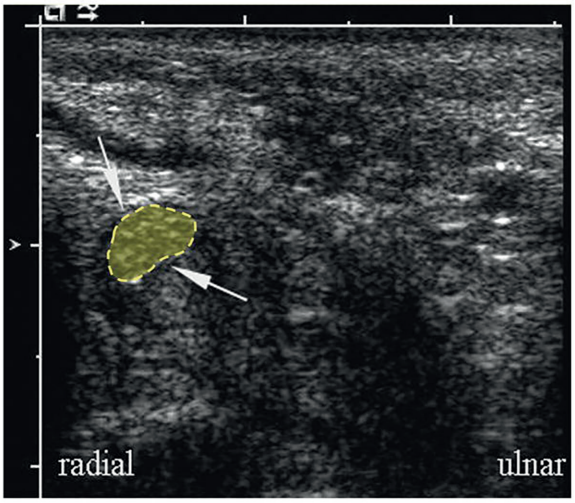


**Figure 4** The location of median nerve at the end of wrist ulnar deviation: the median nerve (arrows) was located between the flexor pollicis longus tendon and flexor retinaculum.

### *The displacement vector of the median nerve during finger and wrist movements*

Mean vectors and parameters for variation confidence limits - major and minor ellipse axes (a and b) and inclination (ψ) - for all motions are included in Table 2.

There was no significant difference in the motion vector of the median nerve between wrist flexion with finger extension and wrist flexion with finger flexion ($p$=0.067). There was a significant difference in the motion vector of the median nerve between wrist extension with finger extension and wrist extension with finger flexion ($p$=0.012), between finger flexion, wrist flexion with finger extension and wrist ulnar deviation with finger extension ($p$<0.001) (Figure 5), and between finger flexion, wrist extension with finger extension, and wrist extension with finger flexion (all $p$<0.05).

| | p (NU) | θ | a (NU) | b (NU) | φ |
|---|---|---|---|---|---|
| **Finger Flexion** | 0.2 | 117 ° | 0.5 | 0.2 | -16 ° |
| **Wrist Flexion with Finger Extension** | 1.5 | 267 ° | 1.2 | 0.5 | -12 ° |
| **Wrist Flexion with Finger Flexion** | 1.8 | 295 ° | 1.1 | 0.5 | -12 ° |
| **Wrist Extension with Finger Extension** | 0.4 | 226 ° | 0.5 | 0.2 | -8 ° |
| **Wrist Extension with Finger Flexion** | 0.5 | 182 ° | 0.5 | 0.2 | -3 ° |
| **Wrist Ulnar Deviation** | 2.8 | 189 ° | 0.3 | 0.2 | -5 ° |

**Table 2** The mean vector and confidence limits for various parameters (α = 0.05) of the median nerve displacement during finger and wrist movements.
Abbreviations: ρ = vector length, NU; normalized units (is approximately 1.8 mm), θ = vector angle, a = major ellipse axes for variation of the confidence limits, b = minor ellipse axes for variation of the confidence limits, ψ = inclination of the ellipse.

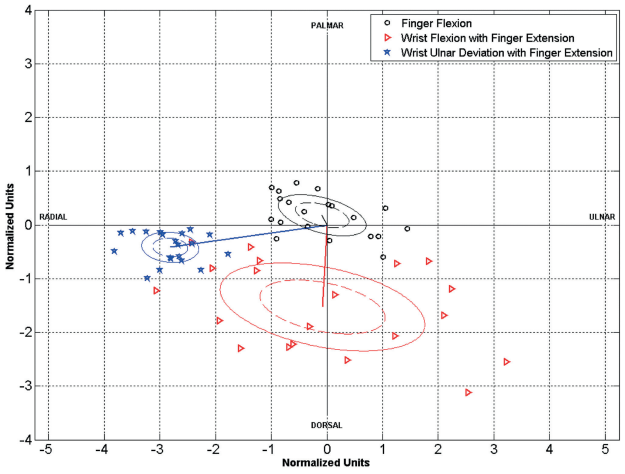


**Figure 5** Median nerve displacement vector for finger flexion, wrist flexion with finger extension and wrist ulnar deviation. (Solid ellipses represent standard deviation, dashed ellipses represent 95% confidence limits and the radial line represents the mean vector for each group.)

***The amplitude of median nerve displacement during finger and wrist movements***

There was a significant difference in the amplitude of the median nerve displacement among the movements ($p$<0.001) (Figure 6). The mean amplitudes of the median nerve displacement in wrist flexion with finger extension (2.360.79± NU), wrist flexion with finger flexion (2.460.84± NU) and wrist ulnar deviation with finger extension (2.86±0.51 NU) were higher than those in finger flexion (0.82±0.33 NU), wrist extension with finger extension (0.770.46± NU) and wrist extension with finger flexion (0.81±0.58 NU). There was no difference in the amplitude of the median nerve displacement between wrist flexion with finger extension, wrist flexion with finger flexion, and wrist ulnar deviation with finger extension ($p$=0.120) or between finger flexion, wrist extension with finger extension and wrist extension with finger flexion ($p$=0.956).

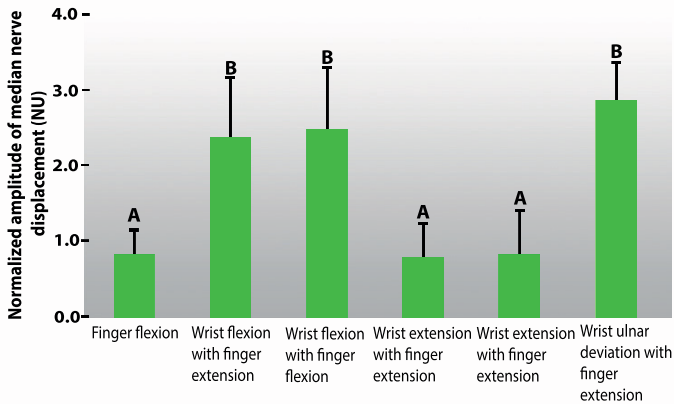


**Figure 6** The amplitude of median nerve displacement. The amplitude of median nerve motion in finger flexion, wrist extension with finger extension and wrist extension with finger flexion (A) were significantly less compared to wrist flexion with finger extension, wrist flexion with finger flexion and wrist ulnar deviation (B) (p<0.0001).

***Intra- and inter-observer agreement of median nerve measurements***

Intra- and inter-observer agreement for the area, perimeter, aspect ratio of the MER, circularity and displacement of median nerve are summarized in Table 3. The intra-observer and inter-observer agreements were good to excellent for all measurements, with the ICCs ranging from 0.86 to 0.98.

| First image | Intra-rater ICC (CI 95%) | Inter-rater ICC (CI 95%) |
|---|---|---|
| Area | 0.96 (0.61-0.99) | 0.95 (0.67-0.99) |
| Perimeter | 0.94 (0.79-0.98) | 0.93 (0.71-0.99) |
| Aspect ratio | 0.97 (0.84-0.99) | 0.96 (0.78-0.99) |
| Circularity | 0.86 (0.65-0.97) | 0.89 (0.60-0.97) |
| **Final image** | | |
| Area | 0.97 (0.87-0.99) | 0.97 (0.61-0.99) |
| Perimeter | 0.95 (0.78-0.99) | 0.91 (0.68-0.98) |
| Aspect ratio | 0.98 (0.93-0.99) | 0.97 (0.86-0.99) |
| Circularity | 0.93 (0.72-0.98) | 0.89 (0.68-0.97) |
| **Amplitude of median nerve displacement** | 0.91 (0.67-0.98) | 0.90 (0.60-0.98) |

**Table 3** Intra- and inter-rater intraclass correlation coefficient (ICC) and 95% confidence interval (CI) of the median nerve deformation and displacement in wrist maximal flexion with finger extension.

## DISCUSSION

Studying the transverse movement and shape of the median nerve in the carpal tunnel is important to understand the kinematics of the median nerve in both physiological and pathophysiological states. Ultrasound is a useful tool for such purposes, because it can obtain dynamic information about the deformation and displacement of the median nerve throughout the full range of wrist and finger motion.

Repetitive wrist movements are associated with CTS.[13,14] The motion of wrist flexion is also used as a provocative test to diagnose CTS. The most common test for CTS is the Phalen test in which the patient is asked to hold their wrists in complete and forced flexion (pushing the dorsal surfaces of both hands together) for 30–60 seconds. Characteristic symptoms such as burning, tingling or numb sensation over the thumb, index, middle and ring fingers indicates a positive test result and suggests CTS.[25] Our results show that some wrist movements, such as maximal flexion and ulnar deviation, cause significant transverse displacement of the median nerve in the carpal tunnel. In addition, we have shown that the transverse motions are less affected by finger movement. This was as expected, since it is more logical that finger motions have a greater effect on longitudinal nerve motion than on transverse motion.

In this study, we quantitatively evaluated the deformation of the median nerve during different wrist movements. We found that the circularity of the median nerve was increased and the aspect ratio of the MER and perimeter were decreased during maximal wrist flexion and ulnar deviation. Other studies also found that the median nerve deforms during wrist movement, although their results were qualitative, depicting the shape of median nerve simply as flattened, oval or round.[15,16] The significant deformability of the median nerve during wrist flexion and ulnar deviation in normal subjects may be related to its internal structure. Histologically, a peripheral nerve is composed of axons, which are bundled by 3 connective tissue layers; the endoneurium, the perineurium, and the epineurium. These connective tissues contain collagen fibrils, elastic fibres and endoneurial fluid.[26] During extraneural compression induced by wrist movement, the median nerve could have transient and reversible deformation due to displacement of nerve fascicles in the nerve trunk. Although continuous compression would eventually cause endoneurial fluid displacement, as it would flow to the edges of a compressive cuff,[27] this endoneurial fluid displacement is likely to occur during a relatively slow course, and is probably not related to the deformation of the median nerve that we observed in association with wrist movement. In contrast, longstanding compression might produce progressive fibrosis in the epineurial and perineurial connective tissues. This has been observed in experimental animals as well as autopsy retrieved human specimens with nerve compression. This fibrosis would result in a permanently decreased compliance of the median nerve.[28-30] We hypothesize that the deformation capability of median nerve may be impaired in patients with CTS. Further studies in patients with CTS are needed to validate this hypothesis.

The analysis of the vector and amplitude of median nerve displacement in this study showed that wrist flexion and wrist ulnar deviation cause significant displacement of the median nerve, as compared to finger flexion without wrist movement, or with wrist extension. This significant difference in displacement of the median nerve may be due to the influence of adjacent tissues, either pushing or pulling the median nerve into certain directions. During wrist flexion, the flexor tendons move palmarly within the carpal tunnel, as the flexor tendons change their pulling angle and glide directly against the flexor retinaculum.[31] As these tendons move palmarly towards the position of the nerve, the nerve can experience one of the following two phenomena: it can remain in situ, and likely be compressed by the palmarly advancing tendons, or it can move to the locations that the tendons have vacated to escape the compression. We observed the latter median nerve kinematics in the normal hands in this study. Similarly, as the wrist deviates ulnarly the tendons would tend to move to the ulnar side of the wrist, thereby pushing the nerve radially. It is well known that patients with CTS demonstrate fibrosis of the synovial tissue within the carpal tunnel.[32-36] In such cases, one might expect diminished motion, and resulting deformation of the nerve with finger and wrist movement. Indeed, this has been observed as well.[10]

Aside from the amplitude of nerve motion being different based on different combinations of wrist and finger motion, we also identified motion patterns in which the direction of nerve motion changed, even if the amplitude did not, such as between finger flexion and finger extension with the wrist extended.

In addition to nerve motion as a result of direct physical contact with the tendons, the nerve may also move under the influence of fluid pressure shifts within the carpal tunnel. Pressures within the carpal tunnel can rise substantially during finger and wrist motion.[37,38] However, other studies have shown that this pressure elevation is primarily due to contact pressure, and not fluid pressure.[39,40] A study using bulb pressure to evaluate the contact pressure on the median nerve showed that the pressure increased markedly as the wrist flexion angle and ulnar deviation angle increased.[41]

We believe that our normal data will be helpful to understand the pathomechanics in patients at risk for or suffering from early stages of CTS. The subsynovial connective tissue (SSCT), which fills the space between the tendons, and the space between the tendons and the median nerve, is normally filmy and supple, and thus could facilitate the smooth gliding of the median nerve between the flexor tendons and flexor retinaculum during finger and wrist movements. In patients with CTS, the SSCT becomes fibrotic and stiff, which could alter the gliding characteristics of the SSCT, and, thus of the nerve as well.[32,33,42-44] We hypothesize that nerve and tendon motion patterns that are altered by SSCT fibrosis might be useful to identify CTS prodromes, and perhaps even as 'biomarkers' that might suggest treatments to restore or preserve nerve mobility before symptoms become so severe that surgery is needed, and we plan to investigate this possibility in future studies.

Our study has several shortcomings. First, our study has a small sample size. Yet the promising results of this study do indicate that evaluating the transverse plane movement of the median nerve during wrist motion could provide more information about the mobility and deformability of the median nerve, and may prove useful in the assessment of CTS. Second, in this initial study we only analysed the initial and final images, but the advantage of ultrasound is that the entire movement can be captured and analysed. However, such an analysis is far more complex than that is needed to identify a simple vector from initial to final position, and so we have begun with this simpler analysis. Now that we have demonstrated that ultrasound can, indeed, capture useful images of the overall movement, we plan to return and reanalyse the entire movement path, for more insights. Finally, the median nerve kinematics was only characterized in normal subjects. However, we consider this a necessary first step before analysing abnormal conditions. The data presented in the current study will be useful as a baseline for future studies in CTS patient populations.

In summary, our study quantitatively evaluated the transverse plane displacement and deformation of the median nerve under different finger and wrist movements in the healthy wrist. Maximal wrist flexion and ulnar deviation may be useful for evaluating the displacement and deformation of the median nerve, since these motions produced the

largest displacements and deformations of the normal median nerve. Further studies of transverse plane ultrasound of the median nerve are necessary to assess its clinical value in patients with CTS.

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# 7

# ALTERED MEDIAN NERVE DEFORMATION AND TRANSVERSE DISPLACEMENT DURING WRIST MOVEMENT IN PATIENTS WITH CARPAL TUNNEL SYNDROME

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## ABSTRACT

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome. Strong pinch or grip with wrist flexion has been considered a risk factor for CTS. Studying median nerve displacement during wrist movements may provide useful information about median nerve kinematic changes in CTS patients. The purpose of this study was to evaluate the deformability and mobility of the median nerve in CTS patients compared to healthy subjects. Dynamic ultrasound images were obtained in 20 affected wrists of 13 patients with CTS. Results were compared to complementary data obtained from both wrists of 10 healthy subjects reported in a previous study. Initial and final median nerve shape and position were measured and analysed for six defined wrist movements. The deformation ratios for each movement were defined as the median nerve area, perimeter and circularity of the final position normalized by respective values assessed in the initial position. The median nerve displacement vector and amplitude were also calculated. The deformation ratio for circularity was significant less in CTS patients compared to healthy subjects during wrist flexion and wrist ulnar deviation ($P<0.01$). The mean vector of median nerve displacement and the displacement amplitude of the median nerve during wrist flexion and wrist ulnar deviation were significantly different between CTS patients and healthy subjects ($P<0.05$). CTS patients differ from normal subjects with regard to mobility and deformability of the median nerve.

## INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome, and its precise aetiology remains largely unclear. Like other peripheral nerves, the median nerve is exposed to various mechanical stresses related to limb postures and movements. In the case of the median nerve in the carpal tunnel, the relevant movements are of the fingers and wrist. The median nerve response to these stresses is a combination of displacement and deformation.[1] Both displacement and deformation are known to vary from normal in CTS patients, due to increased carpal tunnel pressure and to fibrosis in the median nerve and the surrounding tissue in the carpal tunnel.[2,3]

Actuated by finger or wrist motion, the median nerve can displace in three dimensions. Longitudinal sliding of the median nerve in the carpal tunnel has been observed both in vitro and in vivo.[4-9] Reduced longitudinal excursion of the median nerve at the carpal tunnel has been identified in CTS patients.[5,10] Transverse motion of the median nerve has also been studied in the carpal tunnel in normal subjects[11,12] and CTS patients.[1,13] Nakamichi et al. found reduced transverse motion of the median nerve during passive flexion and extension of the index finger in CTS patients.[1] Erel et al. studied the transverse motion of the median nerve during passive extension of the digits at the metacarpophalangeal joint from 90° flexion to neutral. Their results showed that in CTS patients there was a significant reduction in transverse movement on the more symptomatic side compared to the contralateral side.[13]

Compared to finger movement, wrist movements may have more influence on the pathomechanism of CTS. Activities performed with the wrist flexed or extended have been considered to be risk factors for CTS.[14] Wrist position affects not only the interstitial fluid pressure in the carpal tunnel,[3,15,16] but also the direct contact pressure on the median nerve from the adjacent tissues, including the flexor tendons, subsynovial connective tissue (SSCT) within the carpal tunnel and the flexor retinaculum.[15,17,18] The shear strain index between the tendon and median nerve is higher at 60 degrees of wrist flexion compared to 30 degrees of flexion, full wrist extension or neutral wrist positions.[19] The gliding resistance of flexor tendons against the flexor retinaculum is also significantly increased at 60 degrees of wrist flexion compared to the neutral position.[20]

Despite the importance of wrist position in the pathomechanism of CTS, there are few studies that have addressed the transverse deformation and mobility of the median nerve associated with wrist movement.[21-24] For normal subjects, quantitative data of the median nerve displacement and deformation were obtained either by magnetic resonance imaging or high frequency ultrasound.[21,24] Consistent findings, which showed the median nerve adopting a rounder shape with the wrist flexed compared to the wrist in neutral position were reported in these studies. Allmann et al. investigated the median nerve during wrist flexion and extension in CTS patients. However, only qualitative displacement

results were reported, and the deformation of the median nerve was not described.[25] To our knowledge, no studies have compared quantitatively the median nerve motion and deformation during wrist motion between CTS patients and healthy controls.

In this study, we investigated both the deformation and mobility of the median nerve in the transverse plane during six different hand and wrist motions in CTS patients and compared these results to those previously reported for normal subjects.[21] Our hypothesis was that the deformability and mobility of the median nerve in response to maximal wrist flexion, extension or ulnar deviation may be reduced in patients with CTS. We believe that such information could be valuable to the study of kinematics of the median nerve in patients with CTS.

## MATERIALS AND METHODS

Thirteen patients with clinically diagnosed CTS were recruited (6 men, 7 women, mean age 50.9 with a range of 41-60 years) according to the diagnostic criteria of the Quality Standards Subcommittee of the American Academy of Neurology.[26] Among them, 7 patients had bilateral CTS and the remaining 6 patients had unilateral CTS, thus a total of 20 wrists with CTS were included in this study. Patients were excluded if they had the following conditions: rheumatoid arthritis; osteoarthritis; degenerative joint disease in the hand or wrist; flexor tendinitis in the hand or wrist; space occupying lesions of the wrist; coexistent neurologic diseases, such as polyneuropathy, proximal median neuropathy, cervical radiculopathy, diabetes mellitus; history of fractures or other trauma to the hand or wrist; other systematic diseases. Similar methods were applied in a previous study of healthy subjects, which reported on 10 healthy volunteers (4 men, 6 women, mean age 39 year with a range of 25-56 years) with no clinical signs or symptoms of CTS.[21] Both wrists were evaluated in healthy subject. Thus a total of 20 wrists were examined in the previous study, which will serve as a control group for the current study.

### *Ultrasound examination*

Each subject was imaged while sitting with the shoulder in the neutral position and the forearm supinated. The forearm of the subject was placed on a custom-made table with the wrist in the neutral position. An ultrasound scanner (Acuson Sequoia C512, Siemens Medical Solutions, Malvern, PA, USA) was used, equipped with a linear array transducer (15L8; frequency: 8-14MHz). The depth of the ultrasound image was adjusted to 25-30 mm, depending on the tissue thickness of the examined hand. Ultrasound examinations were performed by a radiologist with more than 5 years of experience in musculoskeletal ultrasound. The image acquisition frame rate was set to 70 Hz with minimal image compression.

The transducer was placed at the proximal carpal tunnel. The proximal carpal tunnel was defined as the area between the pisiform and the scaphoid tubercle; these two landmarks are palpable on the palm of the hand and could be easily identified on ultrasound with the characteristics of hyperechoic surface and strong posterior acoustic shadowing. The transducer was maintained perpendicular to the median nerve in order to get clear images and to avoid anisotropic artefact. To stabilize the transducer during finger or wrist motion and to minimize compression of the tissue within the carpal tunnel, a custom-made transducer-fixing device was fastened at the subjects' palm.[21] To measure the wrist angle during wrist movement, a 2-axis tilt sensor (CXT102, Crossbow Technology, Inc., Milpitas, CA, USA) functioning as a goniometer was fixed to the back of the hand. Both dorsal-palmar and radial-ulnar rotational motion was collected during the wrist movements. The tilt sensor only registers angulation relative to the gravity vector. To allow it to measure wrist angle for both motion planes, different orientations of the wrist and sensor relative to the wrist were required. It was mounted with its base parallel to the dorsal plane of the hand for the wrist dorsal-palmar movement (the first position of the wrist was at the horizontal plane). For the wrist radial-ulnar movement, the forearm was rotated such that wrist radial-ulnar movement followed the vertical plane, and the tilt sensor was repositioned to allow its base to again be parallel with the horizontal plane. Tilt sensor data measuring wrist angles were collected concurrently with ultrasound data at a sample rate of 36 Hz.

Dynamic ultrasound images were obtained during the following finger and wrist movements:

1. Finger flexion, defined as the wrist held in the neutral position while all four fingers and the thumb moved from full finger extension to maximal flexion to make a fist;
2. Wrist flexion with finger extension, defined as wrist motion from the neutral position to maximal flexion while all fingers were held in full extension;
3. Wrist flexion with finger flexion, defined as wrist motion from the neutral position to maximal flexion while all fingers were flexed to form a fist;
4. Wrist extension with finger extension, defined as wrist motion from the neutral position to maximal extension while all fingers were held in full extension;
5. Wrist extension with finger flexion, defined as wrist motion from the neutral position to maximal extension while all fingers were flexed to form a fist;
6. Wrist ulnar deviation with finger extension, defined as wrist motion from the neutral position to maximal ulnar deviation while the fingers were held in full extension.

Before data collection, the subjects would practice the motion 2-3 times with the examiner. All movements were repeated again 3 times for the experiment. The clip in which the median nerve was observed most clearly was chosen for final analysis.

### *Image analysis*

Images were evaluated using Analyze 11.0 software (Mayo Clinic, Rochester, MN, USA). After the initial and final frames of the motion were selected, the median nerve was outlined manually using a continuous boundary trace just within the echogenic boundary of the nerve.[27] The following parameters of the median nerve were calculated automatically: area, perimeter, circularity, and the centroid coordinates. Circularity was defined as:

$$circularity = 4\pi \cdot \frac{area}{perimeter^2} \quad \text{Eq. 1}$$

If the circularity was 1, the outlined polygon resembled a perfect circle; a value less than 1 indicated a deviation from a circle (e.g., oval or irregular shaped polygon). The centroid was defined as the centre of area of the outlined median nerve and was expressed in Cartesian coordinates x (radial-ulnar axis) and y (palmar-dorsal axis).

To assess the deformability of the median nerve, we calculated deformation ratios for area, perimeter and circularity. The deformation ratio was defined as the value in the final position normalized by the respective value in the initial position. Deformation ratios closer to 1 imply that the measurements of the parameter calculated in the initial and final positions were very similar. The more the deformation ratio deviates from 1 the greater the difference between the measurement of the parameter in the first and final positions.

To assess the mobility of the median nerve, we calculated the displacements in radial-ulnar (*x*) and palmar-dorsal directions (*y*) by comparing the initial and final centroid positions. The median nerve displacement vector was defined as the final position of median nerve relative to its initial position in each wrist movement. The amplitude of the median nerve displacement was defined as:

$$displacement = \sqrt{x^2 + y^2} \quad \text{Eq. 2}$$

The sign convention for motion analysis was such that the palmar and ulnar directions were defined as positive and the radial and dorsal directions were defined as negative values.

### *Normalization of measurements*

Displacement vector and displacement amplitude of the median nerve were normalized to hand length. Hand length was defined as the distance from the tip of the middle finger to the midline of the distal wrist crease when the forearm and hand were supinated on a table and was measured with a ruler on which the minimal scale was millimetre.[28] Normalized results were presented as Normalized Units (NU) in which 1 NU = 1% of the normalized length. Thus for example, if the hand length was 100 mm and the displacement amplitude of the median nerve was 3 mm, the measurement would be expressed as 3 NU (i.e., 3% of the normalized length). The mean hand length of all wrists of CTS patients in this study was 184.55 ± 9.85 mm. Thus, one NU was roughly 1.85± 0.10 mm.

### *Statistical analysis*

JMP 9.0 (SAS Institute, Cary, NC, USA) and Matlab (MathWorks Inc., Natick, MA, USA) were used for statistical analysis. Mardia's bivariate test for normality was performed on median nerve displacement data. All results are expressed as a mean ± standard deviation (SD). The unpaired t- test and one-way ANOVA was used to analyse the differences in the means of maximal wrist angles, deformation ratios, and normalized displacement amplitude of the median nerve between patient data collected in this study and data of healthy subjects previously reported.[21] The difference of the median nerve displacement vector between patient data of this study and data of healthy subjects previously reported[21] was analysed using the bivariate Mardia's two-sample test and the Mardia-Watson-Wheeler non-parametric test.[29] The mean vector was used to represent the sample centre. The standard ellipse, representative of sample variation, and Hotelling's confidence ellipse parameters ($\alpha = 0.05$) were calculated for each motion to describe sample variation. P-values of less than 0.05 were considered statistically significant. This study protocol was reviewed and approved by the Institutional Review Board of our institution.

## RESULTS

### *Maximal wrist angles during wrist movements*

The wrist angles during wrist extension with fingers extended or flexed in CTS patients (35.75±7.28 degrees and 37.80±10.55 degrees, respectively) were significantly lower than those in healthy subjects (45.66±12.25 degrees and 48.04±10.27 degrees, respectively) (both P=0.004) (Figure 1). There were no differences in wrist angle between CTS patients and healthy subjects for the other movements (P>0.05).

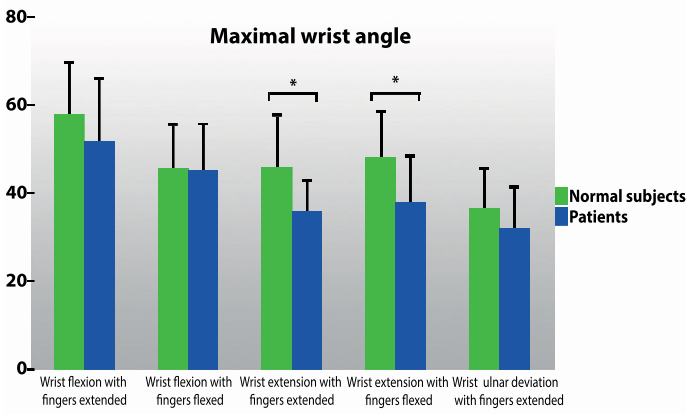


**Figure 1** The comparison of the wrist angles between CTS patients and healthy subjects. The maximal wrist angle during wrist extension with fingers extended or flexed in CTS patients was significantly lower than those in healthy subjects.

### *Deformation ratios of the median nerve*

The deformation ratios of the area, perimeter and circularity of the median nerve during finger and wrist movements are shown in Table 1. For wrist flexion with fingers flexed, the deformation ratio of median nerve perimeter was significantly higher in CTS patients than that in healthy subjects (P=0.024) (ratio for both groups was less than 1). For wrist flexion with fingers extended or flexed and wrist ulnar deviation with fingers extended, the deformation ratio of circularity in CTS patients was significantly less than that in healthy subjects (P=0.009, P=0.004 and P<0.001, respectively) (Figure 2) (ratio for both groups was bigger than 1). For finger flexion and wrist extension with fingers extended or flexed, no difference in any deformation ratio of the median nerve was found between the CTS patients and healthy subjects.

| Wrist motions | Area deformation ratio | Perimeter deformation ratio | Circularity deformation ratio |
|---|---|---|---|
| **Finger flexion** | | | |
| Patients | 1.00±0.16 | 0.98±0.08 | 1.05±0.13 |
| Healthy subjects | 0.99±0.12 | 0.98±0.09 | 1.09±0.15 |
| **Wrist flexion with finger extension** | | | |
| Patients | 0.93±0.20 | 0.87±0.16 | 1.23±0.16** |
| Healthy subjects | 1.06±0.24 | 0.86±0.16 | 1.49±0.38 |
| **Wrist flexion with finger flexed** | | | |
| Patients | 0.98±0.21 | 0.89±0.13* | 1.25±0.28** |
| Healthy subjects | 0.94±0.22 | 0.79±0.15 | 1.57±0.36 |
| **Wrist extension with finger extension** | | | |
| Patients | 1.01±0.20 | 1.02±0.14 | 0.99±0.20 |
| Healthy subjects | 1.03±0.15 | 0.97±0.11 | 1.12±0.19 |
| **Wrist extension with finger flexed** | | | |
| Patients | 0.97±0.20 | 1.00±0.12 | 0.99±0.20 |
| Healthy subjects | 0.98±0.15 | 0.98±0.12 | 1.05±0.22 |
| **Wrist ulnar deviation** | | | |
| Patients | 0.97±0.20 | 0.90±0.12 | 1.19±0.16** |
| Healthy subjects | 1.02±0.27 | 0.93±0.20 | 1.53±0.32 |

**Table 1** Median nerve deformation ratios.
* p<0.05, ** p<0.01

### *Displacement vector of the median nerve*

Mean vectors for all movements are shown in Table 2. Included are vector magnitude (ρ) and vector direction (θ), major and minor confidence ellipse axes (a and b) and inclination of the ellipse (ψ). Solid ellipses represent standard deviation, dashed ellipses represent 95% confidence limits and the radial line represents the mean vector for each group. This table includes data published previously, with regard to the normal subjects,[21] and compares that

data with those in the patients studied here. With the exception of wrist flexion with fingers extended, all motions were found to have a normal distribution. A significant difference in the mean median nerve displacement vector was found between CTS patients and healthy subjects for wrist flexion with fingers extended or flexed ($P<0.01$), wrist extension with fingers extended ($P<0.05$) and wrist ulnar deviation with fingers extended ($P<0.01$) (Figures 3A-D). No significant difference was found between healthy subjects and patients for movements of finger flexion ($P=0.217$) or wrist extension with fingers flexed ($P=0.106$) (Figures 3E-F).

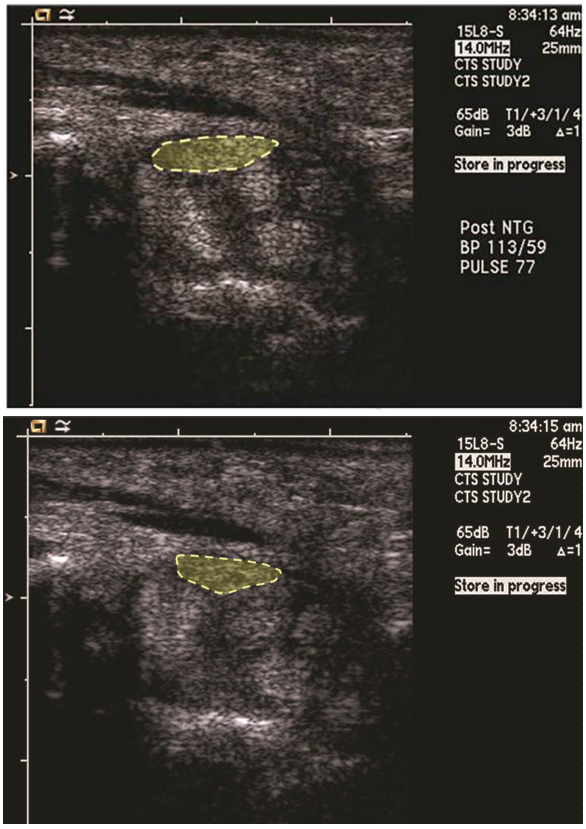


**Figure 2** The median nerve at the carpal tunnel in a patient with CTS. At the start (first image) of wrist maximal flexion with fingers extended, the enlarged median nerve (dashed ellipse) was located between the flexor retinaculum and flexor tendons on ultrasound scans in the transverse plane. At the end (last image) of the movement the median nerve (dashed ellipse) was still located between the flexor retinaculum and flexor tendons and had moved only slightly towards the ulnar side of the carpal tunnel.

### *Normalized amplitudes of the median nerve displacement*

The normalized amplitudes of median nerve displacement are shown in Table 3. The normalized amplitudes of median nerve displacement in CTS patients were significantly less compared to those in normal subjects in wrist flexion with and without finger flexion and wrist ulnar deviation ($P=0.016$, $P=0.010$ and $P=0.005$, respectively). No significant difference was found for the normalized amplitude of median nerve displacement for finger flexion and wrist extension with fingers extended or flexed between the two groups ($P>0.05$).

| | Mean ρ (NU) | Mean θ | a (NU) | b (NU) | ψ |
|---|---|---|---|---|---|
| **Finger flexion** | | | | | |
| Patients | 0.1 | 28.9 ° | 0.5 | 0.2 | 9.1 ° |
| Healthy subjects | 0.2 | 117.3 ° | 0.5 | 0.2 | -16.0 ° |
| **Wrist flexion with finger extension** | | | | | |
| Patients | 0.8 | 137.3 ° ** | 1.0 | 0.3 | -6.2 ° |
| Healthy subjects | 1.5 | 267.1 ° | 1.2 | 0.5 | -11.9 ° |
| **Wrist flexion with finger flexion** | | | | | |
| Patients | 1.0 | 331.4 ° ** | 1.0 | 0.4 | 4.5 ° |
| Healthy subjects | 1.8 | 295.0 ° | 1.1 | 0.5 | -11.7 ° |
| **Wrist extension with finger extension** | | | | | |
| Patients | 0.2 | 144.4 ° * | 0.7 | 0.2 | -12 ° |
| Healthy subjects | 0.4 | 225.6 ° | 0.5 | 0.2 | -7.8 ° |
| **Wrist extension with finger flexion** | | | | | |
| Patients | 0.6 | 184.4 ° | 0.5 | 0.2 | -0.7 ° |
| Healthy subjects | 0.5 | 182.0 ° | 0.5 | 0.2 | -2.5 ° |
| **Wrist ulnar deviation** | | | | | |
| Patients | 1.8 | 190.9 ° ** | 0.8 | 0.3 | 14.6 ° |
| Healthy subjects | 2.8 | 188.5 ° | 0.3 | 0.2 | -5.2 ° |

**Table 2** The mean vector and confidence limits for various parameters of the median nerve displacement during finger and wrist movements in patients with CTS and healthy subjects. Abbreviations: ρ = vector length, NU; normalized units (is approximately 1.8 mm), θ = vector angle, a = major ellipse axes for variation of the confidence limits, b = minor ellipse axes for variation of the confidence limits, ψ = inclination of the ellipse. * $p<0.05$, ** $p<0.01$

| | Amplitude of median nerve displacement (NU) |
|---|---|
| **Finger flexion** | 0.75±0.44 |
| Patients | |
| Healthy subjects | 0.85±0.33 |
| **Wrist flexion with finger extension** | |
| Patients | 1.74±0.78* |
| Healthy subjects | 2.36±0.79 |
| **Wrist flexion with finger flexion** | |
| Patients | 1.71±0.90** |
| Healthy Subjects | 2.46±0.84 |
| **Wrist extension with finger extension** | |
| Patients | 0.90±0.68 |
| Healthy subjects | 0.77±0.46 |
| **Wrist extension with finger flexion** | |
| Patients | 0.85±0.56 |
| Healthy subjects | 0.81±0.58 |
| **Wrist ulnar deviation** | |
| Patients | 1.93±1.23** |
| Healthy subjects | 2.86±0.51 |

**Table 3** The normalized amplitudes of the median nerve displacement during the finger and wrist movements in patients and healthy subjects. * $p<0.05$, ** $p<0.01$

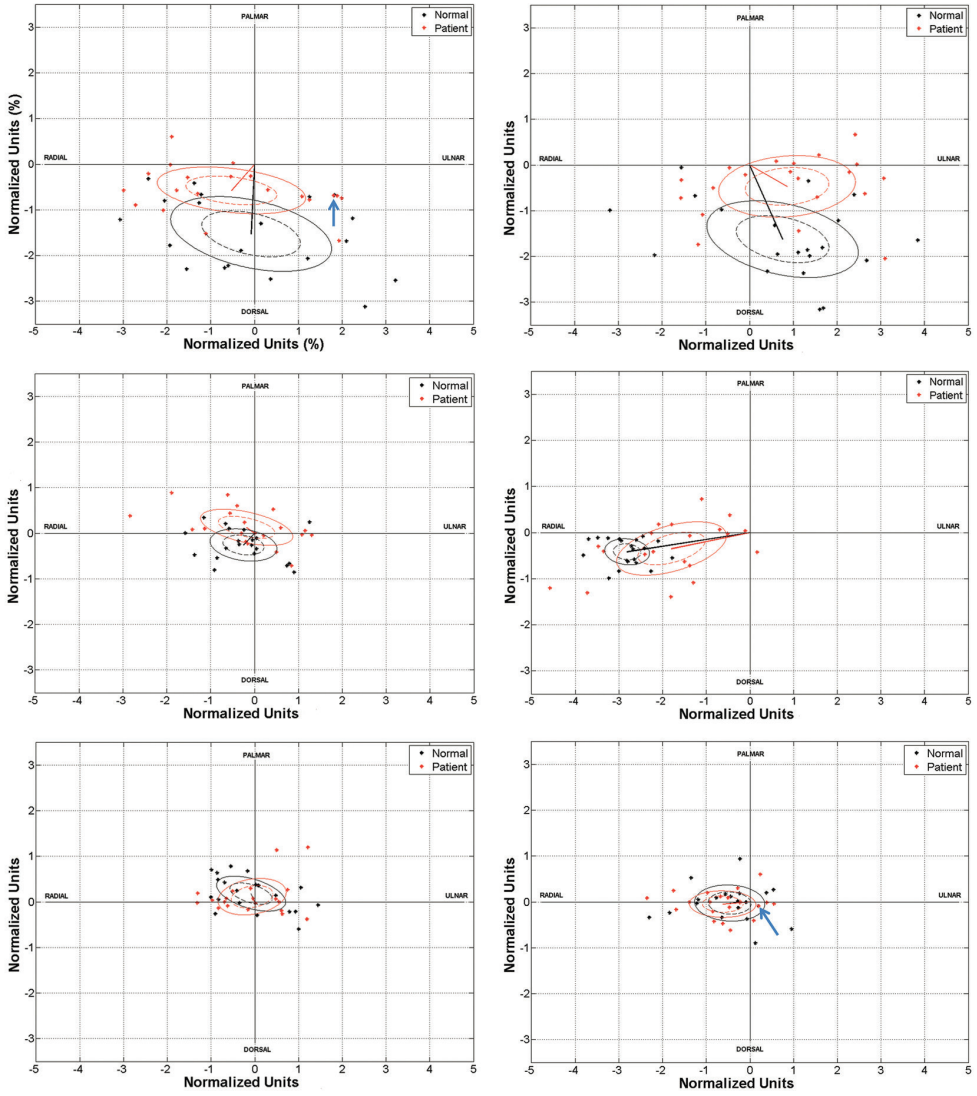


**Figure 3 A-F** The median nerve displacement vectors in CTS patients. Solid ellipses represent standard deviation, dashed ellipses represent 95% confidence limits and the radial line represents the mean vector for each group. **A**. Wrist flexion with fingers extended. The arrow indicates two superimposed points from a patient and a healthy subject respectively. **B**. Wrist flexion with fingers flexed. **C**. Wrist extension with fingers extended. **D**. Wrist ulnar deviation with fingers extended. **E**. Finger flexion. **F**. Wrist extension with fingers flexed. The arrow indicates two superimposed points from a patient and a healthy subject respectively.

## DISCUSSION

Associations have been made between repetitive hand and wrist motions and the possible effect on the development of CTS.[30,31] Therefore, it is important to understand the kinematics of the median nerve during different wrist motions. In this study we evaluated the deformability and mobility of the median nerve at the proximal carpal tunnel during finger and wrist movements in CTS patients and compared these results to those previously reported for normal subjects.[21] We found that with maximal wrist flexion with or without finger flexion and maximal ulnar deviation, the median nerve deformed and moved less in patients with CTS compared to healthy subjects.

Many studies have investigated deformation and mobility of the median nerve using imaging modalities, such as magnetic resonance imaging and ultrasound.[11,13,21,24,32-34] Most studies have focused on the effect of finger motion.[11-13,34] Fewer studies have investigated median nerve displacement in the transverse plane during wrist movement.[21,22,24,32,33] Most of these studies investigated the effect of wrist motion on median nerve shape and/or displacement in healthy subjects.[22,35,36] They found that the median nerve remained palmar during wrist extension and, in most subjects, moved dorsally during wrist flexion. Greening et al. found reduced median nerve displacement in the transverse plane in patients with non-specific arm pain.[32,33] No CTS patients were included in their studies. Allmann et al. found that in 65% of the CTS patients included in the study, the median nerve moved less and remained near the flexor retinaculum during wrist flexion while the same occurred in only 27% of normal subjects.[25] These results are consistent with our findings.

We observed that the deformation of the median nerve in CTS patients was decreased compared to healthy subjects. The normal median nerve deforms to accommodate finger or wrist movement.[11,12,22] This may be related to the specific internal structure of median nerve. Histologically, the median nerve is composed of axons, which are bundled by several connective tissue layers.[37,38] The extensibility of these layers is critical for the nerve to accommodate tensile or compressive stress by elongating, gliding or deforming. In CTS progressive fibrosis has been found in the epineurial and perineurial connective tissues.[39,40] This fibrosis may result in a permanently decreased compliance of the median nerve during its movement in the carpal tunnel. Orman et al. used ultrasound elastography to evaluate the stiffness of median nerve in the carpal tunnel.[41] They found that the median nerve was stiffer in patients with CTS than in normal subjects, which is consistent with the results of our study.

We also observed that the mobility of the median nerve was decreased in CTS patients. In the healthy carpal tunnel the tendons and nerve are surrounded by subsynovial connective tissue (SSCT), which is filmy and supple, and thus can facilitate smooth gliding and deformation of the median nerve in the carpal tunnel. In patients with CTS, the SSCT is fibrotic,[42-44] which may cause the median nerve and tendons to become attached to

adjacent structures, preventing the nerve from moving freely and causing it to become compressed between tendons and the flexor retinaculum during wrist flexion. This may explain why CTS symptoms are provoked by Phalen's maneuver. Enlargement of the median nerve may also impair its mobility. An increased median nerve cross-sectional area is a well-known finding in CTS patients.[45,46] The decreased cross-sectional area of the carpal tunnel in wrist flexion combined with the enlarged median nerve may further hinder the median nerve from moving dorsally between the flexor tendons.[36]

Lastly, we found that the decreases in deformation and displacement of the median nerve in CTS patients were more evident during wrist flexion. This may be related to changes in the anatomy or pressure within the carpal tunnel during wrist flexion, compared to wrist extension or the neutral wrist position. In wrist flexion both the proximal and distal part of the carpal tunnel cross-sectional area are decreased compared to the neutral position.[36,47,48] Furthermore the flexor tendons move palmarly with wrist flexion.[49] Palmar movement of the flexor tendons may further contribute to the increased contact pressure on the median nerve.

Our study has several limitations. First, our study has a small sample size. Yet even with this small sample size we were able to note significant differences between CTS patients and healthy subjects.[21] Second, the ultrasonographic results could not be correlated with the severity of the CTS due to the small sample size. Future studies with a larger sample size are necessary to explore the relationship between the mobility and deformability of the median nerve and the severity of CTS. The data presented in the current study will serve as a useful baseline for future studies. Third, although we performed dynamic ultrasound of the median nerve, we only analysed the median nerve in the first and final image of the movement. Dynamic changes, such as the path of motion, were not analysed. This may provide additional useful information. However, analysis of the median nerve motion path is labour intensive and quantification is difficult. Measurement of the median nerve parameters in the first and last image is therefore a simple method for evaluating the mobility and deformability of the median nerve during wrist movement.

In summary, our study showed that CTS patients have a decreased deformability and mobility of the median nerve at the proximal carpal tunnel in the transverse plane with wrist flexion and ulnar deviation of the wrist. This study has revealed differences in median nerve transverse kinematics in the carpal tunnel between CTS patients and healthy subjects. Further studies with a larger sample of patients are necessary to determine if changes of kinematics of the median nerve can be related to severity of CTS and if these measurements may be useful for predicting treatment response.

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8

# MULTIDIMENSIONAL IMAGING OF THE WRIST: CHANGES OF THE MEDIAN NERVE AND TENDON SHAPE AND DISPLACEMENT IN CARPAL TUNNEL SYNDROME

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## ABSTRACT

Dynamics of structures within the carpal tunnel may be different in carpal tunnel syndrome (CTS) due to fibrotic changes and increased carpal tunnel pressure. Ultrasound may be able to visualize these changes, making ultrasound potentially a diagnostic tool. To study this, we imaged the carpal tunnel of 113 patients and 42 controls. CTS severity was classified according to validated clinical and nerve conduction study (NCS) classifications. Transverse and longitudinal displacement and shape (changes) were calculated for the median nerve, tendons and surrounding tissue. To predict diagnostic value of ultrasound binary logistic regression modelling was applied. Reduced longitudinal nerve displacement ($p \leq 0.019$), increased nerve cross-sectional area ($p \leq 0.006$) and perimeter ($p \leq 0.007$), and a trend of relatively changed tendon displacements were seen in CTS patients. Changes were more convincing when CTS was classified as more severe. Binary logistic modelling to diagnose CTS showed a sensitivity of 70% and specificity of 80 to 84%. In conclusion, CTS patients have altered dynamics of structures within the carpal tunnel.

## INTRODUCTION

Carpal tunnel syndrome (CTS) is the most commonly diagnosed compression neuropathy of the median nerve (MN), with an incidence of 3 to 4% in most epidemiological surveys.[1,2] The clinical CTS diagnosis is generally confirmed with nerve conduction studies (NCS). However, NCS can be false-negative in a significant number of patients.[3-5] Moreover, NCS findings are not strongly correlated with clinical severity and treatment outcome,[3] leaving room for improvement of tools to diagnose CTS and to predict which patients respond best to which treatment.

Ultrasound has gained interest as a diagnostic tool to confirm clinically suspected CTS. Changes of the MN, tendon and surrounding subsynovial connective tissue (SSCT) dynamics have been found and these can be visualized using, amongst others, ultrasound. As an imaging tool, ultrasound has several advantages, including its low cost, painless application and its capability of detecting underlying pathology. In addition, ultrasound is often already used in staging associated disorders like rheumatoid arthritis.[6-9]

Static ultrasound imaging has been used predominantly to study CTS. Differences between CTS patients and controls for area and circularity of the MN are frequently found. The MN area has proven to be strongly correlated with NCS results, and has shown similar specificity and sensitivity as NCS in confirming the diagnosis of CTS.[10-13]

Dynamic ultrasound imaging, whereby alterations of shape and displacement of the structures in the carpal tunnel were measured during motion, have also been investigated to detect potential biomechanical changes in CTS patients.[14-17] Decreased longitudinal MN displacement, altered transverse MN motion and changed longitudinal tendon displacement have been found in CTS patients when comparing the most affected side with the least affected side.[15,18,19]

In the present study, we analysed carpal tunnel structures in the longitudinal and transverse planes using both dynamic ultrasound scans and static ultrasound images, and correlated these results to the clinical and NCS classified severity of CTS. Investigating both static and dynamic measurements can add knowledge on dynamical changes of carpal tunnel structures in CTS patients. This may help to develop a diagnostic tool that has a high sensitivity and specificity to diagnose CTS. To study this, a prospective study was undertaken correlating the severity of CTS based on clinical and NCS classifications with static and dynamic multidimensional ultrasound imaging measurements.

## METHODS

This is a well-designed case-control study (level III evidence). The Medical Ethics Committee (METC) of Erasmus Medical Centre and the Mayo Clinic Institutional Review Board (IRB) have approved this research. We obtained written informed consent from all study participants.

In order to maintain patient confidentiality, and consistent with the medical ethics and IRB approvals, solely deidentified image files and data sets were shared between institutions.

### *Subjects*

Controls and patients were included from the Erasmus Medical Centre (Rotterdam, the Netherlands) and Mayo Clinic (Rochester, MN, USA). The sample size was determined by a power calculation. Based on previously published data whereby the same methods were used and based on pilot data,[15,16] we estimated a standard deviation of MN area results to be 3.3 $mm^2$ and an expected delta of 3.4 $mm^2$. For the longitudinal MN displacement results we estimated a standard deviation of 1.35 mm and an expected delta of 1.1 mm. Next, taking into account that the study group would be subdivided in 5 different clinical or NCS classes, and assuming similarity in our data with previously published data and pilot data, a sample size of 129 study subjects or more would provide a 80% power to detect differences with an $\alpha$ of 0.05 and a $\beta$ of 0.20.

All controls had no clinical signs or symptoms of CTS and patients had symptoms of CTS as determined by a neurologist, neurosurgeon, orthopaedic surgeon or plastic surgeon. Controls and patients filled in the Boston Carpal Tunnel Questionnaire (BCTQ), and were classified according to a validated clinical classification.[20,21] The clinical classification was based on the historical objective (Hi-Ob) scale.[20] All patients underwent a NCS test and results were graded according to the criteria of Padua et al.[22] Reference values of Buschbacher et al. were used for the assessment of NCS results.[23]

In CTS patients, only the most affected side was included, which was based primarily on the Hi-Ob scale and NCS classification. If inconclusive, the BCTQ score was decisive. In the control group, at random, the right or left hand was included. Subjects were excluded if they had a medical history of upper extremity surgery, other peripheral nerve pathology or fractures of the hand or wrist.

### *Clinical classification*

The Hi-Ob score rates symptoms as either:

1. No CTS if patients had no CTS symptoms;
2. Minimal CTS if patients had nocturnal paraesthesia in the MN distribution (numbness, tingling, pain, burning);
3. Mild CTS if patients had nocturnal and diurnal paraesthesia in the MN distribution;
4. Moderate CTS if patients had sensory deficit in the MN distribution of the hand;
5. Severe to extreme CTS if patients had a motor deficit, hypotrophy of the MN innervated muscles of the hand or severe impaired motor function of the by the MN innervated thenar muscles.

### *The BCTQ*

The BCTQ is a validated patient-orientated questionnaire. The BCTQ evaluates CTS symptoms, assessed by 11 questions, and function, assessed by 8 questions.[21] Each item includes 5 possible responses, and the score is calculated as the mean of the responses of the individual items.

### *NCS classification*

All patients underwent NCS at entry to the study using the Viking Select or Viking EDX EMG machine (CareFusion, San Diego (CA), USA). As described in the guidelines of the American Association of Electrodiagnostic Medicine; ring electrodes located on digits 4, 1 and 3 were used for recording sensory latency, velocity and sensory nerve action potential amplitude, and surface electrodes for recording the distal motor latency (DML), velocity in the forearm and compound muscle action potential amplitude from the abductor pollicis brevis muscle.[24]

1. No CTS (i.e., normal sensory and motor responses);
2. Minimal CTS (i.e., abnormal segmental test (third digit to palm/palm to wrist ratio of <1) or a distal sensory latency difference of ≥0.5 between the ulnar and median nerve, and normal MN sensory nerve conduction velocity (SNCV) and normal DML);
3. Mild CTS (i.e., abnormal MN SNCV (<40 ms), normal DML);
4. Moderate CTS (abnormal MN SNCV, abnormal DML (≥4.7 ms for men and ≥4.4 ms for women));
5. Severe or extreme CTS (absence of median sensory response, abnormal DML or total absence of motor responses).

### *Ultrasound measurement protocol*

Subjects were seated with the arm positioned on a table. The arm was supinated, elbow slightly flexed in 120 degrees, and the wrist in neutral position. Subjects were asked to flex their fingers in 8 seconds until the tip of their fingers touched the palm of the hand. High frequency ultrasound scans were made in the longitudinal and transverse plane of the MN, the flexor digitorum superficialis tendon of the middle finger (FDS3) and the flexor digitorum profundus tendon of the middle finger (FDP3) with surrounding tissue. We used the Philips iU22 and iU33 machines (Philips Electronics, Best, the Netherlands) with respectively a 5-12 MHz linear array transducer and a 7-15 MHz linear array transducer. The transducer was placed at the distal wrist crease at the level of the inlet of the carpal tunnel, which was identified by the pisiform bone and the scaphoid tubercle. A trained physician (AF) with experience in musculoskeletal ultrasound of the upper extremity did all imaging at both institutions.

### *Data processing*

#### *Analysis of longitudinal plane ultrasound scans*

The process of data analysis to calculate longitudinal displacement of the structures within the carpal tunnel has been described previously.[25] In brief, ultrasound images were exported as uncompressed Audio Video Interleave (AVI) files using OsiriX (version 4.1.2 64-bit, http://osorix-viewer.com). The uncompressed AVI's were exported to and analysed with a validated in-house developed Matlab-based speckle-tracking algorithm (Version 2011a, The MathWorks Inc., Natick (MA), USA).[25] In the first frame of the scan a region of interest was placed within the structure to be measured and the speckle-tracking program calculated the total displacement of this structure (Figure 1A-C). The following parameters were calculated: displacement of the MN, FDS3 tendon, FDP3 tendon and the tissue (SSCT) surrounding each of these structures. In addition, to normalize data, displacement ratios of the MN and tendons were calculated.

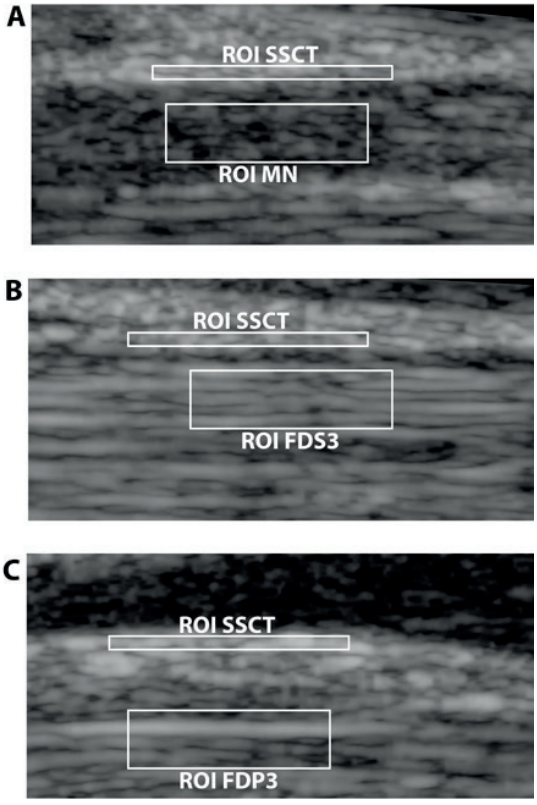


**Figure 1A-C.** Placement of the region of interest (ROI) for
**A**. The MN with SSCT.
**B**. The FDS3 tendon with SSCT.
**C.** The FDP3 tendon with SSCT.

*Analysis of transverse plane ultrasound scans*

The process of data analysis to calculate shape and transverse plane displacement parameters of the MN, FDS3 tendon and FDP3 tendon has been described previously.[14] Briefly, an in-house developed Matlab-based image processing software program (Version 2011a, The MathWorks Inc., Natick (MA), USA) was used. Polygons were placed manually on the outside border of the MN, FDS3 tendon and FDP3 tendon in 10 frames of the AVI file (Figure 2A-B). From the polygons, the following outcome parameters were calculated: area, perimeter, circularity, area deformation ratio, perimeter deformation ratio, circularity deformation ratio, and center of mass (CoM). The deformation ratio was defined as the value in the final position divided by the value of the initial position. Transverse endpoint displacement of the MN and tendons were based on CoM calculations.[14]

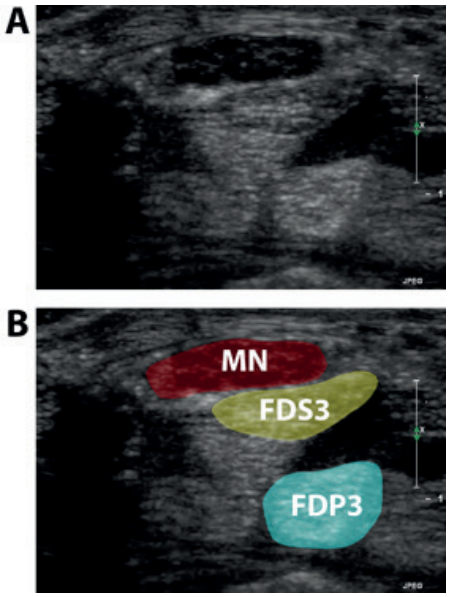


**Figure 2A-B. A.** A transverse plane ultrasound image at the carpal tunnel inlet of a CTS patient during extension of all fingers. **B**. Manually placed polygons on the outside border of the MN, FDS3 tendon and FDP3 tendon.

## *Statistical analysis*

The test-retest reliability of the longitudinal ultrasound measurements was calculated. To do so, the MN, tendons and surrounding SSCT were imaged twice, converted and analysed separately by the same investigator. Following the guidelines of Wolak et al., we analysed repeated measures of each structure in 50 subjects, based on an expected excellent intraclass correlation coefficient (ICC) of >0.80.[26] The ICC random mixed model with absolute agreement was used. No test-retest reliability was calculated for transverse ultrasound measurements, since the test-retest reliability for the transverse ultrasound imaging has been reported previously to be approximately 0.75 for shape measurements and 0.85 for displacement measurements of the MN and tendons.[14,27]

To compare group characteristics (i.e., gender, age, body mass index (BMI) and hand side) of the controls and CTS patients, we used the unpaired T-test for continuous data and Chi-squared test for binominal data. Next, CTS patients were classified according to the clinical and NCS classification. The one-way ANOVA with Bonferroni correction was used to analyse potential differences for the various ultrasound measurements between the different classes of CTS severity based on the clinical and NCS classification. A p-value of $<0.05$ was considered significant.

To predict diagnostic value of ultrasound for CTS, we applied binary logistic regression modelling with stepwise elimination using the maximum-likelihood function. Two models were defined; in model one the clinical classification was the dependent variable and in the second model the NCS classification was the dependent variable. All statistical analyses were performed using the Statistical Package for Social Science software version 17.0 (SPSS, Chicago (IL), USA).

## RESULTS

The majority of controls and CTS patients (29 controls (69%) and 90 patients (80%) respectively) were recruited and imaged at the Erasmus Medical Centre; 13 controls (31%) and 23 patients (20%) were included at the Mayo Clinic. The control and patient group characteristics are shown in Table 1. Except for the hand side, no differences existed between groups.

| | **Controls (N=42)** | **Patients (N=113)** | **P-value** |
|---|---|---|---|
| Gender (Female) | 32 (76%) | 82 (73%) | 0.729 |
| Age | 46.3 (SD 11.3) | 40.0 (SD 12.1) | 0.088 |
| BMI | 28.0 (SD 8.2) | 29.7 (SD 5.5) | 0.066 |
| Right hand included | 36 (86%) | 78 (69%) | 0.036 |
| **Clinical classification** | | | |
| - no CTS | 42 (100%) | | |
| - minimal CTS | | 13 (12%) | |
| - mild CTS | | 66 (58%) | |
| - moderate CTS | | 28 (25%) | |
| - severe CTS | | 6 (5%) | |
| **NCS classification** | | | |
| - no CTS | 42 (100%) | 19 (17%) | |
| - minimal CTS | | 22 (19%) | |
| - mild CTS | | 24 (20%) | |
| - moderate CTS | | 29 (26%) | |
| - severe CTS | | 19 (17%) | |

**Table 1** Study group characteristics.
Abbreviations: N=number; SD=standard deviation; BMI=body mass index.

### *Ultrasound measurement of longitudinal displacements*

The test-retest ICCs for the displacement of the MN (ICC=0.83) and its surrounding tissue (ICC=0.49), the FDS3 tendon (ICC=0.70) and its surrounding tissue (ICC=0.73), and the FDP3 tendon (ICC=0.85) and its surrounding SSCT (ICC=0.68) were moderate to good, with the repeatability of the surrounding SSCT measures being lower than for the tendons and nerves, except for the SSCT surrounding the FDS3 tendon.

Less MN displacement was seen in patients clinically classified as having mild or moderate CTS ($p \leq 0.019$) compared to the control group (Table 2). Less MN displacement was also seen in patients having moderate and severe CTS according to the NCS classification system ($p \leq 0.001$) compared to the control group and the patients with a NCS result negative for CTS (Table 3). No differences in displacements were found between controls and CTS patients for the FDS3 tendon, FDP3 tendon or the SSCT surrounding the nerve and tendons.

| | Controls | Minimal CTS | Mild CTS | Moderate CTS | Severe CTS |
|---|---|---|---|---|---|
| **Longitudinal plane** | | | | | |
| Subjects (N) | 42 | 13 | 66 | 28 | 6 |
| MN displacement (mm) | 4.1 | 3.9 | 3.1 | 2.7 | 3.1 |
| | SD 1.9 | SD 1.2 | SD 1.6 | SD 1.5 | SD 1.5 |
| **Transverse plane** | | | | | |
| Subjects (N) | 42 | 13 | 57* | 27* | 6 |
| MN area ($mm^2$) | 9.6 | 9.4 | 13.6 | 14.1 | 15.9 |
| | SD 2.3 | SD 2.7 | SD 4.5 | SD 5.8 | SD 3.2 |
| MN perimeter (mm) | 15.4 | 14.4 | 17.5 | 17.2 | 19.1 |
| | SD 2.6 | SD 2.9 | SD 3.1 | SD 3.6 | SD 2.7 |
| Circularity ratio | 1.14 | 0.99 | 1.02 | 1.04 | 1.04 |
| | SD 0.24 | SD 0.16 | SD 0.14 | SD 0.12 | SD 0.10 |
| Perimeter ratio | 0.94 | 0.99 | 1.00 | 0.99 | 0.96 |
| | SD 0.11 | SD 0.12 | SD 0.10 | SD 0.08 | SD 0.06 |

**Table 2** Displayed are the ultrasound parameters that were significantly different between controls and clinically graded CTS patients. *Transverse ultrasound data is missing in 9 patients with mild CTS and 1 patient with moderate CTS.
Abbreviations: N=number; SD=standard deviation.

When analysing the ratios of the MN to FDS3 tendon and FDS3 to FDP3 tendon, a trend of decreasing MN to FDS3 tendon ratios and increasing FDS3 to FDP3 tendon ratios was observed with increasing severity of the CTS (Figure 3A-B, Figure 4A-B, Table S-1 and Table S-2).

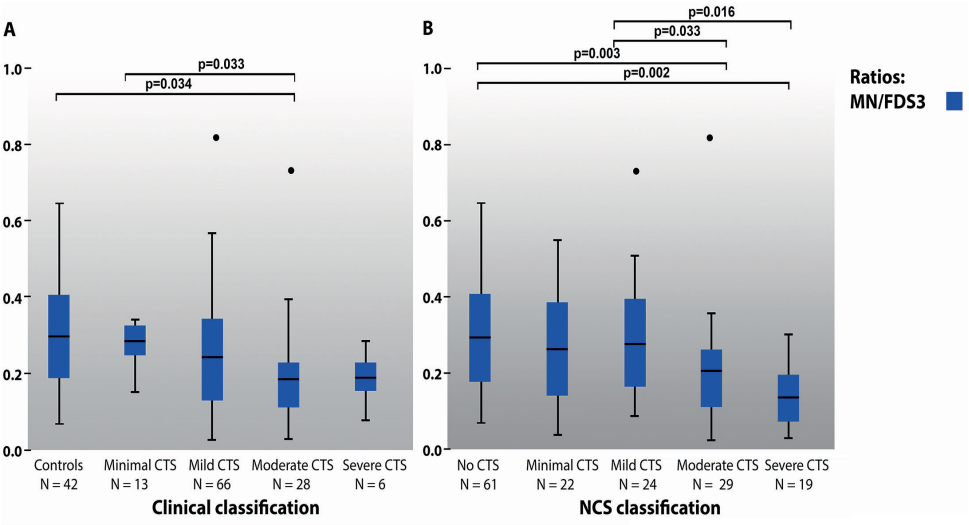


**Figure 3A-B** MN to FDS3 tendon ratio based on the longitudinal displacement of these structures. Significant differences are identified with corresponding p-values. **A**. Clinically graded CTS patients. **B**. CTS patients graded according to the NCS classification. Outliers are displayed as dots.

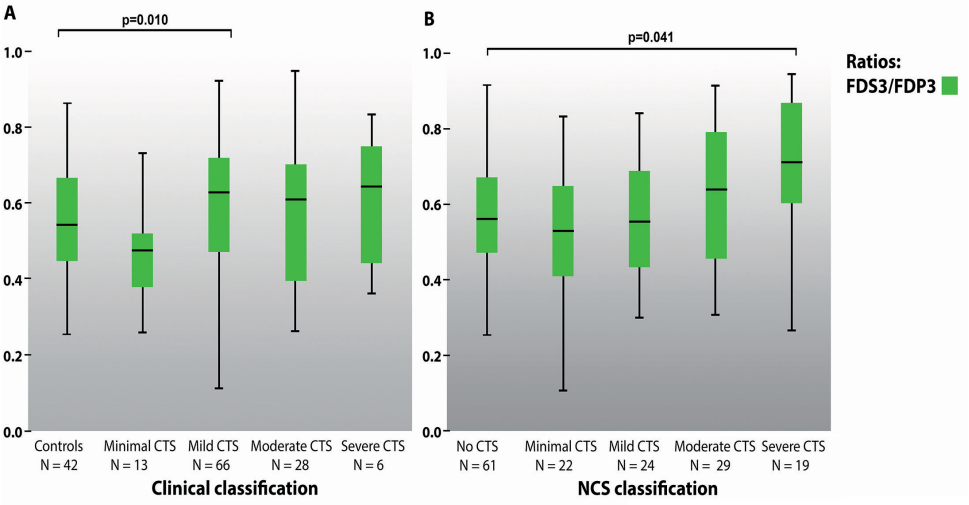


**Figure 4A-B** FDS3 to FDP3 tendon ratio based on the longitudinal displacement of these structures. Significant differences are identified with corresponding p-values. **A**. Clinically graded CTS patients. **B**. CTS patients graded according to the NCS classification. Outliers are displayed as dots.

| | Controls or no CTS | Minimal CTS | Mild CTS | Moderate CTS | Severe CTS |
|---|---|---|---|---|---|
| **Longitudinal displacement (mm)** | | | | | |
| Subjects (N) | 42 | 13 | 66 | 28 | 6 |
| MN | 4.1 (SD 1.9) | 3.9 (SD 1.2) | 3.1 (SD 1.6) | 2.7 (SD 1.5) | 3.1 (SD 1.5) |
| Surrounding SSCT | 2.3 (SD 2.2) | 2.0 (SD 1.1) | 1.5 (SD 1.1) | 1.8 (SD 1.3) | 1.4 (SD 1.2) |
| FDS3 | 14.3 (SD 4.3) | 11.7 (SD 3.3) | 15.1 (SD 4.7) | 14.8 (SD 5.5) | 15.9 (SD 3.2) |
| Surrounding SSCT | 7.6 (SD 5.4) | 6.6 (SD 3.5) | 8.9 (SD 5.3) | 7.7 (SD 6.1) | 6.2 (SD 3.3) |
| FDP3 | 26.7 (SD 5.5) | 26.7 (SD 5.4) | 24.6 (SD 5.3) | 25.1 (SD 3.8) | 25.8 (SD 5.7) |
| Surrounding SSCT | 24.3 (SD 5.4) | 25.4 (SD 7.0) | 23.4 (SD 5.2) | 23.6 (SD 6.0) | 25.9 (SD 5.8) |

**Table S1** Longitudinal displacement of the MN, FDS3 tendon, FDP3 tendon and surrounding SSCT of the controls and clinically graded CTS patients.
Abbreviations: N=number; SD=standard deviation.

| | Controls or no CTS | Minimal CTS | Mild CTS | Moderate CTS | Severe CTS |
|---|---|---|---|---|---|
| **Longitudinal displacement (mm)** | | | | | |
| Subjects (N) | 61 | 22 | 24 | 29 | 19 |
| MN | 4.1 (SD 1.8) | 3.1 (SD 1.5) | 3.4 (SD 1.7) | 2.6 (SD 1.4) | 2.4 (SD 1.0) |
| Surrounding SSCT | 2.2 (SD 2.0) | 1.9 (SD 1.4) | 1.7 (SD 1.0) | 1.4 (SD 1.1) | 1.5 (SD 1.2) |
| FDS3 | 14.7 (SD 4.5) | 14.0 (SD 4.1) | 12.9 (SD 4.6) | 15.2 (SD 5.2) | 16.4 (SD 4.6) |
| Surrounding SSCT | 8.5 (SD 5.8) | 7.5 (SD 4.6) | 8.0 (SD 5.8) | 8.3 (SD 4.7) | 6.9 (SD 4.8) |
| FDP3 | 26.7 (SD 5.0) | 25.3 (SD 4.2) | 2.36 (SD 5.2) | 25.5 (SD 5.6) | 24.2 (SD 5.3) |
| Surrounding SSCT | 24.5 (SD 5.3) | 23.8 (SD 4.1) | 23.0 (SD 6.6) | 24.8 (SD 6.1) | 22.7 (SD 5.9) |

**Table S2** Longitudinal displacement of the MN, FDS3 tendon, FDP3 tendon and surrounding SSCT of the controls and CTS patients graded according to the NCS classification.
Abbreviations: N=number; SD=standard deviation.

### *Measurements of the transverse plane ultrasound imaging*

Increased MN area was found for patients with clinically classified mild to severe CTS ($p \leq 0.006$) and moderate to severe CTS ($p < 0.001$) according to the clinical and NCS classification compared to controls or patients with NCS results negative for CTS (Table 2 and 3). The perimeter was increased in patients clinically classified as having mild CTS ($p \leq 0.007$) and patients with moderate to severe CTS according to the NCS classification ($p < 0.001$) compared to controls or patients with NCS results negative for CTS. No significant differences were found between groups for circularity based on either the clinical classification or the NCS classification. A significantly decreased MN circularity and perimeter ratio was found in patients with clinically graded mild CTS ($p \leq 0.019$). Patients with minimal CTS had a significantly smaller circularity ratio ($p = 0.014$). No significant difference was found between controls and CTS patients for displacement of the MN or tendons in the transverse plane (Figure 5A-D).

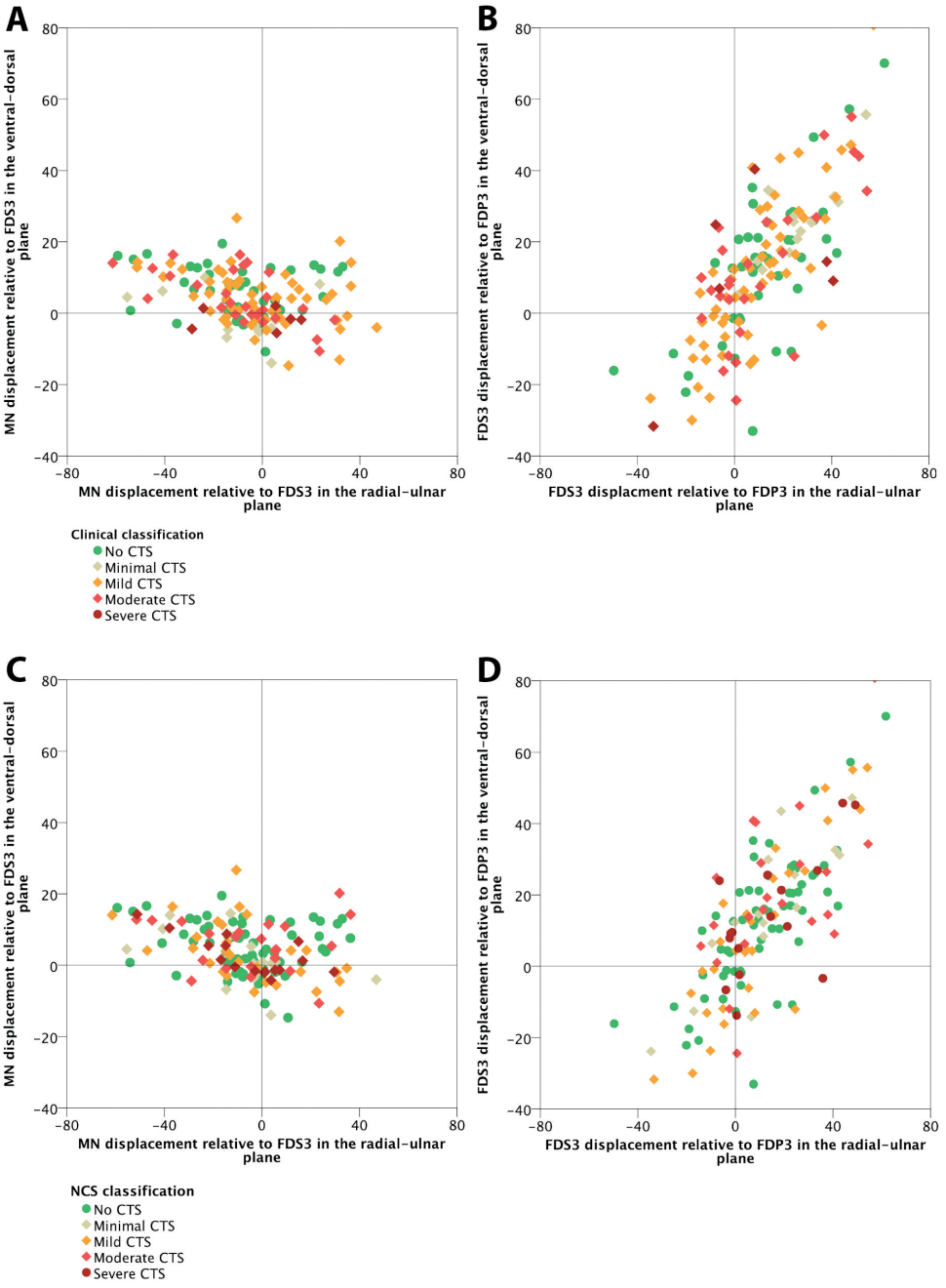


**Figure 5A-D** Transverse displacement in millimeters in the x (radio-ulnar) and y (palmar-dorsal) plane of the MN relative to the FDS3 tendon and the FDS3 tendon relative to the FDP3 tendon. **A-B**. Clinically graded CTS patients. **C-D**. CTS patients graded according to the NCS classification.

| | Controls or no CTS | Minimal CTS | Mild CTS | Moderate CTS | Severe CTS |
|---|---|---|---|---|---|
| **Longitudinal plane** | | | | | |
| Subjects (N) | 61 | 22 | 24 | 29 | 19 |
| MN displacement (mm) | 4.1 | 3.1 | 3.4 | 2.6 | 2.4 |
| | SD 1.8 | SD 1.5 | SD 1.7 | SD 1.4 | SD 1.0 |
| **Transverse plane** | | | | | |
| Subjects (N) | 60* | 19* | 24 | 25* | 17* |
| MN area ($mm^2$) | 10.0 | 11.4 | 11.7 | 15.4 | 17.6 |
| | SD 2.4 | SD 4.0 | SD 3.6 | SD 4.6 | SD 5.8 |
| MN perimeter (mm) | 15.5 | 15.7 | 16.0 | 18.5 | 19.7 |
| | SD 2.5 | SD 2.6 | SD 2.7 | SD 3.4 | SD 3.8 |
| Circularity ratio | 1.11 | 0.96 | 1.06 | 1.04 | 0.99 |
| | SD 0.22 | SD 0.15 | SD 0.14 | SD 0.13 | SD 0.11 |
| Perimeter ratio | 0.95 | 1.01 | 0.98 | 1.00 | 1.02 |
| | SD 0.10 | SD 0.11 | SD 0.11 | SD 0.08 | SD 0.06 |

**Table 3** Ultrasound parameters that showed significantly different results between controls and CTS patients graded according to the NCS classification. *Transverse ultrasound data are missing in one patient with no CTS according to the NCS classification, 3 patients with minimal CTS, 4 patients with moderate CTS and 2 patients with severe CTS. Abbreviations: N=number; SD=standard deviation.

| | β | SE | EXP (β) | 95% CI | p-value |
|---|---|---|---|---|---|
| **Model 1** | | | | | |
| MN displacement (mm) | -1.94 | 1.39 | 0.14 | 0.01-2.18 | 0.162 |
| FDP3 displacement (mm) | -0.94 | 0.48 | 0.39 | 0.15-1.00 | 0.051 |
| FDP3/FDS3 ratio | 2.09 | 1.52 | 8.10 | 0.41-160.32 | 0.170 |
| Area ($mm^2$) | 0.45 | 0.10 | 1.57 | 1.30-1.90 | <0.001 |
| Circularity ratio | 1.95 | 1.69 | 7.04 | 0.26-192.7 | 0.248 |
| Perimeter ratio | 6.75 | 3.04 | 850.60 | 2.20-329354.57 | 0.026 |
| Transverse displacement MN (mm) | -0.03 | 0.2 | 0.97 | 0.94-1.01 | 0.088 |
| Constant | -10.71 | 4.85 | | | 0.027 |
| **Model 2** | | | | | |
| MN displacement (mm) | -1.42 | 1.45 | 0.24 | 0.01-4.14 | 0.328 |
| FDS3 displacement (mm) | -1.94 | 0.80 | 0.14 | 0.03-0.69 | 0.015 |
| FDS3/FDP3 ratio | 4.23 | 2.02 | 68.93 | 1.33-3584.36 | 0.036 |
| Area MN ($mm^2$) | 0.33 | 0.07 | 1.39 | 1.21-1.60 | <0.001 |
| Circularity | 2.57 | 2.44 | 13.01 | 0.11-1538.77 | 0.292 |
| Circularity ratio | 4.46 | 1.93 | 86.41 | 1.96-3811.07 | 0.021 |
| Perimeter ratio | 7.62 | 3.15 | 2031.11 | 4.23-976196.37 | 0.016 |
| Transverse displacement MN (mm) | -.0.03 | 0.02 | 0.97 | 0.94-1.00 | 0.081 |
| Transverse displacement FDS3 (mm) | 0.03 | 0.02 | | | 0.159 |
| Constant | -18.43 | 5.46 | 1.03 | 0.99-1.07 | 0.002 |

**Table 4** Binary logistic modelling to predict the diagnostic value. Explanatory variables included in the logistic model. Model 1: clinical symptoms as the dependent variable. Model 2: NCS results as the dependent variable. Abbreviations: β = direction, SE=standard error, CI=confidence interval.

***Binary logistic regression modelling***

To determine the associations between the ultrasound parameters and the clinical or NCS classification, we evaluated two different logistic regression models (Table 4). Model 1 predicted the clinically diagnosed CTS and was found to have a sensitivity of 70% and specificity of 84%. Model 2 predicted the NCS-diagnosed CTS and was found to have a sensitivity of 70% and specificity of 86%.

## DISCUSSION

In this prospective study, the severity of CTS, based on clinical and NCS classifications, was compared with the results of static and dynamic multidimensional ultrasound imaging. The main findings were reduced longitudinal displacement of the MN and increased area of the MN. These changes became more pronounced when the severity of the CTS increased. When using binary logistic modelling, the diagnostic predictive value of ultrasound had a 70% sensitivity and a 84% specificity with clinical symptoms as dependent variable and a 70% sensitivity and a 86% specificity with NCS results as dependent variable.

Changes in longitudinal displacement without changes in the transverse displacement were found for various structures within the carpal tunnel. Recently, decreased longitudinal displacement of the MN has been reported in CTS patients.[15,19] In addition, Korstanje et al. demonstrated increased FDS3 tendon as well as decreased FDP3 tendon mobility in CTS patients when the most affected side was compared with the least affected side.[15] We did not find these differences, possibly because of great inter-subject variability. However, we did find an increased FDS3 to FDP3 tendon ratio and we saw a trend of decrease in absolute FDP3 tendon displacement in combination with an increase in absolute FDS3 tendon displacement. This may be the result of fibrotic SSCT causing the tendons to adhere to each other, or it may be that CTS patients flex their hands differently.

In contrast to the decreased longitudinal movement of the MN, no change for transverse displacement was found in CTS patients. This reduced longitudinal motion without a combined decrease in transverse displacement could potentially be explained by the concept of a disconnected or ruptured SSCT in CTS patients.[28] If the SSCT between the tendon and MN is disconnected, the MN will not be pulled along by the tendons in the longitudinal plane and may move transversely towards all possible directions within the carpal tunnel in response to the anterior motion of the tendons with finger flexion.[18] It has also been hypothesized that in some CTS patients the MN becomes relatively fixed to the tendons by means of fibrosis of the SSCT, although most often the SSCT between the MN and flexor tendons appears to be completely disrupted.[28-31] In the present study, two patients with mild and moderate CTS had MN movement, which was nearly simultaneously with the FDS3 tendon in the longitudinal plane. The MN to FDS3 tendon ratios were 0.73 and 0.82, which was higher than in any of the controls (maximum MN to FDS3 tendon ratio

was 0.65). This may suggest that in a small number of patients the fibrotic SSCT results in fixation of the MN to the tendons.

Altered cross-sectional MN area was the best discriminator between controls and CTS patients. Many studies have described that MN area is one of the most diagnostic measurements.[10,11,13] In this study, we found that other shape parameters (e.g., circularity ratio) changed as well in CTS patients, which may help to increase the diagnostic accuracy of ultrasound imaging.

About 20% of the CTS patients had symptoms of CTS with a negative NCS test result.[13] Witt et al. showed that 50% of CTS patients with negative NCS did have benefit from treatment and in 33% of the patients treatment had a negative effect.[3] This illustrates the need for a more adequate diagnosis. Ultrasound could potentially be that new diagnostic tool. Various studies have found that in 16-34% of the CTS patients with negative NCS results static ultrasound measurement may be useful in diagnosing CTS.[3,13,24]

We found that multidimensional ultrasound measurements had approximately a sensitivity of 70% and specificity of 85% for diagnosing CTS using clinical and NCS outcome as a reference. However, when developing a new tool, choosing the most appropriate treatment may be the most important outcome measure. Therefore, future studies are needed to correlate ultrasound measurements to outcome after different interventions.

The strength of this study is that we included 42 controls and 113 CTS patients, subdivided based on CTS severity. Many ultrasound studies did not subdivide the study population into severity subgroups, did not include a control group or included control groups that had significant lower BMI, younger ages or included both hands of one subject.[10,11,15-17,19,32] These are all confounding factors that could influence results (e.g., smaller areas of the MN of the control group, reduced standard deviations). In our control group gender, BMI and age were not statistically different from the CTS patient group, although, there was a trend of decreased BMI and increased age in the control group. Whether this may have affected our results is questionable; a positive correlation between BMI and MN area has been reported by one study while others found none.[33-35] Regarding age, a positive correlation with MN area has been found.[33] However, since the average age of the control group was higher than that of the CTS patient group this may have only underestimated the differences of MN area between controls and patients.

Our study has several limitations. First, there were significantly more right hands included in the control group. However, Filius et al. found that there was no difference between the right and left side within the same subject when applying transverse plane ultrasound scans.[14] Second, test-retest ICC for the longitudinal displacement results of the MN, tendons and SSCT were not all found to be excellent,[36] which should be considered when interpreting the ultrasound results. Partly, small speckle tracking errors may have affected results. However, more likely, results may have been affected by differences between consecutive recording due to, for example, subtle changes in the amount of

finger flexion of the subject, difference in recording locations and differences in image quality. Measuring finger movement ex vivo may partly solve this issue. Third, the transverse ultrasound images of ten patients lacked. Due to IRB regulations, the transverse ultrasound imaging was approved after approval of the longitudinal ultrasound imaging. However, it is unlikely that this has affected our results since the majority of these patients were classified as having mild and moderate CTS, which were relatively the largest subgroups. Lastly, 3D displacement cannot be assessed since this would require simultaneous acquisition of the orthogonal views, and thus, a 3D matrix transducer would be required operating at a frequency of at least 8MHz with high frame rates. Such transducers do not exist yet. The frame rate of current mechanically scanning 3D transducers is far too low to perform speckle-tracking algorithms as performed in the present study.

In summary, this study demonstrates that changes in shape and motion occur in CTS patients, particularly regarding the MN, and these changes are related to the severity of CTS. These findings provide insight in the dynamical changes that occur in CTS patients, which may help to get a better understanding of the pathogenesis of CTS and may help to develop an ultrasound-based tool that can diagnose CTS accurately.

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# 9

# DISCUSSION

# DISCUSSION

Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve in the carpal tunnel and accounts for approximately 90% of all compression neuropathies.[1] Compression and irritation of the median nerve causes paraesthesia of the radial side of the hand and muscle weakness of mostly the thumb.

High-velocity and highly repetitive hand and wrist motions have found to be a risk factor for CTS.[2-5] Hand motions are a result of coordinated displacements of various tendons at various velocities. Tendon motion can cause damage to the subsynovial connective tissue (SSCT) surrounding the nerve and flexor tendons in the carpal tunnel.[6,7] The SSCT serves as a friction-reducing unit when tendons are in motion.[8] Damaged SSCT initiates a repair process, which leads to replacement of the damaged SSCT by fibrotic SSCT,[9-13] a predominant histological finding in CTS.[12] The fibrotic SSCT is thickened, has increased capabilities to absorb interstitial fluids and decreased permeability.[14-16] Moreover, fibrozation of the SSCT causes adhesions or disconnection between adjacent tissues. These changes could affect carpal tunnel pressure and dynamics of structures in the carpal tunnel, which may subsequently cause median nerve neuropathy.

Part I of this thesis focused on biomechanical and dynamical behaviour of the SSCT, and the relation between (high-velocity) tendon gliding and SSCT damage. Part II focused on possible changes in dynamics of the median nerve, flexor tendons and SSCT in CTS patients using ultrasound and we investigated if ultrasound is an accurate diagnostic tool for CTS (Figure 1). Here I will discuss the main findings of this thesis, their clinical importance and possible limitations. Moreover, directions for future research will be considered.

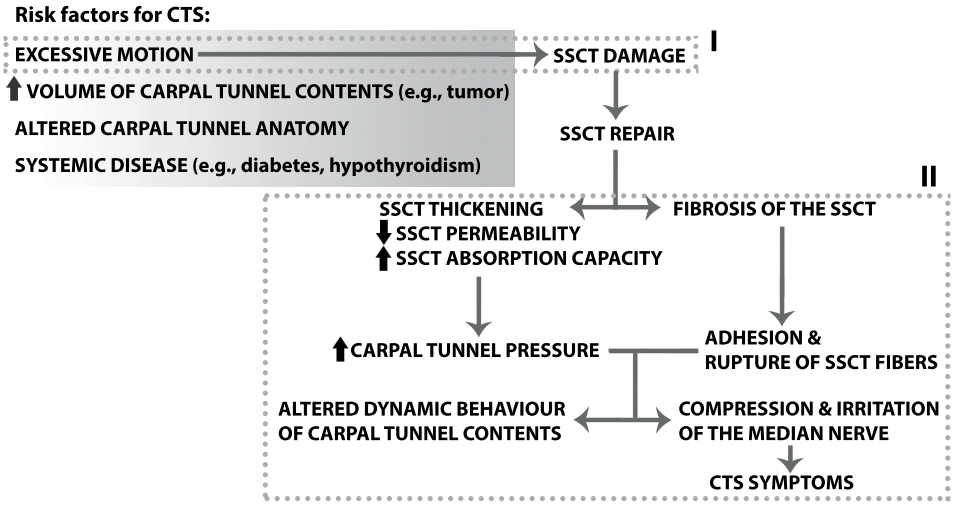


**Figure 1** Outline of this thesis.

### *Part I. The potential link between hand motions and the development of CTS*

The occurrence of CTS is associated with high-velocity, repetitive hand and wrist motions and hand vibration.[2-5,17,18] In **chapter 2** we showed that the SSCT of human cadaver hands is damaged earlier within the range of motion at higher tendon excursion velocities. The lowered SSCT damage threshold as a result of higher tendon excursion velocities gives an explanation why high-velocity repetitive motions of the hand are a risk factor for CTS.[2-5]

In **chapter 3** we investigated in detail the different components contributing to tendon gliding resistance. We demonstrated that the total tendon gliding resistance is the result of SSCT deformation, poroelastic properties (i.e. stress-induced fluid flow) of the tendon, and possibly the SSCT, and contact friction between structures. Changes in any of these components due to fibrozation and damage of the SSCT can increase gliding resistance.[13] Increased gliding resistance is seen when there is increased carpal tunnel pressure, which is the main characteristic of CTS.[19]

In **chapter 4** we explored in CTS patients and healthy subjects the effect of tendon excursion velocity on median nerve displacement using ultrasound. We found that the relative nerve displacement increased at higher tendon excursion velocities in healthy subjects as well as in CTS patients. Based on the results of the chapters 2 and 3 this is most likely the result of increased stiffness. Overall less median nerve displacement was seen in CTS patients compared to the healthy subjects. In vivo and ex vivo studies have shown that the interconnecting SSCT fibrils can rupture, which may result in SSCT-flexor tendon or SSCT-median nerve dissociation.[6,8,20] Rupture of the SSCT could therefore be the mechanism responsible for decreased median nerve motion found in our study.

When interpreting the findings of **chapter 2, 3 and 4**, several *limitations* need to be taken into account. First of all, in **chapter 2 and 3** we have studied SSCT properties in human cadaver hands. Although a human cadaver hand study may be a good experimental method to mimic the in vivo situation, the in vitro conditions differ from in vivo conditions, which need to be considered when interpreting the results. Secondly, the results of **chapter 4** are contradictory to the findings of Oh et al. and Yoshii et al. who found decreased SSCT and median nerve displacement at higher tendon excursion velocities.[21,22] However, these studies used lower tendon excursion velocities and were performed in cadaver hands whereby openings were made proximal of the carpal tunnel, which may have affected the internal environment. This makes the comparability of theirs and our study debatable. Lastly, accurate imaging of the SSCT remains a challenge. The SSCT is a layered structure of solely 1 mm thick that deforms during motion. Therefore the SSCT displacement measurements are prone to errors when using speckle-tracking analysis. However, future developments, such as very-high frequency ultrasound imaging (e.g., Visual Sonics Vevo 2100), will enable better visualisation of the SSCT and may (partly) resolve these issues.

*In conclusion*, high-velocity hand motions are considered risk factors for CTS. High-velocity tendon excursion increases gliding resistance of the tendon. It causes the SSCT to

stiffen and the SSCT gets damaged at a lower tendon excursion rate. Increased stiffening of the SSCT can explain the increased median nerve displacement at higher tendon excursion velocities. Ruptured interconnecting SSCT fibers can explain the decreased median nerve displacement in CTS patients.

Several recommendations can be given regarding *future research*. First, more research is needed regarding SSCT damage patterns, preferably in vivo. For this, animal test models may be useful; but using animal models to study non-life-threatening syndromes remains an ethical point of debate. Also, recently very-high frequency ultrasound machines (e.g., Visual Sonics Vevo 2100) are being developed with increased quality of imaging and capacity. Improved imaging machines may enable more detailed imaging of the SSCT and allow smaller region of interest-boxes. Usage of these machines for in vivo research should therefore be considered in the nearby future. Completing the discovery of carpal tunnel biomechanics, a definite element model of the carpal tunnel should be created, which could be used to investigate alternatives for high-risk motions to decrease the chance of getting CTS.

### *Part II. Changes in carpal tunnel content mechanics in CTS patients and the value of ultrasound as diagnostic tool*

Increased carpal tunnel pressure and fibrotic SSCT are the most prominent features of CTS.[12,13,23,24] The exact pathophysiology of idiopathic CTS is however unknown. One often proposed hypothesis is that damaged SSCT triggers a non-inflammatory repair process resulting in fibrotic SSCT and increased carpal tunnel pressure, which subsequently compresses the median nerve.[13,14,25] Fibrozation of the SSCT may lead to adhesiolysis of the median nerve and flexor tendons or to dissociation of the SSCT from the nerve and tendons if the SSCT is ruptured.[26] We hypothesised that these changes influence the dynamics of the median nerve, flexor tendons and SSCT within the carpal tunnel and may be of diagnostic value. Ultrasound is the only modality capable of non-invasively, real time imaging of moving tissues, and therefore the most ideal tool to investigate the dynamics of these structures in vivo during hand and wrist motions.[27]

Although high frequency ultrasound allows precise real time imaging, ultrasound imaging and reviewing of the scans are rater-dependent.[28] Excellent test-retest results have been reported for measurements of various transverse plane ultrasound parameters, however no reliability between various reviewers was reported.[29] In **chapter 5** we found fair to excellent intrarater and interrater reliability for transverse shape measurements of the median nerve and most flexor tendons. We also reported excellent intrarater and interrater reliability for transverse displacement measurements. For longitudinal displacement measurements small intrarater and interrater errors have been found using this speckle tracking method,[30] however no test-retest reliability was investigated. In **chapter 8** we have performed a test-retest in 50 subjects. The test-retest reliability for longitudinal displacement measurements

of the median nerve, superficial flexor tendon of the middle finger and the deep flexor tendon of the middle finger were found to be good to excellent. The test-retest reliability for longitudinal displacement measurements of the SSCT measurements was concluded to be moderate to good. These results together demonstrate that ultrasound measurements are reliable and that these measurements can be used to investigate carpal tunnel dynamics.
When investigating the dynamics of carpal tunnel structures during various hand and wrist motions and comparing the results of healthy subjects with CTS patients, a number of differences were discovered, as described in **chapter 6 and 7**. First, flexion and ulnar deviation of the wrist had the most prominent effect on the median nerve circularity; less median nerve deformation was seen in CTS patients. Next, although finger flexion did not affect deformation of the nerve in this relatively small case-control study (**chapter 7**), in the larger study less deformation of the median nerve was seen during finger flexion when comparing the healthy subjects with patients with severe CTS (**chapter 8**). Lastly, we found less median nerve motion and the nerve moved towards a different direction during wrist flexion and ulnar deviation in CTS patients compared to healthy subjects.

In **chapter 8** we studied the dynamics of carpal tunnel structure in the longitudinal plane. We found a decrease in median nerve displacement and a trend of increasing superficial flexor tendon displacement and decreasing deep flexor tendon displacement in CTS patients. Others have reported similar changes in the relative motion of the median nerve and tendons.[31-33] Different factors such as enlarged size of the median nerve, ruptured SSCT and increased carpal tunnel pressure may play a causative role. Contrary to our expectations was the decreased longitudinal median nerve displacement without a conjoint decrease of transverse median nerve displacement. A possible rationale could be that the amplitude of transverse displacement during finger flexion might be relatively too small to detect differences. Calculating the area of the median nerve, a static measurement, was found to be the most discriminating parameter for CTS; most patients with CTS have an increased cross-sectional area. In addition, measuring the median nerve area is also the simplest parameter to measure. Other shape measurements of the median nerve were less discriminating, but can easily be obtained through area calculations.

Although we have tried to analyse the changes of carpal tunnel content dynamics as detailed as possible by incorporating a large number of patients, investigating numerous ultrasound parameters and using a matched case-control study design, there are several *limitations*. To begin with, ultrasound parameters were compared with clinical and nerve conduction study classifications due to lack of a golden standard for CTS. As a result, it was not possible to examine superiority of ultrasound in diagnosing CTS compared to the nerve conduction test. Secondly, analyzing the ultrasound scans is a laborious process; it may take up to 40 minutes for one patient, and requires a substantial amount of data storage; up to 20 gigabytes for one hand. This limits its clinical usability. However, with current technical developments, we expect this to become easier in the near future. At

last, although we have assumed that the change in dynamics is probably the result of variations of pressure and fibrosis of the SSCT, we could only indirectly measured this. It seems reasonable that structural changes in the carpal tunnel are the main cause of changed motion patterns. However, it is possible that patients have a predisposing motion pattern that leads to increased shear of the SSCT and secondary to that SSCT damage, which subsequently can lead to SSCT fibrosis and increased carpal tunnel pressure. Large longitudinal prospective studies would be needed to answer this question. Nevertheless, such motion patterns may be useful in distinguishing affected from unaffected individuals.

*In conclusion*, deformation and mobility of the median nerve and flexor tendons are different in patients with CTS and this becomes more prominent with increasing severity of CTS. In CTS patients we found an increased median nerve area, decreased circularity and decreased displacement during wrist flexion and ulnar deviation in the transverse plane. In the longitudinal plane, CTS patients had decreased median nerve displacement and an increased superficial to deep flexor tendon ratio. Lastly, ultrasound is a reliable tool to investigate these changes in dynamics of carpal tunnel structures.

We can make several recommendations for *future research*. This thesis showed that changes in dynamics of carpal tunnel contents occur in CTS patients and that ultrasound can measure these changes reliably. Future research should focus therefore on defining cut off values for ultrasound parameters, improving the user-friendliness of the programs used to analyse the ultrasound scans, and new ultrasound machines (i.e., Visual Sonics Vevo 2100) with increased imaging quality and capacity should be considered for investigating carpal tunnel dynamics. Next, a comparison with treatment outcome, using a randomized controlled trial study design, will give more clinically useful information about the diagnostic value of ultrasound. Third, we did find an increased superficial to deep flexor tendon ratio in some patients, we hypothesized that this could be the result of adhesions between the superficial and deep flexor tendon of corresponding fingers. However, it could as well be the result of alterations in motion patterns, suggesting that CTS patients move their fingers differently. We have not studied the motion of the fingers, but this would be interesting to measure. Lastly, it may be interesting to differentiate whether the change in dynamics of carpal tunnel contents in CTS patients is the direct result of SSCT changes or increased carpal tunnel pressure. This can be investigated when scanning CTS patients' wrist before and after a carpal tunnel release preferably combined with carpal tunnel pressure measurements and histological SSCT analysis.

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# 10

# SUMMARY

## SUMMARY

The aim of this thesis is (part I) to extend the knowledge about biomechanical and dynamic behaviour of the subsynovial connective tissue (SSCT) during tendon gliding, and (part II) to establish possible changes in dynamics of the carpal tunnel contents in patients with carpal tunnel syndrome (CTS) using ultrasound, and to investigate whether ultrasound could be a reliable and accurate diagnostic tool for CTS.

## PART I

CTS is an entrapment neuropathy of the median nerve in the carpal tunnel. Fibrosis of the SSCT in the carpal tunnel is a predominant histological finding in CTS, which is considered to be the result of a damage repair process of the SSCT. Once the SSCT is fibrotic, it is more susceptible to damage, entering a vicious circle, which leads to more production of fibrosis. The damage to the SSCT can be caused by tendon motion.

In **chapter 2** we studied the effect of tendon excursion velocity in the generation of SSCT damage. Previous studies found that low-velocity tendon excursions can irreversibly damage the SSCT within the normal range of motion. This may be different at higher tendon excursion velocities. Nine human cadaver wrists were used. Three repeated cycles of ramp-stretch testing were performed simulating 40%, 60%, 90%, and 120% of the physiological excursion of the superficial middle finger flexor tendon with a tendon excursion velocity of 60 mm/s. Gliding resistance energy and force were calculated and values of the second and third cycle were normalized by values obtained in the first cycle for each excursion level. The data was compared with the data of a similar experiment whereby a tendon excursion velocity of 2mm/s was used. For high-velocity tendon excursions, a significant drop in the excursion energy ratio, indicative for SSCT damage, was first observed at an excursion level of 60% of the physiological excursion of the tendon. For low-velocity tendon excursions the drop in the excursion energy ratio was first observed at an excursion level of 90% of the physiological excursion of the tendon. In conclusion, we found that increasing tendon excursion velocity lowers the SSCT damage threshold. This finding may be relevant for understanding the pathogenesis of SSCT damage and fibrosis, such as that accompanying CTS, and the relationship of CTS with occupational factors.

In **chapter 3** we investigated the different components contributing to gliding resistance within the carpal tunnel resulting from tendon motion. Four pairs of human cadaver wrists (8 wrists in total) were used. Tendon gliding resistance was measured under different conditions; with and without intact SSCT, at 2mm/s and 6omm/s tendon excursion velocity, and with and without relaxation time between test cycles. Gliding resistance force, energy and stiffness were calculated. SSCT stretching was found to play a substantial role. When isolating the SSCT gliding resistance, more force, energy and a trend of increased stiffness were observed at high-velocity tendon excursions compared to low-velocity

tendon excursions. Poroelastic properties (i.e., elastic properties of fluid-infiltrated porous tissues) of the tendon, and possibly the SSCT, played a role as well because relaxation time significantly increased gliding resistance force and energy. At high-velocity tendon excursions with relaxation time we found increased gliding resistance energy and force compared to low-velocity tendon excursions with relaxation time and these differences were amplified with higher tendon excursion velocities. Lastly, without relaxation time there was still gliding resistance observed, however no difference in gliding resistance force and energy was found between different tendon excursion velocities, suggesting contact friction. When increasing carpal tunnel pressure, increased gliding resistance was observed. The fibrotic changes, thickening, increased absorption capacity, and decreased permeability of the SSCT in CTS patients can consequently effect any of the above-mentioned components and result in increased gliding resistance.

In **chapter 4** we studied the in vivo effect of tendon excursion velocity on median nerve displacement and indirectly SSCT displacement. Increased strain rates increases stiffness in viscoelastic tissues, and thereby its capacity to transfer shear load. SSCT is like most biological tissues thought to be viscoelastic. Therefore, if higher tendon excursion velocities increase SSCT stiffness it may increase the median nerve displacement, since the median nerve is a relatively loose structure that cannot move actively, but can solely be moved passively. However, in CTS the SSCT may be ruptured from the median nerve or tendon and therefore it may disconnect the tendon from the median nerve. This can also affect median nerve displacement. In this study, ultrasonography was performed on 14 wrists of healthy subjects and 25 wrists of CTS patients during controlled hand motions performed at three different velocities. Longitudinal median nerve and tendon excursions were assessed and compared across the three different velocities. In both the healthy subject group as well as the CTS patient group the median nerve displacement increased with increasing tendon excursion velocity. CTS patients exhibited significantly less median nerve motion than the healthy subjects. These findings are consistent with the current knowledge of SSCT mechanics in CTS, in which in some patients the fibrotic SSCT appears to have ruptured from the tendon surface and can no longer pull along the median nerve.

## PART II

Increased carpal tunnel pressure, SSCT thickening and fibrosis that may lead to adhesions or disconnections between carpal tunnel structures, and decreased permeability and increased absorption capacity of the SSCT can all effect the dynamics of the median nerve, SSCT, and flexor tendons within the carpal tunnel. Studying these structures during hand and wrist motions in healthy subjects and CTS patients may reveal useful information about possible changes of the dynamics of these structures in patients with CTS. Ultrasound can visualize these potential changes, which potentially makes it a diagnostic tool.

Unfortunately, reliability and reference values are not well established for most dynamic sonographic measurements of the median nerve, SSCT and flexor tendons. In **chapter 5** we imaged 40 wrists of 20 healthy subjects using ultrasound. Ultrasound scans of the carpal tunnel inlet were acquired during hand motion. Based on shape and displacement measurements of the median nerve and flexor tendons, intra- and interrater reliability and reference values were calculated. The mean intra- and interrater reliability for measurements of the median nerve and most flexor tendons were 0.79 for shape parameters and 0.89 for displacement parameters. These results demonstrate that cross-sectional shape and displacement measurements of the median nerve and most flexor tendons had a high reliability. Next, we concluded that during motion, the median nerve flattened with ulnar movement, flexor tendons became more circular, and flexor tendons of corresponding fingers moved toward each other. The reference values reported in chapter 5 may be useful for future ultrasound research on the diagnosis of CTS.

In **chapter 8** we included reliability testing for longitudinal ultrasound measurements. We performed a test-retest in 50 subjects, since others have already reported on intrarater and interrater reliability and found small errors. The test-retest reliability for the displacement of the median nerve, flexor tendons of the middle finger and SSCT was moderate to excellent, with a mean reliability of 0.71. Hereby the overall reliability of the median nerve and flexor tendons was higher compared to the reliability of the SSCT.

In **chapter 6** we evaluated the deformation and displacement of the median nerve in healthy subjects at the proximal carpal tunnel level on cross-sectional ultrasound images during different wrist movements, to establish a baseline for comparison with abnormal movements. Dynamic ultrasound images of both wrists of 10 healthy subjects were obtained during six different hand and wrist motions: maximal wrist flexion with fingers flexed or extended, extension with fingers flexed or extended, ulnar deviation, and fingers flexion. To simplify the analysis, the initial and final shape and position of the median nerve were measured and analysed. The circularity of the median nerve increased and the perimeter decreased during wrist flexion with finger extension or flexion and ulnar deviation. There were significant differences for the median nerve displacement amplitude and direction between finger flexion, wrist flexion with fingers extended, and wrist ulnar deviation. The mean amplitudes of median nerve displacement during wrist flexion with finger extension or flexion and ulnar deviation were higher than during finger flexion and wrist extension with finger extension or flexion. In conclusion, in the normal carpal tunnel, wrist flexion and ulnar deviation could induce significant transverse displacement and deformation of the median nerve in healthy subjects.

The aim of **chapter 7** was to evaluate the deformability and mobility of the median nerve in patients with CTS and compare the results with the data of healthy subjects. Dynamic ultrasound images were obtained in 20 affected wrists of 13 patients with CTS. Results were compared to data obtained from both wrists of 10 healthy subjects reported

in chapter 6. Shape and position of the median nerve on the initial and final image were measured and analysed for six wrist and hand movements. The deformation ratios for each movement were defined as the median nerve area, perimeter, and circularity of the final position normalized by values assessed in the initial position. Furthermore, the median nerve displacement vector and amplitude were calculated. The deformation ratio for circularity was significantly less in patients with CTS compared to healthy subjects during wrist flexion with finger extension or flexion. The vector of median nerve displacement during wrist flexion with finger flexion or extension was different between patients with CTS and healthy subjects. The displacement amplitude of the median nerve was found to be less in patients with CTS compared to healthy subjects during wrist flexion with finger extension or flexion and ulnar deviation. In conclusion, patients with CTS differ from normal subjects with regard to mobility and deformability of the median nerve during wrist flexion and ulnar deviation.

In **chapter 8** the dynamics of the carpal tunnel contents were analysed in multiple planes. Hundred-and-thirteen patients with clinically confirmed CTS and 42 controls were included. CTS severity was classified according to validated clinical and nerve conduction study classifications. Ultrasound was used to image the carpal tunnel in the cross-sectional and longitudinal plane during hand motion. Cross-sectional and longitudinal displacement and shape (changes) were calculated for the median nerve, tendons, and SSCT. To predict the diagnostic value of ultrasound for CTS we applied a binary logistic regression model. Less longitudinal median nerve displacement was seen both in patients with clinically suspected CTS and when CTS was confirmed based on nerve conduction study results. Moreover, in CTS patients a trend of increasing superficial flexor tendon displacement and decreasing deep flexor tendon displacement was seen, and we found an increased median nerve area and perimeter. These changes were increasingly profound in more severely classified CTS patients. Binary logistic modelling showed 70% sensitivity and 84% specificity with clinical symptoms as dependent variable and 71% sensitivity and 80% specificity with nerve conduction study results as dependent variable. This study demonstrates that changes in shape and mobility of the median nerve and flexor tendons occur, and that these changes can be related to the severity of CTS.

Summarizing, the aim of this thesis was (part I) to extend the knowledge of biomechanical and dynamical behaviour of the SSCT during (high-velocity) tendon gliding, (part II) to establish potential changes in dynamics of the carpal tunnel contents of CTS patients using ultrasound, and to investigate whether ultrasound could be a reliable and accurate tool to diagnose CTS. In part I we found that higher tendon excursion velocities increase gliding resistance, which was largely the result of SSCT deformation; SSCT stiffens at higher tendon excursion velocities. This can explain the increased median nerve displacement at higher tendon excursion velocities. In addition, higher tendon excursion velocities lower the damage threshold. In part II we found that deformation and mobility of the flexor

tendons and median nerve are changed in CTS patients and this becomes more prominent with increasing severity of CTS. In CTS patients an increased median nerve area is seen in the transversal plane, as well as decreased circularity, and decreased displacement during wrist flexion and ulnar deviation. In the longitudinal plane CTS patients had a decreased median nerve displacement and an increased superficial to deep flexor tendon ratio. Last of all, ultrasound is a reliable tool to investigate these changes in dynamics of carpal tunnel contents.

# SAMENVATTING

Het doel van dit proefschrift is om (deel I) meer kennis te verwerven over de biomechaniek en dynamiek van het subsynoviale bindweefsel (SSCT) gedurende een peesexcursie en (deel II) om mogelijke veranderingen in de dynamiek van structuren in de carpale tunnel bij carpaal tunnel syndroom (CTS) patiënten vast te stellen met behulp van echografisch onderzoek. Daarnaast onderzochten we of echografisch onderzoek een betrouwbaar en nauwkeurig aanvullend diagnosticum zou kunnen zijn bij het vaststellen van CTS.

## DEEL I

CTS is een drukneuropathie van de nervus medianus in de carpale tunnel. De meest typerende histologische bevinding in CTS is fibrose van de SSCT, hiervan wordt aangenomen dat dit het resultaat is van beschadigd en daarna hersteld SSCT. Het fibrotische SSCT is gevoeliger voor nieuwe beschadigingen, waardoor er een vicieuze cirkel ontstaat welke leidt tot een toename van fibrose van de SSCT. Deze schade aan de SSCT kan veroorzaakt worden door peesexcursie.

In **hoofdstuk 2** onderzochten we het verband tussen de snelheid van de peesexcursie en het ontstaan van schade aan de SSCT. Eerdere studies hebben aangetoond dat er schade kan ontstaan aan de SSCT binnen het normale bewegingsbereik van de pees en bij een lage peesexcursiesnelheid. Mogelijk heeft een hogere peesexcursie een ander effect op het ontstaan van SSCT schade. In deze studie hebben we negen menselijke kadaverpolsen gebruikt. Drie herhaalde cycli van ramp-stretch-testen werden uitgevoerd op 40%, 60%, 90% en 120% van het normale bewegingsbereik van de oppervlakkige middelvingerbuigpees met een excursiesnelheid van 60 mm/s. De energie en kracht die nodig waren voor deze peesexcursies werden gemeten. De data van de tweede en derde cycli van elk excursieniveau werden genormaliseerd naar de data verkregen in de eerste cyclus van het desbetreffende excursieniveau. De uitkomsten werden vergeleken met de uitkomsten van eenzelfde experiment waarbij een peesexcursiesnelheid van 2mm/s was gebruikt. Voor de peesexcursies met hoge snelheid werd een significante daling van de energieverhouding, indicatief voor SSCT schade, voor het eerst waargenomen bij een excursieniveau van 60% van het normale bewegingsbereik van de pees. Bij een lage excursiesnelheid werd deze daling pas voor het eerst waargenomen bij een excursieniveau van 90% van het normale bewegingsbereik van de pees. Op basis hiervan concluderen we dat hogere snelheid van peesexcursie sneller schade geeft aan de SSCT. Deze bevindingen dragen bij aan de kennis omtrent het pathologische proces van SSCT fibrotisering en het ontstaan van SSCT schade, welke een rol speelt bij CTS, en het verband tussen peesbewegingen en het ontstaan van CTS.

In **hoofdstuk 3** bestudeerden we de diverse componenten die bijdragen aan de weerstand bij peesexcursie in de carpale tunnel. Vier paar menselijke kadaverpolsen (8 polsen in totaal) werden gebruikt. De weerstand bij peesexcursie in de carpale tunnel

werd gemeten onder verschillende omstandigheden: met en zonder intact SSCT, peesexcursiesnelheden van 2mm/s en 60mm/s en met en zonder relaxatietijd tussen de testcycli. De energie en kracht die nodig waren voor deze peesexcursies werden gemeten en op basis van de weerstand-curve werd de stijfheid berekend. SSCT had een aanzienlijk effect op de weerstand bij peesexcursie in de carpale tunnel. We vonden dat bij een peesexcursiesnelheid van 60mm/s, in vergelijking met een peesexcursiesnelheid van 2mm/s er meer kracht en energie voor SSCT deformatie nodig was en dat er ook een toegenomen SSCT stijfheid werd waargenomen. Poro-elastische eigenschappen van de pees, oftewel de elastische eigenschappen van de pees rekening houdend met interstitele vloeistof, en mogelijk van de SSCT, speelden ook een rol in de weerstand van de peesexcursie. Dit omdat de benodigde kracht en energie voor peesexcursie toenam als er een tijdsperiode tussen de verschillende test cycli zat en daarnaast de benodigde kracht en energie voor peesexcursie tussen 2mm/s en 60mm/s peesexcursiesnelheid met relaxatietijd eveneens verschillend was en dit verschil toenam wanneer er een hogere peesexcursie snelheid werd gebruikt. Tot slot vonden we dat er zonder relaxatietijd nog wel weerstand bij peesexcursies was, maar deze was ongeveer gelijk bij 2mm/s en 60mm/s peesexcursiesnelheid, wat suggestief is voor wrijving tussen weefsels. Fibrotische veranderingen, verdikking, verminderde doorlaatbaarheid en het verhoogde absorptievermogen van de SSCT in CTS patiënten kunnen effect hebben op alle eerder genoemde componenten die bijdrage aan de peesexcursie weerstand in de carpale tunnel en kunnen mogelijk de oorzaak zijn van de verhoogde peesexcursie weerstand die gevonden wordt bij CTS patiënten.

In **hoofdstuk 4** onderzochten we bij CTS patiënten en gezonde personen middels echografie de effecten van de peesexcursie snelheid op de nervus medianus verplaatsing en indirect op de SSCT verplaatsing. Verhoogde snelheid van weefseldeformatie verhoogt de stijfheid van visco-elastische weefsels, en daarmee het vermogen gewicht te kunnen verschuiven. De meeste biologische weefsels zijn visco-elastisch. Daarom zou een hogere SSCT stijfheid als gevolg van snellere peesexcursie kunnen leiden tot meer zenuwverplaatsing. Echter, bij CTS patiënten kan de SSCT afgescheurd zijn van de zenuw of pees, deze verbroken verbinding tussen zenuw en pees zal van invloed zijn op de verplaatsing van de nervus medianus. In deze studie maakten we echo's van 14 polsen van gezonde personen en 25 polsen van CTS patiënten tijdens een gecontroleerde handbeweging op drie verschillende snelheden. Longitudinale verplaatsing van de zenuw en pezen van de middelvinger werden berekend en de uitkomsten verkregen bij de drie verschillende bewegingssnelheden werden vergeleken. In beide groepen nam de zenuwverplaatsing toe bij toenemende snelheid van de peesbeweging. Daarnaast was er bij CTS patiënten aanzienlijk minder zenuwverplaatsing dan bij de gezonde personen. Deze bevindingen komen overeen met de huidige inzichten ten aanzien van SSCT bij CTS patiënten. Bij sommige patiënten lijkt de fibrotische SSCT te zijn afgescheurd van de pees, waardoor de nervus medianus niet meer passief kan worden meegetrokken bij peesbewegingen.

## DEEL II

Verhoogde druk in de carpale tunnel, verdikking van de SSCT en fibrose van de SSCT leidend tot verklevingen of disconnectie van structuren in de carpale tunnel, verminderde doorlaatbaarheid en meer absorptie capaciteit van de SSCT kunnen allemaal effect hebben op de dynamiek van de nervus medianus, SSCT en pezen in de carpale tunnel. Het bestuderen van de dynamica van deze structuren gedurende hand- en polsbewegingen bij zowel gezonde personen als CTS patiënten kan informatie opleveren over mogelijke veranderingen in de dynamica van deze structuren bij CTS. Echografisch onderzoek kan deze potentiële veranderingen visualiseren, waardoor echo wellicht een waardevolle diagnostische test zou kunnen zijn.

Echter, de betrouwbaarheid en referentiewaarden zijn onbekend voor de meeste dynamische echografische metingen van de nervus medianus, SSCT en buigpezen. In **hoofdstuk 5** hebben we 40 polsen van 20 gezonde deelnemers geëchood. Echo opnames werden gemaakt van het proximale deel van de carpale tunnel tijdens handbewegingen. Intra- en interbeoordelaarsbetrouwbaarheid en de referentiewaarden werden berekend voor metingen van de vorm en de verplaatsing van de zenuw en pezen. De gemiddelde intra- en interbeoordelaarsbetrouwbaarheid van de nervus medianus en de meeste buigpezen waren 0.79 voor transversale vorm metingen en 0.89 voor metingen van transversale verplaatsing, wat duidt op een goede betrouwbaarheid. Daarnaast constateerden we dat tijdens de handbeweging de nervus medianus afvlakte en verplaatste naar ulnair en dat de pezen meer cirkelvormig werden en de buigpezen van corresponderende vingers naar elkaar toe bewogen. De gerapporteerde referentiewaarden in hoofdstuk 5 kunnen gebruikt worden bij echografisch onderzoek naar de diagnostiek bij CTS.

In **hoofdstuk 8** hebben we ook de test-hertest betrouwbaarheid onderzocht van longitudinale buigpees- en zenuwverplaatsingen op basis van echofilms bij 50 personen. We vonden dat de test-hertest betrouwbaarheid voor de verplaatsing van de nervus medianus, buigpezen en SSCT redelijk tot zeer goed was, met een gemiddelde betrouwbaarheid van 0.71. Daarbij constateerden we ook dat de test-hertest betrouwbaarheid van zenuw- en peesverplaatsingen beter was dan die van de SSCT.

In **hoofdstuk 6** bestudeerden we de transversale vervorming en verplaatsing van de nervus medianus in gezonde personen in het proximale deel van de carpale tunnel tijdens verschillende polsbewegingen. Echofilms van 10 gezonde personen werden gemaakt van beide polsen gedurende de volgende zes hand- en polsbewegingen: maximale polsflexie met vingerextensie of -flexie, maximale polsextensie met vingerextensie of -flexie en ulnaire deviatie met vingerextensie of alleen vingerflexie. Om de analyse te vereenvoudigen werden de vorm en positie van de nervus medianus op het echobeeld van de beginpositie en eindpositie gemeten en geanalyseerd. De circulariteit nam toe en de perimeter nam af van de nervus medianus tijdens polsflexie met vingerextensie of -flexie en ulnaire deviatie. Er waren significante verschillen in de amplitude en richting van verplaatsing van

de nervus medianus tussen vingerflexie, polsflexie met vingerextensie en ulnaire deviatie. De gemiddelde amplitudes van verplaatsing van de nervus medianus waren hoger tijdens polsflexie met vingerextensie of -flexie en ulnaire deviatie in vergelijking met andere hand- en polsbewegingen. Op basis hiervan concluderen we dat met name polsflexie en ulnaire deviatie aanzienlijke transversale beweging en vervormingen kan geven van de nervus medianus bij gezonde personen.

In **hoofdstuk 7** bestudeerden we de transversale vervormbaarheid en de mobiliteit van de nervus medianus bij 20 polsen van 13 CTS patiënten en vergeleken ze met 20 polsen van 10 gezonde personen. De vorm en positie van de nervus medianus werden gemeten op het echobeeld van de beginpositie en eindpositie van zes eerder genoemde pols- en handbewegingen. De vervormingsratio's tijdens elke polsbeweging werden gedefinieerd als de nervus medianus oppervlakte, omtrek en circulariteit gemeten op het echobeeld met de eindpositie van de betreffende beweging en genormaliseerd door dezelfde metingen op basis van het echobeeld met de beginpositie. De richting en amplitude van verplaatsing werden eveneens berekend. De vervormingsratio voor circulariteit was minder bij CTS patiënten in vergelijking met gezonde personen tijdens polsflexie met vingerflexie of -extensie. De gemiddelde amplitude en richting van de nervus medianus verplaatsing tijdens polsflexie met vingerflexie of -extensie was verschillend tussen CTS patiënten en gezonde personen. De verplaatsing van de nervus medianus was minder bij CTS patiënten tijdens polsflexie met vingerflexie of -extensie en ulnaire deviatie. Op basis hiervan concluderen we dat in CTS patiënten de vervormbaarheid en mobiliteit van de nervus medianus tijdens polsflexie en ulnaire deviatie significant anders is dan bij gezonde personen.

In **hoofdstuk 8** onderzochten we de dynamica van carpale tunnel structuren in meerdere vlakken. Honderddertien patiënten met CTS en 42 controles werden geïncludeerd in deze studie. De ernst van CTS werd ingedeeld volgens gevalideerde klinische en zenuwgeleidingsonderzoek classificaties. Echografie werd gebruikt om de carpale tunnel te bekijken in het transversale en longitudinale vlak. Transversale en longitudinale verplaatsing en vormveranderingen werden berekend voor de nervus medianus, pezen en SSCT. Minder longitudinale zenuwverplaatsing werd gezien, zowel bij CTS patiënten met klinisch verdenking op CTS en CTS bevestigd middels zenuwgeleidingsonderzoek. Daarnaast was er een trend van toenemende excursie van de oppervlakkige buigpees en afnemende excursie van de diepe buigpees en een vergroot transversaal oppervlak en omtrek van de zenuw. Deze veranderingen waren evidenter in de ernstiger geclassificeerde CTS patiënten. Binaire logistieke regressie analyse toonde 70% sensitiviteit en 84% specificiteit wanneer de klinische diagnose als afhankelijke variabele werd gekozen en 71% sensitiviteit en 80% specificiteit wanneer de resultaten van het zenuwgeleidingsonderzoek als afhankelijke variabele werden gekozen. Hiermee hebben we aangetoond dat er veranderingen in vorm en mobiliteit van de zenuw en de pezen optreden bij CTS patienten en deze veranderingen kunnen worden gerelateerd aan de ernst van CTS.

Samenvattend was het doel van dit proefschrift (deel I) om meer kennis te verkrijgen over het biomechanische en dynamische gedrag van de SSCT tijdens peesexcursies (met hoge snelheid), (deel II) om mogelijke veranderingen in dynamiek van de carpale tunnel structuren bij CTS patiënten vast te stellen middels echografie en te onderzoeken of echografie een betrouwbaar en nauwkeurig diagnosticum voor CTS zou kunnen zijn. In deel I vonden we dat een hogere peesexcursiesnelheid meer weerstand gaf die grotendeels was toe te schrijven aan SSCT vervorming; bij een hogere peesexcursiesnelheid werd de SSCT stijver. Dit is een verklaring waarom bij een hogere peesexcursiesnelheid meer zenuwverplaatsing werd gevonden. Bovendien raakte de SSCT sneller beschadigd bij een hogere peesexcursiesnelheid. In deel II vonden we dat de vervorming en de mobiliteit van de buigpezen en de mediane zenuw veranderden in CTS patiënten en dat dit meer zichtbaar werd bij patiënten met een ernstigere vorm van CTS. In het transversale vlak vonden we bij CTS patiënten dat de oppervlakte van de zenuw toenam en de vervorming en verplaatsing minder was bij polsflexie en ulnaire deviatie. In het longitudinale vlak zagen we dat de zenuwverplaatsing verminderde bij CTS patiënten en er een trend was van toenemende excursie van de oppervlakkige buigpees en afnemende excursie van de diepe buigpees. Tot slot hebben we aangetoond dat echografie een betrouwbare methode is om vormveranderingen en verplaatsingen van de zenuw, pezen en SSCT in de carpale tunnel te meten en een mogelijke diagnostische test is voor CTS.

# 11

LIST OF PUBLICATIONS

PHD PORTFOLIO

DANKWOORD

CURRICULUM VITAE

## List of publications

**A. Filius**, M. Scheltens, J.G. Bosch, P.A. Van Doorn, H.J. Stam, S.E.R. Hovius, P.C. Amadio, R.W. Selles.
Multidimensional imaging of the wrist: changes of the median nerve and tendon shape and displacement in carpal tunnel syndrome.
*J Orthop Res.* 2015 Sep; 33 (9):1332-40

**A. Filius,** A.R. Thoreson, Y. Wang, S. Passe, C. Zhao , K.-N. An, P.C. Amadio
The effect of tendon excursion velocity on longitudinal median nerve displacement: differences between carpal tunnel syndrome patients and controls
*J Orthop Res.* 2015 Apr; 33 (4):483-7

Y. Wang, **A. Filius**, C. Zhao, S. Passe, A.R. Thoreson, K.-N. An, P.C. Amadio
Altered median nerve deformation and transverse displacement during wrist movement in patients with carpal tunnel syndrome.
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Y. Wang, A.R. Thoreson, S. Passe, **A. Filius**, C. Zhao, K.-N. An, P.C. Amadio
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**A. Filius,** A.R. Thoreson, T.-H. Yang, M. Vanhees, K.-N. An, C. Zhao, P.C. Amadio
The effect of low- and high-velocity tendon excursion on the mechanical properties of human cadaver subsynovial connective tissue.
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Maternal psychological outcome after early onset preeclampsia and preterm birth.
*J of Matern Fetal Neonatal Med*. 2012 Mar; 25 (3):272-6

**A. Filius**, J.M. Zuidam, J.B. Jaquet, H.P. Slijper, J.H. Coert
Modification of the use of extensor retinaculum for reducible distal radioulnar joint instability: technique and results.
Submitted to Am J Hand Surg.

**A. Filius,** A.R. Thoreson, Y. Osaza, K.-N. An, C. Zhao, P.C. Amadio
Delineation of the mechanisms of tendon gliding resistance within the carpal tunnel.
Submitted to J of Orthop Res.

# PhD portfolio

| | | | |
|---|---|---|---|
| Name PhD student: | A. Filius | PhD period: | 07-11 till 08-15 |
| Erasmus MC Department: | Plastic Surgery & Rehabilitation Medicine | Promotoren: | prof.dr. S.E.R. Hovius<br>prof.dr. H.J. Stam |
| Research School: | Nihes | Supervisor: | dr. R.W. Selles |

| | Year | Workload (ECTS) |
|---|---|---|
| **Courses and academic skills** | | |
| - Biomedical English Writing and Communication | 2012 | 3 |
| - Introduction of Research in Medicine | 2011-2012 | 1 |
| - Principles of Research in Medicine | 2011-2012 | 1 |
| - Biostatistics for Clinicians | 2011-2012 | 1 |
| - Musculoskeletal Ultrasound course, Harrogate, United Kingdom | 2011 | 2 |
| - Microsurgery Training, Erasmus Medical Centre, Rotterdam, the Netherlands | 2011-2012 | 3 |
| - Microsurgery Course, Mayo Clinic, Rochester, United States | 2013 | 1 |
| - Hand surgery grand rounds and research meetings | 2011-2013 | 3 |
| **Presentations** | | |
| - International presentations | 2011-2015 | 3 |
| - National presentations | 2010-2013 | 6 |
| **Lecturing and supervising** | | |
| - Supervising microsurgery (international and national) course | 2011-2012 | 1.5 |
| - Teaching 1st and 4th years medical students about the anatomy of the arm and hand | 2012 | 3 |
| - Invited presentation for hand therapists training day, Rotterdam, the Netherlands | 2013 | 1 |
| - Supervising BSc students at Erasmus MC and Mayo Clinic | 2012-2013 | 3 |


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IVENOPPORTUNITIES PROFAN
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RJAN NEUROLOGIE PATIENTEN
PAP&MAM STEUN RDAM HAN
-DU-PAPE FESTIVAL LIEF
UBROTTERDAM FEEDBACK
OLKER PROMOTIECOMMISSIE
DINERS AMBER BABES SOOF
JK CARO MARGRIET NICK JULIA

## Curriculum vitae

Anika Filius was born on November 5th, 1985 in Deil, the Netherlands. In 2004 she graduated from the Koningin Wilhelmina College in Culemborg. Hereafter she moved to Rotterdam for medical school. During medical school she did one year of Health Policy and Management. After graduating cum laude from medical school she was accepted as a PhD student at the department of Plastic and Reconstructive Surgery and Hand Surgery and the department of Rehabilitation Medicine and Physical Therapy, Erasmus MC, Rotterdam (supervisors: prof.dr. S.E.R. Hovius and prof.dr. H.J. Stam). During her PhD she went to the Orthopaedic Biomechanics lab at the Mayo Clinic, Rochester (MN), United States, for a research fellowship under the supervision of professor Amadio. Based on the research done there, a NIH grant was awarded, which has resulted in a collaboration project between the Mayo Clinic and Erasmus MC. Halfway 2014 she started working as a resident at the department of Plastic and Reconstructive Surgery and Hand Surgery, Erasmus MC, Rotterdam and Isala Clinics, Zwolle. After this period she changed her direction and moved towards another field within medicine. After having worked for 7 months at the Cardiology department, Maasstad Hospital, Rotterdam, she started residency training on April 2015 in Anaesthesiology, Erasmus MC, Rotterdam.