Summary

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. CTS may be reliably diagnosed clinically. However, if operative therapy is considered, an objective test is often required to confirm the clinical diagnosis. Electrodagnostic examination is endorsed as the test of choice, but ultrasonographic examination of the median nerve is applied increasingly.

In this thesis technology assessment, reassessment, and the application of specific nerve conduction tests in confirming the clinical diagnosis CTS will be described (Part I). Furthermore, an exploration of specific cases in which ultrasonographic examination of the median nerve can be useful is performed (Part II).

PART I - Nerve Conduction Studies

Nerve conduction studies (NCS) are important in the electrodagnostic testing of polyneuropathies and mononeuropathies such as CTS. Since temperature influences different variables of nerve conduction studies, it is recommended to perform NCS with skin temperatures of at least 31°Celsius. This often makes it necessary to warm the limbs prior to electrodagnostic testing. Since warming cold limbs by hot water immersion may be laborious in certain patients, we examined whether hot packs are as effective as hot water immersion for warming cold limbs in chapter 2. In 10 healthy persons the cold limbs were warmed; in half of patients this was first done by hot packs, then with hot water immersion, and vice versa in the other half of subjects. Motor and sensory NCS of the lower and upper extremities were performed before and after both different warming techniques. Mean temperatures were higher after warming with hot packs compared with hot water immersion and there were no differences in nerve conduction velocities (NCVs). Moreover, subjects preferred hot packs for reasons of convenience. Furthermore, hot packs are safe, clean and easy to use.

Another important advantage is that when nerve conduction studies in multiple extremities have to be performed, hot packs may be removed only then when a limb has to be studied in order to keep it at the appropriate temperature. We conclude that hot packs are as effective as and more convenient than hot water immersion for warming cold limbs. All nerve conduction studies in the thesis have been performed with this technique of warming the hand and forearm.
The electrophysiological hallmark of CTS is the decrease in NCV of the median nerve across the carpal tunnel. Often, NCV of the median nerve fibers across the carpal tunnel is compared with those distal from the tunnel i.e. the segment in the palm of the hand. 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. In a prospectively conducted study, we included 157 patients with clinically defined CTS, and reassessed a modification of the classic PALM-test. Reference values were derived from 47 healthy, asymptomatic volunteers. All were tested in the same laboratory according to the same electrodiagnostic test protocol. In all patients, antidromic sensory NCS were performed and the NCV of the median nerve was computed in 3 segments: forearm, wrist, and palm, and recorded from digit 2 and 3. The difference in NCV as well as the ratio of the NCV between the different segments were computed. Sensitivity of comparing the median NCV of the forearm with the wrist segment was 79.6% and 82.8% for the second and third digit, respectively, vs. 65.6% (digit 2) and 65.0% (digit 3) for comparing the NCV of the palm with the wrist. Applying the ratio led to slightly higher sensitivities (82.8% and 85.4% for the second and third digit, respectively). We conclude that this modification of the palmar test is a sensitive and robust method in diagnosing CTS. We recommend to use the sensory NCV of the median nerve of the forearm as a reference, instead of that of the palm. Since the sensitivity of the PALM test recorded from digit 3 is higher compared with the sensitivity of digit 2, we also recommend to record from digit 3.

In the hand the size of the nerve segments in the most commonly used nerve conduction tests in confirming CTS is relatively small. These short distances between stimulus cathode and recording electrode often cause disturbing stimulus artifacts. Consequently, defining onset latencies, as needed for determining NCV, can be difficult. Alternatively, peak latencies may be used. In chapter 4 we compared the diagnostic accuracy of onset versus peak latency measurements of sensory nerve action potentials (SNAPs) in electrodiagnostic studies for diagnosing CTS in a prospectively conducted study that included 156 patients with clinically defined CTS. Standardized NCS were performed (DIG1, DIG4, PALM3) and both onset and peak latency were measured. We constructed Bland-Altman plots to assess the agreement. Overall agreement, positive and negative per cent agreement, and Kappa coefficient were computed. The Bland-Altman plots, positive and negative per cent agreement
show a good overall agreement for all performed sensory NCS. The Kappa was 0.850, 0.847, and 0.815 for DIG1, DIG4 and PALM3, respectively. We conclude that onset and peak latencies in sensory NCS in diagnosing CTS show a good overall agreement, but sensitivities for all three tests are higher for onset latency measurements. Because onset latency represents the fastest conducting fibers, we recommend to use initially onset latencies. If accurate defining of onset latencies is not possible, peak latencies can be used instead.

Despite all efforts, SNAPs can sometimes not be elicited. This occurs especially in severe cases of CTS. Motor NCS are important in the documentation of motor fiber involvement in CTS and even more so if SNAPs cannot be elicited. In chapter 5 we prospectively tested the sensitivity of different motor nerve conduction tests in confirming CTS and compared it with the aforementioned sensory NCS. In 162 consecutive patients with clinically defined CTS we performed the following motor nerve conduction tests: (1) the distal motor latency of the compound muscle action potential (CMAP) of the thenar muscles (DML-APB); (2) lumbrical-interosseous comparison study (2L-INT). For both, terminal latency index (TLI) and residual motor latency were calculated. Sensitivity for the sensory tests was 79.4% (DIG1), 85.2% (DIG4), 81.8% (PALM3). The sensitivity for TLI-APB was 81.3%. All other motor nerve conduction tests showed considerably lower sensitivities. If SNAPs of DIG1, DIG4, and PALM3 could not be elicited, all motor nerve conduction tests are very sensitive (95.8% to 100%). If median nerve SNAPs are not recordable, but a CMAP is recordable to the abductor pollicis brevis muscle, the 2L-INT has no additional value.

To conclude:

- Hot packs are as efficient as hot water immersion in warming cold limbs prior to electrodiagnostic testing; it is far less laborious and more practical and it is therefore the preferable procedure.
- The modified segmental palmar test is a sensitive, robust, and easily applicable method in diagnosing CTS. The median sensory NCV in the forearm, instead of that in the palm, is recommended to be used as a reference. Since the sensitivity of the PALM test recorded from digit 3 is higher compared with the sensitivity of digit 2, recording from digit 3 is recommended.
- Onset and peak latencies show a good overall agreement in confirming the clinical diagnosis of CTS. Since onset latency measurements represent NCV of the fastest conducting fibers, the use of onset latency
is recommended.

- Sensory nerve conduction tests and terminal latency index have a high sensitivity in the electrodiagnostic confirmation of CTS. If no SNAPs can be elicited, all motor nerve conduction tests have a high sensitivity, but the lumbrical-interosseous comparison test had no additional value.

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

NCS may be perceived as unpleasant by some patients. Ultrasonography is painless and it gives additional anatomical and morphological information about the median nerve and its surrounding tissue. Enlargement of the cross-sectional area (CSA) of the median nerve at the inlet of the carpal tunnel is a characteristic finding. Originally, normal values of the CSA of the median nerve are based solely on gender, and range from 9 to 11 mm². Recently, new ultrasonography criteria were developed that take wrist circumference into account, which can predict the upper limit of normal (ULN) more accurately compared to an absolute cut-off point. In chapter 6 we compared the electrodiagnostic confirmation of clinical diagnosis of CTS with ultrasonography, using these new normal values. Furthermore, we determined whether electrodiagnostic examination can be replaced by ultrasonography to confirm the clinical diagnosis of CTS. We prospectively collected 156 patients with clinically defined CTS; all underwent neurological, electrodiagnostic, and ultrasonographic examinations. Upper limit of normal CSA of the median nerve was established using regression equations based on left/right side and circumference of the wrist. Of 156 patients with clinically defined CTS, 130 (83.3%) met the electrodiagnostic criteria of CTS, 26 (16.7%) did not. Ultrasonographic examination adjusted for wrist circumference was abnormal in 89 patients (57.1%), only 3 of these patients had normal electrodiagnostic test results. Ultrasonography was normal in 67 patients (42.9%), within this group 44 patients (65.7%) had abnormal electrodiagnostic test results. We conclude that ultrasonography cannot replace electrodiagnostic examination for the confirmation of the clinical diagnosis of CTS and that it does not have the same diagnostic value as NCS in confirming CTS. However, in case of an abnormal ultrasonographic test result, 96.6% also had abnormal electrodiagnostic test results.
As described in chapter 6 and according to other studies, the CSA of the median nerve is not enlarged in a substantial number of patients with CTS. In chapter 6 we did not include patients with severe thenar atrophy. We hypothesized that the CSA of the median nerve in these patients is not enlarged but in fact may be reduced because of secondary atrophy after severe axonal damage. In chapter 7 we tested this hypothesis in a prospectively collected cohort of 14 patients with clinically and electrophysiologically defined severe CTS. The CSA of the median nerve was measured and compared with controls. Since the patient group appeared to be rather old (mean 71.8 years, range 52-86), we also collected and examined a group of asymptomatic elderly subjects. This group fitted well within the reference values for CSA. The CSA of the median nerve exceeded the ULN in the majority of patients with severe CTS; mean CSA 17.7 mm\(^2\) (SD, 5.22). We conclude that atrophy of the median nerve in severe CTS does not explain the negative ultrasonographic test results. Instead, the CSA of the median nerve is enlarged in most patients with severe CTS.

The use of imaging studies for diagnostic purposes in CTS has led to an increase in the recognition of morphological or anatomic anomalies such as bifid median nerves. It is suggested that a bifid median nerve may facilitate compression of the nerve because of larger CSA at the level of the carpal tunnel. Data about frequency, and association with CTS are, however, conflicting. Data about electrophysiological findings and outcome are scarce. In chapter 8 we tested the hypothesis that a bifid median nerve predisposes to the development of CTS and we investigated differences in electrophysiological findings and outcome in a prospectively conducted study with 259 consecutive patients with clinically defined CTS. 54 healthy asymptomatic volunteers were investigated ultrasonographically. We found a bifid median nerve in 41 patients (15.8%), 6 of whom bilateral, so, in patients a bifid median nerve was found in 47 of 518 wrists (9.1%). In contrast, ten control subjects (18.5%) had a bifid median nerve, all unilateral. We found no clinical differences in patients with bifid vs. non-bifid median nerves, but electrophysiological and ultrasonographic abnormalities were more pronounced in patients with non-bifid median nerves. Some outcome measurements show a better outcome after surgical decompression in patients with non-bifid median nerves. We conclude that a bifid median nerve is not an independent risk factor for development of CTS, but some of our data suggest the outcome to be different.
To conclude:

- **Ultrasonography cannot replace electrodiagnostic examination for confirmation of the clinical diagnosis of CTS.**

- Atrophy of the median nerve does not explain negative ultrasonographic test results. Instead, the CSA of the median nerve is practically always enlarged in patients with severe CTS.

- A bifid median nerve is found in patients as well as in healthy controls and is not an independent risk factor for the development of CTS. However, outcome in patients with a bifid median nerve may be different.
Chapter 9

Summary

General Discussion
General discussion

Carpal tunnel syndrome (CTS) can be reliably diagnosed clinically, but most surgeons require confirmation by supplementary quantitative testing when operative therapy is considered. For this, nerve conduction studies (NCS) are more frequently applied than ultrasound.\textsuperscript{1-3} Both techniques are the subject of this thesis.

\textbf{Nerve conduction studies}

Several sensory and motor NCS have been proved to be adequate for the confirmation of the clinical diagnosis of CTS. However, the sensitivity of these tests varies greatly. In accordance with previous studies we have demonstrated that the sensitivity of DIG4 is the highest among these techniques (85.2 to 86.0\%) (\textit{chapter 3 and 5}).\textsuperscript{4-5} This high sensitivity may be explained by the method of this test, which is comparing the test results with those from the presumably unaffected ulnar nerve fibers recorded from the same finger. Thus, both responses will be more or less equally influenced by age, skin temperature and height, as well as by physical parameters such as conduction distance and geometrical issues. More importantly, the median nerve fibers to the ring finger may be more subject to compression due to the position of the fibers to the ring finger in the outer margin of the median nerve beneath the transverse carpal ligament.\textsuperscript{5}

The sensitivity of the other sensory NCS, which is the subject of this thesis, ranges from 65.6\% to 82.8\% (PALM2; with the conduction velocity in the palm as a reference and PALM3; with the forearm conduction velocity as a reference, respectively, \textit{chapter 3}). The sensitivity of DIG1 is found to be 80.3\% and it is, rather unexpectedly, slightly lower than the DIG4-test, even though it has the same methodological reasoning. A possible explanation is the large variability in temperature differences between radial nerve fibers and median nerve fibers to the thumb. However, with our rather rigid method of warming the limb, this seems to be a less satisfying explanation. Since conduction distances in the DIG1-test are generally smaller than those in the DIG4-test, larger measurement errors may influence the sensitivity. Furthermore, regarding the topographical anatomy, the measured distance between the stimulation and the recording site in the DIG1 test, reflects far less accurately the conduction distance in the nerve fibers than that in the DIG4 test. Moreover, it is also dependent on the thumb position. Therefore, it is recommended to perform the DIG1-test...
in the same manner as when collecting reference values, and with the thumb
extended.⁵ There are specific cases, however, in which DIG1 can be particularly
useful. In these cases, the ulnar nerve cannot be used as a reference, because
of concomitant ulnar nerve pathology. It is suggested that the ulnar nerve is
sometimes also affected in the carpal tunnel syndrome.⁶,⁷ The radial nerve is
probably less often compromised in carpal tunnel syndrome and therefore DIG1
can be used instead. We often find relatively low conduction velocities in radial
and median nerve fibers to the first digit, compared with those to the fourth digit
in both patients and in healthy persons. It may be that fibers to the first finger are
physically different, as has been found to be the case in nerve fibers of the radial
nerve.⁸ It is therefore very important to collect reference values in each individual
laboratory⁴ and to apply the same procedure if DIG1-test is performed.

The observation that PALM3 has a higher diagnostic yield compared with
other sensory nerve conduction (comparison) studies can be explained by the
fact that in carpal tunnel syndrome there is a focal entrapment leading to a focal
compression. The detection of a focal slowing will be best demonstrated in short
distances, as used in PALM3. Slowing of the nerve conduction of the median
nerve fibers distal as well as proximal to the entrapment in the carpal tunnel
presumably occurs as a result of axonal degeneration of fibers outside the carpal
tunnel.⁹ It is far more frequently observed in fibers distal of the carpal tunnel than
in median nerve fibers of the forearm.⁵,⁶,¹⁰,¹¹ Therefore, the forearm sensory nerve
conduction velocity (NCV) is preferred as a reference in the PALM test. Probably,
this test may appear to be particularly useful in patients with polyneuropathy in
whom, obviously due to prevalent distal slowing, the DIG4 and DIG1 test are
not feasible. Moreover, in patients whose median SNAP cannot be recorded
from DIG1 or DIG4 it is not very surprising that it will however, be possible from
PALM3, as two digital nerves contribute to the SNAP amplitude at this site. So,
in these patients, the PALM3 test is particularly valuable.

In obese patients especially, it may be more difficult to stimulate the median
nerve supramaximally at the elbow as compared to the wrist, as the median
nerve may be deeply buried in the region of the elbow. In our cohort, obese
patients are well represented: 55.3% of patients had a body mass index > 25
(range 18.41 - 48.44).

The TLI-APB has a comparatively large diagnostic yield (81.3 to 81.5%) and
even has a higher sensitivity than most of the sensory nerve conduction tests
in confirming CTS (chapter 5). In this study, the terminal latency index (TLI)
was abnormal in 18 patients out of 45 patients (40.0%) with normal DML-APB,
which indicates that this test is more sensitive in diagnosing CTS. Otherwise,
when the DML-APB was abnormal, the TLI turned out to be normal in just 3 patients (2.6%). Reported sensitivity of TLI-APB in the literature ranges from 50.0%\textsuperscript{12,13} to 90.1%\textsuperscript{14} with reported specificity ranging from 53.9%\textsuperscript{14} to 94%\textsuperscript{13}, largely explained by differences in inclusion criteria and technical differences. It is suggested that TLI in particular, gives additional information to conventional electrophysiological studies in mildly affected motor nerves.\textsuperscript{12}

As defined by the values of the upper limit of normal and the lower limit of normal in our reference values, one abnormal test implies a 5% risk of false positivity. The presence of at least two abnormal electrodiagnostic test results further reduces this risk sufficiently for the reliable electrodiagnostic confirmation of CTS.\textsuperscript{5,16} Therefore, in clinical practice we recommend to use at least two abnormal test results for the electrodiagnostic confirmation of clinically defined CTS (Table 1). Furthermore, based on the results of our studies, we recommend starting with DIG4 and TLI-APB as a combination of sensory and motor NCS. In some CTS patients in whom the NCV in ulnar nerve fibers is also low, the latency difference in DIG4 will turn out to be within normal limits and the DIG4 test seems to be normal. Subsequently, the PALM3 test with the NCV of the forearm as a reference is recommended. In borderline cases, performing extra tests such as DIG1 may also be helpful. In our opinion, the 2L-INT test should only be performed if a CMAP of the APB cannot be recorded. In case of a recordable CMAP to the APB, this test has no additional value.

A proposal for a flowchart regarding NCS in confirming clinical CTS is shown in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Criteria for clinically defined CTS\textsuperscript{15}</th>
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<tbody>
<tr>
<td><strong>Criteria I to IV must be fulfilled:</strong></td>
</tr>
<tr>
<td>I pain and/or paresthesia in and restricted to median nerve distribution</td>
</tr>
<tr>
<td>II and 2 or more of the following:</td>
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<tr>
<td>- nocturnal paresthesias</td>
</tr>
<tr>
<td>- aggravation of paresthesias by activities such as car driving, bicycling, holding a book or telephone</td>
</tr>
<tr>
<td>- relieve of symptoms by shaking the hand (Flick sign)</td>
</tr>
<tr>
<td>III no aggravation of complaints by neck movements</td>
</tr>
<tr>
<td>IV complaints not originating from neck or shoulder</td>
</tr>
</tbody>
</table>
Figure 1. Proposed flowchart regarding nerve conduction studies in confirming clinically defined CTS.

Table 2. Normal values

<table>
<thead>
<tr>
<th>TEST</th>
<th>Onset latency</th>
<th>Peak latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG1</td>
<td>≤0.54 ms</td>
<td>≤0.81 ms</td>
</tr>
<tr>
<td>DIG4</td>
<td>≤0.34 ms</td>
<td>≤0.44 ms</td>
</tr>
<tr>
<td>PALM3</td>
<td>≤17.6 m/s</td>
<td>≤16.6 m/s</td>
</tr>
</tbody>
</table>

DIG1, distal sensory latency difference (median – radial nerve); DIG4, distal sensory latency difference (median – ulnar nerve); PALM3, median sensory nerve conduction velocity difference forearm vs. wrist.
**Technical issues**

It is important to be aware of physical and physiological factors that may influence the test results of NCS and the interpretation of its data. Stimulus artifacts and background noise of the signal amplifier may hamper especially the accurate measurement of sensory nerve action potentials. In most cases electronic signal averaging, lowering electrode impedance by scrubbing and cleaning the skin will be efficacious. Placing the ground electrode between stimulus and recording site and varying the stimulus strength and duration mutually may significantly reduce large stimulus artifacts. A very rewarding method is changing the direction of the electrical field of the stimulator electrodes by rotating the position of the anode without changing the position of the cathode. However, in NCS with short distances, which especially concern NCS in confirming entrapment neuropathies, stimulus artifacts may mask the onset latency of SNAPs. In the way that we performed the NCS described in this thesis we could refrain from small conduction distances to prevent these artifacts. However, if onset latency remains obscured by stimulus artifacts, despite all efforts to reduce them, peak latencies can be used instead (chapter 4). Peak and onset latency measurements show a good overall agreement in sensory NCS in confirming CTS empirically. Only onset latency represents the fastest conducting fibers, which is the only means to measure conventional nerve conduction velocity. Therefore, peak latency measurements may, in our opinion, not be applied to estimate nerve conduction velocities. In addition, when peak latencies are used, appropriate reference values have to be applied (see Table 2).

One of the most important physiologic factors, known to influence the nerve conduction velocity considerably, is temperature. In order to accurately interpret the results of NCS, the temperature of the limbs should ideally be minimally 32°C. In some laboratories one does not warm cold limbs because it is seen as too much work or as a laborious procedure. Sometimes it is not feasible in for instance old, bedridden patients or in the Intensive Care Unit. Some use correction factors for NCV. However, since these temperature correction factors probably have only been studied in healthy nerves and do not correct for other nerve conduction parameters, the procedure with warming cold limbs is generally recommended. It has been shown that general correction factors do not apply to patients with CTS and therefore, warming the limb before performing NCS is recommended. Warming cold limbs with hot packs (chapter 2) is an efficient, effective, hygienic, and comfortable alternative to hot water immersion or warming with external heaters; the latter moreover induces electrical noise. More
importantly, hot packs can be kept in place until the specific limb is studied, thereby preventing cooling down again and optimizing external circumstances in performing NCS and interpreting the results of these studies correctly. The minimal effective warming time has not been studied, nor has the effectiveness of hot packs in warming cold limbs of patients with suspected polyneuropathy, mononeuropathy, etcetera. However, it is known that temperature dependency of nerve conduction variables is different in diseased as compared to normal nerve fibers.\textsuperscript{19-21}

Despite all efforts made to optimize the NCS in confirming CTS technically, the results of all types of applied NCS may be normal in patients with classical CTS symptoms (clinically defined CTS). This phenomenon may be explained by the fact that paresthesias, an often very prominent complaint of CTS patients, may be caused by the generation of ectopic action potential by transient ischemia. In contrast to the physiological consequences of conduction block or axonal degeneration, these positive symptoms cannot be detected by conventional NCS.

**Ultrasound studies**

Had the accuracy of ultrasonographic testing been equivalent to electrodiagnostic testing, then the first would be preferred as it is more patient friendly. In daily practice, ultrasonography may be regarded as complementary to NCS for additional morphological information about the contents of the carpal tunnel and the presence of anatomical variations of the nerve apart from information about cross-sectional area (CSA) of the median nerve.

To date, NCS is still the first choice examination,\textsuperscript{3} among other reasons, possibly because sensitivity and specificity of ultrasonography show a large variation. In order to try to reduce this variation, normal values of the upper limit of normal for the CSA taking the wrist circumference into account, were developed.\textsuperscript{22} These were applied in a population with clinically defined CTS and compared with NCS. It appears that the sensitivity of ultrasonography for the confirmation of clinically defined CTS is lower than that of NCS when these values are applied (57.1\%) (\textit{chapter 6}). However, in case of abnormal ultrasonographic test results, 96.6\% of patients had abnormal electrodiagnostic test results. Even though ultrasonography may not completely replace NCS in all patients with clinical classic CTS, the clinical diagnosis could be confirmed in a substantial number of patients. Therefore, it could be a strategy to start
with ultrasonography to confirm the clinical diagnosis. In our study, we found that the CSA is not enlarged in a substantial number of patients with CTS. Atrophy of nerve fibers have been described in peripheral nerves of patients with amyotrophic lateral sclerosis.\textsuperscript{23} Therefore, we hypothesized that secondary axonal degeneration could be an explanation for the phenomenon that median nerve CSA is not always enlarged in CTS patients. As we found that the CSA is enlarged in 78.6\% of patients with severe CTS, it is not very likely that secondary axonal atrophy of median nerve fibers is an explanation for this phenomenon (chapter 7). So, if ultrasonography turns out to be normal, it is necessary to perform NCS to confirm the clinical diagnosis of CTS.

However, in case of postoperative complaints only NCS can discriminate recurrent or persistent CTS, by comparing test results with preoperatively performed conduction studies. It is important to bear in mind that, postoperatively, minor conduction abnormalities may persist even if the complaints have gone.\textsuperscript{24} Therefore, ultrasonography cannot be used to disclose insufficient recovery or deterioration postoperatively as yet.

Only ultrasonography allows the demonstration of the presence of a bifid median nerve (chapter 8). However, this may not be an argument for ultrasonography in the confirmation of CTS, as we have demonstrated bifid median nerves in 15.8\% of patients with CTS and in 18.5\% of healthy controls; this is obviously not a risk factor for developing CTS. At the moment, it is not clear which method for normal values has to be applied in the presence of a bifid median nerve, since the summated CSA appeared to be smaller in patients with a bifid median nerve compared to those with non-bifid nerves. The number of healthy subjects with a bifid median nerve was too small to compute normal values for this specific group. However, the mean of the summated CSA of bifid median nerve was within our previously assessed upper and lower limits of normal for non-bifid median nerves.\textsuperscript{22}

There are arguments that the presence of a bifid median nerve is associated with a relatively worse outcome after an operation, while preoperative electrophysiological severity was certainly not worse compared with patients with non-bifid median nerve. Likewise, electrophysiologically more severe CTS is associated with worse outcome.\textsuperscript{25} One may hypothesize that CTS patients with a bifid median nerve have to be treated differently. However, this subject was not within the scope of this thesis.

To conclude, NCS cannot be completely replaced by ultrasonography in confirming CTS. In a substantial proportion of patients with classical symptoms
suggestive of CTS, ultrasonography may be performed as an examination of first choice. Otherwise, ultrasonography may be complementary to NCS as additional information on anatomical variations and surroundings of the median nerve can be demonstrated. A proposal for a flowchart in confirming the clinical diagnosis with NCS and/or ultrasonography is shown in Figure 2.

Figure 2. Proposed flowchart regarding NCS and/or ultrasonography in confirming clinically defined CTS.

* see Table 1
** see Figure 1
Recommendations and directions for future research

Warming cold limbs prior to performing nerve conduction studies (NCS) is an important quality condition, which can be easily and effectively achieved by the application of hot packs during 30 minutes. The minimal necessary warming time using this method has yet to be established. If 10 to 15 minutes would prove to be sufficient, this would be considerably more efficient in daily practice.

When performing sensory NCS in confirming carpal tunnel syndrome (CTS), it is recommended to use onset latency measurements, since these represent the fastest conducting fibers. If it is not possible to define onset latencies accurately, for instance because of disturbing stimulus artifacts, peak latency measurements can be used instead. In this case it is imperative that other reference values are applied. It has been shown that inter- and intra-examiner reliability is higher for peak latency measurements compared with onset latency measurements. However, the reliability of peak and onset latency measurements in short-segment studies has not been studied thus far and further research is necessary.

In this thesis, only patients with typical CTS and healthy volunteers were included. As a consequence only sensitivity could be computed. This means that only clinically defined CTS patients could be discriminated from healthy controls. To estimate the specificity of all tests, patients with non-specific complaints of the hand in whom the diagnosis of CTS is considered but not proved, have to be tested according to our protocol.

A substantial number of patients in the cohort of patients with severe CTS suffered from diabetes. Patients with clinical signs of polyneuropathy were excluded from this study. It has been reported that the cross-sectional area (CSA) of the median nerve in the carpal tunnel of patients with diabetic polyneuropathy was larger than in patients without diabetic polyneuropathy, but it has also been reported that the CSA of the median nerve at the wrist was larger in diabetic patients with CTS, regardless of the presence of a coexisting polyneuropathy. Further studies are needed to collect reference values of ultrasonography in diabetics. Except for chapter 7, patients with severe thenar atrophy were excluded. Since these patients were excluded, we are probably not enough informed about the value of NCS in this specific group of patients. A previously performed study, however, has demonstrated only 5% prevalence rate of severe thenar wasting in a large CTS population. The sensitivity and specificity of the nerve conduction tests in patients with severe thenar atrophy
has to be established in the future.

Outcome in CTS patients with a bifid median nerve seems to be worse, despite the fact that the electrophysiological abnormalities are less severe compared to patients with non-bifid median nerves. One can hypothesize that worse outcome is caused by persistent entrapment of one branch of the median nerve or perhaps iatrogenic injury to one branch. Are there more complications in this patient group? Is the prevalence of a bifid median nerve in patients with surgical failure or poor outcome after surgery different? If so, this could be an argument that the surgical planning, for instance, has to be different. To date, ultrasonography has been used only in confirming the clinical diagnosis. Further study is needed to establish the role of ultrasonography in determining the prognosis in patients with CTS.

Diagnostic testing has been the main topic of this thesis. However, patients and their physicians are particularly interested in outcome after treatment. Therefore, it is relevant to study whether pre-treatment test results could predict the outcome in CTS patients.

Diagnostic tests to confirm the clinical diagnosis may have the disadvantage to withhold CTS patients from treatment in the case of false negative test results. It would be of value to study treatment outcome in clinically defined CTS patients who are treated irrespective of test outcome. In that way electrodiagnostic and ultrasonographic test results may prove to be of value in predicting outcome instead of merely confirming the clinical diagnosis of CTS.
References


