Chapter 1

General Introduction and Thesis Outline
The carpal tunnel syndrome: general introduction

History
In 1854, Sir James Paget (1814-1899), Professor of Anatomy and Surgery at the Royal College of Surgeons of England, was the first to recognize that the median nerve could be compressed at the wrist. He described a case of a patient with hand symptoms resulting from a radial fracture. This patient had ulceration of the first three digits, which was cured only by fixation of the wrist in order to prevent pressure on the nerve. In 1880, James Jackson Putnam (1846-1918) presented a description of a series of 37 patients with symptoms of median nerve compression at the wrist, at that time known as Putnam’s acroparesthesia. Since then, the clinical syndrome was described increasingly, supported by autopsy and surgical studies. It was McArdle (1949, personal communication, Oral communication to the Association of British Neurologists in October 1951) who suggested that compression of the median nerve at the wrist was the cause of the paresthesias, which could be resolved by transsection of the flexor retinaculum. Since that decade, the clinical syndrome has generally been designated as the carpal tunnel syndrome (CTS) and currently it is the most frequently diagnosed entrapment neuropathy.

Epidemiology
CTS has an estimated prevalence of 9% in women and 0.6% in men, with a peak incidence in the fifth decade. The dominant hand is affected most often. There are many conditions associated with CTS: pregnancy, use of hormonal agents and oophorectomy, diabetes mellitus, rheumatoid arthritis, obesity (in younger patients), hypothyroidism, and Colles fracture.

Anatomy
The transverse carpal ligament or flexor retinaculum, is a sheath of connective tissue that runs medially from the hamate pisiform bone and is attached laterally to the scaphoid and trapezium bone and forms the roof of the carpal tunnel. The other borders (lateral, medial and lower) are formed by the pisiform bone and the tubercle of the scaphoid (proximally), and the hook of the hamate and
tubercle of the trapezium bone (distally). The median nerve traverses through the tunnel along with the nine flexor tendons (Figure 1) and divides in the palm into motor and sensory branches. The abductor pollicis brevis muscle and the opponens pollicis muscle are the main muscles supplied by the motor branch at this level. Generally, the medial half of the thumb, the index and middle finger, and the lateral half of the fourth finger are supplied by the sensory fibers of the median nerve. The sensation of the thenar eminence is innervated by the palmar cutaneous sensory branch, which does not pass through the carpal tunnel, and is therefore not affected in CTS.\textsuperscript{13,14}

\textbf{Figure 1.} Cross section of the wrist and carpal tunnel
Pathophysiology

The semi-closed carpal tunnel causes the median nerve to be vulnerable to local compression. Increased carpal canal pressures have been recorded in several studies and the pressure often approximates 30 mm Hg with the wrist in neutral position, which is the critical value to induce symptoms of neural deficit.\textsuperscript{15} The pressure increases when the wrist is flexed or extended. In acute compression, a sudden increase in pressure is caused, which probably causes local ischemia. Firstly, myelinated fibers are affected by the ischemia and this causes conduction block. Another consequence of compression is displacement of nodes of Ranvier during compression.\textsuperscript{16} Secondly, axoplasmic transport may be blocked which may result in anterograde axonal atrophy. However, even in chronic nerve entrapment, unmyelinated fibers tend to be spared.\textsuperscript{15} Thirdly, the pressure of the median nerve at the carpal tunnel varies diurnally and may also show variation with stretching and shearing.\textsuperscript{17} Fourthly, chronic compression causes endoneurial edema and inhibition of intraneural microvascular blood flow.\textsuperscript{17,18} If the compression is severe enough or chronic, secondary Wallerian degeneration and axonal loss may result.\textsuperscript{14} Ischemia and demyelination cause ectopic pulse generation in sensory fibers that may lead to paresthesias and pain. Weakness occurs in case of motor fiber conduction block or eventually in case of axonal degeneration and muscle atrophy.\textsuperscript{15} In chronic compression, sympathetic nerve fibers are relatively spared. Therefore, anhydrosis and vasomotor dysfunction are uncommon in carpal tunnel syndrome.

Signs and symptoms

CTS is characterized by paresthesias and numbness involving the median nerve innervated fingers (because of ectopic pulse generation, caused by ischemia and demyelination), typically occurring at night or present on awakening. Patients often mention relief of paresthesias, burning or subjectively swollen feeling or sensation of uselessness in the fingers by shaking,\textsuperscript{19} and hanging the arm out of bed or rubbing the hand (Flick maneuver).\textsuperscript{20} Muscular weakness is less frequently mentioned.\textsuperscript{6}

Some patients experience pain localized to the wrist or even radiation to the forearm. Typically, paresthesias are reported in the median nerve innervated area (median thumb, index, middle, and lateral ring finger). However, paresthesias or sensory symptoms are variably reported between patients, and a substantial part of patients report an extra-median rather than strictly median distribution of the paresthesias or sensory disturbance.\textsuperscript{21} It is suggested that a typically
median nerve distribution is associated with more severe cases of CTS.\textsuperscript{22} Other symptoms associated with CTS are worsening of paresthesias and pain by, for instance, driving a car, riding a bicycle or holding a phone or a book.

The neurological examination is often unremarkable in CTS patients, but sensory disturbances in the median nerve distribution (hypesthesia, hypalgesia) may be found.\textsuperscript{20} Thenar atrophy and weak thumb abduction are other signs that can be present on neurological examination, but probably exclusively in severe cases.\textsuperscript{14} Patients may experience (increase of) paresthesias in the distribution of the median nerve when the examiner taps the distal wrist crease over the median nerve (Hoffmann-Tinel’s sign\textsuperscript{23}) or when the patient flexes both wrists 90 degrees for 60 seconds (Phalen’s maneuver\textsuperscript{24}). However, in a recent study by Westerman et al.,\textsuperscript{25} the additional value of the neurological examination for the diagnosis CTS was low. The neurological examination rarely changed the diagnosis based on history.\textsuperscript{25} There are several hypotheses as to why these clinical findings are not useful in diagnosing CTS. Sensory findings are for instance often subjective, and atrophy occurs only in longstanding cases and can also be the result of other causes than CTS.\textsuperscript{20}

Diagnostics

\textit{Electrophysiology}

In 1956, a focal slowing of the median nerve motor conduction velocity was demonstrated for the first time electrophysiologically by nerve conduction studies.\textsuperscript{26}

Until then, neurophysiological confirmation of the clinical diagnosis was dependent on the demonstration of denervation on electromyography of the muscles supplied by the median nerve. However, electromyographic findings are often normal or only mildly abnormal in an early stage of CTS.\textsuperscript{14} Ever since, progress has been made in the electrophysiological diagnosis of CTS, a result of improved techniques of recording neurophysiological signals from peripheral nerves. Even detection of small abnormalities of nerve conduction is possible.

Myelin dysfunction and disruption at the nodes of Ranvier result in slowed nerve conduction velocity (NCV) and conduction block.\textsuperscript{27} Conduction slowing or conduction block in median nerve fibers across the carpal tunnel is the electrophysiological hallmark of a distal median neuropathy. However, nerve conduction studies are not only performed to confirm the diagnosis, but also to exclude other causes with symptoms similar to CTS.
Despite the fact that the clinical diagnosis remains the criterion standard, many surgeons require electrodiagnostic confirmation of the clinical diagnosis\textsuperscript{28} and Consensus Committees\textsuperscript{29} have endorsed electrodiagnosis as the diagnostic test of choice due to a high a sensitivity (85%) and specificity (95%) of nerve conduction studies.\textsuperscript{5}

The principle of the nerve conduction studies is based on the demonstration of focal nerve conduction slowing of the median nerve over the carpal tunnel. In general, sensory nerve conduction velocities (NCVs) of the median nerve across the wrist are compared with sensory NCVs of (radial and ulnar) nerve fibers, which are presumed to be normal. Normally, the NCV is approximately 50 m/s, but there is quite a range of variety. Therefore, it is commonly accepted that adjacent segments of the median nerve or other nerves near the median nerve can be used as a reference. Comparing the distal median sensory latencies with either the ulnar or the radial distal sensory latencies allows the greatest accuracy for confirming the diagnosis of CTS.\textsuperscript{27} However, generally, abnormal results in more than a single test are preferred over a single one to confirm the clinical diagnosis in order to minimize the chance of a false positive diagnosis. \textsuperscript{27,30,31}

One of the most sensitive tests is the so-called DIG4 test, in which the distal sensory latency of the median nerve is compared with the ulnar distal sensory latency over the same distance between the wrist and ring finger.\textsuperscript{5} (Figure 2A) If the NCV of the ulnar nerve is normal and the distal sensory latency difference between the median and ulnar nerve over the same conduction distance is more than 0.4 ms, this difference is considered significant and it suggests a median nerve conduction slowing, supporting the clinical diagnosis of CTS.\textsuperscript{27} Another sensory test is the so-called DIG1 test, in which the distal sensory latency of the median nerve is compared with the distal sensory latency of the radial nerve, both over the same distance (Figure 2B).\textsuperscript{27} According to our laboratory’s reference values the upper limit of normal (ULN) of this test is 0.6 ms.

Short segment studies have improved the diagnostic accuracy.\textsuperscript{5} Comparison of the NCV of median nerve fibers across the carpal tunnel with those distal from the carpal tunnel (PALM test) is also a sensitive test,\textsuperscript{32,33} and is frequently used in the electrodiagnostic testing for CTS (Figure 3). It has the advantage of measuring the median NCV selectively over the carpal tunnel. Since CTS is a focal neuropathy, the conduction slowing over a small segment is more easily detected when applying small conduction distances and it may be important to demonstrate a decrease in sensory NCV over a short segment.
Figure 2.
A. DIG1: comparison of distal sensory latency of radial nerve with median nerve.
B. DIG4: comparison of distal sensory latency of ulnar nerve with median nerve.
Black circle, cathode; White circle, anode

Figure 3. PALM3. Stimulation sites palm, wrist, and elbow.
Black circle, cathode; White circle, anode.
Additionally, it is generally recommended to perform a motor nerve conduction study of the median nerve recording from the thenar eminence in order to measure the distal motor latency (DML). The median nerve is stimulated at the wrist, usually with a distance of 6 cm between the stimulation and recording site (Figure 4). According to our laboratory’s reference values the ULN of the DML is 4.0 ms. Other motor nerve conduction studies are (1) the absolute value of the DML of the compound muscle action potential (CMAP) of the second lumbrical muscle; (2) comparison of the motor latency of the CMAP of the lumbrical muscle with that of the interosseous muscle after stimulation of the median and ulnar nerve; and (3) the terminal latency index of the thenar CMAP.

The use of needle electromyography as a standard electrodiagnostic test in CTS has been abandoned. Until the 1980s, compound muscle action potentials were recorded with concentric needle electrodes. At the time concentric needles were applied, it appeared that positive sharp waves and fibrillation potentials were rarely found in the abductor pollicis brevis muscle. Nowadays it is common use to apply surface electrodes over the muscle belly of the abductor pollicis brevis muscle; needle electromyographic examination is not routinely performed. If one considers a cervical radiculopathy, plexopathy, other focal neuropathies, or potential axonal loss, needle electromyography may be considered.

Figure 4. DML. The median nerve is stimulated at the wrist, a CMAP is recorded from the thenar. Black circle, cathode; White circle, anode.
Ultrasonography

As mentioned above, prior to surgical treatment, many surgeons require electrodiagnostic testing in order to confirm the clinical diagnosis. Moreover, Consensus Committees have endorsed electrodiagnostic confirmation as the diagnostic test of choice. Nerve conduction studies, however, may be perceived as unpleasant by some patients. During the past few years, imaging studies in CTS have caught on. High-frequency ultrasonography of the median nerve is emerging as a diagnostic test in CTS, and has been proved to be a patient-friendly, low-cost test. It is painless and, moreover, it gives additional anatomical and morphological information about the median nerve and its surrounding tissues. Ultrasonography is performed with a 5-17 MHz linear-array transducer. The nerve is first visualized proximal to the carpal tunnel in a longitudinal plane and then in transverse planes to confirm identification of the median nerve. Then, the cross-sectional area (CSA) of the median nerve is measured at the inlet of the carpal tunnel by using the direct tracing method.

An enlarged CSA of the median nerve at the inlet of the carpal tunnel is an important and characteristic ultrasonographic finding in CTS. Normal values range from 9 to 11 mm$^2$ or even up to 15 mm$^2$. Other reported findings are flattening of the median nerve at the level of the hook of the hamate and an increase in CSA at the level of the pisiform bone compared with the CSA of the median nerve in the forearm.

Generally, normal values of the CSA of the median nerve in adults are based solely on gender. More recently, new ultrasonography criteria that take wrist circumference into account were developed.

In up to 30% of patients with clinically defined and electrophysiologically confirmed CTS, the CSA is not enlarged. To date, it is not clear why the CSA in these patients remains normal.

The increasing use of imaging studies in CTS has led to an improved recognition of morphologic anomalies, such as bifid nerves. It is suggested by others that the presence of a bifid median nerve is associated with the occurrence of CTS, for example because of facilitation of compression as a consequence of a larger summated CSA. Data about incidence of bifid nerves and CTS are ambiguous.
Treatment

Several conservative treatment options are available. Wrist splinting is one example of conservative treatment that, in some cases, may improve symptoms. However, the results of a Cochrane Review suggest that surgical treatment of CTS relieves symptoms significantly better than splinting. Local corticosteroid injections may be suitable and effective in mild CTS according to electrodiagnostic criteria. In a more recent study, steroid injections were considered to be effective in the short term but, in the end, 75% of patients were operated within one year.
Aims and outline of this thesis

For research purposes the clinical diagnosis remains the gold standard. In daily practice, confirmation of the clinical diagnosis is often wanted prior to surgical intervention. Nerve conduction studies are most frequently used to confirm the clinical diagnosis and are also endorsed as the supplementary diagnostic test of choice; moreover, they are preferred over other diagnostics such as ultrasound or MRI.

The general aim of this thesis was technology assessment, reassessment and application of specific nerve conduction tests in confirming the clinical diagnosis CTS. Furthermore, we investigated whether ultrasonography can replace nerve conduction studies and we aimed to define specific cases in which ultrasonographic examination of the median nerve is particularly useful. We have chosen to study a group of patients with CTS based solely on strictly defined clinical criteria.

PART I - Nerve Conduction Studies

An important technical aspect of the nerve conduction studies is warming the limbs in order to ascertain the reliability of the results. Temperature influences different variables of nerve conduction studies in several ways. It is generally recommended to perform nerve conduction studies with a skin temperature of at least 31°C. In order to achieve these temperatures, warming of the limbs will often be necessary. A commonly used and proven effective method is warming cold limbs by using hot water immersion for 15-30 minutes. However, this procedure may be laborious or even impossible in elderly or bedridden subjects. Also, when more time is needed for the diagnostic procedure, the limb temperature may have dropped considerably in the meantime. In many instances, the nerve conduction studies are even performed without warming the limbs, because of lack of time. A cheaper and less unwieldy method is the application of hot packs; another potential advantage is that the hot packs may be removed shortly before testing, which prevents an unwanted drop of the temperature.

In chapter 2 we investigated whether application of hot packs over the skin of cold limbs is as efficient in warming the limbs as the more commonly used hot
water immersion method.

Sensory nerve conduction studies in general have several disadvantages, despite the fact that these are the most sensitive tests in diagnosing CTS. Firstly, sensory nerve action potentials (SNAPs), even when the studies are performed antidromically, are very small and are often negatively influenced by electrical noise, artifacts, etc. Secondly, SNAPs are more prone to (distal) temperature differences and other circumstances such as, polyneuropathy.

Another important factor that can introduce inaccuracy in these tests is the inherent small conduction distance. Short distances introduce relatively large measurement errors. In addition, conduction slowing in segments distal from the carpal tunnel in CTS patients is often found. Consequently, this segment may be less appropriate as a reference.

Nevertheless, since CTS is a focal neuropathy, the conduction slowing over a small segment is more easily detected when applying small conduction distances and it is therefore important to try to demonstrate a decrease in NCV over this short segment, for example with the so-called PALM-test in which originally the median sensory NCV over the wrist is compared with that over the palm. Since conduction slowing in sensory median nerve fibers over the forearm is rarely found, this segment can be used as a reference instead.

In chapter 3 we tested our hypothesis that comparing the sensory NCV of the median nerve across the wrist with that of the forearm is more sensitive than comparing it with that of the palm in the electrodiagnostic confirmation of CTS and we reassessed the diagnostic value of the segmental palmar test.

Conduction distances in the usually applied sensory nerve conduction studies in the hand are rather small. Because of the small distance between the stimulus cathode and recording electrodes in short segment sensory nerve conduction studies, stimulus artifacts make it often difficult to accurately define onset latencies. Measurement of peak latencies of the SNAP is less influenced by stimulus artifacts. However, these peak latencies cannot be used to compute nerve conduction velocities, since they do not represent the fastest conducting fibers. On the other hand, peak latencies of the median nerve can be compared to peak latencies of other nerves in the hand, which are presumed to be normal, if conduction distances are kept equal.

We investigated the diagnostic accuracy of onset versus peak latency measurements of SNAPs in electrodiagnostic studies in diagnosing CTS. This is
described in chapter 4. Many patients with CTS have normal motor nerve conduction studies: abnormally increased DML is 63% sensitive and 98% specific for diagnosing CTS.\(^5\) Accordingly and generally, to confirm CTS with electrodiagnostic testing, one should focus on sensory nerve conduction tests. However, in more severe cases, SNAPs may not be recordable.\(^6\) Then, motor nerve conduction studies are necessary and the only means to confirm the diagnosis.

In chapter 5 we tested the sensitivity of different motor nerve conduction tests in comparison to those of sensory nerve conduction tests in a group of clinically defined CTS patients. We also investigated the subgroup of patients whose SNAPs are not recordable separately.

PART II - Ultrasonography: An Alternative or Additional Test to Nerve Conduction Studies?

The ultrasonographic determination of the CSA of the median nerve at the level of the carpal tunnel is applied increasingly in confirming the clinical diagnosis of CTS. Since ultrasound is less bothersome and more patient-friendly than nerve conduction studies, it might be preferable to replace the nerve conduction studies by ultrasonographic examination if the accuracy is better than or at least equal to nerve conduction studies in confirming CTS. Previously, a new set of normal values taking wrist circumference into account was developed.\(^4\)

In chapter 6 we investigated whether ultrasonography, when using these new normal values, can replace nerve conduction studies in confirming clinically defined CTS.

Rather frequently, a normal CSA of the median nerve is observed in patients with clinically typical CTS. In up to 30% of patients with electrodiagnostically confirmed CTS, the CSA of the median nerve at the wrist is not enlarged.\(^3\) To date, it is not clear what is the cause of the normal CSA in these patients.

In an old study of patients with CTS with thenar atrophy, a reduction in fiber size of the median nerve under the flexor retinaculum was found.\(^6\) Also, in a more recently performed study it was shown that median nerves in amyotrophic lateral sclerosis patients have smaller CSA compared with healthy controls.\(^6\)
In **chapter 7** we tested our hypothesis that in patients with severe CTS, the CSA of the median nerve is reduced, instead of being enlarged, because of severe axonal damage.

The use of imaging studies such as ultrasonography in CTS has led to an increase in the recognition of anomalies such as bifid median nerves and persistent median arteries. The presence of these anomalies is also described in healthy controls.\(^{63}\) To date, it is not clear whether the presence of a bifid median nerve is associated with CTS. Likewise, data about electrophysiological findings and outcome in these patients are scarce.

In **chapter 8** we describe the results of a prospectively conducted study in which we tested our hypothesis that a bifid median nerve predisposes to the development of CTS. Moreover, we investigated differences in electrophysiological findings and outcome.

The main findings of this thesis are summarized in **chapter 9**, followed by a discussion of the results and recommendations for future research.
References


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