Ultrasonographic assessment of carpal tunnel biomechanics

Margriet van Doesburg

The printing of this thesis was financially supported by:
Allergan B.V., Arthrex Nederland B.V., Bauerfeind, Biomet, Junior Vereniging voor Plastische Chirurgie, Martin Nederland/Marned B.V., Nederlandse Vereniging voor Plastische Chirurgie, Oudshoorn Chirurgische Techniek B.V., QuaMedical, Van Wijngaarden Medical, www.mijncarpaletunnel.nl

Cover, layout and printing: Optima Grafische Communicatie, Rotterdam

ISBN: 978-94-6169-255-9

Ultrasonographic assessment of carpal tunnel biomechanics

Echografische beoordeling van biomechanica in de carpale tunnel
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 28 juni 2012 des middags te 2.30 uur

door

Margaretha Harmke Maria van Doesburg

geboren op 30 juli 1984
te Geldermalsen

Promotor: Prof.dr. M. Kon

Co-promotor: Dr. A.B. Mink van der Molen

Voor mijn moeder

Apply thine heart unto instruction,
and thine ears to the words of knowledge.

Proverbs 23:12

CONTENTS

Non scolae, sed vitae discimus.

Seneca

CHAPTER 1

General introduction

1

INTRODUCTION

The carpal tunnel is a closed space in the human wrist that is bounded by the carpal bones on the dorsal, medial and lateral side and by the flexor retinaculum (carpal ligament) on the palmar side (Figure 1). It contains nine different flexor tendons and the median nerve, surrounded by a lining called the subsynovial connective tissue. Carpal tunnel syndrome is a compression neuropathy of the median nerve which causes tingling and numbness of the fingers innervated by the median nerve. This thesis focuses on the biomechanical characteristics of motion in the carpal tunnel using ultrasound.

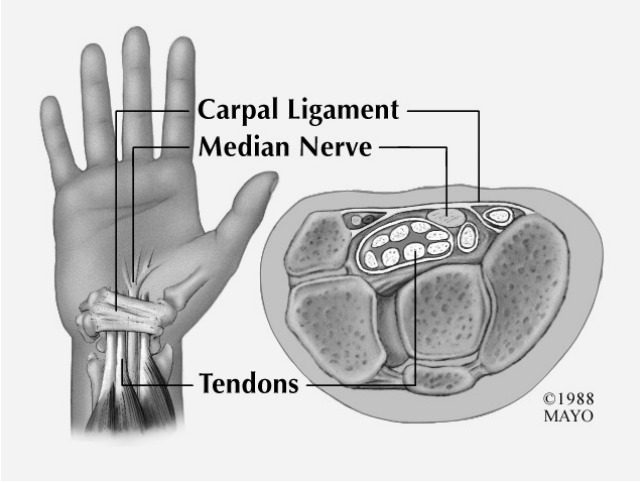

Figure 1 · *Cross-section of the wrist (reprinted with permission)*

History of carpal tunnel syndrome

Carpal tunnel syndrome (CTS) is a condition that is only definitively described since World War II. Retrospectively however, it was already known under a wide variety of different names in the past. The first description of CTS was made by Sir James Paget in 1854, in a report where he describes two patients in which he believed the median nerve was injured [44]. Both cases had a fractured distal radius and were treated by amputation because of intolerable pain, and splinting respectively, the latter being a therapy still used in the treatment of CTS today. In 1880 James Putnam published a study of 37 patients with pain in the distribution of the median nerve, sharing a common symptom of nocturnal numbness or even pain [51]. He concluded that these symptoms were caused by changes in blood supply and suggested treatments including phosphorus and cannabis. These findings were confirmed by Schultz, calling the

symptoms 'acroparesthesia' [45]. In the years after these publications, the focus shifted towards the motor deficiency symptoms of median nerve compression, such as thenar atrophy and weakness of the hand. Patients were considered to have brachial plexus compression and were treated by cervical rib excision, a treatment that was carried out during the first four decades of the twentieth century. In 1913, Marie and Foix published an anatomic and histopathologic study of median nerve lesions at the wrist [33]. They were the first to describe an increase in median nerve volume and thinning at the level of the transverse ligament. Also, they were the first to suggest that transection of the ligament could potentially stop development of this disease. Unfortunately, only little notice was put to this thought, as it took 30 years before Learmonth published a study on the surgical release of the transverse carpal ligament [29].

All of these publications however, described post-traumatic symptoms. The first publication describing non-traumatic symptoms of compression of the median nerve was published by Moersch in 1938, although he concluded that the sensory and motor deficits were caused by different lesions in the carpal tunnel [36]. In 1941, the neurologist Woltman at the Mayo Clinic was the first to state that compression of the median nerve may be caused by an increase in soft tissue in the carpal tunnel. He proposed that compression of the median nerve was caused by pressure due to hyperplastic tissue in the carpal tunnel [45,63]. A few years later, Cannon and Love, also from the Mayo Clinic, performed the first carpal tunnel release for "spontaneous" carpal tunnel syndrome [7].

In the next few decades of the twentieth century, several patients were described with compression of the median nerve due to causes such as ischemia of the nerve with subsequent edema of the nerve and chronic tenosynovitis. The related publications were mainly written by Phalen, who is best known for his clinical test for CTS, the "Phalen's sign", where flexion of the wrist for a period of one minute evokes numbness and paresthesias in the fingers of the patient [46-48]. He also introduced splinting and corticosteroid injections as conservative treatment before surgical treatment [48]. By the 1960's, carpal tunnel syndrome included all different causes of median nerve compression, and as a result the number of patients rapidly increased, with a reported prevalence of up to 5% in the general population these days [2].

Understanding the etiology of carpal tunnel syndrome

The causes of carpal tunnel syndrome can be divided into three groups: it is the result of anatomical or systemic conditions, or idiopathic as in most cases. In the past, various anatomical and occupational factors such as repetitive use of the wrist and digits have been described as potential causative factors [10,65]. Anatomical factors include space-occupying ganglion cysts, persistent median artery and tumors, all leading to

compression of the median nerve due to higher pressure in the carpal tunnel [3,9,39,56,58]. Systemically, CTS has a higher incidence in several diseases such as diabetes mellitus, arthritis and also in pregnancy [35,58]. The cause for CTS in these cases probably lies in fluid retention or deposition of, for example, amyloids. The idiopathic form of this disease occurs mostly in middle aged women and not much is known about its etiology [10,37,58]. Much attention has gone to occupational factors as a cause for carpal tunnel syndrome like repetitive use of the wrist and digits in certain occupations such as poultry- and construction workers [1,8,40]. Recently, a meta-analysis showed several occupational risk factors for developing CTS; vibration [odds ratio (OR) 5.40; 95% CI 3.14, 9.31], hand force (OR 4.23; 95% CI 1.53, 11.68) and repetitive motion (OR 2.26; 95% CI 1.73, 2.94) [4]. Other suggested biomechanical factors that might influence the development of CTS are finger posture, wrist position and fingertip force during motion [19,25,26,35]. Histopathologically, the major finding in carpal tunnel syndrome is fibrosis of the subsynovial connective tissue (SSCT), which changes the motion characteristics of the SSCT, tendons and median nerve, as noted during intraoperative inspection in cases of carpal tunnel release [15,16,32,42].(Figure 2) These changes may cause elevated strain and pressure in the carpal tunnel, which ultimately leads to CTS [32,59]. Ettema et al. suggest that a vicious circle evolves in which changes in the SSCT cause altered motion patterns, which with the subsequent elevated strain and shear to the structures in the carpal tunnel, lead to even more fibrosis [15,16]. The altered motion patterns are potentially useful to differentiate between healthy controls and carpal

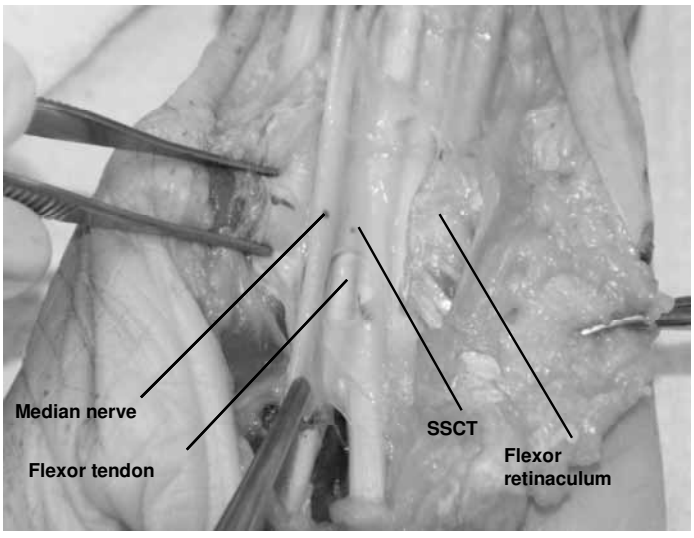

Figure 2 · *Open carpal tunnel with dissected flexor retinaculum, median nerve, flexor tendon and in between the subsynovial connective tissue (SSCT).*

tunnel syndrome patients and it would therefore be useful to know the normal motion pattern of the different tendons and the median nerve in the carpal tunnel.

Diagnosis

Nowadays, the diagnosis of carpal tunnel syndrome is based on clinical signs, and is usually confirmed with electrodiagnostic studies like electromyography (EMG). However, these studies may be normal in 16-34% of the patients who are clinically suspected of having CTS [17,24,62]. This high rate of false-negative results led to the use of other modalities such as magnetic resonance imaging (MRI) and ultrasound (US) for diagnostic purposes. Rahmani et al. evaluated the use of ultrasound in a group of patients with symptoms of CTS but with negative EMG results. They set up a prediction model for CTS, using the cross-sectional area of the median nerve, its hypoechogenicity and hypervascularity as determining factors [52], and found a probability of 35%, 70% and 90% in persons who had one, two or three of these ultrasonographic signs, respectively. Deniz et al. compared several diagnostic modalities including ultrasound and EMG to clinical diagnosis as the gold standard, and found similar accuracies for the diagnosis of CTS for all diagnostic tools [12]. These studies suggest that there may be a role for ultrasound as a diagnostic tool for those patients who are clinically suspected of CTS, but who have normal EMG results. The advantage of ultrasound is that it is less expensive and painful than electrodiagnostic studies. The use of ultrasonography as a method for diagnosing CTS has been extensively studied previously [38,43,49]. However, most research has focused on the use of static cross-sectional imaging of the carpal tunnel, measuring several parameters such as the cross-sectional area and shape of the median nerve, and bowing of the flexor retinaculum [27,28,53,54,61]. These parameters within the carpal tunnel have been assessed both in cadaver models and clinically [13,49,55,64]. Measuring the cross-sectional area of the median nerve has been done before and reports of its sensitivity for diagnosing CTS rise to 94% while specificity rates are reported as high as 98% [6,13,30,31,64]. Recently, Fowler et al. showed in their meta-analysis an average sensitivity for diagnosing CTS with ultrasound of 80.2% and a specificity of 78.7% when using electrodiagnostic tests as a gold standard [17]. Despite the fact that many studies describe static cross-sectional characteristics of the median nerve, only few describe the ulnar-radial and dorsal-palmar movements of the median nerve and tendons in the carpal tunnel. It is known that the median nerve can also slide transversely within the carpal tunnel and responds to these forces by becoming interposed in various positions between the superficial flexor tendons [14,57]. Ugbolue et al. studied these transverse motions and concluded that they are only small and irregular, but this study was only done in cadav-

ers with passive motion [59]. A more precise study of motion pattern differences in vivo would be useful, to see if there are substantial differences and therewith indications for carpal tunnel syndrome pathology.

Besides the cross-sectional imaging of the carpal tunnel, ultrasound studies have focused on the longitudinal motion of the tendons and the median nerve as well, mainly by using Doppler imaging [14,20]. However, the carpal tunnel is a three dimensional structure, and ultimately three dimensional motion over time (i.e., 4D) motion analysis will be necessary to truly understand the kinematics within the carpal tunnel.

Therapy

Management decisions of carpal tunnel syndrome rely on several factors including the severity of symptoms and patient preference. In mild cases, conservative therapy is the initial treatment and consists of splinting and corticosteroid injections. Nocturnal immobilization of the wrist in neutral position improves symptoms after about 2 weeks [22,41,50]. Local corticosteroid injections improve symptoms in up to 77% of the patients after 4 weeks, although the long-term effects are unclear and many patients still need surgery in a later stage of the disease [11,18,22,34]. When conservative therapy fails, surgery may be indicated. Decompression through an open or endoscopic carpal tunnel release is effective in about 75% of the patients, although in 8% of the patients the symptoms worsen [5]. Two randomized controlled trials showed, that surgical intervention is more effective than no treatment or corticosteroid injections in the midterm [21,60], but long term effectiveness of the different treatment options for CTS are lacking [23]. This moderate effectiveness of therapy may be due to a lack of knowledge about the precise etiology of CTS.

Aim and outline of this thesis

Not much is known about tendon and nerve biomechanics in the carpal tunnel in both healthy individuals and in cases of carpal tunnel syndrome. Ultrasound is the only modality capable of real-time imaging of motion in the carpal tunnel. Assessing the motion direction and biomechanics of the different structures in the carpal tunnel could give us more insight in whether these dynamics relate to carpal tunnel syndrome. Therefore, the overall aim of this thesis is to provide more insight in the biomechanics in the carpal tunnel, using ultrasound as a real-time imaging modality. Since we believe that the subsynovial connective tissue plays a key role in the development of CTS, we tried to image this structure with ultrasound as well.

The first part of this thesis addresses the question if it is possible to image the subsynovial connective tissue in the carpal tunnel with ultrasound and to measure if there is a difference in its thickness between carpal tunnel syndrome patients and healthy persons (**Chapter 2**). The second part copes with the transverse motion pattern and deformation of the flexor tendons and median nerve and answers the question if there is a difference in these parameters between carpal tunnel syndrome patients and healthy persons (**Chapter 3-5**). The third part addresses the longitudinal motion of the tendons in the carpal tunnel in both healthy controls and CTS patients and contains a validation study for the methods used for longitudinal motion measurement (**Chapter 6 and 7**). In the last part of this thesis, the results are discussed and suggestions for future research are made.

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PART I

Subsynovial Connective Tissue Thickness

It is unfortunate that so few appreciate from what small causes diseases come.

Charles H. Mayo

CHAPTER 2

Sonographic measurements of subsynovial connective tissue thickness in patients with carpal tunnel syndrome

Margriet H.M. van Doesburg, Aebele B. Mink van der Molen, Jacqueline Henderson, Stephen S. Cha, Kai Nan An, Peter C. Amadio

Journal of Ultrasound in Medicine. 2012 Jan;31(1):31-6.

ABSTRACT

Objective: A major pathological finding in patients with idiopathic carpal tunnel syndrome (CTS) is non-inflammatory fibrosis and thickening of the subsynovial connective tissue (SSCT). The objective of this study was to determine the ability of ultrasound (US) to detect this thickening by comparing SSCT thickness in CTS patients and normal controls.

Methods: Longitudinal ultrasonograms of the middle finger superficial flexor tendon and SSCT were obtained at three levels: at the wrist crease (proximal tunnel), the hook of the hamate (mid-tunnel) and at the distal edge of the transverse carpal ligament (distal tunnel). The thickness of the SSCT perpendicular to the direction of the tendon, and the diameter of the FDS tendon at the same level was measured. Then, a thickness ratio (TR) was created.

Results: At all three levels, the SSCT was thicker in patients than in controls ($p<0.0001$) with a thickness ranging from 0.60mm to 0.63mm in patients and 0.46mm to 0.50mm in controls. The thickness ratio was significantly greater in patients at the mid-tunnel and distal level ($p=0.018$ and $p=0.013$ respectively).

Conclusion: With this study we have shown that it is possible to measure SSCT thickness with ultrasound and that the SSCT is thicker in CTS patients than in healthy controls.

INTRODUCTION

Within the carpal tunnel, the subsynovial connective tissue (SSCT) is the lining around tendons that allows movement between the flexor tendons and median nerve, and it plays a fundamental role in terms of nutrition of the structures embedded in it[8]. Although the precise etiology of carpal tunnel syndrome (CTS) has remained elusive, it is known that one major pathological finding in idiopathic CTS is non-inflammatory fibrosis and thickening of the SSCT[3,7,12,13]. Some investigators have suggested that the pathological changes of SSCT may be a cause, rather than a consequence of CTS[13].

The use of diagnostic ultrasonography has greatly enhanced the ability to diagnose injuries of tendons and tendon sheaths. Recently, steps have been made to image the SSCT with ultrasound as well[2,11,14]. The principal advantages of ultrasonography are its low cost, short study time, availability, and the possibility of dynamic imaging. In addition, the utility of ultrasonography in the evaluation of CTS has been favorably compared to electromyography because of its non-invasiveness[12]. The usefulness of ultrasonography in monitoring carpal tunnel syndrome has been investigated by many authors. Static ultrasound imaging has been described to detect pathologies such as restricted median nerve sliding in the carpal tunnel[3,7,14], tendinous and ligamentous injuries and swelling of the median nerve in the proximal part of the carpal tunnel, and flattening of the median nerve in the distal part of the carpal tunnel[2,11,16]. These approaches however, are only able to capture late changes. A method that could identify earlier anatomic differences in, for example, patients who have symptoms but normal EMG results, could potentially help identify novel therapies to prevent transition into a permanent neuropathy. We believe a promising opportunity is presented in imaging the SSCT by ultrasound, because the ability to image changes in this structure would not only be a possible aid in understanding CTS, but could also be used for further investigation of carpal tunnel evolution and treatment.

Therefore, the objective of this study was to investigate the SSCT thickness in carpal tunnel syndrome patients with ultrasound and compare these results with normal controls.

METHODS

Data Acquisition

To analyze the local anatomy and assess SSCT thickness, longitudinal ultrasonograms of the middle finger superficial flexor tendon and SSCT were obtained at three levels: at the wrist crease (proximal tunnel), the hook of the hamate (mid-tunnel) and at the distal edge of the transverse carpal ligament (distal tunnel). The middle finger FDS tendon was selected for measurement because it is the most palmar tendon and thus moves directly against the carpal flexor retinaculum during finger motion and because it is adjacent to the median nerve within the carpal tunnel. This study was approved by our Institutional Review Board.

We recruited 34 healthy volunteers (17 men, 17 women, mean age 34.3 years, range 22-67) in whom bilateral images were taken, and 31 CTS patients (11 men, 20 women, mean age 51.0 years, range 26-70) of whom 4 had unilateral and the other 27 bilateral images taken. Patients were selected from among those undergoing diagnostic work up for CTS in the pre-treatment period. CTS diagnosis was confirmed both clinically and by electrodiagnostic studies in all patients. Clinical evaluations included sensibility (two point discrimination) in the median nerve distribution of the hand, Phalen's test, Tinel's sign, manual muscle testing of the abductor pollicis brevis, and notation of the presence and extent of thenar muscle atrophy. Patients with any history of upper extremity surgery, as well as any disorder associated with a higher incidence of CTS were excluded.

After getting informed consent, the ultrasound measurements were performed. All ultrasound studies were done by the same examiner, who was not blinded to whether the subject was a patient or a control. Each subject was imaged lying supine with the shoulder abducted to 45 degrees, with the elbow fully extended and the forearm in supination. The forearm of the examinee was fastened on a custom-made table with the wrist in the neutral position. An ultrasound scanner (Acuson Sequoia C512, Siemens Medical Solutions, Malvern, PA) equipped with 15L8 linear array transducer was set to a 15MHz acquisition frequency. The transducer was placed on the palmar wrist surface to make it parallel to the long axis of the middle finger FDS tendon (Figure 1). Positioning of the transducer was assured by identification of anatomical structures: while flexing and extending the middle finger, the third FDS tendon was identified as a moving, striated structure. More palmarly, the SSCT was recognized as a non-moving low-echogenic layer. To minimize compression of the SSCT, the scan head was applied to the skin without additional pressure. The scanning was optimized for depth, focus,

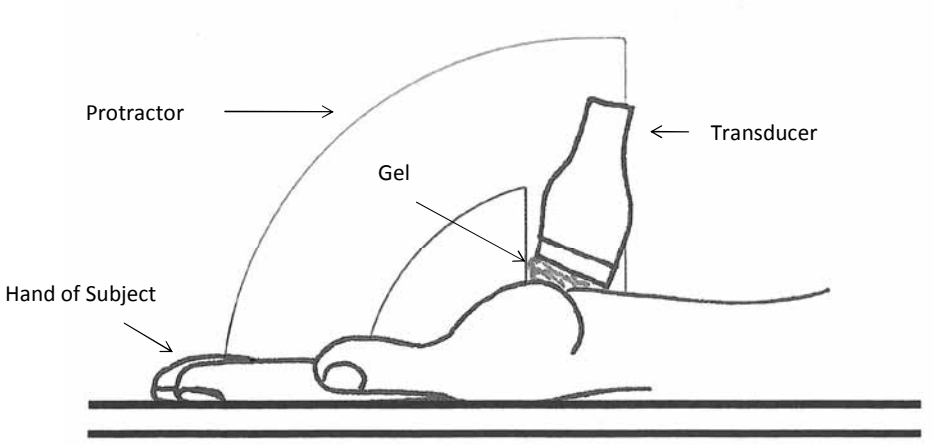

Figure 1 · *Graphic representation of the study set-up with the subject's hand on the custom-made table and the ultrasound transducer longitudinally placed on the wrist.*

gain, dynamic range and maintained throughout the exam for consistency. Then, three still images at the three different levels were taken.

Data Analysis

The still images were uploaded into ImageJ software (Figure 2). Using the Analyze menu, we measured the thickness of the SSCT, drawing a line perpendicular to the direction of the tendon where after the software calculated the thickness. The diameter of the FDS tendon at the same level was also measured the same way as a reference for data analysis. The SSCT was defined as the thin echogenic layer at the border of the tendon, between the median nerve and the FDS tendon as first described by Ettema et al.[5]. To compensate for differences in hand size, especially between men and women, the SSCT thickness was normalized to the FDS tendon diameter at the same level, using the thickness ratio (TR), calculated as: SSCT thickness/tendon thickness = thickness ratio. To calculate the correlation between SSCT thickness and the electrodiagnostic results, we divided the electrodiagnostic results into mild, moderate or severe, based on the grading scheme for CTS severity described by Stevens[15].

The results were summarized in descriptive statistics (mean, standard deviation, median, and range) and by subject groups. A mixed model with repeated measures adjustment from individuals was used to compare the thickness measurements between CTS patients and healthy controls. Individuals were repeated factors, left and right hands were random effects, CTS patient and controls and the three different locations were taken as fixed effects. Pearson correlation coefficient and its p-value

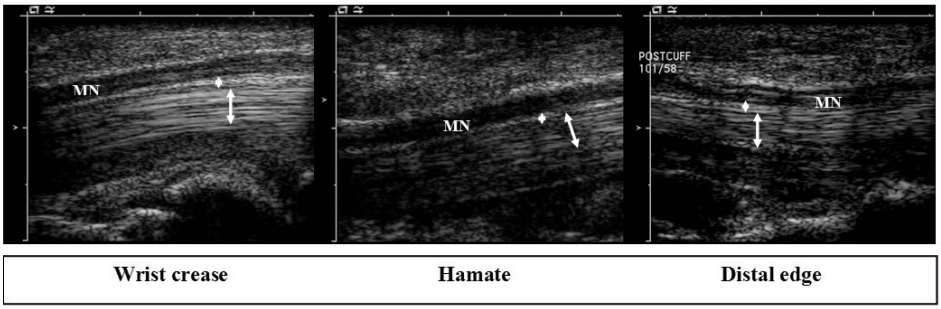

Figure 2 · *Longitudinal ultrasound image at three levels within the carpal tunnel. Long arrow: flexor tendon diameter measurement. Arrowheads: SSCT diameter measurement. MN: median nerve.*

were used to describe the relationship between two factors. Any p-value less than 0.05 was considered statistically significant. All statistical analyses were performed by SAS version 9.3 software (SAS institute Inc., Cary, NC).

RESULTS

Results are shown in Table 1 and Figure 3. At all three levels, the SSCT was thicker in patients than in controls ($p<0.0001$) with a thickness ranging from 0.60mm to 0.63mm in patients and 0.46mm to 0.50mm in controls. The thickness ratio was significantly greater in patients at the hamate and distal level ($p=0.018$ and $p=0.013$ respectively).
We did not find any correlation between SSCT thickness and electrodiagnostic results with Pearson *r* ranging from -0.17 to 0.21.

DISCUSSION

With this study we have shown that it is possible to assess SSCT thickness with ultrasound, and that on average the SSCT is thicker in CTS patients than in healthy controls. The importance of this study is twofold. First, thickening of the SSCT might be an early indicator/predictor of CTS, supporting a clinical diagnosis when electrodiagnostic studies are normal. Of course, this would need much further study. Second, these results are potentially a first step in developing a new, non-invasive method that may help in the care of CTS patients in the future.

Table 1 · *Mean thickness of tendon and SSCT with standard deviation (SD) and range in CTS patients and controls. P-values show significance between patients and controls.*

		Tendon thickness in mm (95% CI) Range		SSCT thickness in mm (95%CI) Range		ST ratio (95%CI) Range	
Wrist crease	Control	**2.06 (1.56-3.10)** 1.27-3.85	p=0.002	**0.46 (0.23-0.70)** 0.21-0.91	p<0.0001	**0.24 (0.10-0.38)** 0.11-0.40	p=0.234
	Patient	**2.36 (1.42-30)** 1.39-3.46		**0.63 (0.20-1.06)** 0.23-1.62		**0.27 (0.09-0.45)** 0.13-0.74	
Hamate	Control	**2.40 (1.36-3.44)** 1.52-3.92	p=0.009	**0.48 (0.30-0.81)** 0.31-0.80	p<0.0001	**0.21 (0.11-0.31)** 0.11-0.35	p=0.018
	Patient	**2.58 (1.80-3.36)** 1.68-3.51		**0.60 (0.29-0.91)** 0.29-1.27		**0.24 (0.12-0.36)** 0.13-0.44)	
Distal edge	Control	**2.49 (0.91-3.55)** 1.42-4.70	p=0.099	**0.50 (0.29-0.72)** 0.22-0.78	p<0.0001	**0.20 (0.10-0.30)** 0.10-0.31	p=0.013
	Patient	**2.63 (1.69-3.59)** 1.64-3.74		**0.61 (0.40-0.83)** 0.29-1.04		**0.23 (0.13-0.33)** 0.12-0.34	

Several studies have already shown that fibrosis and thickening of the subsynovial connective tissue are present in patients with carpal tunnel syndrome, but not in individuals without this diagnosis. Jinrok et al. and Donato et al. showed pathologic vascular proliferation, vascular hypertrophy, and vascular obstruction with wall thickening in the SSCT in patients[1,9]. Ettema et al. showed that CTS patients have thicker fibrous bundles between the layers of SSCT than did normal controls. Of note, the normal controls used in Ettema et al were cadaver specimens with no antemortem history of CTS, while the patients were middle aged adults, suggesting that the fibrosis is not a function of age, but of disease[4].

Of course, it is unclear at this point whether the SSCT fibrosis causes the neuropathy, or whether both the fibrosis and neuropathy are caused by some other, as yet unidentified, factor. Regardless, the measurement of SSCT thickness could be clinically useful for several reasons. It could be used to support a clinical diagnosis of CTS when clinical signs are abnormal but electrodiagnostic studies are normal. Studies of SSCT thickness might also be helpful in patient care. It is possible, for example, that a thicker SSCT might be associated with a poorer response to interventions such as steroid injection, splinting, or simple decompression. We plan to look for these correlations in future studies. We found a wide variation of normal results in this study. However, this study was meant as a first step towards potentially using SSCT thickness measurements in diagnosing CTS. To our knowledge, these measurements have never been done in patients before and we want to give

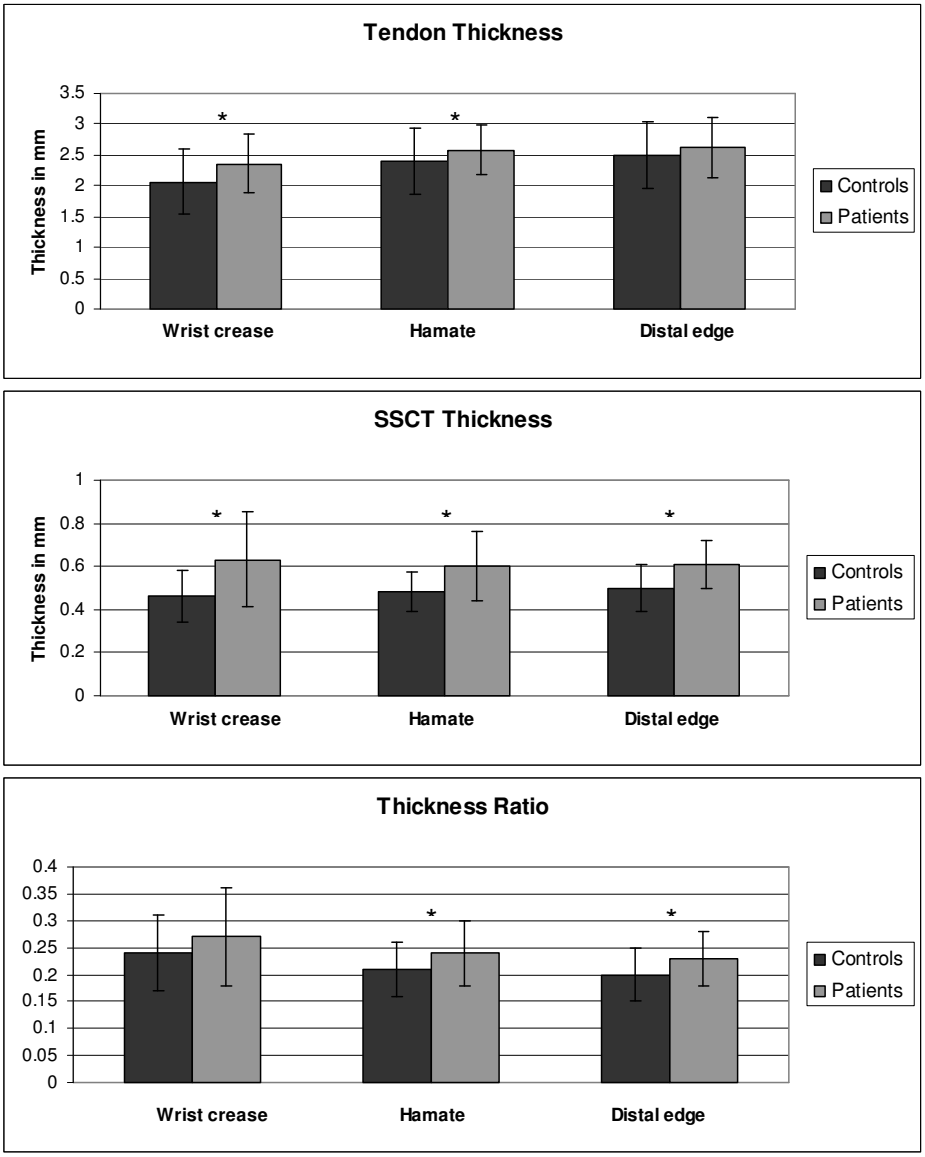

Figure 3 · *Mean thickness of tendon and SSCT and thickness ratio with standard deviation (SD) in CTS patients and controls. *p<0.05.*

a general idea of this method and its potential (future) applications. Now we have shown that it is possible to measure SSCT using ultrasound and that there is a difference between controls and patients, we can focus on the specifics such as reliability and diagnostic performance in future studies. Even though we tried to

base our ultrasound settings on other studies with similar purposes, we will need to improve this in the future to get less variable and better clinically applicable results.

In this study, we only measured SSCT thickness at one time point. It would be more ideal to study the thickening of the SSCT over time, and to compare the progression of SSCT thickening and clinical neuropathy. Such data will help to clarify whether SSCT thickening is an early, concomitant or late finding in patients with clinically diagnosed CTS.

Several parameters that might be potentially useful for clinical use were measured in this study. Ettema et al. showed that no significant differences were noted between the thickness of SSCT measured by ultrasound and that measured during cadaver dissection[5]. They found an SSCT thickness in normal controls ranging from 0.62mm at the wrist crease level to 0.66mm at the hamate and distal edge level. Our results in normal controls are slightly lower, but this difference might be due to the use of color Doppler by Ettema et al, which angle dependency might alter measurements. In both their and our study, the SSCT is thicker at the hamate and distal edge level. This could be due to the fact that within the carpal tunnel, pressure and shear are higher at the proximal level which is the entrance of the carpal tunnel. The thickness of both tendons and SSCT could be dependent on hand size and gender and to rule these factors out, we created the thickness ratio. Therefore, this parameter would be most reliable and clinically most useful.

In the future, further research needs to be done to make thickness measurements more clinically applicable. The ability of this method to discriminate between pathologically thick and normal SSCT needs to be investigated, as well as the cut-off values. We did not find any correlation between SSCT thickness and EMG severity in this study; however it would be useful to repeat these measurements with a greater sample size. Interestingly, a recent publication does show a correlation between a different measure of SSCT pathology (neovascularization) and outcome. As in our study, there was no correlation of electrodiagnostic severity in this study with either SSCT pathology, preoperative symptomatology, or clinical outcome.[6]

Finally, the presented method is laborious and should be modified for clinical use. One possible disadvantage of the thickness ratio is that if both the tendon and the SSCT thicken by an equal percentage, then the ratio would remain unchanged. An option to identify and correct for this would be to also measure the total thickness of the tendon and SSCT together, a possibility which remains for future studies.

The tightness of the carpal tunnel is probably best represented at the hook of the hamate level, since this is right in the middle of the carpal tunnel. The proximal level is measured at the wrist crease, which is just at the entrance of the carpal tunnel.

We encountered some difficulties during this study. During image acquisition, we noticed that FDS tendon and SSCT imaging are much easier on the proximal part of

the carpal tunnel. Imaging at the middle and distal part of the carpal tunnel required applying some pressure to the transducer because of the thicker subcutaneous tissues of the palm. Even though we tried to avoid applying pressure, this may have affected the analysis. Another limitation of this study is that we did not use a gold standard for our measurements, nor did we do electrophysiological testing in the volunteers to rule out they had CTS. For ethical reasons however, we were not able to directly measure the SSCT and tendon thickness of normal volunteers in vivo, since this would have required a surgical intervention. However, Ettema et al. used cadaveric SSCT measurements as a controls, and showed in their study that no significant differences were noted between the thickness of SSCT measured by ultrasound and that measured during cadaver dissection[5]. Also, we did not test the reproducibility of the technique, even though ultrasound is known for high inter-rater variation. This remains for future studies. However, others have shown that a very similar method is valid.[10]

In conclusion, we have presented a method to measure subsynovial connective tissue thickness using ultrasound, and showed that the SSCT is significantly thicker in carpal tunnel syndrome patients than in healthy controls. These findings suggest that thickening of the SSCT due to fibrosis is a pathological finding in CTS patients and that ultrasound might be useful as a diagnostic aid for early detection of CTS in the future.

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PART II

Transverse Plane Motion and Deformation of the Median Nerve and Flexor Tendons

We are, I think, in the right road of improvement, for we are making experiments.

Benjamin Franklin

CHAPTER 3

Median Nerve Deformation and Displacement in the Carpal Tunnel during Index Finger and Thumb Motion

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Journal of Orthopedic Research. 2010 Oct;28(10):1387-90

ABSTRACT

Purpose: The purpose of this study was to investigate the deformation and displacement of the normal median nerve in the carpal tunnel during index finger and thumb motion, using ultrasound.

Methods: Thirty wrists from 15 asymptomatic volunteers were evaluated by ultrasound. Cross-sectional images during motion from full extension to flexion of the index finger and thumb were recorded. On the initial and final frames, the median nerve, flexor pollicis longus (FPL) and index finger flexor digitorum superficialis (FDS) tendons were outlined. Coordinate data was recorded and median nerve cross-sectional area, perimeter, aspect ratio of the minimal enclosing rectangle, and circularity in extension and flexion positions were calculated.

Results*:* During index finger flexion, the tendon moves volarly while the nerve moves radially. With thumb flexion the tendon moves volarly, but the median nerve moves towards the ulnar side. In both motions the area and perimeter of the median nerve in flexion were smaller than in extension.

Conclusions: We showed that during index finger or thumb flexion, the median nerve in healthy human subjects shifts away from the index finger FDS and FPL tendon while being compressed between the tendons and the flexor retinaculum in the carpal tunnel. We are planning to compare these data with measurements in patients with carpal tunnel syndrome, and believe that these parameters may be useful tools for the assessment of CTS and carpal tunnel mechanics with ultrasound in the future.

INTRODUCTION

The carpal tunnel contains nine flexor tendons and the median nerve. These structures are surrounded by the subsynovial connective tissue (SSCT), which functions as a sliding interface between these structures [7]. The major pathological finding in carpal tunnel syndrome is fibrosis of the SSCT, which changes the motion characteristics of the SSCT, tendon excursion and median nerve, as noted during intraoperative inspection in cases of carpal tunnel release [5,7,11,15]. These changes may also cause elevated strain and pressure in the carpal tunnel, which ultimately can lead to carpal tunnel syndrome (CTS) [11,19].

It is our underlying hypothesis that, due to fibrosis of the SSCT, the kinematics of the nerve and tendons in the carpal tunnel change in patients with CTS. We further hypothesize that these changes are associated with the evolution of CTS, and that these changes can be monitored non-invasively, by ultrasound. An essential first step in testing these hypotheses is to identify the normal motion pattern of the different tendons and the median nerve in the carpal tunnel. These data can then be used as a baseline against which to compare patient data. If, as we hypothesize, there are detectable differences in the SSCT and tendon and nerve kinematics in individuals with CTS, then these differences could be sought in individuals at risk for CTS. If our hypotheses are supported, then ultrasound could become a useful non-invasive tool to study the genesis of CTS, and to monitor at risk individuals.

Ultrasonography is known to be a good imaging technique for the structures in the carpal tunnel. Several different parameters within the carpal tunnel have been assessed using this technology, both clinically and in cadaver models [3,6,16,18,20]. Most ultrasound studies have focused on the longitudinal motion of the tendons and the median nerve. Although the ulnar-radial and dorsal-palmar movement of the median nerve have been assessed, tendon movement in these directions has not been studied in depth [4,9,10,14]. However, the carpal tunnel is a three dimensional structure, and ultimately three dimensional motion over time (i.e., 4D motion analysis) will be necessary to truly understand the kinematics within the carpal tunnel. Recent research from our laboratory evaluated the transverse motion of the middle finger flexor digitorum superficialis (FDS) tendon, because it is superficial, and positioned next to the median nerve in the carpal tunnel [21]. This facilitates image capture. The index finger and thumb, however, are most commonly used in activities like pinching, which can be impaired in patients with CTS [8]. Even though the index finger flexor tendons and the flexor pollicis longus tendon are anatomically further away from the median nerve than the middle finger flexor tendon, they are directly posterior to the nerve, and we believe that it would be useful to know how their motion normally affects the deformation and motion direction of the median nerve

The purpose of this study was, therefore, to investigate the motion direction and deformation of the normal median nerve, the index finger superficial flexor tendon, and flexor pollicis longus tendon in index finger and thumb movement, using ultrasound.

METHODS

This study was approved by our Institutional Review Board. We recruited 15 healthy volunteers (9 men, 6 women) with a mean age of 36.3 +/- 6.9 years. Participants were excluded if they had a history of wrist trauma, wrist surgery or any symptoms related to, or which could mimic carpal tunnel syndrome. After written consent was obtained, we proceeded with the ultrasound on both wrists.

The image acquisition procedure of the cross-sectional plane of the carpal tunnel has been described previously [21]. In brief, the subjects were lying supine with their arm outstretched and their lower arm and wrist fixed on a custom-made device. Image acquisition was done at a frame rate of 30Hz, using an Acuson Sequoia C512 ultrasound machine (Siemens Medical Solutions, Malvern, PA) with a 15L8 linear array transducer (Figure 1). The resolution of the monitor of this system is

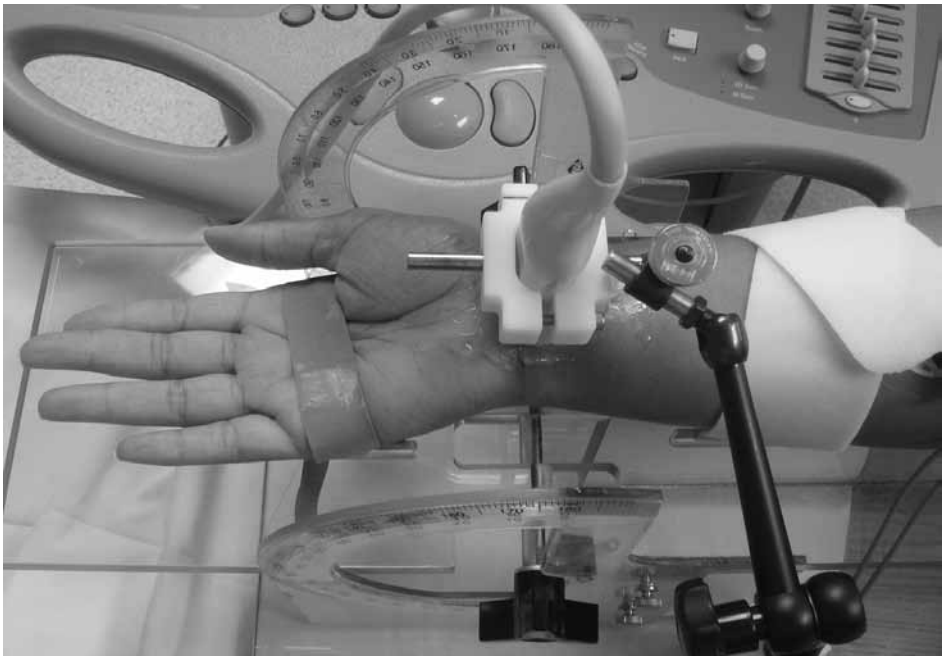

Figure 1 · *Custom-made table with transducer holder.*

640x480pixels (NTSC format). With this combination of transducer and monitor, the pixel size is roughly 0.04 mm^2. The transducer was held in a 90-degree angle to the wrist, without applying any extra pressure to it, to avoid compression of the carpal tunnel. Images were acquired at the wrist crease level, with the transducer parallel to the wrist crease. The participant was asked to fully flex and extend the index finger or the thumb to the sound of a metronome at a pace of 0.8Hz for half a cycle (flexion or extension) After a period of practice with the metronome, five cycles of the flexion-extension motion were recorded. We found in our initial analyses that during finger or thumb extension, the nerve and tendons were furthest away from each other compared to their position in flexion. For this reason we choose to measure the full extension and full flexion positions of both.

After obtaining the data, the images were evaluated using Analyze 8.1 software (Mayo Clinic, Rochester, USA). After the initial and final frames of the motion were selected and reviewed, the median nerve and the tendon were outlined (Figure 2). Area, perimeter, displacement, circularity and the aspect ratio of a minimum enclosing rectangle were measured by the software. The average of the five cycles was calculated. The minimum enclosing rectangle was determined as the smallest possible enclosing rectangle to the image. The aspect ratio was defined as the

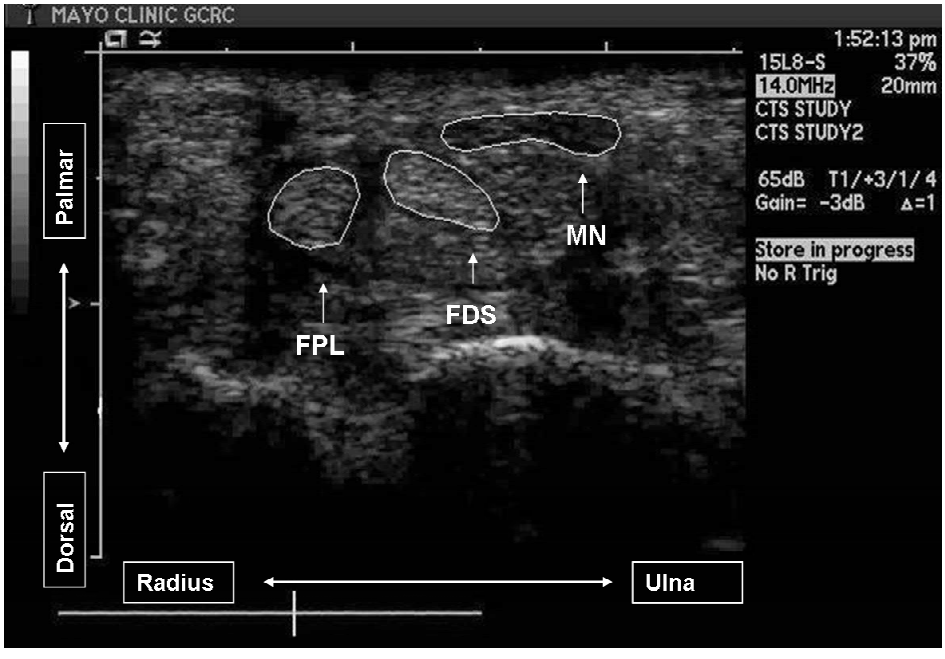

Figure 2 · *Cross-sectional ultrasound image with outlined median nerve, index finger FDS and FPL tendon. FPL = flexor pollicis longus.*

ratio of the minor axis divided by the major axis of this rectangle. In addition, the deformation ratio for each parameter was calculated by dividing the flexion by the extension value. This ratio will give an indication of the deformation of the median nerve during the full extension to flexion motion.
The displacement of the nerve was defined as the difference between the centroid coordinates of the extension and flexion positions. This way, the displacement in ulnar-radial and palmar-dorsal direction could be calculated. The palmar and ulnar directions were defined as positive and the radial and dorsal as negative.

Statistical Analysis

All results were expressed in mean +/- standard deviation (SD). Since we evaluated flexion and extension in both left and right wrist of all participants, we used mixed model approach for statistical analyses where participants were treated as repeated factor, wrists (left and right) as random effect factor, and fingers (thumb and index) or motion direction (Flexion/Extension) as fixed effect factor. A p-value of less than 0.05 was considered significant. The reliability of five measurements was estimated by Intraclass correlation coefficient (ICC). ICC had adopted the interpretation of Kappa statistics and an ICC>0.75 will be rated excellent . All statistical analyses were performed by SAS version 9.1.3 software (SAS institute Inc., Cary, NC).

RESULTS

We did not find any differences between left and right hands (p=0.96), within cycles (p=0.37) or patients (p=0,98) for a worst case series of calculated ratios. Therefore, we decided to use the average for further statistical analysis. Using the same method for a series of measurements of absolute data, we again did not find any difference between cycles (p=0.33) or left and right hands (p=0.17). We did find a difference between patients (p<0.0001), however, using a mixed model with patients as a repeated factor, this difference disappears. Figures 3 and 4 show the results of the direction and amount of movement of the median nerve and the tendons over the course of a full excursion, from full flexion to full extension.

In the palmar-dorsal direction the median nerve moves 0.041mm dorsally with index finger motion and 0.047mm volarly with thumb motion. The motion of the nerve in the palmar-dorsal direction was not significantly different in index FDS or FPL motion. From full extension to full flexion, the FPL moves more volarly

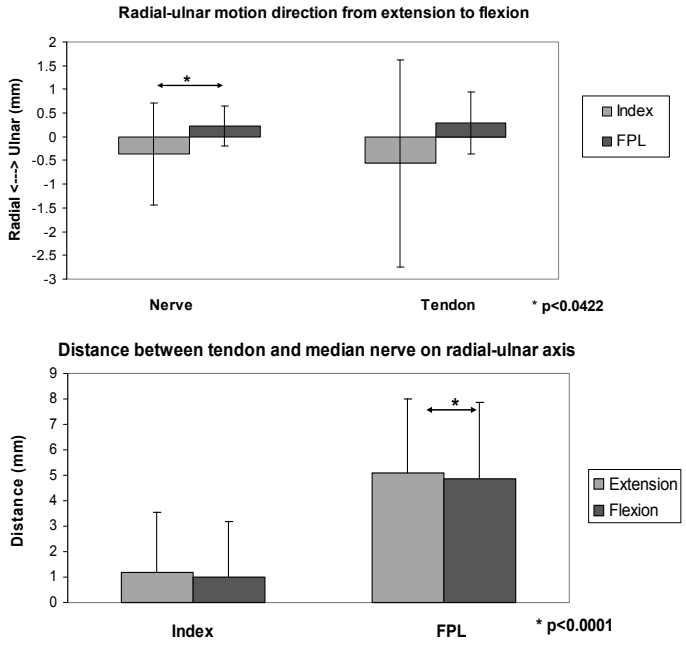

Figure 3 · *Radial-ulnar motion direction and radial-ulnar nerve-tendon distance*

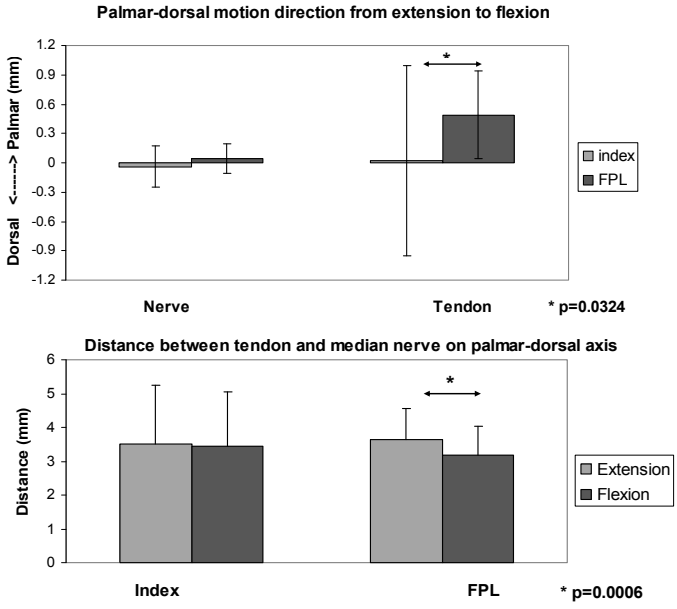

Figure 4 · *Palmar-dorsal motion direction and palmar-dorsal nerve-tendon distance*

(0.49mm, SD 0.44) than does the index FDS (0.03mm, SD 0.97) ($p<0.05$). The radial-ulnar direction of the tendon was not significantly different comparing the index FDS and the FPL, but the median nerve moves differently depending on which tendon is moving, in an ulnar direction with FPL motion (0.23mm, SD 0.43) and in radial direction with index FDS motion (0.36mm, SD 1.08) ($p<0.05$).

The distance between the nerve and the tendon in the radial-ulnar direction was significantly smaller with index FDS motion than with FPL motion ($P<0.0001$). The palmar-dorsal movement of the index FDS and FPL was also not different, but the FPL was significantly closer to the nerve in flexion than it was in extension ($p=0.0006$).

The median nerve parameter indices and deformation ratios are shown in Table 1.

There were no statistical differences between the index FDS and FPL measurements. With respect to the flexion and extension positions within these motions, however, the cross-sectional area and the perimeter of the median nerve were larger in extension compared to flexion.

Aspect ratio of the minimal enclosing rectangle and circularity were not significantly different, nor were the deformation ratios of the four parameters.

In this study we also had the possibility to evaluate intra-observer differences by evaluating the differences between the 5 trials per subject. We calculated the ICC

Table 1 · *Median nerve indices and deformation ratios*

Median nerve indices		Extension Average (SD)		Flexion Average (SD)	**Deformation ratios**
Area (mm^2)	Index	9.93 (1.56)	*	9.55 (1.58)	0.961 (0.044)
	FPL	10.11(1.42)	*	9.62(1.30)	0.955 (0.067)
Perimeter(mm)	Index	14.82(1.83)	*	14.61(2.00)	0.985 (0.038)
	FPL	15.04(1.30)	*	14.72(1.21)	0.980 (0.042)
Aspect ratio	Index	0.37(0.08)		0.39(0.11)	1.060 (0.169)
	FPL	0.36(0.08)		0.37(0.09)	1.015 (0.102)
Circularity	Index	1.78(0.26)		1.81(0.31)	1.013 (0.078)
	FPL	1.81(0.28)		1.83(0.33)	1.008 (0.064)

* $p<0.05$

from a worst case series of measurements and found an excellent ICC of 0.812 (95% CI 0.601-0.928). We expect the ICC to be similar or even better for all measurements.

DISCUSSION

In this study, we showed that with the individual index finger and thumb motion, the tendons move towards the median nerve, thereby pushing the median nerve in either a radial or ulnar direction. As the FPL contracts, causing thumb interphalangeal flexion, its motion is in the palmar direction towards the median nerve, thereby compressing the nerve and pushing it in the ulnar direction. During index finger motion the tendon also moves in a palmar direction, while the nerve moves radially. The area of the median nerve is smaller in flexion than in extension with both index finger and thumb movements, which suggests that there is compression of the median nerve between the tendons and the flexor retinaculum during these single digit motions. There was also no difference in the aspect ratio of the minimal enclosing rectangle and the circularity, indicating that the shape of the median nerve does not change. . In longitudinal ultrasound images taken during the same exam, we did not see longitudinal motion of the median nerve in a proximal or distal direction. We do not, therefore. think that we scanned a different part of the median nerve in extension than we did in flexion.

These results show that in healthy subjects, the median nerve not only undergoes compression during index finger and thumb motions, but also that it can 'escape' the most severe compression, because the nerve is able to move from side to side to avoid the most direct contact with the underlying tendons. We think that this is an important observation, since in carpal tunnel syndrome the median nerve is often noted to be constrained by SSCT fibrosis to the overlying flexor retinaculum and underlying tendons, making it liable to even greater compression.

Yoshii et al. showed in a recent publication that isolated motion of the middle finger affects median nerve deformation more than fist motion. They also found that in isolated middle finger motion, the flexor digitorum superficialis (FDS III) moved in the radial and dorsal direction, while in fist motion it moved in the ulnar and palmar direction. These findings are consistent with our own findings, and suggest that different hand activities, for example pinching versus gripping, might have quite different effects on median nerve compression, and thus might be helpful in better understanding the etiology of carpal tunnel syndrome, a condition which is both extremely common and most often idiopathic [1,2].

While tendon motion in the carpal tunnel has not been commonly studied, several authors have studied transverse displacement of the median nerve [4,13,17]. Nakamichi

and Tachibana observed a transverse sliding of the median nerve beneath the flexor retinaculum in passive motion of the proximal and distal interphalangeal joints of the index finger [12]. They found that the median nerve slides 1.75 ± 0.49 mm in the ulnar direction. This is not consistent with our findings. We think the difference relates to the fact that Nakamichi and Tachibana measured passive flexion of the proximal and distal interphalangeal joints, while our subjects flexed the PIP, DIP and metacarpophalangeal joints actively.

The strength of this study is that we studied active in-vivo measurements of the motion direction of the median nerve and the index finger and FPL. We believe that with these results, we have shown that in single digit motion of either the index finger or the thumb, compression of the median nerve occurs. Fibrosis of the surrounding SSCT might result in even more compression of the median nerve.

This study also has several shortcomings. First, we did not evaluate intra- and interobserver differences. Ultrasound is known for having a significant variation between examiners. However, in our ultrasound setting, we found several ways to avoid differences in imaging. The subject's arm and hand were tied to the custom-made table to prevent it from moving (Figure 1). Second, the transducer was held in place with an adjustable arm. This allowed the examiner to focus on the image acquisition, while the transducer did not move.

Finally, our study has a small sample size, but based on previous research we believe that these results give a good indication of the motion direction and deformation of the carpal tunnel contents, and were quite consistent between subjects.

We believe that the results here presented may be useful as baseline data for future studies of the motion direction and deformation of the carpal tunnel contents in both healthy human subjects and in patients with CTS. Based on the data collected here, which shows that our measurement methods are feasible, we plan a future study to compare these data to measurements in patients with CTS.

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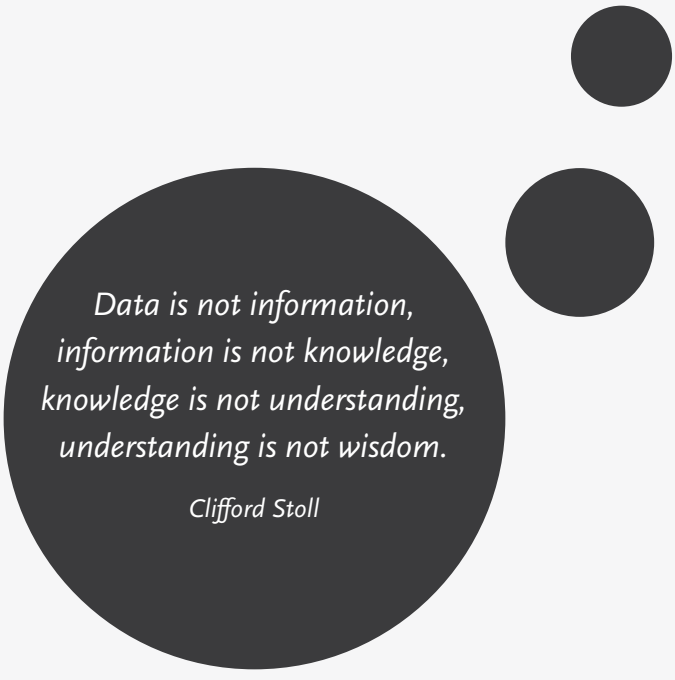
Data is not information,
information is not knowledge,
knowledge is not understanding,
understanding is not wisdom.
Clifford Stoll

CHAPTER 4

Median Nerve Deformation in Differential Finger Motions: Ultrasonographic Comparison of Carpal Tunnel Syndrome Patients and Healthy Controls

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Journal of Orthopedic Research. 2012;30(4):643-8

ABSTRACT

Purpose: We investigated the median nerve deformation in the carpal tunnel in patients with carpal tunnel syndrome and controls during thumb, index finger, middle finger and a four finger motion, using ultrasound.

Methods: Both wrists of 29 asymptomatic volunteers and 29 patients with idiopathic carpal tunnel syndrome were evaluated by ultrasound. Cross-sectional images during motion from full extension to flexion were recorded. Median nerve cross-sectional area, perimeter, aspect ratio of the minimal enclosing rectangle, and circularity in extension and flexion positions were calculated. Additionally, a deformation index was calculated. We also calculated the intra-rater reliability.

Results: In both controls and patients, the median nerve cross sectional area became significantly smaller from extension to flexion in all finger motions ($p<0.05$). In flexion and extension, regardless of the specific finger motion, the median nerve deformation, circularity and the change in perimeter were all significantly greater in CTS patients than in controls ($p<0.05$). We found excellent intra-rater reliability for all measurements (ICC>0.84).

Conclusions: With this study we have shown that it is possible to assess the deformation of the median nerve in carpal tunnel syndrome with ultrasonography and that there is more deformation of the median nerve in carpal tunnel syndrome patients during active finger motion. These parameters might be useful in the evaluation of kinematics within the carpal tunnel, and in furthering our understanding of the biomechanics of carpal tunnel syndrome in the future.

INTRODUCTION

Carpal tunnel syndrome is a compression neuropathy of the median nerve in the wrist. Patients with carpal tunnel syndrome (CTS) experience pain and weakness in the hand, and numbness and paresthesias in the first three digits. These symptoms were first described by Sir James Paget in 1854, although widespread recognition of the condition only happened in the 1950s because of the work of Phalen.[10] However, the etiology of carpal tunnel syndrome remains idiopathic in most cases. Various anatomic, systemic and occupational factors such as repetitive use of the wrist and digits have all been described as potential causative factors.[1,14] In other studies, the focus has been on biomechanical factors that might influence the development of CTS.[5,6,8] The carpal tunnel contains nine different tendons and the median nerve, bound by the carpal bones on the dorsal side and the transverse carpal ligament on the volar side. Recent studies have demonstrated that even in healthy people, the median nerve gets compressed between the flexor retinaculum and the tendons during active finger motion.[12,14] In addition, several studies have shown that there is reduced longitudinal gliding of the median nerve in CTS patients.[3,9] This suggests that monitoring the motion and deformation of the median nerve by ultrasound may offer new insights into the mechanics within the carpal tunnel, and potentially serve as a new means by which CTS can be better understood, or perhaps even diagnosed. It is therefore important to characterize the deformation of the median nerve during finger motion in both CTS patients and normal controls. We hypothesized that there are detectable differences in deformation and motion of the median nerve in individuals with CTS, compared to healthy controls. If our hypothesis is supported, then these parameters would potentially be useful to use ultrasound as a non-invasive tool to study the genesis of CTS, and to monitor at risk individuals.

METHODS

Image Acquisition

This study was approved by our Institutional Review Board, and all participants gave written informed consent. We recruited 29 healthy volunteers (15 women, 14 men, age range 22-67 with a mean age of 35.5 years) without any history of CTS, and 29 patients with idiopathic CTS (18 women, 11 men, mean age 51.1 years with a range of 26-70 years) which was diagnosed by electrophysiological studies. All but two volunteers

had bilateral CTS. CTS patients with a history of systemic disease associated with a higher incidence of carpal tunnel syndrome, such as thyroid disease, obesity or rheumatoid arthritis, as well as all patients with any upper extremity surgery in their medical history, were excluded. We evaluated both left and right wrists in the healthy volunteers; in CTS patients we evaluated the affected side(s). Cross-sectional images of the carpal tunnel were obtained by placing the 15L8 linear array transducer of a Siemens Sequoia C512 ultrasound machine (Siemens Medical Solutions, Malvern, PA) set to a 15 MHz acquisition frequency, transversely at the wrist crease and perpendicular to the long axes of the forearm, just proximal to the carpal tunnel. The participants were positioned with the supinated hand fixed in a custom made device, with the wrist in neutral position. They were asked to flex and extend all four fingers (index, middle, ring, little) together as well as to move three digits (either middle finger, index finger or thumb) independently, from 0 degrees (i.e., full) finger extension to the maximum flexion, that is, until the finger tip touched the palm. In the case of single digit motion, the participant was asked to keep the other fingers as much extended as possible. Five cycles of motion were recorded for each of the four movements. Using Analyze 8.1 software (Mayo Clinic, Rochester, MN) the recorded clip was reviewed and the initial and final frames of the motion cycle were selected. Based on these images, the outer hypoechogenic rim of the median nerve was outlined for both the full extension and the full flexion positions (Figure 1). We then calculated the median nerve cross sectional area and perimeter. We also calculated the circularity, defined as:

$$\text{Circularity} = (\text{nerve perimeter})^2 / (\text{nerve area} \cdot 4\pi) \quad \text{(Equation 1)}$$

Also, the aspect ratio of the median nerve minimum enclosing rectangle (MER), was an indication of the flattening of the median nerve. To calculate the aspect ratio

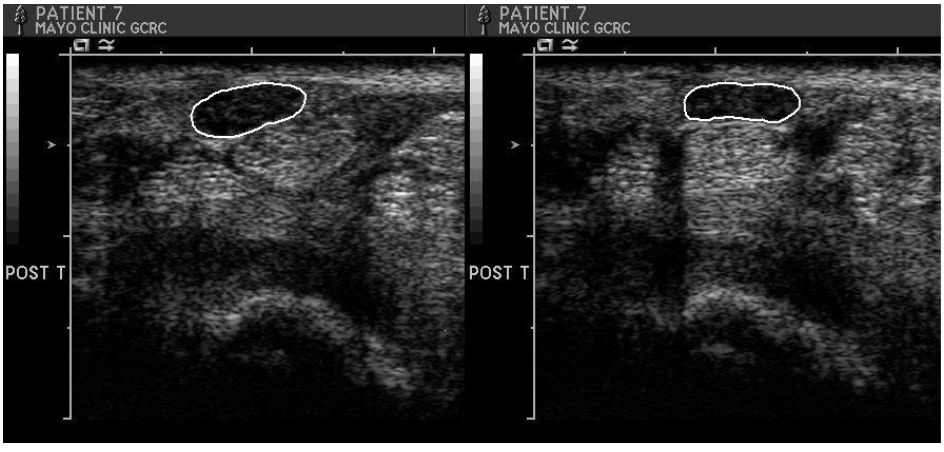

Figure 1 · *Example of outlining of the median nerve in middle finger motion from extension (left) to flexion (right) where the median nerve becomes smaller and squarer*

of the MER, the software calculated the smallest possible rectangle that would fit around the cross section of median nerve and divided the short axis by the long axis. We then created a deformation index (DI), calculated as:

DI = flexion/extension (Equation 2)

DI is an indication for the amount of deformation of the median nerve throughout an extension to flexion motion. Since we recorded five cycles of each finger motion within each participant, we were able to calculate the intra-rater reliability from these measurements.

Statistical Analysis

All results were expressed in mean +/- standard deviation (SD). Since we evaluated flexion and extension in both left and right wrist of healthy participants and patients with bilateral CTS, we used SAS procedure MIXED model approach for statistical analyses where participants were treated as repeated factor, wrists (left and right) as random effect factor, and fingers (4 fingers, middle finger, index finger and thumb) or motion direction (flexion/extension) as fixed effect factor. An overall p-value of less than 0.05 was considered significant for finger and motion differences. The post hoc comparisons were checked by the LSD rule. The reliability of five measurements was estimated by intraclass correlation coefficient (ICC). ICC had adopted the interpretation of Kappa statistics and an ICC>0.75 was rated excellent. All statistical analyses were performed by SAS version 9.2 software (SAS institute Inc., Cary, NC).

RESULTS

The results of the absolute parameter measurements of the median nerve for all finger motions are shown in Table 1 and the deformation indices in Table 2.

Table 1 · *Absolute indices for the cross section of the median nerve. *p<0.05 between controls and patients, SD= Standard Deviation*

INDIPARAMETERS		Four finger motion		Middle finger		Index finger		Thumb	
		Extension	Flexion	Extension	Flexion	Extension	Flexion	Extension	Flexion
Area, mm² (SD) (range)	Control	9.76 (2.42) (6.73-14.56)	9.20 (2.46) (6.29-14.12)	9.85 (2.35) (6.13-13.50)	9.31 (2.50) (6.12-13.91)	9.57 (1.99) (5.49-11.98)	8.95 (1.91) (5.08-12.07)	9.44 (2.00) (6.43-12.39)	8.90 (1.86) (5.80-12.04)
	Patient	11.26 (4.05) * (7.15-22.37)	10.24 (3.59) * (6.34-19.59)	11.16 (3.86) * (7.09-21.03)	10.29 (3.69) * (6.82-20.87)	10.75 (3.65) * (7.09-20.72)	9.82 (3.42) * (6.52-20.00)	10.77 (3.97) * (6.92-23.10)	9.94 (3.72) * (6.53-22.22)
Perimeter, mm (SD) (range)	Control	14.41 (2.68) (10.93-20.14)	14.30 (2.66) (10.79-19.79)	14.52 (2.73) (11.10-18.35)	14.77 (2.83) (11.30-19.36)	14.46 (2.12) (10.88-18.46)	14.19 (2.15) (10.62-18.96)	14.56 (2.00) (11.15-18.09)	14.22 (1.89) (10.76-17.52)
	Patient	14.59 (4.06) (10.77-20.09)	14.19 (3.87) (10.57-19.42)	14.50 (3.97) (10.99-19.02)	14.11 (3.86) (10.92-20.10)	14.38 (3.93) (10.85-18.53)	14.09 (3.87) (10.48-19.52)	14.22 (3.97) (11.22-21.29)	14.05 (3.92) (11.00-20.55)
Aspect ratio of MER (SD) (range)	Control	0.37 (0.11) (0.22-0.62)	0.34 (0.08) (0.22-0.49)	0.35 (0.10) (0.21-0.56)	0.32 (0.09) (0.20-0.51)	0.37 (0.09) (0.21-0.54)	0.37 (0.12) (0.23-0.74)	0.35 (0.09) (0.21-0.55)	0.35 (0.10) (0.19-0.54)
	Patient	0.38 (0.14) (0.23-0.73)	0.36 (0.12) * (0.24-0.68)	0.38 (0.14) * (0.24-0.75)	0.36 (0.13) * (0.24-0.69)	0.37 (0.13) (0.23-0.63)	0.34 (0.12) * (0.23-0.57)	0.38 (0.13) * (0.25-0.65)	0.36 (0.13) (0.25-0.67)
Circularity (SD) (range)	Control	1.72 (0.36) (1.29-2.51)	1.81 (0.35) (1.36-2.53)	1.74 (0.37) (1.26-2.52)	1.90 (0.40) (1.38-2.63)	1.71 (0.41) (1.29-2.49)	1.77 (0.44) (1.26-2.49)	1.81 (0.30) (1.43-2.70)	1.84 (0.33) (1.35-2.97)
	Patient	1.54 (0.43) * (1.19-2.22)	1.59 (0.44) * (1.22-2.20)	1.53 (0.43) * (1.20-2.15)	1.57 (0.43) * (1.18-2.12)	1.56 (0.44) * (1.24-2.32)	1.64 (0.47) * (1.30-2.39)	1.52 (0.44) * (1.21-2.24)	1.62 (0.48) * (1.24-2.46)

Table 2 · *Deformation indices for the median nerve from extension to flexion motion.*

DEFORMATION INDEX		Four finger motion	Middle finger	Index finger	Thumb
Area (SD) (range)	Control	0.94 (0.08) (0.74-1.12)	0.95 (0.09) (0.75-1.17)	0.94 (0.05) (0.80-1.05)	0.94 (0.06) (0.81-1.11)
	Patient	0.91 (0.05) * (0.75-1.02)	0.92 (0.06) * (0.78-1.07)	0.91 (0.05) * (0.76-1.04)	0.92 (0.05) * (0.80-1.07)
Perimeter (SD) (range)	Control	1.00 (0.06) (0.88-1.18)	1.02 (0.07) (0.84-1.16)	0.98 (0.04) (0.88-1.06)	0.98 (0.04) (0.89-1.06)
	Patient	0.97 (0.03) * (0.90-1.07)	0.97 (0.05) * (0.88-1.09)	0.98 (0.04)* (0.84-1.09)	0.99 (0.03) * (0.90-1.08)
Aspect ratio of MER (SD) (range)	Control	0.94 (0.19) (1.56-1.55)	0.94 (0.24) (0.55-1.79)	1.01 (0.18) (0.74-1.59)	1.00 (0.10) (0.83-1.26)
	Patient	0.97 (0.11) (0.71-1.21)	0.96 (0.17) (0.64-1.64)	0.94 (0.12) * (0.75-1.23)	0.95 (0.08) * (0.78-1.18)
Circularity (SD) (range)	Control	1.06 (0.11) (0.81-1.48)	1.10 (0.14) (0.79-1.62)	1.03 (0.09) (0.84-1.27)	1.01 (0.06) (0.90-1.15)
	Patient	1.04 (0.06) * (0.86-1.18)	1.03 (0.085) * (0.82-1.20)	1.05 (0.06) (0.91-1.17)	1.06 (0.05) (0.94-1.19)

** p<0.05 between controls and patients, SD= Standard Deviation*

Four Finger Motion

The cross-sectional area of the median nerve was greater in CTS patients in both extension and flexion positions than in controls (p<0.0001), but the perimeter, however, was not different between the two groups. For the deformation index, there was a significant difference for both area and perimeter (p=0.0004 and p=0.0009 respectively), showing that there is a change in shape between extension and flexion. The circularity was less in patients than in controls, as was the DI for circularity (p<0.0001 and p=0.0063 respectively), meaning that the shape of the median nerve is closer to a perfect circle in patients. The aspect ratio of the minimal enclosing rectangle was 0.34 in controls and 0.36 in patients (p=0.002).

Middle Finger Motion

The area of the median nerve was greater in patients than in controls in both flexion and extension (p<0.0001), with a significant difference in deformation index (p=0.002). There were no significant differences in absolute perimeter measurement, although

the DI was smaller in patients ($p<0.0001$). Circularity measurements were greater in controls than in patients in both flexion and extension ($p<0.0001$), as was the DI ($p<0.0001$). The aspect of the minimal enclosing rectangle was higher in patients ($p>0.05$).

Index Finger Motion

The cross-sectional area of the median nerve was smaller in controls than in patients ($p<0.0001$) in both flexion and extension. The deformation indices for both the area and the perimeter were significantly different between both groups, with p-values of <0.0001 and 0.0009. The circularity of the median nerve was greater in controls than in patients ($p<0.0001$ in extension and $p=0.0065$ in flexion), showing that the nerve in patients is closer to a perfect circle than in controls. For the aspect ratio of the MER, there was a difference between the groups in flexion ($p=0.0045$), while the deformation index was smaller in patients ($p<0.0001$).

Thumb Motion

In thumb motion, the cross sectional area of the median nerve was smaller in controls than in patients, in both flexion and extension ($p<0.0001$). There was no difference in perimeter, but the deformation index for both area measurements as well as for perimeter were significantly different between the two groups. The median nerve was more circular in patients than in controls in both flexion and extension ($p<0.0001$). For the aspect ratio of the MER, there was only a difference in extension ($p=0.001$) and in DI ($p<0.0001$).

Reliability

For all measurements the intraclass correlation coefficient was excellent with values ranging from 0.84 to 0.98.

DISCUSSION

In this study we have shown that in flexion and extension, regardless of the specific finger motion, the median nerve cross sectional area and deformation of the median nerve are greater in CTS patients than in controls. We believe that these are important observations for several reasons.

The tendons and median nerve move in a three dimensional plane during finger motion.[12,14] Because the carpal tunnel is a closed space, the median nerve cannot move away from the tendons and thus gets compressed causing a change in shape and area. As noted by others, these parameters may be useful as a tool for diagnosing CTS with ultrasound.[2-4,7,9] Our results show that the best parameters seem to be the cross-sectional area and the area deformation index (Table 1 and 2). While circularity measurements were also different in all finger motions, this deformation index was only significantly different in four finger and middle finger motion, so this measure would probably not be useful for clinical purposes. As shown in Table 1 and 2, the results of perimeter and MER measurements are also too inconsistent for clinical use. Other investigators have studied median nerve cross-sectional area in CTS, with reported values ranging from an average cross-sectional area of the median nerve at the distal wrist crease of 7-9 mm^2 in asymptomatic volunteers to 13.7-16.8 mm^2 in CTS patients.[2,7,11,13] Klauser et al. compared the cross-sectional area of the median nerve (CSA) at two different levels. They found an average CSA of 16.8 mm^2 in patients and 9.0 mm^2 at the carpal tunnel level, and 9.5 mm^2 in patients and 8.7 mm^2 in controls at a more proximal level.[7] They also calculated the difference between those two measurements and found a 99% sensitivity and 100% specificity for these measurements. However, absolute value measurements in the carpal tunnel may also be dependent on confounders such as gender and wrist size. We believe that the amount of compression is therefore best shown by a deformation index, as calculated in this study, since it is unaffected by absolute size. Since the measurements for the median nerve area were different both in normal measurements as well as in deformation index, we believe this would be the best potential parameter to distinguish between patients and healthy individuals in supporting a clinical diagnosis of CTS. Sernik et al. showed the median nerve cross-sectional area was increased compared to their control group and they suggest a cut off point of 10 mm^2, but the reliability, specificity and sensitivity of such measures were not rigorously compared to other diagnostic measures, such as electrodiagnosis, clinical findings, or differences between flexion and extension values.[11] Other studies suggest cut-off values of 9-11 mm^2, with high sensitivity and specificity levels.[2,13] Based on our results we would suggest using a cut-off value of 10 mm^2, measuring the area with middle finger motion since we noticed during image acquisition that the third

superficial flexor digitorum tendon is the easiest tendon to recognize compared to the other tendons.

Finally, and most importantly, we believe the measures described here may be useful in noninvasive study of mechanical behavior related to the median nerve in health and disease. A combination of longitudinal and cross sectional data could generate three dimensional images of the carpal tunnel contents; the dynamic aspect imparts a fourth dimension, that of movement over time. Such imaging could be used to investigate, and even monitor, the mechanical behavior of the nerve and tendons within the carpal tunnel, not only for simple motions, as described here, but also for more task-related activities, such as pinching, gripping, or keyboarding. Such investigations may shed further light on activities likely to deform the median nerve.

Our study has some short comings. As shown in Table 1 and 2, differences in healthy volunteers are very small between flexion and extension, and one finding was different from the general trend in results: the perimeter in middle finger motion was higher at flexion than in extension in controls.

Ultrasound is known to have measurement errors due to operator-differences like experience, but also technical differences like the angle of the transducer to the wrist. Even though fixed the transducer in a special holder, motion of the patient may have influenced the results. The angle in which the transducer is placed on the patients' wrist is also important: in case of a smaller angle (than 90 degrees, like ours) the cross section of the median nerve might become bigger, for example. Another cause could be the level of the carpal tunnel at which the measurement is taken: our measurements were taken at the wrist crease level, just proximal to the tunnel. If images were taken more distally, within the tunnel, the median nerve might be more compressed. Also, during finger motion, the tendons move towards the median nerve, thereby compressing it. This happens in both healthy controls and in CTS patients, as shown with this study. It is logical to think that the median nerve might flatten with finger flexion, as the tendons press against the nerve from below. For a given cross section, a circular shape will have a smaller perimeter than an elliptical shape. This means that even in healthy subjects, due to the change in shape, the perimeter might change as well, but this effect might differ between different locations along the course of the nerve.

Secondly, our results are not categorized by severity of CTS. We do believe it would be useful to study the relation between duration of symptoms, severity of the electrophysiological changes and deformation of the median nerve. This would be a useful next step towards using ultrasound parameters for diagnosing CTS in an early stage. There was a statistically significant age difference between our patient and control groups which may have caused bias in our results, since theoretically

the difference in shape may have been caused by a normal aging process rather than disease.

The intra-rater reliability was calculated from five repetitions within each finger motion measurement, all done by one not-blinded investigator within the same session. Ideally, a more true representation of the intra-rater reliability would have been to compare multiple repetitions within more than one session. Also, even though it is known that ultrasound is a highly operator-dependent tool, we did not calculate inter-observer reliability. This remains for future studies.

We conclude that it is possible to investigate the deformation of the median nerve in carpal tunnel syndrome by ultrasonography and that there is more deformation of the median nerve in carpal tunnel syndrome patients during active finger motion. These parameters might be useful in the future as an additional tool for diagnosing or assessing the biomechanics of carpal tunnel syndrome.

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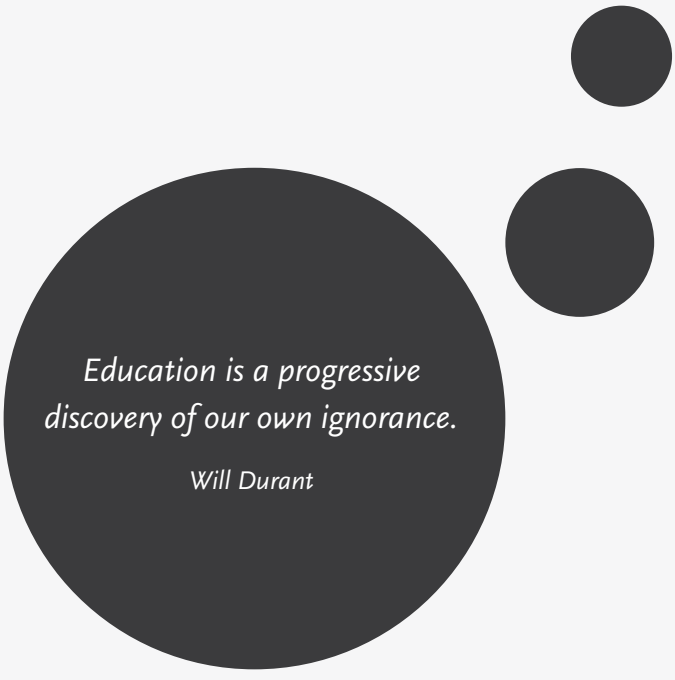
Education is a progressive discovery of our own ignorance.
Will Durant

CHAPTER 5

Transverse Plane Tendon and Median Nerve Motion in the Carpal Tunnel: Ultrasound Comparison of Carpal Tunnel Syndrome Patients and Healthy Volunteers

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Accepted in PLoS ONE

ABSTRACT

Background: The median nerve and flexor tendons are known to translate transversely in the carpal tunnel. The purpose of this study was to investigate these motions in differential finger motion using ultrasound, and to compare them in healthy people and carpal tunnel syndrome patients.

Methods: Transverse ultrasounds clips were taken during fist, index finger, middle finger and thumb flexion in 29 healthy normal subjects and 29 CTS patients. Displacement in palmar-dorsal and radial-ulnar direction was calculated using Analyze software. Additionally, the distance between the median nerve and the tendons was calculated.

Results: We found a changed motion pattern of the median nerve in middle finger, index finger and thumb motion between normal subjects and CTS patients ($p<0.05$). Also, we found a changed motion direction in CTS patients of the FDS III tendon in fist and middle finger motion, and of the FDS II and flexor pollicis longus tendon in index finger and thumb motion, respectively ($p<0.05$). The distance between the median nerve and the FDS II or FPL tendon is significantly greater in patients than in healthy volunteers for index finger and thumb motion, respectively ($p<0.05$).

Conclusion: Our results suggest a changed motion pattern of the median nerve and several tendons in carpal tunnel syndrome patients compared to normal subjects. Such motion patterns may be useful in distinguishing affected from unaffected individuals, and in studies of the pathomechanics of carpal tunnel syndrome.

INTRODUCTION

Carpal tunnel syndrome is a peripheral compression neuropathy for which several potential pathophysiological explanations have been proposed. Some studies focus on fibrosis of the subsynovial connective tissue (SSCT) as a cause [2,4,8], while other studies focus on dynamic causes, such as a changed motion pattern of the median nerve [3,7]. Of course, it is possible that the two may be interrelated, in that the fibrosis may affect the motion. Ettema et al. showed that the gliding characteristics in CTS patients are altered, while Osamura et al. showed that the material properties are changed in patients as well [6,11]. They suggest that these changes may be due to fibrosis of the subsynovial connective tissue and that alterations in the gliding characteristics of the SSCT may affect tendon gliding motion [6].

Even though tendon displacement has been studied before, not much is known yet about the tendon rearrangements within the carpal tunnel with differential finger motion. A pilot study from our institution showed that in index finger and thumb flexion, the motion direction of the median nerve and flexor tendons differs between healthy normal subjects and carpal tunnel syndrome patients, and that it is possible to display these motions with high frequency ultrasound [14]. A change in the biomechanics in the carpal tunnel may be another clue towards identifying the etiology of idiopathic carpal tunnel syndrome, and better insight in the movement of the tendons and the median nerve in the carpal tunnel may assist in designing rehabilitation protocols after surgery.

Ultrasound techniques have been used to examine median nerve and tendon motions in the past [1,3,9]. The median nerve is known to move longitudinally within the carpal tunnel, and studies have shown that both the median nerve and the tendons have greater longitudinal excursion in healthy wrists than in symptomatic wrists [3,7,9]. The median nerve can also slide transversely within the carpal tunnel and responds to these forces by becoming interposed in various positions between the superficial flexor tendons [3,12].

In this study, we hypothesized that the motion direction and the displacement of the median nerve and the flexor tendons during differential finger flexion and extension will be altered in CTS patients compared to healthy controls.

METHODS

Ethics Statement

This research has been approved by the Mayo Clinic Institutional Review Board. We obtained written informed consent from all participants in the study.

Image Acquisition

After acquiring approval from our Institutional Review Board, we recruited 29 healthy volunteers (15 women, 14 men, age range 22-67 with a mean age of 35.5 years) without any history of CTS, and 29 volunteers with idiopathic CTS (18 women, 11 men, mean age 51.1 years with a range of 26-70 years) which was clinically diagnosed and confirmed by electromyography. All but two volunteers had bilateral CTS. CTS patients were excluded if their medical records showed a history of systemic disease associated with a higher incidence of carpal tunnel syndrome, such as thyroid disease, obesity, rheumatoid arthritis, or any trauma or surgery of the lower arm. The preliminary results from some of the normal subjects in our study population have been published before [14]. In this paper however, we describe the results of the total population compared to CTS patients. Transverse images of the carpal tunnel were obtained using a Siemens Sequoia C512 ultrasound machine (Siemens Medical Solutions, Malvern, PA), with a 15L8 linear array transducer set to a 15 MHz acquisition frequency, placed transversely at the wrist crease and perpendicular to the long axes of the forearm. After obtaining a clear image, the transducer was fixed at its position in a custom made fixture. The depth was set to 20 mm, focus was adjusted to the level of the tendon. The frame rate was set to 30 Hz. The participants were lying down with their hand supinated and strapped to a custom made device, with the wrist in neutral position. Participants were asked to flex and extend their middle finger, index finger and thumb independently from full extension to flexion, until the finger tip touched the hand palm. Also, they were asked to flex four fingers at the same time (index, middle, ring, little finger). In the case of single digit motion, the participant was asked to keep the other fingers as much extended as possible. For all four motions, five cycles of were recorded. Images were reviewed using Analyze 8.1 software (Mayo Clinic, Rochester, MN), selecting the initial and final frames of the motion cycle. The outer hypoechogenic rim of the median nerve and the outer hyperechogenic rim of the tendons were outlined for both the full extension and the full flexion positions. Depending on which motion investigated, we choose to outline the FDS II tendon in case of index finger motion, while

in fist and middle finger motion the FDS III tendon and in thumb motion the flexor pollicis longus tendon were measured. Total displacement in both X and Y direction of the tendon and the nerve, the distance between the tendon and the median nerve in flexion and extension, as well as the motion direction of the tendon and the nerve could be calculated, using the centroid of the outlined tendon and nerve (Figure 1). The displacement was defined as the difference in the midpoint coordinates between the extension and flexion position. The intra-rater reliability was calculated from the five cycles that were of each finger motion within each participant. All participants gave written informed consent for this study.

Statistical Analysis

All results were expressed in mean +/- standard deviation (SD), and all statistical analyses were performed by SAS version 9.2 software (SAS institute Inc., Cary, NC). We used SAS procedure MIXED model approach for statistical analyses, since we evaluated flexion and extension in both left and right wrist of all participants. Participants were treated as repeated factor, wrists (left and right) as random effect factor, and fingers (4 fingers, middle finger, index finger and thumb) or motion direction (flexion/extension) as fixed effect factor. An overall p-value of less than 0.05 was considered significant for finger and motion differences.

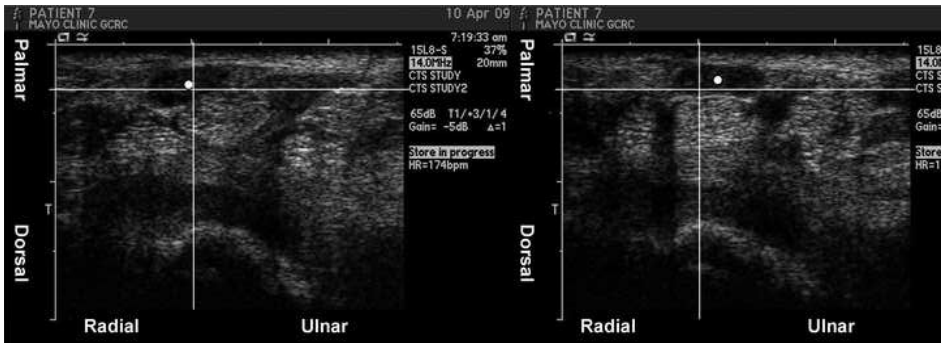

Figure 1 · *Example of median nerve motion direction measurement in middle finger motion in a patient. The centroid of the median nerve (white dot) was taken in extension (left picture) and flexion (right picture) to calculate motion direction. The grid shows the change in position of the median nerve centroid in ulnar-palmar direction.*

RESULTS

The results are summarized in Table 1 and 2, and in Figure 2.

Motion Direction

As shown in Table 1 and Figure 2, for four finger motion, there was no difference in median nerve motion direction between normal subjects and patients. The FDS III tendon however, moved more towards the ulnar and palmar side in patients than in normal subjects (p=0.008 and p=0.0008 respectively). In middle finger motion the median nerve moved more ulnarly in patients than it did in normal subjects (p<0.0001), while the FDS tendon of the middle finger moved more towards the dorsoradial side (p<0.05). In index finger motion both the median nerve and the FDS II tendon moved more ulnarly in patients, while in normal subjects the tendon moved slightly radial (p=0.038 and p=0.027 respectively). In thumb motion the median nerve moved dorsoradial patients, while it moved palmarly and ulnarly in normal subjects (p<0.05). The FPL tendon moved slightly radial and dorsal in patients as well, while it did not in normal subjects.

Table 1 · Motion of the median nerve, flexor digitorum superficialis tendons and the flexor pollicis longus tendon. *For fist and middle finger motion the FDS III tendon was measured, for index finger motion the FDS II tendon and for thumb motion the FPL tendon. Measurements in millimeter (mm). *p<0.05 between controls and patients.*

		Ulnar (+) or Radial (-) Motion of Nerve Mean (SD)	Palmar (+) or Dorsal (-) Motion of Nerve Mean (SD)	Ulnar (+) or Radial (-) Motion of Tendon Mean (SD)	Palmar (+) or Dorsal (-) Motion of Tendon Mean (SD)
Fist Motion	Control	1.40 (1.95)	0.18 (0.39)	0.26 (2.28)	0.15 (0.83)
	Patient	1.63 (2.29)	0.09 (0.39)	1.79 (2.73)*	0.61 (1.01)*
Middle Finger Motion	Control	1.13 (2.13)	0.09 (0.38)	-0.62 (1.23)	-0.07 (0.69)
	Patient	1.90 (1.64)*	0.19 (0.33)	-0.88 (1.41)*	-0.50 (0.82)*
Index Finger Motion	Control	0.49 (1.61)	0.04 (0.35)	-0.03 (2.35)	0.28 (1.00)
	Patient	1.25 (1.43)*	0.13 (0.31)	0.68 (1.55)*	0.36 (1.13)
Thumb Motion	Control	0.17 (0.84)	0.02 (0.23)	0.17 (0.99)	1.30 (0.61)
	Patient	-0.63 (0.76)*	-0.10 (0.21)*	-0.17 (0.70)*	-0.51 (0.55)*

Table 2 · Displacement and distance between median nerve an flexor tendons. *Total displacement (mm) of the median nerve and the different tendons, and distance between median nerve and tendon during finger motion. For fist and middle finger motion the FDS III tendon was measured, for index finger motion the FDS II tendon and for thumb motion the FPL tendon. *p<0.05 between controls and patients.*

		Total Displacement Nerve Mean (SD)	Total Displacement Tendon Mean (SD)	Distance between Nerve and Tendon in Extension Mean (SD)	Distance between Nerve and Tendon in Flexion Mean (SD)
Fist Motion	Control	1.93 (1.48)	1.90 (1.54)	4.34 (1.45)	4.29 (1.58)
	Patient	2.20 (1.80)	2.79 (1.90)*	4.25 (1.15)	4.99 (1.91)*
Middle Finger Motion	Control	2.00 (1.40)	1.29 (0.95)	4.18 (1.45)	3.75 (1.22)
	Patient	2.15 (1.34)	1.61 (1.04)*	4.11 (1.08)	3.66 (0.89)
Index Finger Motion	Control	1.37 (1.02)	2.08 (1.50)	4.38 (1.33)	4.46 (1.33)
	Patient	1.54 (1.09)	1.72 (1.15)	5.33 (1.13)*	5.56 (1.33)*
Thumb Motion	Control	0.59 (0.63)*	0.90 (0.80)	6.58 (2.29)	6.46 (2.30)
	Patient	0.81 (0.61)	0.92 (0.49)	7.82 (1.91)*	7.69 (2.05)*

Transverse Distance

As shown in Table 2, in middle finger and four finger motion, the FDS III tendon's total motion was greater in patients than in normal subjects ($p=0.0042$ and $p<0.0001$ respectively), as well as the median nerve total motion in thumb motion ($p=0.0003$). In both index finger and thumb motion, the distance between the nerve and the FDS II and FPL tendon respectively, was greater in CTS patients in both extension and flexion, as well as in fist flexion.

DISCUSSION

This study suggests that there is a changed motion pattern of the median nerve and the flexor digitorum superficialis tendons in the carpal tunnel in CTS patients compared to normal subjects. Also, there seems to be a greater change in distance between the median nerve and the tendon for index finger and thumb motion in CTS patients in comparison to healthy controls.

Many studies have focused on longitudinal motion patterns of the tendons and median nerve in the carpal tunnel [3,7,9], while only few have focused on transverse

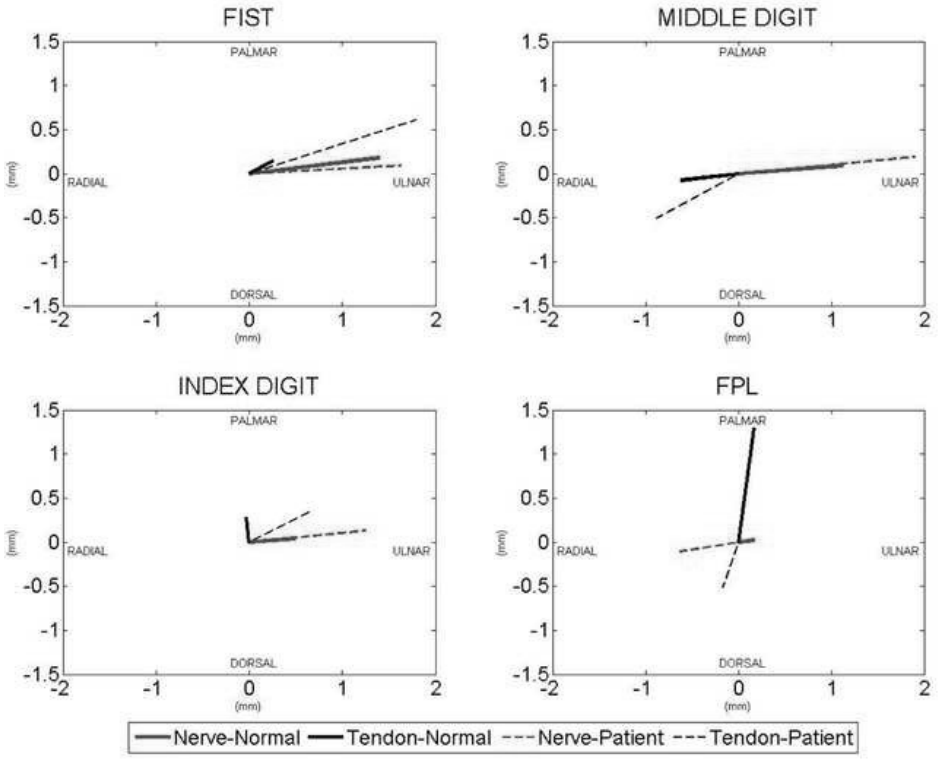

Figure 2 · *Representation of flexor tendon and median nerve motion direction in CTS patients and normal subjects. For fist and middle finger motion the FDS III tendon was measured, for index finger motion the FDS II tendon and for thumb motion the FPL tendon.*

plane motion [10,13,15]. To our knowledge no studies have investigated the motion patterns during differential finger motion or have distinguished the exact motion direction of the nerve and the tendons. Our results show greater motion in patients than in normal subjects, while some other studies show irregular and small transverse displacement [3,13]. Nakamichi and Tachibana studied transverse sliding of the median nerve in asymptomatic human cadavers, using ultrasound [10]. They found a mean transverse sliding of 2.1 mm. Ugbolue et al. found in their study of cadaver hands, with simulated active tendon motion, that the transverse displacement of the index finger and middle finger FDS tendon and the median nerve is relatively small compared to the longitudinal motion [13]. They found values ranging 1.4-5.1 mm transverse displacement in the median nerve and 1.9-7.3 mm for the tendons. These measurements were done in cadavers with no history of CTS. The range of their results is comparable to ours, although they do not specify for each motion in which direction the median nerve or FDS tendon moves specifically. Erel et al. examined

both CTS patients and healthy controls, and found that the flexor tendons move palmarly and the median nerve moves radially from flexion to extension, with radial translation values having a mean of 0.89 mm in their 17 CTS patients and a mean of 1.55 mm in their 19 normal subjects [3]. Our results show mostly an ulnar translation. However, while we and Erel et al studied similar subjects, the methods used were quite different. Our measurements were taken from extension to flexion, while Erel et al. measured from flexion to extension. There were several other differences between our study and that of Erel et al, including software, hardware, and image acquisition rate (Erel et al at 10 frames per second versus ours at a full video rate of 30 frames per second), but the most important difference may be that we measured full fist motion, while Erel et al. held the wrist and interphalangeal joints fixed, and thus only measured the effect of metacarpophalangeal joint motion. This important difference in the motion that was evaluated may well explain the difference in results.

During image acquisition and analysis, we noticed in the ultrasound clips that sometimes the median nerve would move suddenly, to rapidly snap to a new position, while in most other measurements, the median nerve would slide smoothly in the transverse plane. There seemed to be a trend that these particular patients also showed greater displacement results, but we did not do any statistical analysis of this observation because of the small number of patients showing this pattern. This snapping phenomenon could possibly be explained by a hypothesis provided by Ettema et al. previously: in late stages of SSCT fibrosis the tendons sometimes break free from the adherent synovium, and actually increase their motion relative to the synovium [5]. Indeed, Ettema et al noted on direct surgical observation that the patients appeared to fall into two groups: those whose tendons and synovium were more adherent than normal, and those in whom the tendons were completely unattached to the synovium. They hypothesized that the latter group represented an end stage situation. Both groups of patients could be distinguished from normal hands (cadavers in their study), where the tendon and synovial motion had intermediate values. This may explain the higher displacement results in our CTS patients. It remains hard to determine which occurs first: fibrosis which might cause a changed motion pattern and then CTS, or a different motion pattern which makes a person prone to develop fibrosis and possibly CTS.

The strength of this study is that we describe, for the first time, the specific motion direction of the median nerve and the different tendons in the carpal tunnel during differential finger motion. We also showed that it is possible to investigate these motions with ultrasound, thus, this method and our results may help to understand carpal tunnel biomechanics. Knowing the changes in biomechanics within the carpal tunnel may aid in understanding the pathophysiological process causing compression neuropathies such as carpal tunnel syndrome. In a more clinical setting, better

knowledge of the median nerve and tendon motion in the carpal tunnel may also be helpful in identifying patients with motion patterns similar to CTS patients, who do not have neurological symptoms; it might be useful to follow such patients to determine if neurological symptoms develop in the future, or if the motion patterns can be affected by rehabilitation exercises.

One of the weaknesses of our method is that ultrasound is known for great operator dependency and the variability in our results could be caused by this, even though all image acquisition was done by the same investigator. Because all measurements were done by the same investigator, we were not able to measure interobserver reliability. Second, there is a difference in the mean age between the patient and the control group, which may have caused bias in our results. However, CTS is known to be more frequent in women and less common in young people, a trend that is represented in our patient group. It is possible though, that the higher average age in the patient group has caused greater differences in measurements, which could be due to a normal aging process and not so much to the development of CTS. Third, it would be interesting to see if there is any correlation between the displacement of the nerve and the tendons and the severity of electrophysiological studies, this study did not correlate our results to severity of electrophysiological studies. Despite our study not having enough power, preliminary analysis seems to show a trend that the more severe the EMG results are, the lesser the median nerve moves. This would correspond with earlier findings and also with intra-operative observations. Therefore, for future studies it would be interesting to know if there is any correlation between electrophysiological severity and median nerve motion in the carpal tunnel. We did our measurements with the wrist in neutral position. Yoshii et al showed in a cadaver study that median nerve and tendon motion decrease with wrist flexion. Since they looked at longitudinal motion, it would be interesting to see if wrist position also affects transverse motion of the structures within the carpal tunnel [16].

In conclusion, our results suggest that with index finger and thumb motion, there is more distance between the nerve and the tendon in CTS patients than in normal subjects. This may aid in understanding the biomechanics within the carpal tunnel and further research needs to elucidate if this method may be useful to assess pathological changes within the carpal tunnel.

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PART III

Longitudinal Motion of the Median Nerve and Subsynovial Connective Tissue


Perseverance is not a long race; it is many short races one after the other.
Walter Elliot

CHAPTER 6

Speckle Tracking Ultrasound Assessment of Longitudinal Motion of the Flexor Tendon and Subsynovial Tissue in Carpal Tunnel Syndrome

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Accepted in Journal of Ultrasound in Medicine

ABSTRACT

Purpose: The aim of this study was to image both tendon and subsynovial connective tissue (SSCT) movement in patients with carpal tunnel syndrome (CTS) and normal controls, using ultrasound with speckle tracking. To estimate accuracy of this tracking method, we used in vivo measurements during surgery to validate the motion estimated with ultrasound.

Methods: We recruited 22 healthy volunteers and 18 patients with CTS. Longitudinal ultrasonograms of the middle finger flexor digitorum superficialis (FDS) tendon and the SSCT were obtained during finger flexion and extension. The images were analyzed with Syngo VVI software, using a speckle tracking algorithm. The ratio of the SSCT velocity to tendon velocity was calculated as the maximum velocity ratio (MVR) and the shear index (SI), the ratio of tendon to SSCT motion, was calculated. For validation we recorded FDS tendon motion during open carpal tunnel release.

Results: The SI was higher in patients than in controls ($p<0.05$), while the MVR in extension was smaller for patients than for controls ($p<0.05$). We found good intra-class correlations coefficients for SI and MVR measurements ($ICC>0.80$) between speckle tracking and in vivo measurements. Bland Altman analyses showed that all measurements remained within the limits of agreement.

Conclusion: Speckle tracking is a potentially useful method to assess the biomechanics within the carpal tunnel, and to distinguish between healthy individuals and patients with CTS. This method however, needs to be further developed for clinical use, with the SI and MVR as possible differentiating parameters between CTS patients and healthy subjects.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve at the wrist level, of which the exact etiology remains unknown. The most commonly reported pathological finding is fibrosis of the subsynovial connective tissue (SSCT), the lining around the tendons within the carpal tunnel[3,5]. Ettema et al. and Osamura et al. showed that the mechanical properties of the SSCT and the motion mechanics in the carpal tunnel are altered in patients with CTS, and suggested that this may be a consequence of the fibrotic changes of the SSCT, causing the synovium to be more tightly tethered to the tendon in patients than in healthy people[6,7,13]. This alteration in SSCT mechanics could predispose to a vicious cycle of shearing injury to the SSCT[20,21].

The diagnosis of carpal tunnel syndrome is mostly clinically, and is usually confirmed with nerve conduction studies. The use of ultrasonography as a new method for diagnosing CTS has been extensively studied previously. However, most research has focused on the use of static cross-sectional imaging of the carpal tunnel, including parameters such as the cross-sectional area and shape of the median nerve, and bowing of the flexor retinaculum[10,11,15-17].

Assessment of the longitudinal motion of the median nerve and tendons within the carpal tunnel during finger motion has been studied as well, using tissue Doppler imaging[9]. Tissue Doppler imaging has one big disadvantage, which is its angle dependency. Recently, a study showed that speckle tracking may be a useful method to evaluate the motions of the tendons and SSCT in the carpal tunnel, showing a better correlation with joint angle measurements than Doppler measurements did[19]. Speckle tracking is a relatively new method, in which speckles in the ultrasound image are tracked from frame to frame, independent of the angle. This method has been used before to measure median nerve excursion in CTS[4]. Yoshii et al. were the first to assess the SSCT using ultrasound, and because of the possible mechanical change in motion of both the tendons and the SSCT in CTS patients, it may be clinically relevant to be able to distinguish both.

The aim of this study was to image both tendons and SSCT movement in patients with carpal tunnel syndrome and compare their results with normal controls, using speckle tracking. This non-invasive evaluation of the tendon and SSCT motion may be useful to better understand biomechanics within the carpal tunnel, and could be a potential diagnostic tool for carpal tunnel syndrome in the future. To estimate the ability of this speckle tracking method to accurately measure tendon and SSCT excursion, we used direct measurements in the carpal tunnel during surgery to validate the motions estimated from ultrasonographic measurement.

METHODS

Ultrasound Measurements

After getting approval from our Institutional Review Board, we recruited 22 healthy volunteers (twelve men, ten women; mean age 35.1 years, ranging from 27-67 years) and 18 patients (five men, thirteen women; mean age 52.1 years, with a range of 34-70 years) with idiopathic carpal tunnel syndrome diagnosed by clinical symptoms and electromyography. This was a sample of convenience; we did not attempt to match age and gender in subjects and controls. Patients were excluded if they had a history of any condition predisposing to CTS, such as arthritis, diabetes mellitus or trauma to the lower arm. After receiving written consent from the participants, longitudinal ultrasonograms of the middle finger flexor digitorum superficialis tendon and the SSCT were obtained by applying the transducer longitudinally from the hook of the hamate level (mid-tunnel) to the wrist crease level (proximal tunnel). We used a 15L8 linear array transducer of a Siemens Sequoia C512 ultrasound machine (Siemens Medical Solutions, Malvern, PA) set to a 15MHz acquisition frequency. The depth was set to 20mm, and the focus was adjusted to the level of the tendon. The frame rate was set to 30Hz. Proper transducer positioning was assured by identifying specific anatomical structures and detecting the FDSIII tendon while flexing and extending the middle finger. Then, more palmarly, the surrounding soft tissue and the flexor retinaculum were identified as nonmoving structures. Tendons are easily recognizable because of their echogenic fibrillar structure consisting of parallel lines. The median nerve was recognized as a structure with multiple hypoechoic areas. In all healthy volunteers, measurements were taken bilaterally. In patients, measurements were taken from the affected arm(s). Participants were asked to flex and extend all fingers (index, middle, ring, little) simultaneously while holding a 1.5 inch diameter cylinder, at a pace of 0.8Hz for each direction of motion. Before data collection, the participants practiced the motion with the examiner. Three motion cycles were recorded using the cine loop function, reducing the speed to 37% of real time motion to maximize the recording frame rate.

The images were analyzed with Syngo VVI software (Siemens Medical Solutions USA, Inc., PA, USA). After uploading the images in the software, the period selector mode was used to set the timing bars to the beginning and end of one motion. Three markers were placed on the FDS tendon tissue speckles, with a distance between the two furthest markers of approximately one millimeter. The markers were placed perpendicular to the tendon motion direction, in the area between the distal radius and the carpal bones which were typically seen on the ultrasound. The SSCT

was defined as the thin echogenic layer at the border of the tendon. Again, the three markers were placed, this time one at each border of the echogenic layer and one in between (Figure 1). Then the software's generic curve mode was selected to perform the analysis, providing the velocity and strain time series data. We then measured the maximum velocity for both flexion and extension positions, and calculated the excursion of both the tendon and the SSCT based on the area under the velocity/time series data.

The analysis of the first cycle was used as a preconditioning analysis. The averaged maximum velocities and excursion for the second and third cycles of both tendon and SSCT were used for further analysis. Two ratios were created, the first being the maximum velocity ratio (MVR), defined as maximum velocity of the SSCT relative to the maximum velocity of the tendon, and the second being the shear index (SI), calculated, using the following equation:

[(Tendon excursion – SSCT excursion) / Tendon excursion] x 100 (%)

This index is an indication of the shearing motion between the two structures.

Validation Measurements

The second part of our study was the in vivo validation of this method, using intra-operative videos of tendon and SSCT motion during flexion and extension. A study

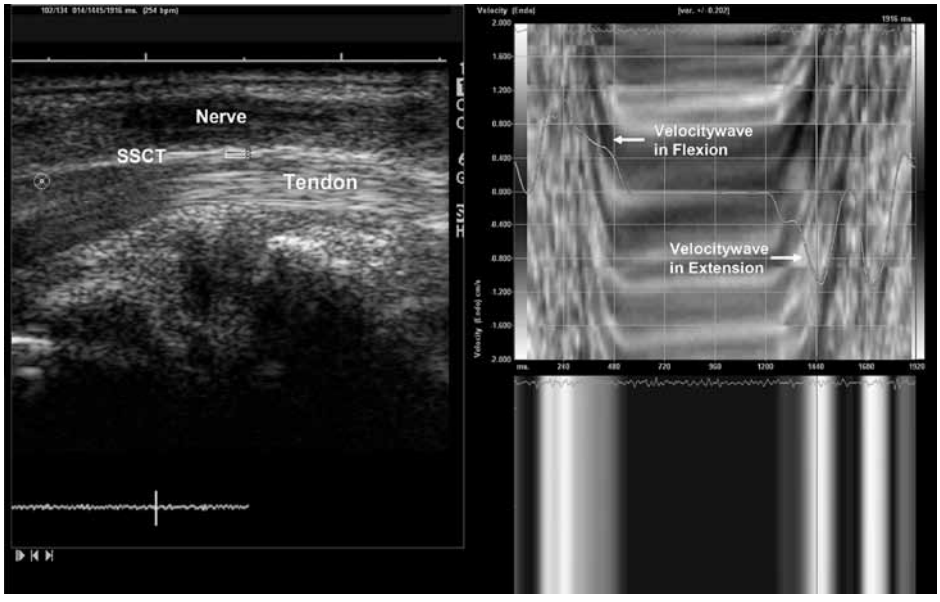

Figure 1 · *Example of SSCT velocity measurements using speckle tracking analyzed with Syngo VVI software*

with a similar intra-operative set-up has been done by Ettema et al[7], who validated this method and reported an intraclass correlation coefficient of 0.88. Based on their study, we calculated that with a sample size of six, we would have 80% power to detect a difference of 1.92mm, which we consider to be potentially clinically significant.

Four patients of the group studied with ultrasound underwent open carpal tunnel release (CTR), two of whom had bilateral CTR and the other two unilateral CTR. After getting written consent, we obtained the intra-operative videos as follows: surgery was performed under local anesthesia without sedation, since that would affect cooperation of the patient. An open surgical incision extending from 1cm proximal to the wrist crease to the mid-palm was made. First the flexor retinaculum was transected, and then the carpal tunnel was exposed by a self-retaining Weitlander retractor. A small window of approximately 3mm diameter was made in the visceral synovium and SSCT to expose the middle finger FDS tendon. With the wrist in the neutral position and the fingers passively extended to 0°, a mark was made on the middle finger FDS tendon surface with a surgical marker. Then, the visceral synovium surface was marked at a level 15mm proximal to the tendon mark. A third mark was made on the cut edge of the flexor retinaculum to serve as a reference point (Figure 2). The patient was asked to flex and extend the four fingers (index, middle, ring, little) with holding 1.5 inch diameter cylinder, while a video camera (StrykeCam In-light Surgical Camera, Stryker Communications, Flower Mound, TX) recorded the motion. A millimeter ruler was included in the camera field, so that the data measured with the camera could be converted into a distance figure. The camera was set perpendicular to the operating table and the wrist, centering the tendons in the middle of the camera field. To avoid measurement errors we did not zoom with the camera. After the motion was recorded, the operation proceeded as normally.

The intra-operation data were digitized to determine the motion characteristics of the three marks using Analyze 8.1 Software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). All X and Y coordinate data were converted from pixels to millimeters using the scale factor conversion obtained from the imaged ruler. The coordinates for the tendon and SSCT were normalized relative to the fixed reference point to correct for any translational motion of the image during data collection. Proximal and distal motions were defined as positive and negative motions, respectively. The coordinates at the initial positions for each marker were defined as zero excursion. For the tendon and SSCT, the distances along the motion direction of the tendon excursion were calculated. Based on these data, we calculated the SI using the formula noted above.

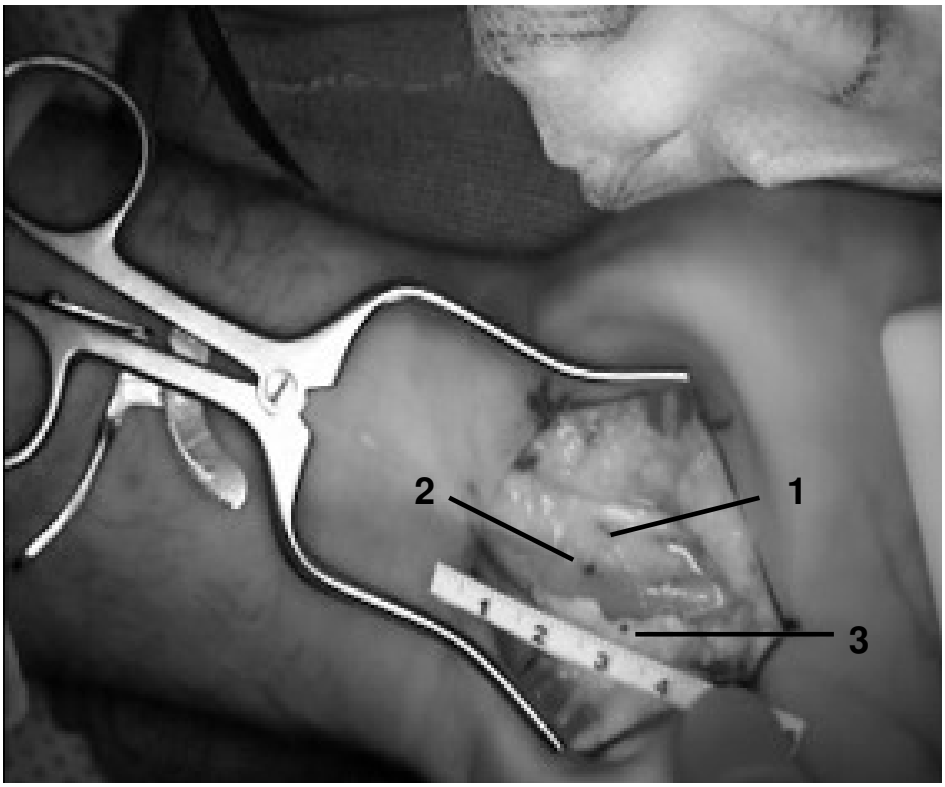

Figure 2 · *Intra-operative setting with surgical markers on 1) FDS tendon, 2) synovium, and 3) reference maker on retinaculum.*

Data Analysis

A repeated measures model was used to compare the differences in shear index and maximum velocity ratio between CTS patients and healthy controls. Controls and patients, as well as left and right hands were fixed effects. For the maximum velocity ratio, the differences in same direction motion (flexion or extension) were compared. For the ultrasound measurements, we recorded 3 motion cycles of each hand in every patient. The first recording was used as preconditioning, while the last two were used for analysis and for intrarater reliability calculation.

The interclass correlation test was used to evaluate the correlation between the tendon excursion from the speckle tracking methods and the intra-operative measurement of the same patient. We used the Bland-Altman analysis to show the agreement between the two measurements. The results are expressed as mean ± standard deviation (SD). P-values of less than 0.05 were considered statistically significant.

RESULTS

The results of the ultrasound measurements and intraclass correlation are summarized in Figure 3. In the excursion of the tendon or subsynovial connective tissue we did not find any differences between patients and controls. The shear index however, was on average 47.8, versus 36.3 in controls ($p<0.05$). The maximum velocity ratio in extension was smaller for patients than for controls (0.66 and 0.54 respectively, $p<0.05$). There was no difference in

the velocity ratio in flexion. The intraclass correlations for intra-rater reliability were variable, ranging from 0.36 for MVR in flexion to 0.83 for SSCT total excursion measurements.

For the comparison between speckle tracking and in vivo measurements, we found good intraclass correlation coefficients for shear index and MVR measurements (ICC 0.86 and 0.83 respectively). The intraclass correlations for tendon and SSCT excursion measurements were moderate (ICC 0.44 and 0.67 respectively). The Bland Altman analyses (Figure 4) showed a mean difference of -0.30mm with a standard deviation (SD) of 0.57mm for tendon excursion. For SSCT excursion the mean difference was -0.02mm (SD 0.48mm), for shear index -4.62 (SD 29.79) and for maximum velocity ratio the mean difference was -0.13 (SD 0.32). All results remained within the limits of agreement.

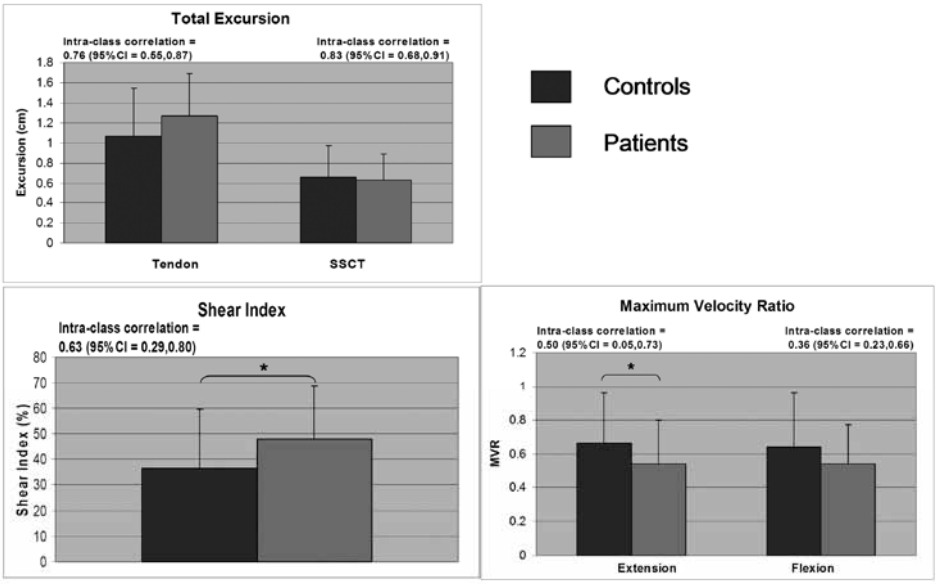

Figure 3 · *Summary of tendon and SSCT velocity and excursion measurements with speckle tracking in controls and CTS patients (* p<0.01).*

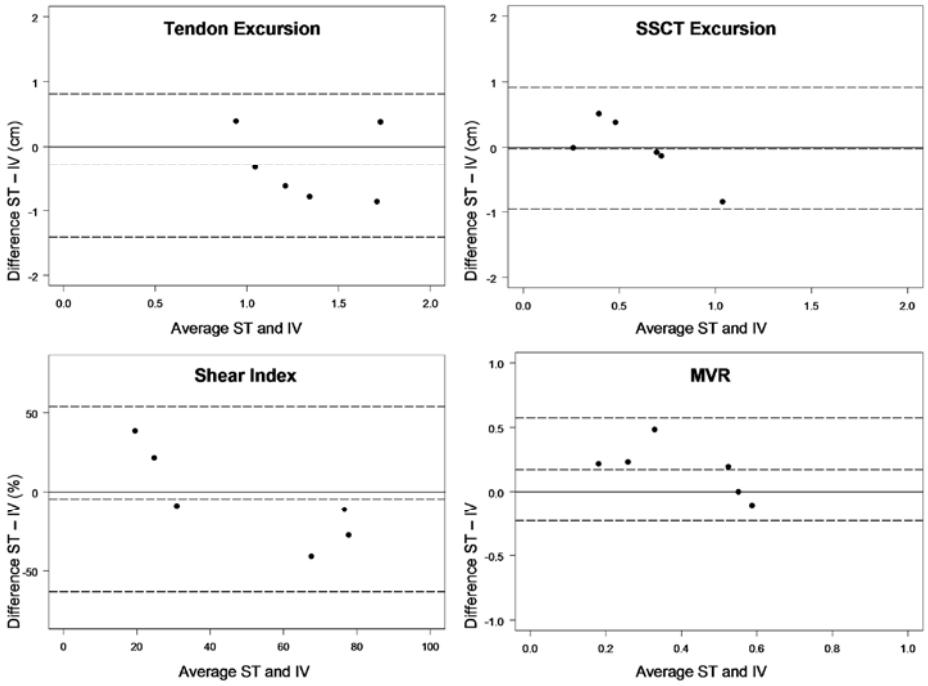

Figure 4 · *Bland-Altman comparative analysis of mean and difference between speckle tracking (ST) and in vivo (IV) measurements.*

DISCUSSION

With this study, we showed that speckle tracking is a potential method to assess the (pathological) biomechanics of tendons and subsynovial connective tissue within the carpal tunnel, as well as to distinguish between healthy controls and patients with carpal tunnel syndrome. To our knowledge, this is also the first method described to dynamically assess subsynovial connective tissue motion within the carpal tunnel.

Speckle tracking, a novel technique to track acoustic signals (speckles) from frame to frame throughout a motion, has been primarily used for analyzing cardiac function [8,14]. Korstanje et al. compared speckle tracking measurements of tendon motion in porcine forelegs and human cadavers to inserted markers, as well as in vivo measurements taking an anatomical landmark as a reference[12]. They found small tracking error rates for all measurements, as well as for their intra-rater reliability. There is however, a technical difference between their study and the method presented in this study. With their method, a stationary region of interest is manually selected in the tendon after which the algorithm automatically distributes a selected number of kernels. Then frame-to-frame displacement is estimated using multiple

overlapping kernels. In our study, we manually placed three markers which were followed through the motion; the region of interest is therefore not fixed. A stationary region of interest assumes limited deformation, which is applicable to tendons but not to SSCT, a much more elastic structure[5,13]. Therefore, the advantage of our method is that it allows one to measure both tendon and SSCT motion resulting in shear measurements which can be useful in evaluating patients.

An important problem we observed during image analysis was out-of-plane motion of the tendon or SSCT which caused the speckles to sometimes lose track of the motion direction of both. This is probably due to the fact that both structures have three dimensional motion directions, while speckle tracking is only able to measure two dimensions. In the future, the algorithm and image acquisition method need to be improved, taking into account the motions direction as well as the material properties of the different structures.

Clinical Implications

Our results show a lower maximum velocity ratio in patients and a higher shear index in patients, which is most probably caused by altered SSCT movement. Studies have shown that rapid, differential finger motion causes higher shear strain to the SSCT leading to shear injury[18,20,21]. Fibrotic subsynovial connective tissue, whether from injury or disease, can cause a delay in initiation of SSCT motion or a decrease in its velocity compared to the tendon, causing a lower velocity ratio as well as less motion of the SSCT and a higher shear between these two structures. We believe these are important results, first because they suggest a role for ultrasound in the noninvasive assessment of carpal tunnel kinematics in healthy and diseased individuals, and second because such a tool may be helpful in further refining prognosis. For example, the degree of impairment of longitudinal motion might correlate with the likelihood of improvement with nonoperative therapy, or with the likelihood of persistent symptoms following surgery, both of which are currently unpredictable. Dynamically measuring tendon motion within the carpal tunnel has been done before, using color Doppler imaging[1,2]. However, Yoshii et al. showed in their recent study that speckle tracking shows a better correlation with tendon excursion than Doppler imaging did [19]. With this study we added to these results that the MVR and SI are not only well measurable with speckle tracking, but that there is a significant difference in these parameters between controls and CTS patients, making them a possible discriminating parameter. Fibrosis of the subsynovial connective tissue may be related to CTS severity as well, in which case the shear index and maximum velocity ratio may be helpful adjuncts to clinical assessment, for example in patients with clinically diagnosed CTS in whom

electrodiagnostic tests are normal, a possibility we plan to assess in the future. However, this study was meant as a first step towards using SSCT and tendon motion as a tool to assess carpal tunnel kinematics, and now that we have shown that these measurements are possible and that there is a difference between controls and patients, it remains for future studies to focus on reliability, improved precision, reproducibility between examiners, and possible clinical applications. If this method would be further developed for clinical use, this might be the first non-invasive, quantitative ultrasound method to aid in the diagnosis of carpal tunnel syndrome.

Technical Considerations

Our results show that, overall, there is variability in intra-observer reliability for the ultrasound measurements. This might be due to several factors. A limitation of all ultrasound assessments is the operator-dependency, specifically with regards to transducer placement and manual placement of the markers during image analysis. We noticed that this technique requires considerable practice on the part of the examiner, especially when it comes to placing the transducer in alignment with the motion direction of the tendon, and getting both tendon and SSCT visualized throughout the whole motion. However, our analyses were all performed by the same examiner, and after the transducer was placed in the correct position, it was fixed into a custom mounting to keep it in place. This way, the investigator was able to focus on image acquisition. As for the placement of the markers we tried to minimize variation in placement by determining that the three markers should be on the structure studied and placed about a millimeter apart from each other. This may have helped in reducing differences in analysis. Even though ultrasound is known for being an operator-dependent process, we were not able to measure inter-rater reliability because of practical reasons. Also, the analyses are very time-consuming and for the future, it would be useful to modify the software to make it more readily available for everyday clinical use. We are planning a study to search for the optimal settings in both software and the ultrasound hardware in an in vitro validation model.

Limitations

This study had several limitations. First of all, we reported data from a small number of patients. Also, there was a difference in age and gender between the both groups. Carpal tunnel syndrome is more frequent in women, with a peak incidence at ages 45-54. This trend is represented in our patient group. We did not specifically attempt,

though, to age and gender match the control group; as noted above, this was a sample of convenience. Since it is possible that SSCT thickening increases normally with age, it is also possible that the higher average age in the patient group has caused greater differences in measurements. This difference could then be due in part to the normal aging process and not entirely due to the development of carpal tunnel syndrome. Because carpal tunnel syndrome is usually bilateral, we chose not to consider the less affected or unaffected contralateral hand of those patients who were not diagnosed with bilateral carpal tunnel syndrome as another variant of normal. In the future, it would be helpful to do a case controlled study to assess the possibility of aging resulting in SSCT thickening outside the context of CTS.

In addition, as noted before, we found that the settings used in this study are not yet optimal. By optimizing the settings for better sensitivity of the velocity tracking and the excursion measurements, we hope to make a step forward towards developing a non-invasive method to assess the biomechanics and possibly to aid in the evaluation of early stage CTS, in which the SSCT is structurally abnormal but the nerve is not. Finally, our measurements are not fully refined, and the failure to show any differences between the groups for certain parameters may simply have been because the method is currently too imprecise. We therefore need to compare this method with other standardized methods in the future, including the need to assess inter and intra examiner reliability.

Conclusions

In conclusion this study shows that speckle tracking is a new, non-invasive method to measure tendon and SSCT mechanics in the human carpal tunnel, with enough accuracy in maximum velocity ratio and shear index measurements to distinguish between healthy controls and carpal tunnel syndrome patients. This method may have clinical utility in the future, and is worthy of further study.

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What saves a man is to take a step.
Then another step.
C.S. Lewis

CHAPTER 7

Phantom model validation for tendon motion speckle tracking

Margriet H.M. van Doesburg, Taylor J. Helmus, Aebele B. Mink van der Molen, Andrew Thoreson, Dirk Larson, Kai-Nan An, Peter C. Amadio

Submitted

ABSTRACT

Background: Speckle tracking ultrasonography is a relatively new technique in which the acoustic speckle pattern generated by the reflected ultrasound beam is tracked frame-by-frame. The aim of this study was to investigate the influence of different angles of tendon and subsynovial connective tissue movement on speckle tracking velocity measurement accuracy in a phantom model in order to validate this method for use in vivo, for example in the assessment of carpal tunnel pathology.

Methods: Motion of markers in a phantom and a human tendon placed in a tissue-mimicking phantom gel was created using a motor driven rocker mechanism and were measured in three different orientation angles: parallel to the transducer and at an angle of 10° relative to both the horizontal and vertical axes. Velocities of model materials were measured using speckle tracking methods and compared to laser sensor measurements of the actuator. Bland and Altman 95% limits of agreement were used for statistical comparison, as well as the intra-class correlation coefficient for variability measurement.

Results: Bland Altman analyses showed good agreement for all conditions. The ICC was moderate to excellent for most measurements in acceleration and deceleration with values ranging from 0.572 to 0.977.

Conclusion: Speckle tracking is a suitable method for measuring both tendon and SSCT motion in the same image and may provide a way to assess the presence or risk of SSCT shear injury within the carpal tunnel, and lead to a better understanding of the role of SSCT shear in carpal tunnel syndrome pathogenesis.

INTRODUCTION

Ultrasound imaging can be used to observe tendon motion for diagnosis of upper extremity disease, for example carpal tunnel syndrome (CTS). Velocity during controlled motion of the different structures in the carpal tunnel has been measured before, mostly using color Doppler imaging [2,4,10]. Disadvantages of this method include dependency on angle between the probe and the resulting velocity and the operator influence on results. Quantitative methods to determine tendon and synovial tissue velocity and function are desired to strengthen the evidence of normal and pathological biomechanics in upper extremity diseases. Speckle tracking ultrasonography is a relatively new technique in which the acoustic speckle pattern generated by the reflected ultrasound beam is tracked frame-by-frame, and displays regional movement from echo images in terms of velocity and direction. It was first introduced as an angle-independent method of measuring strain in myocardial muscle function [8], while more recently Yoshii et al were the first to introduce this method for velocity measurements of tendon and the synovial lining of the tendons in the carpal tunnel, more specifically known as the subsynovial connective tissue (SSCT) [13,14]. This novel image analysis approach could identify and track motion of tendons, nerves and also - considering its relevance to the diagnosis of carpal tunnel syndrome - the subsynovial connective tissue and could assess function of these tissues noninvasively. The advantage of this technique over Doppler imaging techniques is that in Doppler-based techniques, only one component of the velocity vector is estimated, which leads to an underestimation of the actual velocity. However, results of previous studies analyzing motion of tendons and synovium in the carpal tunnel using speckle tracking were highly variable. Also, the speckle tracking algorithm may be sensitive to out-of-plane motion. Therefore, the aim of this study was to investigate the influence of different angles of tendon and SSCT movement on speckle tracking velocity measurement accuracy in a phantom model in order to validate this method for use in vivo. Our hypothesis was that the velocity of objects evaluated with the speckle tracking algorithm will be dependent on the orientation of motion relative to the ultrasound transducer.

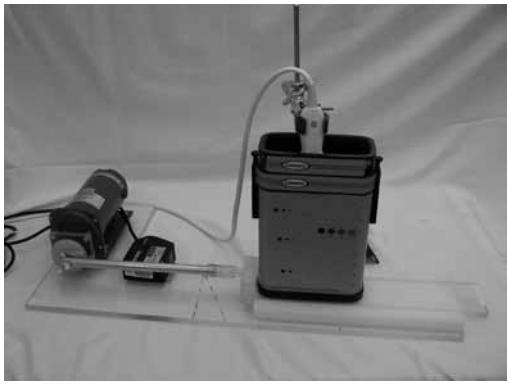
MATERIALS AND METHODS

Two different models were subjected to different orientations of motion: 1) a tissue-mimicking gel phantom with embedded ultrasound-detectable markers made of nylon fibers (Precision Multi-Purpose Phantom Gammex 403GS LE, Gammex Inc., Middleton, WI), and 2) a human cadaver tendon flexor digitorum superficialis (FDS)

tendon –harvested along with some surrounding SSCT – held in place by sutures at each end and embedded in PVA gel (Figure 1). A model was placed onto a plastic slide which was driven by a variable speed motor driven rocker mechanism set at a frequency of approximately 0.5 cycles/s, resulting in reciprocating linear motion. A laser displacement sensor (LK-081, Keyence Corp., Osaka, Japan) was mounted to the base to measure the displacement of the slide. Displacement data was filtered with a 1st order Butterworth low-pass filter with a cut-off frequency of 12.5 Hz. A five-point central difference algorithm was used to calculate slide velocity.

An Acuson Sequoia C512 ultrasound machine with a 15L8 transducer (Siemens Medical Solutions, Malvern, PA) was held in a fixture and placed on the surface of the model gel, after application of acoustic conductive medium (Figure 1). Depth, focus, gain, dynamic range and post processing settings were kept consistent throughout testing. Special attention was paid to maximizing the exported frame rate by slowing down the image to 37% of the real time velocity.

Model motion was oriented in three different directions relative to the transducer: parallel to the transducer (hereafter referred to as "parallel" motion), inclined at 10° in the vertical plane (hereafter referred to as "10° vertical" motion) and at 10° in the horizontal plane relative to the transducer plane (hereafter referred to as "10° horizontal" motion) (Figure 2). To create parallel motion, the plastic slide oscillated along the ground in the transducer imaging plane. To create 10° vertical motion the entire base of the rocker mechanism was inclined using a wedge block to elevate the far edge high enough to achieve the correct 10° angle. Twenty motion cycles for each motion type and for each of the two models were recorded using the cine loop function, reducing the speed to 37% of real time motion to maximize the recording frame rate to 30 frames/s. Twenty consecutive motion cycles of the slide were col-



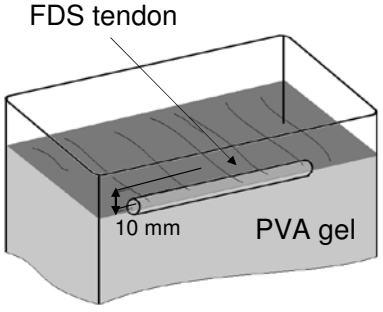


Figure 1 • *Experimental set-up with commercial ultrasound phantom, motor and laser (left), and graphic of tendon-SSCT phantom for speckle tracking verification (right)*

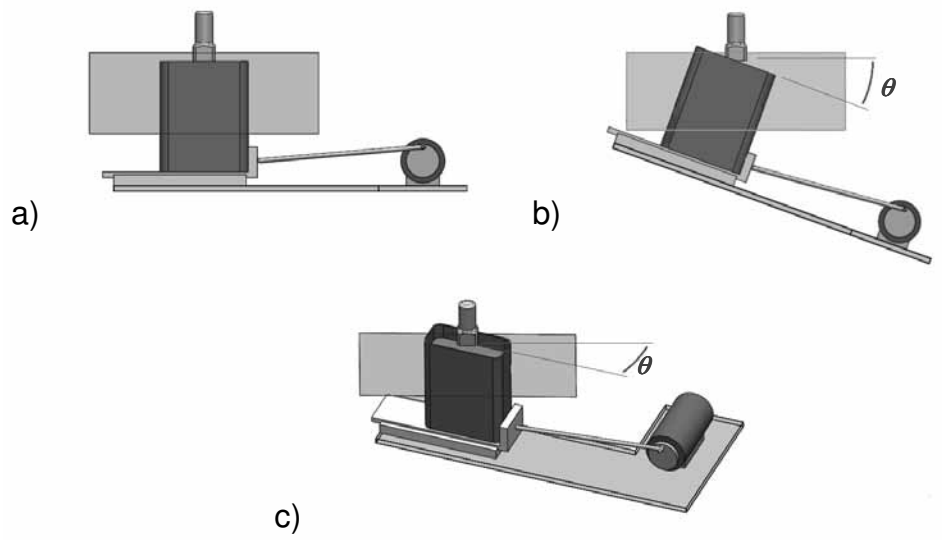


Figure 2 · *Model motion relative to the ultrasound transducer for a) parallel motion b) 10° vertical motion c) 10° horizontal motion*

lected from laser displacement sensor data for each trial at a sample rate of 200 Hz. Since the motion of the slide is periodic, a middle cycle was selected to represent the actual motion of the slide and models mounted on it.

The images were analyzed with Syngo VVI software (Siemens Medical Solutions USA, Inc., PA, USA), tracking the phantom marker, phantom gel, tendon and the SSCT separately. After uploading the images in the software, the period selector mode was used to set the timing bars to the beginning and end of one motion. Three markers were placed on the marker, gel, FDS tendon tissue speckles or the SSCT, with a distance between the two furthest markers of approximately one millimeter on the screen. The markers were placed perpendicular to the motion direction. The software's generic curve mode was selected to perform the analysis, providing the velocity and strain time series data (Figure 3). A custom MATLAB program (MathWorks, Natick, MA) aligned the representative mechanical slide velocity curve to each speckle tracking velocity curve with respect to time. Four different velocity values along the curve were compared, defined by the following events: 1) maximum speckle tracking velocity (positive direction), 2) a point of deceleration (1/8 of the period past the maximum positive velocity), 3) a point of acceleration (3/8 of the period past the maximum positive velocity), 4) maximum speckle tracking velocity (negative direction) (Figure 4).

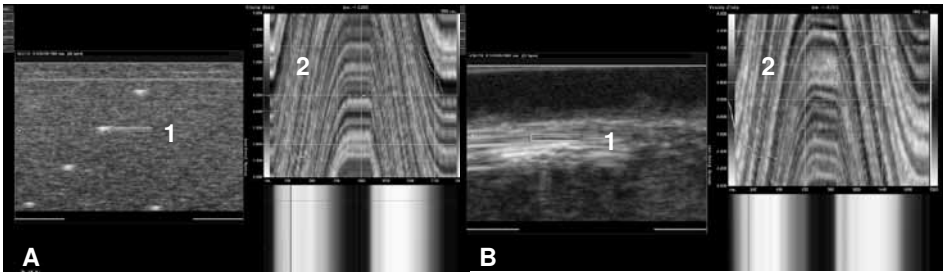


Figure 3 · *Example of VVI results. A. Measurements in parallel angle with markers placed on pin (1), velocity wave of pin (2). B. Measurements in parallel angle with markers placed in tendon (1), velocity wave of tendon (2)*

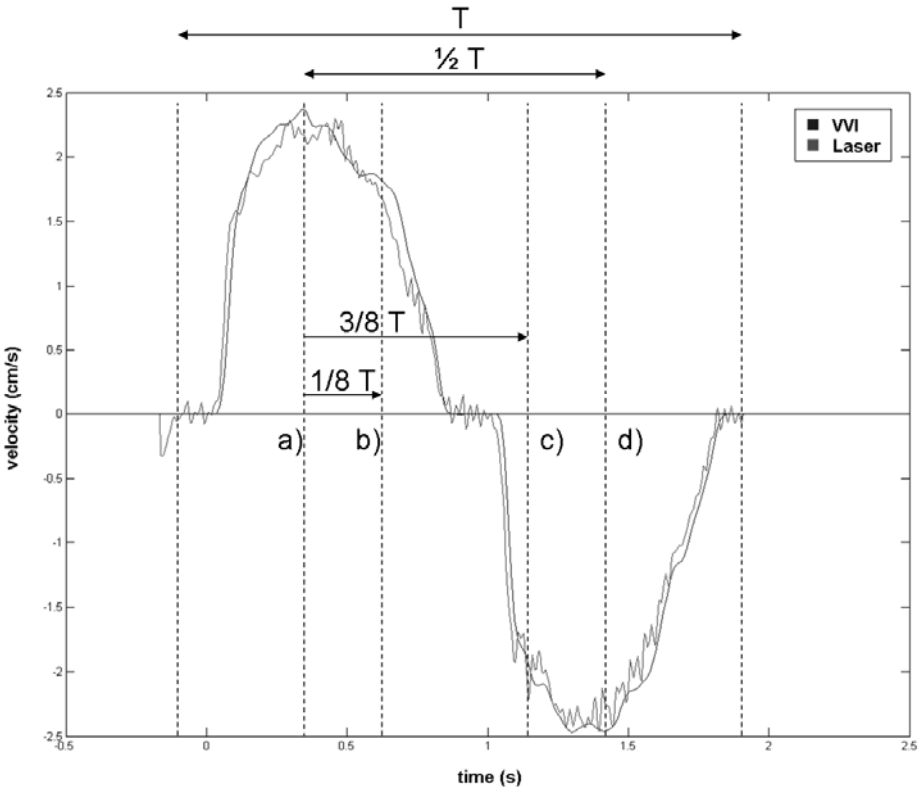


Figure 4 · *Matched velocity curves generated from laser displacement sensor data and speckle tracking. Velocities at four time points were compared a) maximum velocity (positive), b) deceleration, c) acceleration, d) maximum velocity (negative)*

Statistical Analysis

We evaluated the agreement between the laser velocity measurements and the speckle tracking velocity measurements, using the Bland and Altman 95% limits of agreement. For the Bland and Altman plots, the difference between the results of the laser and speckle tracking measurements were plotted against the mean of the two assessments, describing the distribution and variance. We also calculated the intra-class correlation coefficient (ICC) for all conditions, to test the reliability of the speckle tracking method. The ICC was based on a two-way random effects model, and is the ICC(2,1) of Shrout and Fleiss [11]. We considered an ICC of 0.5-0.6 as moderate agreement, 0.7-0.8 as good agreement and above 0.8 as excellent agreement.

RESULTS

Bland and Altman analyses showed good agreement for all conditions. Some example Bland and Altman plots are shown in Figure 5. The ICC's are shown in Table 1 and were moderate for deceleration measurements in parallel motion for tendon and SSCT. In acceleration ICC's were good with values above 0.7 for parallel motion SSCT measurements, 10° horizontal motion tendon measurements and 10° vertical motion gel and SSCT measurements. In deceleration the ICC was good for 10° vertical motion tendon measurements. ICC's were excellent with values above 0.9 for parallel motion pin and gel, and 10° vertical motion pin and tendon tracking in acceleration, as well as parallel motion pin and gel and 10° vertical motion pin, gel and SSCT tracking in deceleration.

DISCUSSION

Modalities such as fluoroscopy and high-frequency Doppler have previously been used to measure tendon velocities, but only more recently speckle tracking has been introduced as an angle independent method to measure longitudinal velocities [2,10,13-15]. Even though this method may not be angle-dependent, out of plane motion may cause problems for accurate measurements, and therefore, we tried to evaluate its accuracy during tendon motion in different angles by comparing speckle tracking velocity measurements in a phantom model to gold standard laser measurements. Excellent accuracy has already been demonstrated for speckle tracking assessment of cardiac function [3,9]. In this study we found good agreement in our Bland and Altman

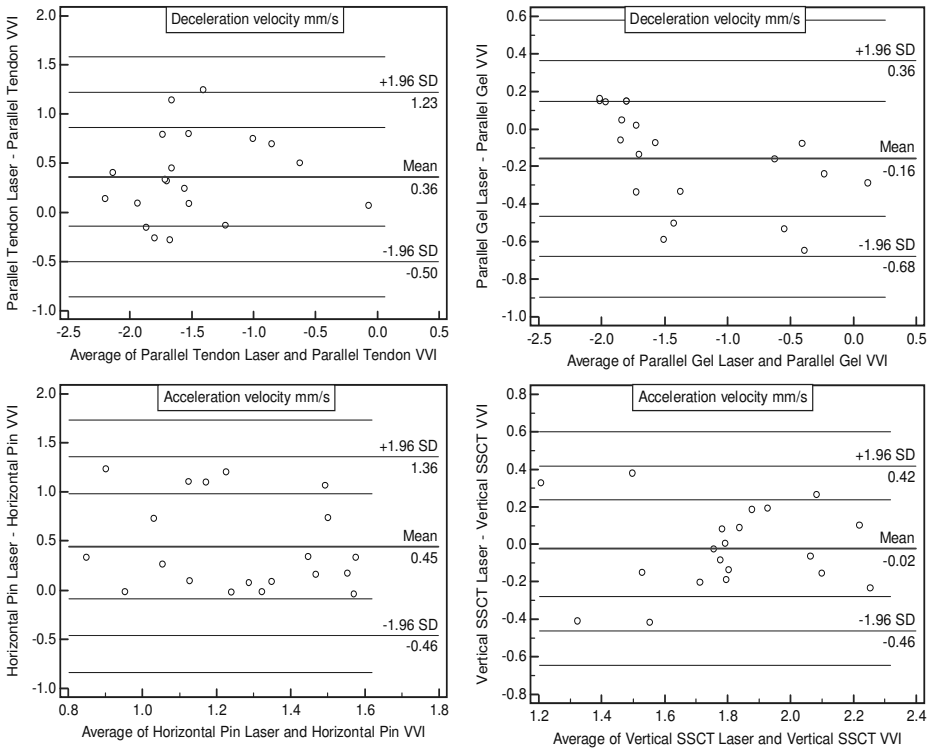


Figure 5 · *Examples of Bland and Altman plots*

analyses between speckle tracking measurements and laser measurements as well. However, the intra-class correlation coefficients were only moderate, indicating that the variability is high. The ICC was in general higher in acceleration and deceleration measurements, showing that the measurements at these points in the velocity curves are more stable than at any maximum point in the curve. During image analysis we sometimes noticed that there seemed to be a delay in tracking at the turning point of the motion cycle: the tracking dots would fall behind and would still be measuring the initial tracking direction. This probably caused an overestimation of velocity at the maximum and minimum points and may have influenced the variability between the laser and speckle tracking data, making it relatively large compared to the variability between the cycles. This could be an explanation why the ICC's at the minimum and maximum velocities are low.

However, Bland and Altman analyses are less influenced by these variabilities and showed good agreement between the two methods. The accuracy of speckle tracking for tendon motion has been assessed before by Yoshii et al. They compared tendon and SSCT excursion measured by Doppler ultrasound and speckle tracking to the excursion measured by the joint angle, and found a higher ICC for speckle tracking

Table 1 · *Intraclass correlation coefficient (ICC) for all conditions.*

Measurement	Motion	Condition	ICC	95% CI
Maximum velocity	Parallel angle	Pin	0.011	(-0.072, 0.118)
		Gel	0.057	(-0.103, 0.310)
		Tendon	0.094	(-0.069, 0.363)
		SSCT	0.014	(-0.030, 0.111)
	Horizontal angle	Pin	0.013	(-0.133, 0.200)
		Gel	0.270	(-0.124, 0.613)
		Tendon	0.251	(-0.587, 0.183)
		SSCT	0.142	(-0.258, 0.524)
	Vertical angle	Pin	0.120	(-0.421, 0.272)
		Gel	0.229	(-0.109, 0.578)
		Tendon	0.053	(-0.151, 0.159)
		SSCT	0.048	(-0.065, 0.250)
Minimum velocity	Parallel angle	Pin	0.026	(-0.081, 0.105)
		Gel	0.074	(-0.060, 0.310)
		Tendon	0.014	(-0.044, 0.064)
		SSCT	0.006	(-0.015, 0.055)
	Horizontal angle	Pin	0.017	(-0.355, 0.420)
		Gel	0.029	(-0.432, 0.465)
		Tendon	0.223	(-0.549, 0.203)
		SSCT	0.212	(-0.253, 0.594)
	Vertical angle	Pin	0.028	(-0.115, 0.145)
		Gel	0.173	(-0,302, 0.230)
		Tendon	0.094	(-0.097, 0.373)
		SSCT	0.022	(-0.288, 0.328)

Acceleration	Parallel angle	Pin	**0.934**	**(0.036, 0.986)**
		Gel	**0.821**	**(0.323, 0.941)**
		Tendon	**0.799**	**(0.557, 0.916)**
		SSCT	**0.671**	**(0.323, 0.857)**
	Horizontal angle	Pin	0.002	(-0.193, 0.286)
		Gel	0.307	(-0.079, 0.637)
		Tendon	**0.665**	**(0.331, 0.852)**
		SSCT	0.122	(-0.308, 0.520)
	Vertical angle	Pin	**0.835**	**(0.634, 0.931)**
		Gel	**0.725**	**(0.422, 0.882)**
		Tendon	**0.923**	**(0.816, 0.969)**
		SSCT	**0.726**	**(0.426, 0.882)**
Deceleration	Parallel angle	Pin	**0.977**	**(0.943, 0.991)**
		Gel	**0.908**	**(0.729, 0.966)**
		Tendon	**0.582**	**(0.074, 0.829)**
		SSCT	**0.572**	**(0.130, 0.814)**
	Horizontal angle	Pin	0.328	(-0.069, 0.654)
		Gel	0.259	(-0.100, 0.630)
		Tendon	0.418	(-0.102, 0.775)
		SSCT	0.458	(-0.091, 0.779)
	Vertical angle	Pin	**0.854**	**(0.544, 0.947)**
		Gel	**0.937**	**(0.848, 0.975)**
		Tendon	**0.717**	**(0.265, 0.891)**
		SSCT	**0.845**	**(0.618, 0.938)**

(0.377 and 0.642 respectively) [14]. Their participants flexed and extended their fingers at a pace of 0.8Hz, while our motor was set to a speed of 0.5cycle/s. In addition to sensitivity for out-of-plane motion, the accuracy of speckle tracking may also be dependent on the velocity of the structure, which may be an explanation for the difference in reliability. However, Korstanje et al. proposed an algorithm optimized for tendon movement using a block-matching scheme and assessed its accuracy at

different velocities in porcine legs, comparing the displacement to manually measured data [6]. They found minimal differences with relative errors of maximally 3.2%. They used an internal reference for these measurements by placing a marker in the tendon instead of using an external reference like the laser in this current study. Even though this may have biased their results, it still shows that the accuracy of speckle tracking largely depends on its underlying algorithm which in this case was unknown to us due to the use of a commercially available program.

To our knowledge, this is the first study to report accuracy of speckle tracking methods in tendon and SSCT in different angles. The present results serve as important baseline data for further improvement of speckle tracking methods because it has many advantages over other ultrasound modalities. Firstly, speckle tracking is independent of anatomical landmarks, whereas other ultrasound techniques often require tracking landmarks such as a musculo-tendinous junction [6,7]. This limits measurements because it is impossible to assess motions that are larger than the window size. Since speckle tracking is independent of these landmarks, it is applicable in a broader sense – for example it can be used for tendons in the hand or the Achilles tendon. Also, speckle tracking has the advantage that it allows for measuring multiple structures in the image, for example tendon and SSCT motion, or even different layers with a tendon [1,5,12], and can potentially be used to assess the effect of tendon rehabilitation protocols on tendon motion and identify adhesions. In the context of carpal tunnel syndrome, it may provide a way to assess the presence or risk of SSCT shear injury within the carpal tunnel, and lead to a better understanding of the role of SSCT shear in CTS pathogenesis.

This study has several limitations. Firstly, synchronized data collection for both the laser displacement sensor and the ultrasound cine for a 20 cycle run would have been ideal. However, the systems which collect the two data types are not interfaced, and the data buffer on the ultrasound machine limits time of data collection to a single period. However, similarity of laser data between cycles was confirmed prior to executing the study. Secondly, there is a necessary mismatch between data type collected as a gold standard (displacement) and the output of the speckle tracking method being verified (velocity). Since velocity is the first time derivative of displacement, one type can be converted into another. However, because there are multiple algorithms to accomplish this, and because the exact algorithm used in VVI software to calculate velocity was not known to us, numerical errors resulting from mismatched numerical methods may be incurred.

We have now shown that in ideal circumstances, speckle tracking has moderate to good accuracy for measuring tendon and SSCT motion. It would be useful though, to repeat these measurements in an in vivo setting to see if its accuracy remains high in less ideal circumstances. For example, the transducer was held in a stable

position throughout the whole motion which would probably not be the case when an ultrasonographer is holding the transducer. Also, in the model presented here, components of motion deviation from the ideal, parallel condition were evaluated individually. However, under in vivo conditions, motion would be more complex, and it would therefore be useful to measure the accuracy of speckle tracking of three dimensional tendon motion and assess this motion at different velocities.

In conclusion, we showed that speckle tracking measurements are most stable at deceleration and acceleration in a velocity curve and are accurate for measuring tendon and subsynovial connective tissue motion. This method allows for measuring motion of multiple structures in the same image and may provide a way to assess the presence or risk of SSCT shear injury within the carpal tunnel, and lead to a better understanding of the role of SSCT shear in carpal tunnel syndrome pathogenesis.

Acknowledgements

The project described was supported by Grant Number AR49823 from NIH/NIAMS, and was performed in our Clinical Research Unit, which is supported by NIH grant RR024150. We would like to thank Nicholas Hangiandreou, Ph.D., Randall Kinnick and Yuexiang Wang, M.D. for their help during the experiments.

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PART IV

Discussion and Summary

Chaque progrès donne un nouvel espoir, suspendu à la solution d'une nouvelle difficulté. Le dossier n'est jamais clos.

Claude Levi-Strauss

CHAPTER 8

General discussion

DISCUSSION

In this thesis, we searched for a way to assess flexor tendon and median nerve biomechanics, as well as subsynovial connective tissue thickness in the carpal tunnel with ultrasound, and tried to see if these patterns would give a clue towards understanding the etiology of carpal tunnel syndrome.

PART I Subsynovial connective tissue thickness

Findings and clinical relevance

The subsynovial connective tissue is a substance containing multiple layers of collagenous fibers around the tendons in the carpal tunnel, and plays a role in tendon gliding and nutrition [5,9]. One of the major pathological findings in patients with idiopathic carpal tunnel syndrome (CTS) is non-inflammatory fibrosis and thickening of the subsynovial connective tissue (SSCT) [3,8,14]. We hypothesized that it would be possible to measure SSCT thickness with ultrasound and that there would be a difference between healthy controls and carpal tunnel syndrome patients. We found indeed that at three different levels in the carpal tunnel, the SSCT is thicker in patients than in controls, with thicknesses ranging from 0.60-0.63mm in patients and 0.46-0.50mm in healthy persons. We also calculated a SSCT-to-tendon ratio to compensate for, for example, difference in hand size. We found that at the midtunnel and distal level, this ratio was greater in patients as well.

The knowledge that there is a difference between CTS patients and controls led to the question whether this may be a potential clue towards unwinding the etiology of idiopathic CTS. However, it is still unclear what pathway causes this thickening. First, thickening may be due to fibrosis since this a condition that has been described before [5,9,14]. Ettema et al. described in their histological study of the SSCT that CTS patients show an increase in fibroblast density, collagen fiber size, vascular proliferation, and TGF-β, all of which are found in healing process following soft-tissue injury [5,6,18]. That raises the question why these changes occur. An explanation could be the increased shear in the carpal tunnel due to a changed motion pattern of the flexor tendons and the median nerve, something that is supported by the fact that the most severe changes in the SSCT are found close to the tendon [5]. Since the SSCT plays a role in facilitating gliding of the tendons in the carpal tunnel, thickening of this structure may cause changes in the mechanical behavior of the tendons. It is however still unclear what comes first: fibrosis that causes changes in motion pattern, or a different mo-

tion pattern that causes fibrosis. The SSCT seems to be sensitive to relatively minor trauma, even in the range of normal tendon excursion [22]. This could mean that even with motions lying within this range, the cascade of injury to the SSCT and fibrosis can already be initiated. Another explanation of the final pathway leading to symptoms of carpal tunnel syndrome could be that people have a predisposing motion pattern of the tendons in their carpal tunnel that leads to shear and fibrosis of the SSCT. This would lead to even more shear, also to the median nerve, and to an increase in carpal tunnel pressure as well. If this is the case, SSCT thickness could be monitored over time and conservative therapy could be started early to prevent from further damage, or recurrent disease. Also, it would be interesting to see if there are ways to inhibit fibrosis of the SSCT to prevent it from causing even more damage. If this method could be used to diagnose SSCT thickening in the carpal tunnel in an early stage, agents that inhibit the pathway leading to fibrosis could be administered thereby slowing down the final pathway leading to CTS. However, fibrosis may also be a normal aging process. Interestingly, Ettema et al. showed that CTS patients have thicker fibrous bundles between the layers of SSCT than did normal controls, however the normal controls used in their study were cadaver specimens with no antemortem history of CTS, while the patients were middle aged adults, suggesting that the fibrosis is not a function of age, but of disease [4]. Additionally, thickening of the SSCT may potentially lead to higher pressure due to an increase in content volume of the carpal tunnel. Also, the pathological vascular changes of the SSCT could cause higher vascular permeability and thus induce edema of the SSCT thereby increasing carpal tunnel pressure [4,7,14,17,23]. The elevated pressure within the carpal tunnel can subsequently lead to the development of symptoms as seen in CTS.

Future directions

This study described the use of ultrasound for thickness measurements of the SSCT, but the presented method is laborious and time-consuming, and needs to be further optimized for use in clinical practice. Knowing that there is a difference in thickness of the SSCT between healthy controls and CTS patients, more research needs to be done to study the specific relationship with carpal tunnel syndrome, if any. This method may not only be useful in a clinical setting in the future, but also as a non-invasive modality to study the relation between the SSCT and carpal tunnel syndrome. Thickening of the SSCT could just be a normal process occurring over time and since our study only measured thickness at one time point, multiple measurements of SSCT thickness over a longer time span could clarify whether this is only an age related process or a pathological process of disease. If there is a relation between SSCT thickness and

carpal tunnel syndrome, thickness measurements could potentially aid in diagnosing CTS. Correlation of the SSCT thickness with EMG results and duration of symptoms of the patient, would be helpful to clarify if this method can be used as a diagnostic tool in the future after validation of this novel method and establishment of cut-off values.

PART II Median nerve and tendon deformation and motion patterns

Findings and clinical relevance

We evaluated the in vivo motion of the flexor tendons and median nerve in the carpal tunnel with ultrasound, to find out if there is a difference in motion patterns of these structures in healthy persons and carpal tunnel syndrome patients. Additionally, we evaluated the cross-sections of the median nerve and tendons to see if the motion patterns also affected the shape of these structures. We found that the median nerve cross sectional area and the total deformation was greater in CTS patients than in controls during finger motion. Also, we found that there is a changed motion pattern of the median nerve and several tendons in carpal tunnel syndrome patients compared to normal subjects.

These findings show that because of the different motion pattern of the tendons, the median nerve gets pushed away and since the carpal tunnel is a closed space, the median nerve thereby gets more compressed. Yet again, the question is whether these changes in motion pattern are a cause or a result of carpal tunnel syndrome. It seems reasonable that structural changes in the carpal tunnel, for example fibrosis of the SSCT or pathological swelling of the median nerve, cause a change in motion pattern because of changes in the rearrangement in the carpal tunnel. However, some people could also have an 'idiopathic' different motion pattern that makes them prone to develop more shear and maybe eventually carpal tunnel syndrome. Such motion patterns may be useful in distinguishing affected from unaffected individuals, and in studies of the pathomechanics of carpal tunnel syndrome.

Even though it is clear that there are changes in the carpal tunnel in CTS patients and that these are visible with ultrasound, its clinical use remains debatable. Ultimately, cut-off values for the median nerve cross-section need to be established, but there is a large variability in the literature. Other investigators have studied median nerve cross-sectional area in CTS, with reported values ranging from an average cross-sectional area of the median nerve at the distal wrist crease of 7-9 mm^2 in asymptomatic volunteers to 13.7-16.8 mm^2 in CTS patients [2,11,20,24]. However, absolute value measurements in the carpal tunnel may also be dependent on confounders

such as gender and wrist size. The advantage of our study was the establishment of the deformation index, since it is unaffected by absolute size. Since the measurements for the median nerve area were different both in normal measurements as well as in deformation index, this would probably be the best potential parameter to distinguish between patients and healthy individuals in supporting a clinical diagnosis of CTS. In comparison to electromyography studies, this would be a more patient-friendly, easy to use and less expensive diagnostic tool in the assessment of CTS.

Even though the clinical applicability of this method is still unclear, ultrasound is useful as a non-invasive method to investigate carpal tunnel biomechanics. Studies have shown that wrist flexion and single digit motion affect shear and compression of the median nerve the most [25-28]. Our study was only done with the wrist in neutral position, however it might be interesting to see what the motion patterns of the different structures are depending on wrist position. This could then identify what kind of motions of the wrist and fingers put persons the most at risk for developing CTS, especially task-related activities such as pinching versus gripping or keyboarding. Ultimately, this could lead to adjustments in work space, treatment, and also in rehabilitation programs to prevent the median nerve from further damage. Comprehension of the three dimensional motion patterns of the median nerve and flexor tendons could be extended to hand surgery rehabilitation protocols, such as after tendon or nerve repair. Korstanje et al. already showed that the longitudinal excursion of the FDS tendon is greater in four finger rehabilitation protocols than in single finger mobilization protocols such as the modified Kleinert protocol [12]. Since tendon motion is a three dimensional motion, this suggests that motion in the transverse plane may also be greater in four finger motion. In our study, we did indeed find an average total displacement of the middle finger FDS tendon in fist motion of 2.79mm versus 1.61mm in single digit motion in CTS patients (Chapter 5). Combining these results into a study of the three dimensional motion in both healthy people and in diseased, could give more insight in the optimal mobilization protocols after surgery.

Future directions

Real time ultrasonography of the carpal tunnel can be used in the future for assessing the biomechanics of the carpal tunnel, both in healthy people and CTS patients. Adding longitudinal images of motion in the carpal tunnel to these two dimensional transverse images, would show us the full three dimensional motion of tendons and the median nerve. Knowing the mechanical behavior of the tendons and the median nerve in a three dimensional fashion could give us more insight in which activities,

for example keyboarding or pinch gripping, are more likely to deform the median nerve and in optimization of rehabilitation protocols. This was the first study to describe a deformation index as a standardized index for measuring median nerve cross-sectional area, and further research is needed to assess its clinical applicability and to establish cut-off values. However, for future studies of the mechanical behavior of the tendons in the carpal tunnel, this method needs to be optimized. A drawback of the ultrasonographic method used in these studies is the need for special training and practice of the sonographer. The method is therefore operator dependent, which may influence its accuracy. Besides that, the calculation method is very time-consuming. Further standardization and decreasing calculation time is essential for broader scientific and clinical use.

PART III Longitudinal motion in the carpal tunnel

Findings and clinical relevance

In the third part of this thesis we evaluated longitudinal motion of the flexor superficialis tendon of the middle finger and the subsynovial connective tissue, using a speckle tracking ultrasound method. Additionally, we set up a validation study with a phantom model for this method since it was mainly used for cardiology purposes and not for tendon velocity measurements. We calculated the shear index, which is an indication of the shear caused by a difference in velocity between the SSCT and the tendon, and found that this index is higher in patients than in controls.

The difference in shear between controls and CTS patients can be caused by either a delay in initiation of SSCT motion or a decrease in its velocity compared to the tendon. Rapid, differential finger motion causes higher shear strain to the SSCT leading to shear injury [28], and this injury on its turn, can affect the SSCT itself or even the median nerve. These observations suggest a role for ultrasound in the noninvasive assessment of carpal tunnel kinematics, and may be a helpful tool in further refining prognosis. For example, the degree of impairment of longitudinal motion may correlate with the likelihood of improvement with nonoperative therapy, or with the likelihood of persistent symptoms following surgery, both of which are currently unpredictable. Additionally, it may also be used to study changes in the structures in the carpal tunnel in recurrent disease or even extended to investigation of stiffness or strain after surgical tendon repair [19,21]. The possibility of measuring motion of multiple structures in the same image can also provide a way to assess the presence or risk of SSCT shear injury within the carpal tunnel, and lead to a better understanding of the role of SSCT

shear in carpal tunnel syndrome pathogenesis. However, the commercially available software program we used for the longitudinal tracking of tendons and the SSCT was originally developed for the measurement of cardiac function [10,13,16]. This means that the algorithm was developed for measuring myocardial tissue, while tendons and the subsynovial connective tissue have different mechanical and structural properties [5,7,15,17]. Tendons have, for example, a more coherent movement and smaller deformation during motion than muscle tissue has, although Arndt et al. recently showed that even within bigger tendons such as the Achilles tendon, non-uniform displacement occurs [1]. The SSCT is a layered structure, and since it is only very thin, measuring the layers separately would be a technical challenge. Because the SSCT is usually only less than 1mm thick, we placed the tracking marker in our study in the middle, thereby giving an average of the velocity which should give reasonable information about the SSCT dynamics [17]. We used a commercially available tracking system with an algorithm that was unknown to us, but in the future, different algorithms need to be developed specified for the measured structure. We showed in our model that speckle tracking measurements are most stable at deceleration and acceleration in a velocity curve and that speckle tracking is still accurate with out-of-plane motion in a vertical angle. However, accuracy decreased in case of horizontal out-of-plane motion, which is probably caused by the fact that in case of horizontally angled motions, the speckles move out of the reach of the ultrasound beam and get lost. In addition to sensitivity for out-of-plane motion, speckle tracking accuracy may also be velocity-dependent, and therefore, future studies will need to focus on combining out-of-plane motion with velocity differences to see if speckle tracking is still reliable in all conditions.

Future directions

Speckle tracking ultrasound is a new non-invasive and accurate method to investigate tendon and SSCT motion in the carpal tunnel. However, future studies need to focus on investigating and improving reliability of this method under different circumstances. For example, its accuracy in different velocities and in different circumstances such as before and after surgery should be clarified. The advantage of this new method above other modalities such as Doppler is that with speckle tracking, multiple structures can be visualized and measured in the same image, and that it is angle-independent. Future studies should focus on using this in further assessment of biomechanical behavior of tendons and the subsynovial connective tissue in diseases such as carpal tunnel syndrome, but also extend this to tendon biomechanics before and after surgery. This knowledge could then be applied not only to understanding etiology, but also to adaptation of therapies and rehabilitation protocols.

Additionally, it would eventually be ideal to have three dimensional images of motion in the carpal tunnel. Combining longitudinal motion imaging with transverse plane motion images would be another step closer to such a model. That way, a more precise picture of the biomechanics of the structures in the carpal tunnel in both healthy controls and carpal tunnel syndrome patients can be depicted.

Main findings and conclusion

This thesis described the motion patterns of the flexor tendons and median nerve in the carpal tunnel, as well as a description of subsynovial connective tissue thickness measurements with ultrasound. Our main findings were:

- The subsynovial connective tissue thickness can be measured with ultrasound
- The SSCT is thicker in CTS patients than in healthy persons
- During active finger motion, there is more compression of the median nerve in CTS patients than in healthy persons
- The flexor digitorum superficialis tendons and median nerve have a changed motion pattern in CTS patients compared to healthy persons
- Speckle tracking ultrasound is a new, non-invasive method to measure tendon and SSCT biomechanics in the human carpal tunnel, and is able to distinguish between carpal tunnel syndrome patients and healthy controls using velocity ratios
- Speckle tracking ultrasound has moderate to good accuracy in measuring tendon and SSCT velocities

These findings can function as baseline data for further research towards understanding the etiology of carpal tunnel syndrome and the role of the subsynovial connective tissue in this disease. Also, these studies aid in the development of ultrasound as a tool for the investigation of tendon and subsynovial connective tissue biomechanics, both in healthy persons and in carpal tunnel syndrome.

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Geef me werk dat bij me past, en ik hoef nooit meer te werken.

Confucius

CHAPTER 9

Summary

SUMMARY

The carpal tunnel is a closed space in the human wrist that contains nine different flexor tendons and the median nerve, surrounded by subsynovial connective tissue (SSCT). Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve which causes tingling and numbness of the fingers innervated by the median nerve. In **Chapter 1** we described that there are several anatomical, systemical and occupational factors such as repetitive use of the wrist and digits suggested as potential causative factors for CTS. Histopathologically, the major finding in carpal tunnel syndrome is fibrosis of the subsynovial connective tissue, which changes the motion characteristics of the SSCT, tendons and median nerve. Potentially, a vicious circle evolves in which changes in the SSCT cause altered motion patterns, which with the subsequent elevated strain and shear to the structures in the carpal tunnel, then lead to even more fibrosis. The altered motion patterns are potentially useful to differentiate between healthy controls and carpal tunnel syndrome patients and it would be useful to know the normal and abnormal motion pattern of the different tendons and the median nerve in the carpal tunnel. Ultrasound is the only modality capable of real time imaging of motion in the carpal tunnel, and therefore, this thesis focused on the biomechanical characteristics of motion in the carpal tunnel using ultrasound.

PART I Subsynovial Connective Tissue Thickness

Since the major pathological finding in CTS is fibrosis of the subsynovial connective tissue, we hypothesized that fibrosis of the SSCT may cause its thickening and that we should be able to visualize this with ultrasound. In **Chapter 2**, we presented a method to sonographically measure subsynovial connective tissue thickness in the carpal tunnel. Longitudinal static images at different levels in the carpal tunnel showed that the SSCT is significantly thicker in CTS patients than in healthy controls, confirming our hypothesis. This was also the first study to confirm that it is possible to measure SSCT thickness with ultrasound. Since fibrosis of the SSCT may be an early sign of carpal tunnel syndrome, this showed that ultrasound might be useful as a diagnostic aid for early detection of CTS.

PART II Transverse Plane Motion and Deformation of the Median Nerve and Flexor Tendons

In **Chapter 3, 4 and 5**, we studied the motion and deformation of the median nerve and the flexor tendons in the transverse plane. In-vivo measurements of the motion direction of the median nerve and the differential flexor digitorum superficialis (FDS) tendons of the index and middle finger and the flexor tendon of the thumb during active finger motion were done. Additionally, we measured the motion direction of the third FDS tendon in fist motion and the change in shape of the median nerve and tendons during flexion and extension. First, we measured median nerve motion and compression in thumb and index finger flexion in healthy people. We found that during flexion of these fingers, the median nerve is pushed away while at the same time compression of the median nerve occurs. Then, we measured the same parameters in both CTS patients and healthy controls and added middle finger and fist motion to our measurements as well. We found that the median nerve deformation was significantly greater in CTS patients than in controls during active finger motion, and that there is a changed motion pattern of the median nerve and several tendons in carpal tunnel syndrome patients compared to normal subjects. These differences show that structural changes in the carpal tunnel, for example fibrosis of the SSCT or pathological swelling of the median nerve, cause a change in motion pattern because of changes in the rearrangement in the carpal tunnel. However, it could also be that people have an 'idiopathic' different motion pattern that makes them prone to develop more shear and maybe eventually carpal tunnel syndrome. Additionally, such motion patterns may be useful in distinguishing affected from unaffected individuals, and in studies of the pathomechanics of carpal tunnel syndrome.

PART III Longitudinal Motion of the Median Nerve and Subsynovial Connective Tissue

Assuming that fibrosis of the SSCT changes the motion pattern of the different structures in the carpal tunnel, we also investigated motion of the median nerve and SSCT in the longitudinal plane. In **Chapter 6** we measured longitudinal excursion and velocity using speckle tracking.

Speckle tracking is a relatively new method, in which speckles in the ultrasound image are tracked from frame to frame, independent of the angle. To estimate the ability of this speckle tracking method to accurately measure tendon and SSCT excursion, we used direct measurements in the carpal tunnel during carpal tunnel release surgery to validate the motions estimated from ultrasonographic measure-

ment. Our results showed a different motion pattern of the SSCT and tendons in CTS patients than in healthy controls with a lower maximum velocity ratio and a higher shear index in patients, which is most probably caused by altered SSCT movement. With this study, we showed that speckle tracking is a potential method to assess the (pathological) biomechanics of tendons and subsynovial connective tissue within the carpal tunnel, as well as to distinguish between healthy controls and patients with carpal tunnel syndrome. To our knowledge, this was the first method described to dynamically assess subsynovial connective tissue motion within the carpal tunnel.

Finally, in **Chapter 7**, we developed an in vitro validation model for the longitudinal ultrasound measurements. Velocity of markers in a phantom and a human tendon placed in a tissue-mimicking phantom gel was evaluated by speckle tracking and a laser in three different orientation angles: parallel to the transducer and at an angle of 10° relative to both the horizontal and vertical axes. We found moderate to good accuracy of the speckle tracking method for measuring velocity, although accuracy was low in the 10° horizontal angle. We concluded that speckle tracking is a valid method for measuring both tendon and SSCT motion in the same image, and that it may provide a way to assess the presence or risk of SSCT shear injury within the carpal tunnel, and lead to a better understanding of the role of SSCT shear in carpal tunnel syndrome pathogenesis.

SUMMARY IN DUTCH – NEDERLANDSE SAMENVATTING

De carpale tunnel is een gesloten ruimte in de pols die negen verschillende flexor pezen en de nervus medianus zenuw bevat, omringd door het subsynoviale bindweefsel (subsynovial connective tissue, SSCT). Carpaal tunnel syndroom (CTS) is een compressie neuropathie van de nervus medianus met als symptomen tintelingen en gevoelloosheid van de vingers die geïnnerveerd worden door deze zenuw. In **Hoofdstuk 1** hebben we beschreven dat er verschillende anatomische, systemische en beroepsfactoren zijn beschreven als mogelijke oorzakelijke factoren voor CTS, zoals intensief gebruik van de pols en vingers bij bijvoorbeeld bouwvakkers en fabrieksmedewerkers. De belangrijkste histopathologische bevinding in carpaal tunnel syndroom is fibrose van het subsynoviale bindweefsel, waarbij onder andere een toename in het aantal fibroblasten en een toegenomen vasculariteit te zien is. Deze fibrose verandert de bewegingen van het SSCT, de pezen en de zenuw in de carpale tunnel en mogelijk ontstaat hierdoor een vicieuze cirkel; veranderingen in het SSCT veroorzaken een veranderd bewegingspatroon en een verhoogde druk in de carpale tunnel, wat dan weer leidt tot meer fibrose. De gewijzigde bewegingspatronen zijn mogelijk nuttig om een onderscheid te kunnen maken tussen gezonde mensen en patienten met carpaal tunnel syndroom en het zou nuttig zijn om het normale bewegingspatroon van de verschillende pezen en de nervus medianus in de carpale tunnel te leren kennen. Echografie is een goede manier om actieve beweging over een tijdsspanne af te beelden en daarom beschrijft dit proefschrift de biomechanische eigenschappen van beweging in de carpale tunnel met behulp van echografie.

DEEL I DIKTE VAN HET SUBSYNOVIALE BINDWEEFSEL

Omdat fibrosering van het subsynoviale bindweefse de belangrijkste histopathologische bevinding in CTS is, veronderstelden wij dat deze fibrose een verdikking van het SSCT kan veroorzaken en dat dit zichtbaar te maken is met echografie. In **Hoofdstuk 2** presenteerden we een methode om de dikte van het subsynoviale bindweefsel te meten door middel van echografie. Op longitudinale statische beelden op verschillende niveaus in de carpale tunnel bleek dat het SSCT beduidend dikker is bij carpaal tunnel syndroom patiënten dan bij gezonde controles, wat onze hypothese bevestigde. Omdat fibrose van het SSCT een vroeg teken van carpaal tunnel syndroom kan zijn, zou echografie mogelijk nuttig kunnen zijn als een diagnostisch hulpmiddel voor vroege detectie van CTS.

DEEL II BEWEGING EN VERVORMING VAN DE NERVUS MEDIANUS EN FLEXORPEZEN IN HET TRANSVERSALE VLAK

In **Hoofdstuk 3, 4 en 5** hebben we de beweging en vervorming van de nervus medianus en de flexor pezen in het transversale vlak gemeten. Met behulp van echografie werden *in-vivo* metingen van de bewegingsrichting van de zenuw en de flexor digitorum superficialis pezen van de wijs- en middelvinger en de flexorpees van de duim gedaan tijdens actief buigen van de betreffende vinger. Daarnaast maten we de bewegingsrichting van de derde FDS pees tijdens het maken van een vuist en de verandering in de vorm van de zenuw en de pezen tijdens het buigen en strekken. Allereerst maten we de beweging en compressie tijdens flexie van de duim en wijsvinger bij gezonde mensen. We vonden dat tijdens flexie van deze vingers, de zenuw wordt weggeduwd en dat deze hierbij wordt gecompromiteerd. Vervolgens hebben we dezelfde parameters gemeten bij zowel CTS patiënten en gezonde controle personen en de metingen uitgebreid met metingen van de middelvinger- en vuistbewegingen. We vonden dat de vervorming van de zenuw significant groter was bij CTS patiënten dan bij controles tijdens flexie van de vingers, en dat er een veranderd bewegingspatroon is van de zenuw en een aantal pezen in carpaal tunnel syndroom patiënten in vergelijking met gezonde personen. De meting van deze bewegingspatronen kan nuttig zijn in het onderscheiden van gezonde mensen van CTS patienten, en in toekomstige studies van de (pathologische) biomechanica van carpaal tunnel syndroom.

DEEL III LONGITUDINALE BEWEGING VAN DE NERVUS MEDIANUS EN HET SUBSYNOVIALE BINDWEEFSEL

Er vanuit gaande dat fibrose van het SSCT het bewegingspatroon van de verschillende structuren in de carpale tunnel verandert, hebben we ook de beweging van de nervus medianus en het SSCT in het longitudinale vlak onderzocht. In **Hoofdstuk 6** hebben we de excursie en bewegingssnelheid hiervan onderzocht met behulp van *speckle tracking*. *Speckle tracking* is een relatief nieuwe methode, waarbij zogenaamde '*speckles*' in het echografisch beeld worden gevolgd van afbeelding naar afbeelding, onafhankelijk van de hoek waaronder de opnames zijn gemaakt. Om de nauwkeurigheid van deze *speckle tracking* methode te meten, gebruikten we directe metingen van de pees- en zenuwexcursie tijdens *carpal tunnel release* operaties om de echografische metingen te valideren. Onze resultaten toonden een ander bewegingspatroon van het SSCT en de pezen in CTS patiënten in vergelijking met gezonde controle personen waarbij een

lagere maximale snelheid en een hogere shear-index dan bij patiënten werd gemeten, hoogst waarschijnlijk veroorzaakt door een veranderde beweging van het SSCT.
Met deze studie hebben we aangetoond dat *speckle tracking* een potentiele methode is om de (pathologische) biomechanica van de pezen en het subsynoviale bindweefsel in de carpale tunnel te onderzoeken, maar ook onderscheid te maken tussen gezonde personen en patiënten. Voor zover wij weten, was dit de eerste beschrijving van een methode om beweging van het subsynoviale bindweefsel binnen de carpale tunnel dynamisch af te beelden en te meten. Tenslotte wordt in **Hoofdstuk 7** een *in vitro* validatie model voor *speckle tracking* beschreven waarbij de snelheid van markers en een pees met SSCT in een fantoom werd gemeten met *speckle tracking* en met een laser. Dit werd gedaan in drie verschillende hoeken: evenwijdig aan de *transducer*, en in een hoek van 10° in horizontale en verticale richting ten opzichte van de *transducer*. We vonden een matig tot goede nauwkeurigheid van de *speckle tracking* methode voor het meten van de sneldheid, hoewel deze laag was voor de metingen in de 10° horizontale hoek. We concludeerden dat *speckle tracking* een goede methode is voor het meten van pees- en SSCT bewegingen en dat dit mogelijk gebruikt kan worden voor verder onderzoek naar de aanwezigheid van, of het risico op schade aan het SSCT in de carpale tunnel en hiermee kan leiden tot een beter begrip van de rol van het SSCT in de pathogenese van het carpale tunnel syndroom.

ABOUT THE AUTHOR

Margriet van Doesburg was born on July 30, 1984 in Geldermalsen, the Netherlands. In 2002 she graduated from high school at the Koningin Wilhelmina College in Culemborg, the Netherlands. That year, she started medical school at the University Medical Center Utrecht during which she participated in several internships abroad, some in Israel and Namibia. In her final year she did a research internship at the Biomechanics Laboratory at Mayo Clinic, Rochester, MN. After graduating from medical school in 2009, she returned to Mayo Clinic as a research fellow for another year. In total she spent a year and a half at Mayo Clinic, after which she started as a surgical resident at the surgery department of Meander Medical Center in Amersfoort. In January 2011 she started residency in Plastic Surgery, spending her first two years in General Surgery at Meander Medisch Centrum, Amersfoort (Head dr. A.J. van Overbeeke). The last years will be spent at the University Medical Center Utrecht (Head dr. A. Schuurman).

LIST OF PUBLICATIONS

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ACKNOWLEDGEMENTS

Na enkele jaren geleden als zesdejaars student aan dit onderzoek begonnen te zijn, ben ik nu dan op het punt aangekomen dat ik deze belangrijke pagina's van mijn proefschrift mag schrijven. Een lichte euforie, vermengd met een vleugje melancholie overvalt me. Het was veel werk, maar wat heb ik er veel voor terug gekregen! Heel veel mensen hebben hier aan bijgedragen en het is onmogelijk iedereen persoonlijk te noemen, maar desondanks wil ik graag een aantal personen die van essentieel belang zijn geweest op deze plaats bedanken.

Prof. dr. M. Kon, geachte promotor, "beste professor". Vanaf het moment dat ik als student bij u langs kwam om onderzoek te kunnen gaan doen binnen de plastische chirurgie, heeft u groot vertrouwen in mij getoond. U heeft altijd de grote lijnen in de gaten gehouden en in het hele proces met (soms) weinig woorden grote steun gegeven. Uw discretie en integriteit zijn een inspirerend voorbeeld voor mij. Ik zie uit naar een even goede samenwerking tijdens mijn vervolgopleiding tot plastisch chirurg!

Dr. A.B. Mink van der Molen, beste Aebele. U heeft de basis gelegd voor de samenwerking met de Mayo Clinic, iets waar ik nu nog steeds heel dankbaar voor ben. Wat een geweldige kansen en ervaringen heeft deze hele reis mij (letterlijk en figuurlijk!) geboden. Heel hartelijk dank voor alle feedback en ondersteuning, en natuurlijk voor het korte maar krachtige bezoek aan het lab in de Mayo Clinic.

Prof.dr. R.M. Castelein, prof.dr. R.L.A.W. Bleys, prof.dr. W. Mali en prof.dr. S.E.R. Hovius, heel hartelijk dank voor het zitting nemen in de beoordelingscommissie en het kritisch doorlezen van mijn proefschrift.

My stay at the Mayo Clinic in Rochester, Minnesota (USA) was a life-changing experience and I would like to thank a few people in particular who contributed to this.

Dr. P.C. Amadio, dear Peter. Thank you so much for all your effort and support during this process. I would not have been able to start or finish this without your guidance. Your quick and clear thoughts have changed my view on research and will be valuable in my career.

Dear dr. Kai-Nan An. Thank you all your support in many ways. It was great knowing I could always knock on your door for answers (being it for a dollar...), but I also still greatly appreciate everything you have done for me outside of the lab. It was great

meeting you and Suei-Ching in church every Sunday, and I am still thankful for making me feel at home in Rochester.

Special thanks go out to my good friends in Rochester: for a year and a half you were my 'family' far away from home and without you it would not have been the same! I will cherish my great memories of all the poolparties and potlucks we had, and of course the trips to several places in the US. My roomie Serena and almost-roomie Anna, we shared so much laughter but also tears in times when it was not so easy being abroad on your own. I know these friendships will stay and I hope we will be able to see each other again soon! Andre, we met in Rochester while I was still not sure if I would get into residency, but now I can finally say we're colleagues! We had a lot of good times together and who knows I might call you to clean up my house in the future...

My colleagues at the Biomechanics Laboratory:

Terri and Melissa, what a great secretaries the both of you are! Thank you so much for all your help during the frustrating moments of handling computers. Andrew Thoreson, you have been of so much help with many of my projects, but especially my last one. You put a lot of time and effort in it, and your more technical way of thinking was very helpful! Jacqueline Henderson, thanks for all our great conversations about Europe, the US, cultural differences, food and of course for inviting me over for Thanksgiving, it was great! All the fellows in the 'submarine': thank you for the good times we shared in our small space without any windows!

Collega's van het Meander Medisch Centrum in Amersfoort:

Dr. A.J. van Overbeeke, beste Adriaan, als ANIOS in het Meander begonnen en straks als AIOS plastische chirurgie met een promotie op zak het pand weer verlaten, wat mooi! Dank voor uw vertrouwen, steun, en natuurlijk uw onderwijs in het chirurgisch vak. Alle collega arts-assistenten chirurgie: wat een gezellige, drukke tijden! Dank voor het delen van verhalen en tips over promoveren, jullie flexibiliteit, en voor de mooie skiweekendjes!

Lieve vrienden en vriendinnen, zoveel dank voor jullie begrip tijdens die keren dat ik niet kon komen omdat ik moest werken aan mijn onderzoek, voor als ik mijn verhaal even kwijt moest, maar ook voor het delen van de mooie momenten. Paralleli's, ladies van het KWC, ik hoop er weer vaker bij te zijn! Allison, ik weet dat ik soms niet kon stoppen met praten over mijn onderzoek, nu gaan we eindelijk al die leuke dingen doen die we al tijden in de planning hebben staan!

Mijn paranimfen Margot Honkoop-de Koning Gans en Hanneke de Groot.

Lieve Margot, jij bent me helemaal in Rochester op komen zoeken, iets dat me destijds heel veel goed heeft gedaan en ik nu nog steeds enorm waardeer! De fotosessies in het ziekenhuis, samen in het Kahler hotel slapen en koken, door de meters sneeuw ploegen met de auto en natuurlijk het uitstapje naar New York zijn blijvende geweldige herinneringen! Daarnaast heb je altijd meegedacht en positieve input gegeven wanneer nodig, en wist ik dat ik altijd even mijn verhaal kwijt kon. Heel veel dank hiervoor!

Lieve Hanneke, als jarenlange huisgenoot en vriendin heb jij dit proces vanaf het eerste mailtje tot aan het organiseren van de feestelijkheden meegemaakt. Ik heb alle kaartjes, cadeautjes en gezellige dingetjes die jij regelmatig uit Nederland naar Rochester stuurde enorm gewaardeerd, en heb er bewondering voor hoe je al deze jaren er altijd bent geweest: als luisterend oor, voor het zetten van een kopje koffie, maar ook om mij af en toe even af te remmen als ik weer eens tot in de late uurtjes achter mijn computer zat.

Lieve meiden, geweldig dat jullie op deze dag naast me staan!

Tenslotte wil ik mijn moeder, broers en schoonzus danken voor hun onvoorwaardelijke steun in de afgelopen jaren. Hoewel het voor jullie misschien lang niet altijd even interessant was, hebben jullie altijd belangstelling getoond en daar ben ik heel dankbaar voor. Lieve mama, de kracht en het doorzettingsvermogen die ik nodig had om dit te volbrengen, heb ik zeker van u geërfd. Dank u wel voor uw betrokkenheid en medeleven, maar ook de praktische hulp! Ik houd van u.