Diplomarbeit

Ultrasound for the diagnosis of carpal tunnel syndrome

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Zusammenfassung

Hintergrund: Das Karpaltunnelsyndrom (CTS) ist das häufigste Kompressionssyndrom peripherer Nerven. Zur CTS Diagnostik kommen neben Klinik und der Messung der Nervenleitgeschwindigkeit nun vermehrt auch hochauflösende Ultraschallgeräte zum Einsatz. Mit Hilfe der Sonographie wird nach morphologischen Veränderungen des N. medianus gesucht. Vor allem die Messung der Querschnittsfläche des N. medianus ist vielversprechend, wobei es aber noch keine allgemein gültigen Schwellenwerte für ein pathologisches Ergebnis gibt.
Die Ziele dieser Arbeit waren die sonographische Vermessung der Querschnittsfläche (cross sectional area, CSA) des N. medianus an unterschiedlichen anatomischen Landmarken zur Bestimmung des optimalen Schwellenwertes für die CTS Diagnose. Zudem wurde die Wertigkeit von Power Doppler (PD)- Signalen innerhalb des N. medianus untersucht.

Methodik: Prospektive Studie an 135 Patienten mit Verdacht auf CTS. Es erfolgten 2 ambulante Kontrollen der Patienten innerhalb von 3 Monaten. Die Diagnosestellung erfolgte durch Kombination des klinischen- und des elektrophysiologischen Befundes. Die CSA des N. medianus wurde an 5 unterschiedlichen Punkten an Unterarm und Handgelenk mit Hilfe der Sonographie vermessen; anschließend die Größenverhältnisse und Differenzen der CSA von Handgelenk und Unterarm zueinander berechnet.
Intraneurale PD-Signale wurden semiquantitativ (subjektive Skala von 0= kein Signal bis 3= starke Vaskularisierung) eingeteilt. Diagnostische Wertigkeiten von unterschiedlichen Ultraschall Methoden, wurden durch „reicever operating characteristic“ (ROC) Kurven mittels SPSS verglichen.

Ergebnisse: Ein CTS wurde bei 111 (45,5%) Handgelenken diagnostiziert; 84 (34,4%) hatten kein CTS und 49 (20,1%) waren mögliche CTS Fälle. Die diagnostische Wertigkeit der Sonographie war für alle Methoden zur Bestimmung der CSA vergleichbar (area under the curve (AUC) Werte zwischen 0,75 und 0,85). Schwellenwerte von 9,8 und 13,8 mm² für die subjektiv größte CSA des N.

medianus erreichten eine Sensitivität von 92% und eine Spezifizität von ebenfalls 92%. Ein PD-Wert von ≥2 erreichte eine Spezifizität von 90% für die Diagnose des CTS. Die sonographische Vermessung des N. medianus ist gut reproduzierbar und zeigte einen „intra-class correlation coefficent“ von 0,90 (95% CI: 0,79-0,95).

Schlussfolgerung: Die Bestimmung der CSA im Bereich des subjektiv größten Durchmessers des N.medianus ist eine gut reproduzierbare Methode und unterstützt die Diagnostik des CTS in der täglichen klinischen Praxis.

Abstract

Objective: Carpal Tunnel Syndrome (CTS) is the most common entrapment syndrome of peripheral nerves. In addition to clinical assessments and nerve conduction studies, high-resolution ultrasound is more and more used for diagnosis of CTS investigating morphologic changes of the median nerve. The determination of the nerve cross-sectional-area (CSA's) is promising; however, no thresholds for an abnormal CSA have been established so far.
The aim of this study was the comparison of sonographically determined median nerve CSA's at different anatomical landmarks for diagnosis of CTS. In addition, the value of power Doppler (PD)-signals within the median nerve was investigated.

Methods: Prospective study on 135 consecutive patients with suspected CTS undergoing two visits within three months. Final diagnosis of CTS was established by clinical and electrophysiological findings. CSA was sonographically measured at 5 different levels at forearm and wrist; and CSA wrist to forearm ratios or differences were calculated. Intra-neural PD-signals were semiquantitatively graded. Diagnostic values of different ultrasound methods were compared by receiving operating characteristic (ROC) curves using SPSS.

Results: CTS was diagnosed in 111 (45.5%) wrists; 84 (34.4%) had no CTS and 49 (20.1%) were possible CTS cases. Diagnostic values were comparable for all sonographic methods to determine median nerve swelling with AUCs ranging from 0.75 to 0.85. Thresholds of 9.8 and 13.8 mm^2 for the largest CSA of the median nerve yielded a sensitivity of 92% and a specificity of 92%, respectively. A PD-score ≥2 had a specificity of 90% for the diagnosis of CTS. Sonographic median nerve volumetry revealed a good reliability with an intra-class correlation coefficient of 0.90 (95% CI: 0.79-0.95).

Conclusion: Sonographic assessment of median nerve swelling and vascularity allows for a reliable diagnosis of CTS. Determination of CSA at its maximal shape offers an easily reproducible tool for CTS classification in daily clinical practice.

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Glossar und Abkürzungen

° C	degree Celsius
AAEM	American Association of Electrodiagnostic Medicine
AUC	area under the curve
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
CS	cervical syndrome
CSA	cross sectional area
CsL	level of largest CSA of the median nerve between the area proximal to the carpal tunnel inlet and the tunnel outlet
CsP	cross sectional area at the proximal border of the pronator quadratus muscle
CsR	proximal margin of the flexor retinaculum
CsS	level of the scaphoid tubercle and pisiform bone
CsT	area of the proximal third of the pronator quadratus muscle
CTS	carpal tunnel syndrome
DDx	differential diagnosis
e. g.	exempli gratia
ECTR	endoscopic carpal tunnel release
EMG	electromyography
ESR	erythrocyte sedimentation rate
HC	healthy controls
Hz	Hertz
i. e.	id est
ICC	intraclass correlation coefficient
m/s	meter per second
mg	milligram
MHz	megahertz
mm	millimeter
mmHg	millimeters of mercury

MRI	magnetic resonance imaging
ms	millisecond
mV	millivolt
N.	Nervus
NCS	nerve conduction study
NSAID	nonsteroidal antiinflammatory drugs
OCTR	open carpal tunnel release
p. o.	per os
PD	power Doppler
PGE2	prostaglandin 2
PS	pronator teres syndrome
RA	rheumatoid arthritis
ROC	receiver operating characteristic
Tab.	table
TOS	thoracic outlet syndrome
U.S.	United States
VEGF	vascular endothelial growth factor

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Introduction

1.1 The Carpal Tunnel Syndrome

1.1.1 Definition

Carpal Tunnel Syndrome (CTS) is the most frequent entrapment syndrome of peripheral nerves caused by an imbalance between the size of the osteo-fibroid canal and its content.[1] Characteristic symptoms are numbness and tingling sensations of the hands especially during the night. In electrophysiologic testing a decreased nerve conduction velocity of median nerve is usually found.

1.1.2 Carpal tunnel anatomy

To understand the pathogenesis of CTS and the need of proper orientation by reference to anatomical landmarks when performing sonography, it's mandatory to know some basic underlying anatomical structures.

At the wrists palmar side the carpal bones are forming a concavity which is radial bounded by the tubercles of the scaphoid and the trapezium bone and on the ulnar side limited to the pisiform bone and the hook of the hamate. Between these boundaries ranges the flexor retinaculum, a stout-fibroid ligament which shapes the roof of the Carpal Tunnel.[2]

As the carpal canal is practically inductile it is apparent that flexions and extensions as well as space-consuming lesions increase the pressure within the tunnel easily causing an irritation of the median nerve. The tightest part is found in the area of the distal carpal bones.

In healthy individuals the average pressure within the carpal tunnel ranges from 3 to 13 mmHg in neutral position whereas during flexion and extension it increases to 10-43 mmHg. In patients with CTS, pressure-peaks up to 110 mmHg were observed.[3,4]

The structures localized within the carpal tunnel are the tendons of the flexor digitorum superficialis, the flexor digitorum profundus, the flexor pollicis longus and the median nerve.

Varieties such as a bifid median nerve (10 - 15%), a persistent median artery (20%) or aberrant muscles are occasionally seen.[5]

1.1.3 Epidemiology

1.1.3.1 Incidence and prevalence

Incidence and prevalence data of CTS vary significantly between the studies depending on the criteria used to classify the disease.[6]

A Dutch survey pointed out a CTS prevalence of 9,2% in females and 0,6% in males. In this study, diagnosis was based on paresthesia in the distribution area of the median nerve occurring at least two times a week.[6,7] In case CTS diagnosis was based on symptoms such as pain, numbness or tingling only the prevalence of CTS increased to 14,4% within the general population.[8] Including the results of clinical examination or electrophysiological testing into CTS classification resulted in rates of 3,8% or 2,7%, respectively.

The incidence of CTS was 276/100.000 person-years in Italy. Women were more commonly affected than men (ratio 3:1)[9][10] and the incidence peaked between the 5th and 6th decade of life [11-14] [8]

1.1.3.2 Economical considerations

CTS causes high socioeconomic costs: Calculations from the United States (U.S.) demonstrated that the average costs emerging from a CTS patient are ~30.000$. These costs include all medical services as well as economic damage arising from the lost workforce.[15] As approximately 4.8 million U.S. workers suffered from CTS in the year 2010 the financial burden from the disease is obviously enormous.[16]

1.1.4 Etiology

In most cases, the cause of CTS is unknown. In a proportion of patients, however, occupational factors and/or certain diseases can be linked with the occurrence of the disease as outlined in Table 1.

The most important ***occupational factors*** related to CTS are highly repetitive movements (e.g. assembly belt, packers), forced flexion and extension of the wrist, especially if combined with a high grip strength. Use of hand-vibrating tools such as chainsaws and pneumatic hammers leads to an increment of the amount of soft tissue within the carpal tunnel and professionals using these tools have an excess risk to develop CTS.[17]

White-collar jobs were long considered to be an occupational risk factor for CTS because of the heavy usage of mouse and keyboards. A systematic review, however, did not confirm such an association.[4,18]

Pregnancy is another risk factor for CTS. Symptoms, however, are usually transient and subside spontaneously within a few months postpartum. Depending on the CTS definition used, 7-62% of pregnant women were reported to develop CTS.[19]

Table 1: Secondary causes of CTS

Rheumatic	Arthritis, Tenovaginitis
Endocrinological	Gravidity, Menopause, Diabetes mellitus, Acromegaly
Mechanically	Compression caused by tumor, Ganglion, Lipoma, Cyst or Osteophyte
Vascular	Persistent median artery
Metabolic	Alcohol abuse, Gout, Amyloidosis
Traumatic	Fractures or luxations at the wrist, Compartment syndrome

1.1.5 Pathogenesis

Although the detailed pathomechanism of CTS has not been identified so far, mechanical compression of the median nerve at the passage of the carpal tunnel as well as the disturbance of nerve microcirculation play critical roles.[20]
As mentioned above pressure within the carpal tunnel can be increased 3-fold in CTS patients either in neutral position as well as during forced flexion or extension.[21,22] Studies in healthy subjects demonstrated that applied pressure at certain thresholds and for defined periods of time provoked symptoms similar to CTS. Paresthesias like tingling and pain for example were observed when pressure was ~30 mmHg, between 40 and 60 mmHg subjects temporarily lost sensory and motor function of the median nerve.[23,24] Removal of the pressure relieved symptoms immediately.
Similarly, the division of the retinaculum flexorum of CTS patients can lead to spontaneous relief of patients' paresthesia and pain. The most important factor contributing to the rapid improvement of CTS symptoms in these cases is decompression of perineural vessles and the reperfusion of the median nerve [25,26]

Prolonged ischemia induces angiogenesis in the tenosynovial tissue as demonstrated in histological studies.[27] This process is triggered by vascular endothelial growth factor (VEGF) and prostaglandin E2 (PGE2)[28] VEGF also increases vascular permeability and is therefore considered to support the formation of subsynovial edema.[28,29] Synovial specimens from CTS patients showed thickened intima and media layers of subsynovial vessels with narrowed or even obstructed lumen.[28]
Besides, compression of venules within the median nerve while arterial flow is still present leads to a higher pressure within capillaries further enhancing vascular permeability and promoting the outflow into the interstitial tissue. The interstitial edema stimulates proliferation of fibroblasts leading to collagen deposition and an increment of the total volume of the median nerve. The high pressure within the carpal tunnel impairs the axonal transport system of nerve cells finally resulting in a degeneration of nerve fibers. Signs of inflammation are usually absent. [30]

1.1.6 Clinical Presentation

The most characteristic symptoms of CTS are tingling, numbness, pain or burning sensations particularly during night. Symptoms are relieved by shaking the hand (Flick's sign) or sticking the hand out of bed. At clinical presentation the majority of patients (66% - 87%) have bilateral symptoms, however, the dominant hand is usually affected more severely.[31,32][33]

In patients with prolonged disease, symptoms also appear during the daytime and are often reported as clumsiness ("dropping things") or weakness. Paresthesia may occur during routine activities such as carrying heavy shopping bags, replacing light bulbs or uncapping tight jars.

1.1.7 Diagnosis

1.1.7.1 Clinical Findings

Currently, a number of clinical tests are used for CTS diagnosis with variable performance: the **Phalen's test** (sensitivity 64%, specificity 83%)[34,35] is positive if the maximal *flexion* of the wrist for ~60 seconds leads to tingling sensations or other paresthesia in the distribution area of the median nerve (digit 1 to 3 and radial half of the 4th digit). An alternative maneuver is the **reverse Phalen's test** where the maximum *extension* of the wrists provokes the same symptoms. The accuracy of Phalen's and reverse Phalen's tests are similar.

For the **Tinel's sign** (Sensitivity 48% - 73%, Specificity 40% - 94%)[35,36] percussion of the heel of the hand is performed leading to electrifying paresthesia.

For the **carpal tunnel compression test** the examiner presses his thumb on the area of the carpal tunnel for ~30 seconds and the test is positive if one or more of the symptoms described for the Phalen's test occur.[37]

To assess functional defects of the median nerve in CTS patients the **Loss-of-Sensibility-Test** (performed by sweeping the examiners finger over the patients'

thenar) and the **Loss-of-2-point discrimination** (differentiation of the smallest possible distance between two points) are usually performed.
Late-onset symptoms as a result of chronic damage of the median nerve include a weakness or atrophy of the abductor pollicis brevis muscle, a reduced sweat secretion and/or dysplasia of the nails.

The most important limitation of all these tests is their uncertain sensitivity and specificity in clinical routine because clinical studies investigating their performance are not easily comparable. Part of studies for example compared CTS patients with healthy controls, whereas others assessed CTS patients, patients with polyneuropathy or other pain syndromes.[38] Besides, the criteria to classify CTS varied between studies. Further studies are required to investigate the diagnostic value of CTS clinical tests in a real-life setting.

1.1.7.2 Electrophysiology

The **nerve conduction study (NCS)** still is the diagnostic tool of choice. According to a literature review of the American Association of Electrodiagnostic Medicine AAEM NCS reaches the highest sensitivity (>85%) and specificity (95%) among currently available tests for CTS.[39]
For NCS the motor branch of the median nerve is primarily investigated, and in case of an inconclusive result the sensory branch is tested as well.
For accurate and reproducible performance of NCS, a standardized procedure is necessary: defined distance between the electrodes, constant skin temperature (34°C), usage of properly maintained device and performance of the measurement by a skilled examiner are the minimal standards.[1]

In CTS patients, a delayed distal motor latency of the median nerve is a characteristic finding in *motor NCS* that is caused by a demyelination of the median nerve. Measurements are usually performed at the median nerve of the symptomatic hand, the ipsilateral ulnar nerve and the contralateral median nerve. A comparison of the results indicates whether the cause of the symptoms is located within the carpal

tunnel, at a higher stage (e.g. at nerves root) or at the level of a systemic disorder (e.g. polyneuropathy).

The *sensory NCS* can quantify the velocity of the impulse of the nerve, measured antidrome from the digit II or III to the wrist. A constant skin temperature (34°C) is essential for this method because higher temperatures may lead to false positive results. Another technique is the measurement of the nerve action impulse from the ring finger back to the wrist. As the ring finger is innervated by both, the median and the ulnar nerve, the skin temperature is less relevant for the accuracy of this method.[40]

With both methods, motor and sensory NCS, a reduced nerve conduction velocity can be determined during early stages of the disease (caused by nerve demyelination), whereas in late phases axon degeneration causes a reduction of the NCS amplitude.[1]

The threshold for normal and abnormal NCS results are depicted in Table 2

Table 2: NCS thresholds

	Median nerve		***Ulnar nerve***	
	sensory	**motor**	**sensory**	**motor**
Distal motor latency (ms)	-	4.2	-	3,5
Amplitude (mV)	15	5	20	7,0
Nerve conduction velocity (m/s)	50	50	50	50

A difference in the distal motor latency between the median and the ulnar nerve of more than 1,5 ms is pathologic.

The **electromyography (EMG)** is usually reserved for a small proportion of patients with unclear NCS results to exclude abnormality of innervation, aplasia of the thenar muscles or pathologically raised stimulation-threshold of the medain nerve.[1]

The principle of this method is similar to the NCS, however, muscle activity is examined invasively using two thin needles (0,45mm) pricked along the muscle of interest.

1.1.7.3 Sonography and magnetic resonance imaging

The introduction of high resolution transducers increased the use of sonography to explore the wrist in patients with CTS symptoms. Whereas NCS results reflect functional changes of the median nerve, ultrasound provides information about the morphology of the median nerve and the other structures within the carpal canal. Sonography is usually better available than NCS, is cheap and has no contraindications.

The diagnostic accuracy of this method, however, is still unclear and reported sensitivities and specificities for CTS diagnosis range from 65% to 97% and 73% to 98%, respectively.[41]

The most important limitation of median nerve sonography is the lack of a consensus regarding CTS specific findings. An increased cross-sectional area (CSA) of the median nerve, for example, is characteristic for CTS, however, the optimal cut-off distinguishing between a normal and abnormal result has not been defined so far.[5,42]

Besides, different anatomical landmarks (such as the scaphoid – pisiform bone, the hook of the hamate – tubercle of trapezium bone or the proximal end of the flexor retinaculum) as well as different methods to determine CSA were proposed in previous studies. [5,41]

Therefore, median nerve sonography does not replace NCS, rather it is used as a complementary method depicting morphological changes within the carpal tunnel (e.g. cysts, lipomas, ganglions, osteophytes, persisting median artery, tenosynovitis, bifid median nerve, accessory muscle ect.).

MRI is an alternative method to ultrasound to investigate the median nerve as well as carpal tunnel morphology. The diagnostic accuracy of MRI is comparable to sonography, however, MRI has the disadvantages of higher costs, contraindications, lower availability and a lower special resolution compare to ultrasound.[43] [44,45] The following criteria are used to diagnose CTS with MRI: increased T2 weighting of the median nerve, bowing of the flexor retinaculum, increased CSA of the median nerve and increased nerve flattening.

1.1.8 Differential diagnosis (DDx)

During diagnostic work-up of CTS patients other entrapment syndromes as well as systemic neuropathies should be excluded: *Cervical Syndrome*/*Cervical Radiculopathy* (CS) for example is one of the most common nerval entrapment syndromes mimicking CTS. CS most frequently affects the segments C6 – C7, however, CS of other segments (such as C4 - C6 or C7 - C8) may also occur. CS is caused by expansive or degenerative processes (e. g. tumors, arthrosis of the intervertebral joints) reducing the space within the vertebral foramen. In addition, lateral and backward movements of the head involving the cervical spine enhance impingement of nerve's root from affected segments.

The characteristic symptom of CS is radiating pain in the area of neck and shoulders triggered by turning the head to the affected side.

CTS and CS are clinically distinguished by the limitation of pain and numbness to the dermatome supplied by the involved segment in CS patients whereas in CTS patients symptoms follow the distributed area of the median nerve. In addition, reduced reflexes (triceps: C6 – C7; biceps: C5 – C6; supinator: C4 – C5) indicate a radicular origin of symptoms.[46]

The Thoracic Outlet Syndrome (TOS) is caused by entrapment of the brachial plexus branches and the subclavian artery in the posterior scalene hiatus. Occasionally, TOS can also be the consequence of post fracture callus formation of the clavicle or a cervical rib. Characteristic symptoms are pain at shoulder and neck, particularly

when arms are in elevated position. In some patients TOS causes symptoms similar to CTS such as nocturnal dysesthesia and/or numbness of the arm or fingers (mostly 4th and 5th digit), weakness, clumsiness, and wasting of the finger muscles.[47]

To differentiate TOS from CTS, imaging procedures such as x-ray, MRI and ultrasound may be helpful demonstrating abnormal bone or soft tissue structures at the thoracic outlet. Additionally, electrophysiologic testing supports the identification of the level of nerve damage.[47]

Pronator Teres Syndrome (PS) is caused by proximal entrapment of the median nerve at the elbow's level between the ulnar and humeral head of the pronator teres muscle. Expansive processes such as hematoma after elbow trauma (e. g. dislocation, fracture), prominent intramuscular ligaments as well as a hypertrophic pronator muscle can increase pressure on the median nerve impairing its function.[48]

Most symptoms of PS overlap with those of CTS.[49,50]

In advanced cases of PS mobility of thumb, index and middle finger is severely restricted due to the missing innervation of the entire digitorum superficialis muscle and the radial portion of the digitorum profundus muscle. In contrast, CTS patients predominately suffer from sensory loss with or without thenar muscle wasting.

Anterior Interosseus Syndrome (Kiloh – Nevin Syndrome) is a lesion of the anterior interosseus nerve originating from the median nerve distal of the pronator teres muscle. The etiology of this syndrome is elusive so far; however, fibrous bands in the pronator muscle are suspected to cause compression of the nerve.[51] In some cases, injury or neuritis of the anterior interosseus nerve may cause the disorder.

Clinically, patients with the Kiloh – Nevin Syndrome present with weakness of the flexor pollicis longus and flexor digitorum profundus muscle I and II leading to the inability to form an "O" with thumb and index finger.[49] Sensory symptoms are usually absent because the interosseus anterior nerve is a motor branch only.

Double- or Multiple Crush Syndrome is defined by a disorder, where the combination of proximal and distal lesions of a peripheral nerve leads to the occurrence of clinical symptoms.[52] Patients with subclinical CTS for example manifest clinically, if cervical compression of the nerve bundles supplying the same dermatome occurs.[52]

1.1.9 Therapy

In general there are two therapeutic approaches for CTS patients: *conservative management* and *surgical intervention*.

Current guidelines of the American Academy of Orthopaedic Surgeons recommend conservative management for mild to moderate CTS patients and reserve surgical interventions for patients with severe, therapy refractory disease.[1,53] Several conservative treatments have been investigated (e. g. splinting, local or systemic steroids, NSAID's, Diuretics, Vitamin B, nerve gliding exercises); however, for most of them insufficient data from clinical trials are available so far. The most commonly used treatment options are summarized below.

1.1.9.1 Splints

Study results concerning the efficacy of splints for treatment of CTS are contradictory. Whereas a recent Cochrane review concluded that there is limited evidence for the effectiveness of splints worn at night for therapy of CTS, other reviews report a good efficacy of this treatment.[54,55] Nevertheless, the use of splinting in mild to moderate cases without permanent nerve damage or disability in daily activity is justified.[56] Particularly in pregnancy, where CTS is self-limiting or in situations of overuse of the wrists, splints may be a good option.

Splints fix the wrist in neutral position particularly during night to avoid additional nerve irritation through unconscious flexion during sleep thus enabling nerve recovery. Several designs of splints have been developed; however, no significant difference between the splint types regarding efficacy has been shown so far.[47,57]

1.1.9.2 Corticosteroids

Corticosteroids effectively reduce interstitial edema thus decreasing the overall pressure within the carpal tunnel.[20,58]

Corticosteroids can be administered orally or can be injected locally into the carpal tunnel. The efficacy of a local injection of 15mg methylprednisolone to reduce CTS symptoms was higher than oral treatment with 25mg prednisone in a 12-week trial.[59,60].[53] In a 2-year follow-up study it was further observed that most patients treated with oral corticosteroids relapsed after a few months: only 10% and 8% were still in remission after 18 and 24 months, respectively.[61] In contrast, a 16-month study on patients with mild CTS demonstrated that local corticosteroids may induce long term relieve of symptoms in the majority (79%) of patients.[62]

Concerning the safety of corticosteroid therapy it is known that long-term use of oral corticosteroids is associated with systemic adverse events such as weight gain, hypertension or diabetes. In contrast, local injections may result in nerve injury or infection in rare cases.

1.1.9.3 Physical Therapy

The term “physical therapy” summarizes various treatments aimed at the mobilization of tendons, nerve and carpal bones in patients with CTS by exercise. Nerve and tendon gliding exercises, carpal bone mobilization, activity modification, chiropractic treatment and yoga, however, all failed to demonstrate efficacy in clinical studies.[63,64][65]

1.1.9.4 Other drug regimens

Diuretics are thought to reduce the amount of interstitial fluid similar to corticosteroids and might therefore decrease pressure within the CT. Clinical trials; however, did not show effective reduction of symptoms by these substances after 2 and 4 weeks of treatment.[66]

NSAID's are commonly used in CTS patients; however, the evidence for the efficacy of these drugs is low.[66,67]

Vitamin B6 (Pyridoxine) is an important co-factor for enzymes involved in the metabolism of peripheral nerves. A lack of Pyridoxine leads to impaired protein synthesis and neuronal dysfunction.[68] Clinical trials studying the efficacy of Vitamin B6 supplementation in CTS patients, however, failed to demonstrate a benefit of this therapy over placebo.[67]

1.1.9.5 Surgical Intervention

Surgical release of the carpal tunnel is more effective than conservative treatments regarding the long-term improvement of CTS symptoms as well as electrophysiological outcome parameters.[69]

Two different surgical techniques are currently used in CTS patients: the conventional *open carpal tunnel release (OCTR)* and the *endoscopic carpal tunnel release (ECTR)*. Both methods aim at the division of the flexor retinaculum and at the removal of scar tissue within the carpal tunnel by neurolysis and/or tenosynovectomy. Both methods can be performed in local anesthesia, intravenous regional anesthesia, peripheral nerve blocks or general anesthesia.[70]

The endoscopic approach was the preferred technique for several years and it was argued that the small incision required to revise the carpal tunnel with ECTR results in less postoperative pain, lower infection rates, lower frequency of scar complications, faster recovery of functional status and lower sickness costs due to an earlier return to workplace. Current studies and systematic reviews, however, were unable to confirm these assumptions.[71,72] The overall complication rates such as nerve-, artery- or tendon damage or even mild unwanted effect such as neuropraxia were comparable between patients operated with ECTR (0.19%) or OCTR (0.49%).[72] Only regarding the risk of surgery induced nerve damage, the ECTR had a slightly worse outcome than OCTR with complication rates of 0,14% and 0,11%, respectively.[73] Besides, a revision operation is more frequently needed in case the ECTR technique is used.[74,75]

The costs for ECTR are 98 £ higher than for OCTR in the United Kingdom.[76] Another 6.482 £ for the initial purchase of the ECTR gear has to be considered.[76] Patients operated with the OCTR method, however, return earlier to work compensating for the slightly higher intrahospital costs. [76] [74,77]

In summary, both surgical methods are established for patients with CTS. As current literature does not favor one method over the other, personal factors such as patients' preference or experience of the surgeon influence the decision about which technique is used for an individual patient.[71]

1.1.10 Prognosis

There are still no good predictors of CTS outcome. For surgical treatment (i.e. OCTR) current data indicate that nicotine and alcohol abuse are related to worse treatment results.[78] Additional negative predictors are thoracic outlet- or double crush syndrome and poor general health status. Patients with a long duration of symptoms usually have worse outcome after operation compared to patients with recent onset disease.[79] Patients suffering from mental disorders such as depression have also worse results in terms of satisfaction and symptoms severity after surgical treatment.[80,81]

1.1.11 Purpose and aim of this research

Ultrasound of the wrist is a diagnostic approach focusing morphologic changes of the median nerve and related structures within the carpal tunnel.

An increased nerve CSA and/or the presence of intranerval PD-signals are characteristic ultrasound signs of CTS.[82] One of the most important factors hampering the routine use of median nerve sonography is the difficulty of determining CSA thresholds (ranging from 9-15mm2).[82-84] Additionally, there is a lack of consensus regarding anatomical landmarks for the measurement of median nerve volume. Calculating the ratio between the median nerve CSA at the proximal forearm and the carpal tunnel improved the diagnostic accuracy.[85-87] However, in these studies reliability testing and adequate control groups lacked.[85-87]

This research examines a large prospective ultrasound study on patients with suspected CTS. The specific aim of the study was to analyze the diagnostic value of sonography-determined CSA at different anatomical landmarks including forearm to wrist ratios and differences. Moreover, the value of intranerval PD-signals as an additional diagnostic tool for CTS diagnosis is assessed.

The results of this research might further contribute the rational implementation of ultrasound as a valuable tool in the diagnose finding of CTS.

2. Methods

Patients:

We performed a prospective study on 135 consecutive patients with suspected CTS undergoing clinical and electrophysiological evaluation between March 2010 and December 2011. In addition, we included 23 healthy controls (HC, mean age 50.4 ± 6.7 years, 78.3% female) for ultrasound studies. The study was approved by the institutional review board of the Medical University Graz and written informed consent was obtained by each patient. Patients presenting with ⩾1 of the following symptoms at one wrist at least were included: (1) paresthesias, pain and/or sensory deficits in the hand in a median nerve distribution, (2) nocturnal/ early morning worsening of paresthesias with disturbed sleep, (3) paresthesias relieved by hand movement or shaking, (4) pain and/or paresthesias in a median nerve distribution provoked by monotone exercises, (5) weakness of fingers supplied by median nerve. Patients with previously diagnosed CTS, conditions resulting in an increased risk of (associated) CTS such as former surgery at wrist, recent wrist fracture, known inflammatory rheumatic disease or pregnancy, patients with known polyneuropathy or contraindications against electrophysiological testing were excluded.[45] Clinical examination consisted of evaluation of muscular strength and trophism, sensory function, and clinical provocation tests including Phalen's, reverse Phalen's and carpal tunnel compression test.

Nerve conduction studies (NCS) were performed at the symptomatic side(s) according to a routine protocol by two neurologists who were unaware of ultrasound results. In brief, NCS was done using commercially available nerve conduction equipment (EMG/NLG/EP-system type Topas, Schwarzer, Munich, Germany). Skin temperature over the dorsum of the hand was kept at 34°C. The antidromic sensory median nerve conduction velocity (normal values 50m/second), the distal motor latency (4.2msec), and the median motor compound muscle action potential (5mV) were determined.[88]

Follow-up visits were performed three months after baseline evaluation. Patients were re-evaluated using clinical and electrophysiological tests as described above.

As there are no uniformly accepted diagnostic criteria for CTS, the final diagnosis was established by the evaluating neurologist based on symptoms, clinical and NCS results.[82,89] The neurologist was asked to indicate his confidence (0-100%) of the diagnosis at each visit.

The diagnosis according to both visits was used as the reference standard in order to increase the validity of the final result: CTS was considered as confirmed with a $\geqslant$90% confidence in diagnosis and excluded if the likelihood for the diagnosis was $\leqslant$10%. Patients with a probable (>10% and <90%) CTS at visit 1 and definite CTS at visit 2 were considered as confirmed CTS. All other cases were rated as possible CTS cases. For those patients not attending the follow-up visit the final diagnosis from baseline visit was taken for the analysis.

Ultrasound protocol

Sonographic evaluations were performed by two rheumatologists experienced in musculoskeletal sonography (C.De.–5 years, M.St.–2 years experience) at the days of baseline and follow-up clinical and electrophysiological testing. Both sonographers were unaware of clinical and NCS results. Patients were examined in sitting position with hands resting in a horizontal supine position on the examination table with fingers semi-extended.[90] We used a Logiq E9 ultrasound device (GE, Milwaukee, WI, USA) with a multifrequence linear transducer (6–15-MHz). A frequency of 15.0 MHz was used for B-mode ultrasound, and imaging parameters were adjusted to maximize the contrast between examined structures. PD-settings were standardized accordingly: frequency 11.9 MHz, pulse repetition frequency 600 Hz (lowest possible avoiding motion artefacts most of the time) and medium persistence. The PD-gain was optimized by increasing gain until noise appeared and then reduced just enough to suppress the noise.[91]

Transverse imaging of the median nerve was done in the area between the distal forearm and the outlet of the carpal tunnel. To minimize sampling errors due to differential loads, a gel pad (thickness 3.3mm; Sonar Aid®, Gestlich Pharma, Wolhusen, Switzerland) was used. CSA of the median nerve was determined by tracing a continuous line at the inner hyperechoic rim with electronic callipers.[85,91] Images were magnified in order to reduce measurement error. CSA was measured at 5 different levels as previously proposed: (a) **C**ross-**s**ectional area at the proximal border of the **P**ronator quadratus muscle (Cs**P**), (b) area of the proximal **T**hird of the

pronator quadratus muscle (Cs**T**), (c) level of **L**argest CSA of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet (Cs**L**), (d) carpal tunnel inlet defined as the proximal margin of the flexor **R**etinaculum (Cs**R**), and (e) in the carpal canal, level of the **S**caphoid tubercle and pisiform bone (Cs**S**) (see Figure 1 for illustration).[85,89,90]

PD-signals were graded from 0–3, in which 0 represented no PD-signal, 1=one single vessel within median nerve, 2=two or three single or two confluent vessels and 3=more than three single or more than two confluent vessels. See figure 2 for examples.

Each assessment was performed twice and the arithmetic mean of the 2 measurements was recorded. The duration of sonography did not exceed 5 minutes per examined wrist (i.e. ⩽10 minutes/patient).

Statistical analysis

Statistical analysis was performed using SPSS (v19.0). Descriptive statistics were used to summarize the data. Proportions were analyzed by the chi-square test and quantitative results were compared using the Mann-Whitney U test (due to non-parametric distribution of the data). Correlations were done with the Spearman's rank correlation test. For final assessment of the diagnostic value of sonography we included the data of the 135 patients with suspected CTS only (excluding HC). To compare the diagnostic values of different methods determining median nerve swelling receiving operating characteristic (ROC) curves were constructed by plotting sensitivity against 1-specificity varying the cut-offs and calculating the area under the curve (AUC). To correct for the fact that wrists were clustered within patients we calculated the mean of AUCs' 95% confidence interval (95%CI) from left and right sites.

Inter-observer variability of B-mode and PD-findings was determined by intra-class correlation coefficient (ICC) and linear weighted kappa coefficient, respectively based on data from 34 patients' wrists analyzed by two ultrasonographers at one visit. Intra-observer variability was investigated by ICC using data from all available patients' wrists. To calculate reliability, CSA of the median nerve at CsP (where median nerve is normal also in CTS patients) as determined by one ultrasonographer was compared between baseline and follow-up visits.

3. Results

A total of 135 patients were included into the study and 111 (82.2%) patients completed baseline and follow-up visits. Clinical characteristics are detailed in Table 3.

Out of the 270 carpal tunnels available for sonography, 4 were excluded because of previous surgery and 22 had a bifid median nerve which was analyzed separately. Abnormal ultrasound findings were present in 11 wrists including effusion (n=8), tenosynovitis (n=2) or intraarticular calcifications (n=1). In one patient rheumatoid arthritis was diagnosed during work-up of CTS.

The final diagnosis of CTS (as outlined in M&M) was made in 111 (45.5%) wrists. CTS was excluded in 59 (24.2%) wrists, 25 were asymptomatic (10.2%) and 49 (20.1%) were considered as possible CTS cases. The prevalences of abnormal NCS findings are summarized in Table 7.

Out of the 46 wrists from HC, two (4.3%) were excluded because of previous fracture and 4 (8.7%) had bifid median nerve.

Table 3: Clinical characteristics of patients with suspected CTS (n=135)

Age at inclusion [years]†	51.9 (±14.5)
Female, n (%)	99 (73.3)
Body mass index [kg/m^2]†	26.8 (±4.3)
Symptom duration [months] ‡	12 (1-362)
ESR [mm/1st hour] (n=102) ‡	8 (2-60)
CRP [mg/L] (n=102) ‡	1.3 (0.6-26.2)
Associated diseases, n (%)	
Diabetes mellitus 2	2 (1.5)
	9 (6.7)
Hypothyroidism	1 (0.7)
Rheumatoid arthritis	
Employment (n=133) , n (%)	
blue-collar jobs	51 (38.3)
white-collar jobs	49 (36.8)
housewives/ charlady	23 (17.3)
pensioners	4 (3.1)
other	6 (4.5)
Manual hobbies (n=107)	79 (73.8)

‡median (range); †mean (standard deviation), n, number, ESR, erythrocyte sedimentation rate (normal values 1-10 mm/1st hour); CRP, C-reactive protein (normal values 0-5 mg/L)

Median nerve sonography

CSAs of median nerve at different anatomical levels are shown in Table 4. CSAs were larger at wrists with confirmed CTS compared to wrists without CTS, asymptomatic sites and wrists of HC. Ultrasound findings correlated with NCS data as depicted in Table 8.

The CSA of bifid median nerves was calculated adding the area of the two nerve bundles. Median CsL at wrists without CTS (n=3) was 9.0mm^2 (range 7.0-13.5), at wrists from HC (n=4) 10.0mm^2 (8.0-10.5) and at wrists from patients with CTS (n=7) 12.0mm^2 (11.0-15.5, differences not significant).

Table 4: Cross-sectional areas of median nerve at different anatomical levels

	CsP	CsT	CsL	CsR	CsS
CTS	7.0 (5.0-11.0)	7.5 (5.0-12.0)	13.0 (9.0-28.5)*	12.0 (8.0-25.5)*	11.5 (7.0-28.0)*
no CTS	7.0 (5.0-12.0)	7.0 (5.0-12.0)	9.0 (6.0-22.0)	9.0 (6.0-20.0)	9.0 (6.0-21.0)
assymp	7.5 (6.0-9.5)	8.0 (6.0-10.5)	9.0 (7.0-15.0)	9.0 (6.5-14.0)	9.0 (7.5-13.0)
possible	7.0 (5.5-12.0)	7.0 (5.5-11.5)	11.5 (6.0-20.5)	11.0 (6.0-16.0)	10.0 (5.5-23.5)
healthy	7.5 (6.0-9.5)	8.0 (5.5-10.0)	8.8 (6.5-13.5)	8.3 (6.0-11.5)	8.0 (6.0-13.0)

CTS, wrists with confirmed carpal tunnel syndrome (as defined in M&M); no CTS, wrists with excluded CTS; assymp, assymptomatic sites; possible, wrists with possible CTS; healthy, wrist from healthy controls

CsP, proximal border of the pronator quadratus muscle; CsT, area of the proximal third of the pronator quadratus muscle; CsL, level of largest cross-sectional area of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet; CsR, carpal tunnel inlet defined as the proximal margin of the flexor retinaculum; CsS, level of the scaphoid tubercle and pisiform bone.

Data indicate median (range) cross-sectional [mm^2] at different levels as indicated; *$p<0.001$ compared to wrists with no CTS, to asymptomatic sites and wrists from healthy controls (not corrected for multiple testing)

Ultrasound determined median nerve swelling for the diagnosis of carpal tunnel syndrome

To directly compare the diagnostic value of different methods determining median nerve swelling ROC curve analysis was performed. Data from wrists with ruled out CTS and asymptomatic sites were pooled, whereas data from HC were excluded for this analysis. The following techniques were compared: (1) determination of CsL, CsR and CsS, (2) ratio CsL/CsP, CsR/CsP, CsS/CsP and CsL/CsT, CsR/CsT, CsS/CsT as well as (3) difference CsL-CsP, CsR-CsP, CsS-CsP and CsL-CsT, CsR-CsT, CsS-CsT.

Comparable diagnostic values were found for all methods with AUCs ranging from 0.75 to 0.85 (see figure 3 for examples). The numerically highest AUC was found for CsL (0.85, 95%CI 0.79-0.91), difference CsL-CsP (0.84, 0.78-0.89) and CsR (0.84, 0.78-0.90).

Similar results were obtained when (1) only diagnoses from baseline visits were considered [CTS: 115 (46.6%), no CTS: 56 (22.5%), asymptomatic: 36 (14.5%), possible CTS: 41 (16.5%; 8 out of them with <50% probability for the diagnosis and 33 with ⩾50% probability)] or when (2) only patients with confirmed diagnosis at both visits (excluding asymptomatic sites and patients with a single visit) were analyzed [CTS: 61 (30.7%) and no CTS: 23 (27.4%)].

For bifid median nerve no ROC curve analysis was calculated because of the low number of cases and controls available.

As a result of ROC curve analysis numerous cut-offs for the ultrasound methods tested were generated with varying sensitivities and specificities. Table 5 illustrates selected cut-offs with a ⩾90% sensitivity or ⩾90% specificity.

Next, we investigated whether the CSA ratio or CSA difference method increases the diagnostic accuracy of sonography in cases CsL resulted in a moderate sensitivity and specificity (i.e. CsL between 9.8 and 13.8mm^2). ROC curve analysis yielded an additional diagnostic value for both CSA ratio and CSA difference techniques with AUCs ranging from 0.60 (0.48-0.72, n.s.; method: ratio CsS/CsT) to 0.68 (0.57-0. 80, p=0.007; method: difference CsL-CsP). Selected cut-offs with corresponding sensitivities and specificities are detailed in Table 9.

Table 5: Sensitivity and specificity of different methods to determine median nerve swelling for the diagnosis of carpal tunnel syndrome

Method	Cut-off	Sensitivity [%]	Specificity [%]
CsL	9.8 mm^2	91.8	60.0
	13.8 mm^2	38.2	91.8
CsR	9.8 mm^2	90.9	61.2
	13.8 mm^2	31.8	91.8
CsS	8.8 mm^2	90.0	44.7
	12.8 mm^2	35.5	91.8
CsL/CsP	1.30	90.9	50.6
	1.81	50.9	91.8
CsR/CsP	1.25	90.9	44.7
	1.68	56.4	91.8
CsS/CsP	1.07	90.9	21.2
	1.66	46.4	91.8
□1.8CsPc	2.5 mm^2	93.6	55.3
	6.5 mm^2	41.8	92.9
□2.9mmPc	1.5 mm^2	96.4	31.8
	5.5 mm^2	51.8	92.9
□2.9mmPc	0.5 mm^2	92.7	16.5
	5.5 mm^2	36.4	95.3

Data are presented for those methods with the highest area under the curve in receiver operating characteristic (ROC) curve analysis. Cut-offs were selected to obtain either a ⩾90% sensitivity or a ⩾90% specificity for each method.

Data indicate cut-offs for the cross-sectional area (CSA) at CsL, the level of largest median nerve swelling observed between the area proximal to the carpal tunnel inlet and the tunnel outlet; the CsR, the level of carpal tunnel inlet defined as the proximal margin of the flexor retinaculum and the CsS, the level of the scaphoid tubercle and pisiform bone. In addition, cut-offs for the CSA ratio between CSL, CSR or CsS and CsP (level of the proximal border of the pronator quadratus muscle) as well as cut-offs for the CSA difference between CSL, CSR or CsS and CsP are shown.

Impact of median nerve vascularisation for diagnosis of CTS

The prevalence and median PD-scores at CsL, CsR and CsS are shown in Table 4. No vascularisation of the median nerve at the level of pronator quadratus muscle was observed.

For calculation of diagnostic value of PD, data from HC were excluded. Considering a PD-score $\geqslant$2 as an abnormal finding resulted in a high specificity of this method: at area CsL sensitivity 47.4% and specificity 89.8%, CsR 40.5% and 90.9%, CsS 19.1% and 96.6%, respectively.

In cases CsL was between 9.8 and 13.8mm^2, a PD-score of $\geqslant$2 led to an additional correct classification of 45.8% of CTS wrists with a specificity of 80% (p=0.017). When CsL was >13.8 mm^2 PD was of no additional value because 42.7% of wrists without CTS had a PD-score $\geqslant$2 in this group.

Table 6: Prevalence of power Doppler (PD)-signals within median nerve and median PD-score at different anatomical levels

	CsL		CsR		CsS	
	n (%)	PD-score	n (%)	PD-score	n (%)	PD-score
CTS	89 (80.9)*[&]	1 (0-3)	87 (79.1)*[&]	1 (0-3)	57 (52.3)*[#]	1 (0-3)
no CTS	23 (39.0)	0 (0-3)	19 (32.2)	0 (0-3)	9 (15.3)	0 (0-3)
assymp	8 (32.0)	0 (0-2)	8 (32.0)	0 (0-2)	6 (24.0)	0 (0-2)
possible	29 (59.2)	1 (0-3)	27 (55.1)	1 (0-3)	14 (28.6)	0 (0-3)
healthy	6 (15.0%)	0 (0-1)	7 (17.5%)	0 (0-1)	7 (17.5%)	0 (0-2)

CTS, wrists with confirmed carpal tunnel syndrome (as defined in M&M); no CTS, wrists with excluded CTS; assymp, assymptomatic sites; possible, wrists with possible CTS; healthy, wrists from healthy controls; CsL, level of largest cross-sectional area of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet; CsR, carpal tunnel inlet defined as the proximal margin of the flexor retinaculum; CsS, level of the scaphoid tubercle and pisiform bone

Data indicate the number (percentage) of wrists with intranerval PD-signals as well as the median (range) PD-score (possible range 0-3) at different levels as indicated.

*$p<0.001$ compared to wrists with no CTS; [&]$p<0.001$ compared to asymptomatic sites and wrists from healthy controls; [#] $p<0.05$ compared to asymptomatic sites and wrists from healthy controls (not corrected for multiple testing)

Reproducibility of ultrasound findings

ICC of CsL (0.90; 95% CI 0.79-0.95) was higher than ICC of ratio CsL/CsP (0.79; 0.62-0.89), whereas ICC of difference CsL-CsP did not differ from the two other methods (0.85; 0.72-0.92). Linear weighted kappa coefficient for PD-assessments at CsL was 0.51 (95%CI 0.32- 0.71). ICC for intra-observer variability was 0.65 (95%CI 0.55-0.73).

4. Discussion

Our data indicate a high diagnostic accuracy and reliability of median nerve sonography for patients with suspected CTS. Determination of CSA at the level of maximal nerve shape had comparable performance to measurement at anatomical landmarks. The calculation of CSA ratio or difference between the site of entrapment and distal forearm was advantageous only in cases of moderate nerve swelling. PD-signals within median nerve improved correct classification of CTS.

We compared different ultrasound methods to determine median nerve swelling to resolve the most important uncertainty resulting from previous studies, namely that the optimal level or anatomical landmark examining CSA is unknown and that published CSA cut-offs are not directly comparable.[82] The majority of earlier studies investigated the median nerve at the scaphoid-pisiform level (CsS), whereas CsL and CsR were less commonly assessed.[82] CSA measurements at the carpal tunnel outlet (level of the hook of the hamate) resulted in a low diagnostic accuracy and reliability in previous publications and were thus not included in our study.[82] Recently proposed CSA ratio or difference methods comparing median nerve at site of entrapment with sites at distal forearm intended to compensate for inter-individual variability of median nerve CSA that may range from 5.5 to 13.5mm^2 in HC.[84-87,92] According to our ROC curve analyses none of these methods can be favored over the other. Assessment of median nerve CSA at its maximal shape (CsL) is probably the simplest way to investigate median nerve swelling in clinical practice and has a high diagnostic accuracy and good reproducibility. Also a recent systematic review favored this technique because the site of maximal median nerve swelling varies between CTS patients.[2,38]

The CSA cut-offs presented in table 3 are arbitrary and depending on the clinical question and pretest probability other cut-offs may perform better.[89] In our setting, we considered two cut-offs as the most relevant ones: one resulting in a high (i.e. $\geqslant$ 90%) sensitivity and a second revealing a high specificity.

Explanations for the fact, that we were unable to confirm the superior performance of CSA ratio/difference over CsL or CsR (as proposed earlier) are the methodological differences between our and the previous studies as well as the possibility that the inter-individual variability of median nerve is not relevant if the CSA cut-off is selected

above the upper range of normal.[84-87] Applying the ratio or difference method to cases with moderate nerve swelling, it was of additional diagnostic value as outlined in supplementary table 3. Another notable finding is the high inter-observer reliability of CsL. A higher reproducibility of the ratio or difference method could be expected given that examiner-dependent variances of manual tracing are “internally” corrected.[85-87] On the other hand, the inner hyperechoic rim of the median nerve is clearly identifiable at wrists resulting in a high reproducibility of CSA at this level.[93,94]

We investigated the presence of PD-signals within median nerve as an alternative/additional tool for CTS diagnosis. A PD-score $\geqslant$2 had a comparable sensitivity and specificity to CsL, and in patients with moderate nerve swelling, a PD-score $\geqslant$2 was associated with a positive likelihood ratio (=sensitivity/1-specificity) of 2.3 to correctly classify these patients. Only one previous study investigated the value of PD-signals systematically;[95] however, this study was retrospective, used ultrasound equipment with a low power and did not grade PD-signals. Semiquantitative scoring was useful to increase specificity of PD, whereas the absence of vascularisation almost excludes CTS.[95]

The diagnostic value of other ultrasound findings such as median nerve flattening ratio or retinacular bulging were not investigated in this study as a low accuracy of these findings is already known.[36,95]

Our study has several strengths: First, we performed the study in the target population of median nerve sonography, namely in patients with suspected CTS. In contrast to previous studies, we excluded HC from ROC curve analyses and did not focus on patients with (long) known CTS because a case–control design might have resulted in a false-high diagnostic accuracy of sonography (partially due to incomplete blinding).[85-87,89,96-98] In our study for example, specificity of CsL (cut-off 13.8mm^2) would have increased from 91.8% to 94.5% if HC were included. Second, the diagnosis was based on clinical and electrophysiological findings from two subsequent visits. Patients with transient symptoms as well as patients with unclear findings were considered as possible CTS cases and were analyzed separately. This approach is conservative resulting in a high number of unclassified cases. Part of them might be considered as “mild CTS” cases, others have a transient disorder resolving without specific treatment and a proportion of patients might develop full CTS to a later time point.[90,99,100] A long term follow-up study investigating this issue is underway.

Many previous studies focused on NCS as the reference standard excluding those 16-34% of patients with clinically characteristic CTS but normal electrophysiological testing.[82,101,102] NCS identifies permanent nerve damage, but not intermittent nerve disturbance in early CTS.[103] Others considered the resolution of symptoms after release of the transverse carpal ligament as sign of definite CTS.[104,105] This approach, however, excludes patients with mild to moderate definite CTS because surgical intervention is usually performed in cases with persistent sensible deficits and/or motor weakness.[1] Physicians' final diagnosis based on clinical and NCS results is therefore the only adequate reference standard to study the diagnostic accuracy of sonography for CTS.[101]

Limitations of our study are the single-center design and the tertiary-care setting. The reproducibility of ultrasound findings in multicenter trials and the diagnostic performance of sonography in primary care (where the ratio between patients with confirmed and excluded CTS might be different) have to be addressed by future studies.

In conclusion, we demonstrated a high diagnostic value and good reliability of ultrasound determination of median nerve CSA in patients with suspected CTS. Measurement of nerve CSA at its maximal shape is the simplest way to investigate median nerve swelling and may thus be the favored in clinical practice. Assessment of intranerval PD-signals improves classification of CTS particularly in cases of moderate nerve swelling.

FIGURES

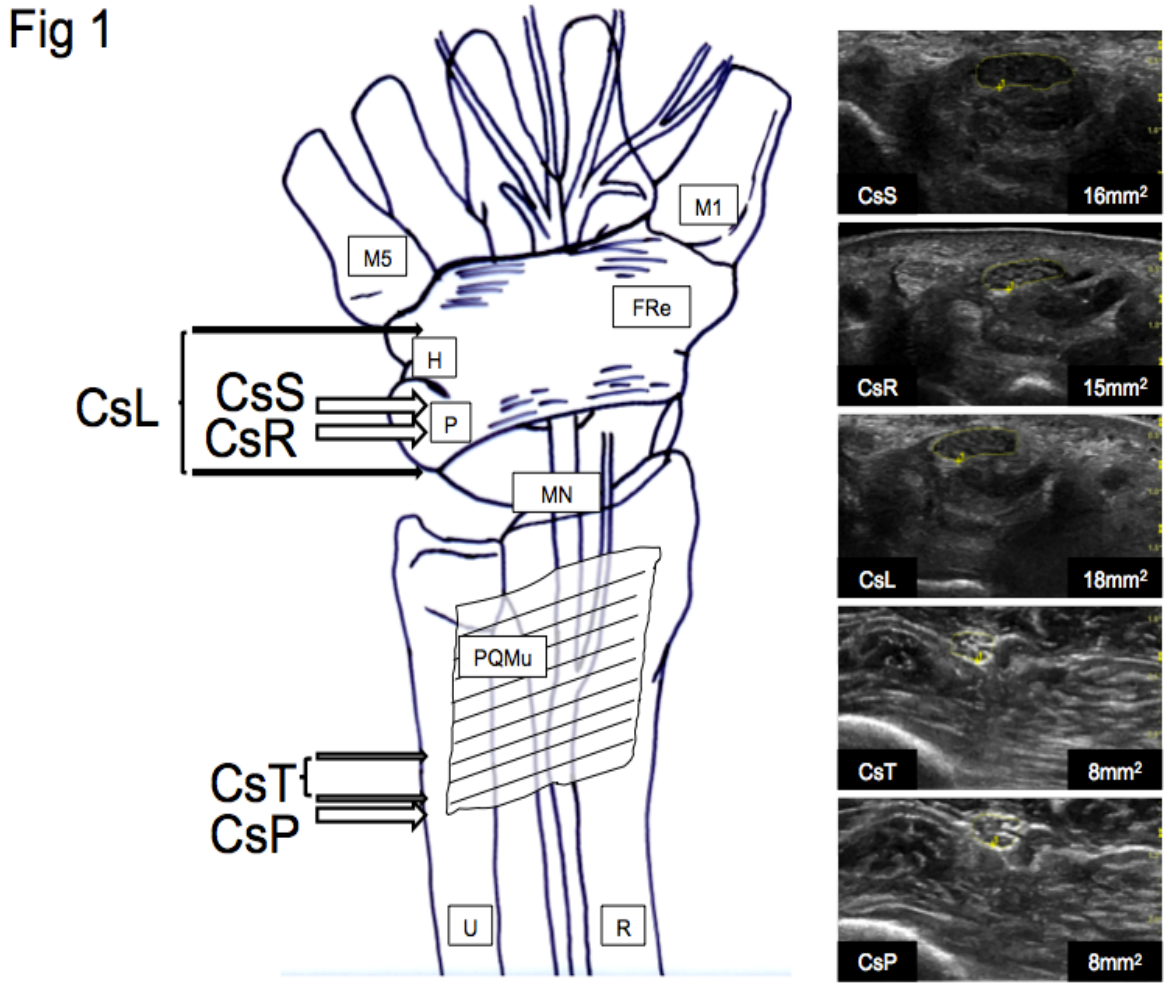


Figure 1: Anatomical levels to determine median nerve cross-sectional area

Illustration indicates anatomical levels where median nerve cross-sectional area (CSA) and power Doppler (PD) signals were assessed. In addition, ultrasound image examples of the median nerve (including CSA in mm2) obtained at each level are shown.

CsP, proximal border of the pronator quadratus muscle; CsT, area of the proximal third of the pronator quadratus muscle; CsL, level of largest CSA of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet; CsR, carpal tunnel inlet defined as the proximal margin of the flexor retinaculum; CsS, level of the scaphoid tubercle and pisiform bone; U, ulna; R, radius, PQMu, pronator quadrates muscle; MN, median nerve; P, pisiform bone; H, hamulus of the hamate bone; FRe, flexor retinaculum; M1,

M5, metacarpal bone 1 and 5

Table 7: Prevalence of abnormal findings by nerve conduction studies at baseline and at 3 months follow-up visit

	Baseline n (%)	Follow-up n (%)
abnormal sensory conduction velocity (V1 n=203; V2 n=150)	133 (65.5)	93 (62.0)
abnormal distal motor latency (V1 n=210; V2 n=152)	101 (48.1)	68 (44.7)
abnormal muscle action potential (V1 n=210; V2 n=152)	27 (12.9)	19 (12.5)

The number of wrists analyzed at baseline (V1) and 3 months follow-up (V2) are indicated. Normal values were: 50m/second for sensory conduction velocity, 4.2msec for distal motor latency, and 5mV for muscle action potential [88]

Table 8: Correlation between ultrasound findings and results of nerve conduction studies at baseline

Sono method	SCV	DML	MAP
CsL	-.53***	.52***	-.30***
CsR	-.50***	.50***	-.27**
CsS	-.36***	.37***	-.20*
CsL/CsP	-.47***	.48***	-.24**
CsR/CsP	-.46***	.46***	-.24**
CsS/CsP	-.29**	.31***	-.17*
□.17**Pt	-.51***	.51***	-.27**
□.27***t	-.49***	.49***	-.25**
□.25***t	-.31***	.33***	-.17*

Data were correlated using the spearman's rank correlation test. Correlation coefficients and corresponding significance levels are shown with ***p<0.001, **p<0.01, *p<0.05 (not corrected for multiple testing)

SCV, sensory conduction velocity; DML, distal motor latency; MAP, muscle action potential; CsL, cross-sectional area (CSA) at the level of largest median nerve swelling observed between the area proximal to the carpal tunnel inlet and the tunnel outlet; CsR, level of carpal tunnel inlet defined as the proximal margin of the flexor retinaculum; CsS, the level of the scaphoid tubercle and pisiform bone. Data for CSA ratio between CSL, CSR or CsS and CsP (level of the proximal border of the pronator quadratus muscle) as well as results for the CSA difference between CSL, CSR or CsS and CsP are also shown.

Table 9: Sensitivity and specificity of CSA ratio or difference method in cases with moderate CsL increment

Method	Cut-off	Sensitivity [%]	Specificity [%]
CsL/CsP	1.28	91.5	11.1
	1.78	40.7	92.6
□2.6CsPc	2.5 mm^2	94.9	11.1
	5.5 mm^2	40.7	92.6

Data indicate the diagnostic value of the cross-sectional area (CSA) ratio between CsL (the level of largest median nerve swelling observed between the area proximal to the carpal tunnel inlet and the tunnel outlet) and CsP (level of the proximal border of the pronator quadratus muscle) as well as the CSA difference between CsL and CsP, in cases CSA measured at CsL lied between 9.8 and 13.8 mm^2. Cut-offs were selected to obtain a high sensitivity or specificity for each method. Only data for methods with a statistically significant area under the curve are shown.

ad Fig. 2 Examples for semiquantitative scoring (0-3) of power Doppler (PD)-signals.

PD-signals within median nerve were semiquantitatively graded from 0 to 3 as outlined in Materials and Methods. Examples show transverse scans of median nerve at CsL (level of largest CSA of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet) or CsS (level of the scaphoid tubercle and pisiform bone, image marked with an asterix) with PD-scores ranging from zero (PD=0) to three (PD=3).

ad. Fig. 3 Receiving operating characteristic (ROC) curve analysis for different methods to determine median nerve swelling.

A comparison of ROC curves for different methods to determine median nerve swelling are shown including (a) assessment of cross-sectional area (CSA) at CsL (level of largest CSA of the median nerve observed between the area proximal to the carpal tunnel inlet and the tunnel outlet), CsR (carpal tunnel inlet defined as the proximal margin of the flexor retinaculum) or CsS (level of the scaphoid tubercle and pisiform bone), (b) CSA ratio between CSL, CSR or CsS and CsP (level of the proximal border of the pronator quadratus muscle), (c) CSA difference between CSL, CSR or CsS and CsP, (d) CsL, ratio CsL/CsP and difference CsL-CsP, (e) CSA ratio between CSL, CSR or CsS and CsT (area of the proximal third of the pronator quadratus muscle), (f) CSA difference between CSL, CSR or CsS and CsT as well as (g) CsL, ratio CsL/CsT and difference CsL-CsT

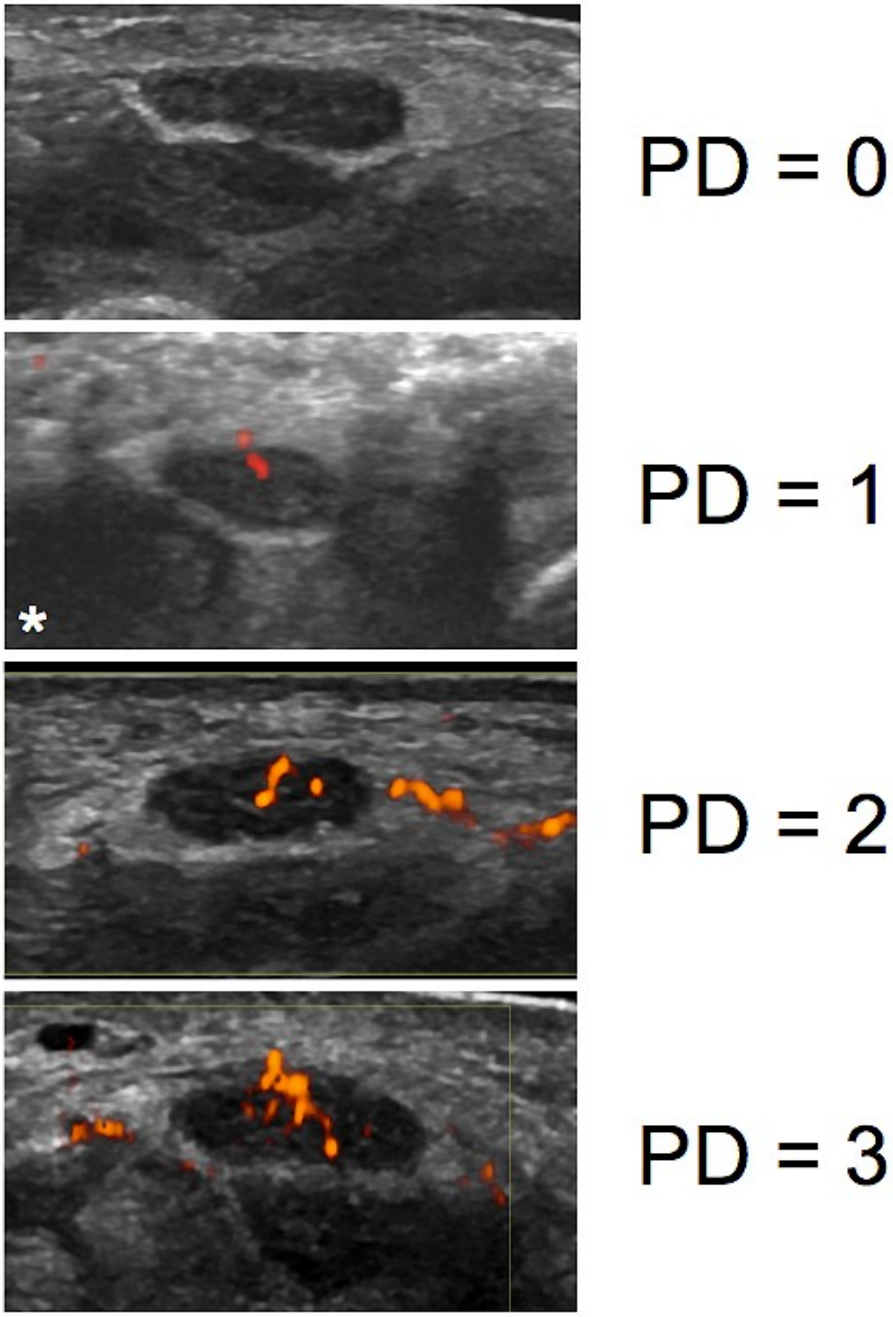


Figure 2: Examples for semiquantitative scoring (0-3) of power

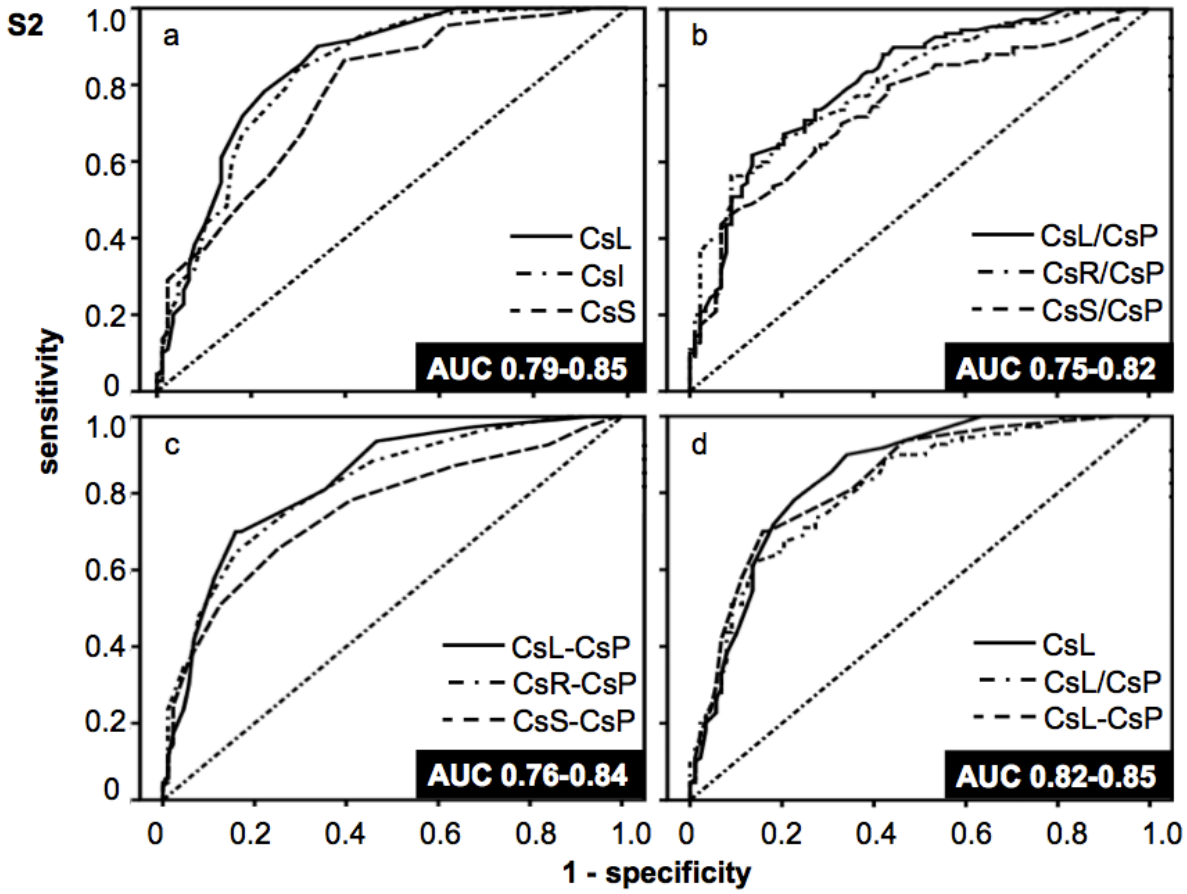
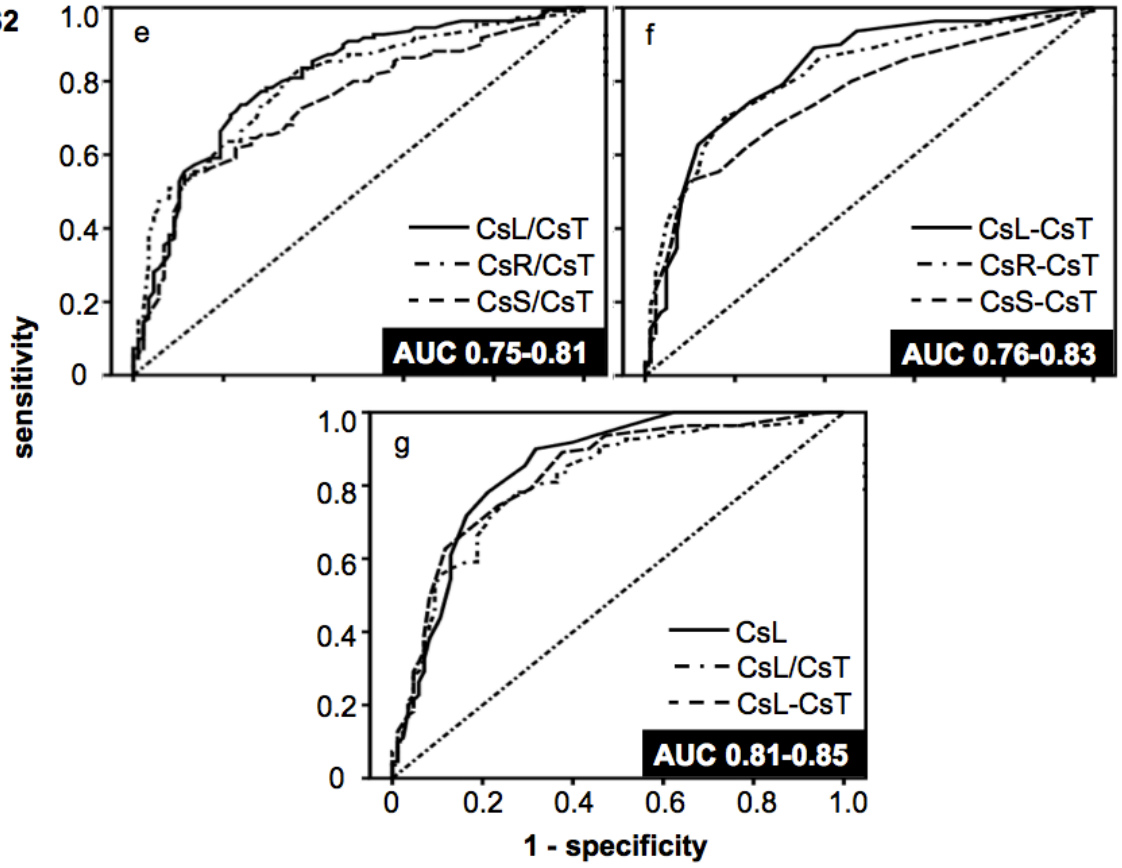


Figure 3: Receiving operating characteristic (ROC) curve analysis for different methods to determine median nerve swelling

S2


e
f
g
sensitivity
1 - specificity
1.0
0.8
0.6
0.4
0.2
0
CsL/CsT
CsR/CsT
CsS/CsT
AUC 0.75-0.81
CsL-CsT
CsR-CsT
CsS-CsT
AUC 0.76-0.83
CsL
CsL/CsT
CsL-CsT
AUC 0.81-0.85

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