**Autonomous University of Barcelona / Universitat Autònoma de Barcelona**

**Department of Medicine, Vall d'Hebrón University Hospital**

## Ph.D. Thesis / Tesis Doctoral

*With Option to European Doctor Mention*

# DIAGNOSTIC ROLE OF REPEATER F-WAVES IN CARPAL TUNNEL SYNDROME WITH SUBCLINICAL RADICULOPATHY

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*To Staffan and our growing family*

# ABSTRACT

***Introduction*:** Repeater F-waves are sometimes seen in Carpal Tunnel Syndrome's (CTS) routine studies. These late responses are particularly useful for the diagnosis of polyneuropathies and proximal nerve lesions at a very early stage.

***Objective:*** The aim of this study was to assess, compare and analyze the incidence and characteristics of repeater F-waves in both peripheral nerve entrapments and cervical radiculopathies.

***Methods*:** We systematically reviewed the clinical significance of repeater F-waves in median and ulnar nerve recordings in consecutive patients with carpal tunnel syndrome, ulnar mononeuropathy and cervical root lesion in different combinations. Peripheral polyneuropathies were excluded from the study. The number of identical F-waves and their repetitions in samples of 20 stimuli were estimated.

***Results*:** A total of 123 patients (197 upper limbs) were studied over a 6-month period. Repeater F-waves occurred significantly more frequently in the nerves of radiculopathy groups than in peripheral nerve entrapments or healthy individuals. Their persistence was negatively correlated with that of non-repeaters F-waves.

***Discussion*:** Our findings suggest that repeater F-waves differentiate between radiculopathy and peripheral nerve entrapment pathology although not between different cervical levels of pathology or when too mild axonal damage. Even in routinely recorded samples of 20 traces, the index of repeater to all F-waves could be used as a nonspecific sign of proximal axonal pathology.

***Conclusions:*** Repeater F-Waves in peripheral nerve entrapment syndromes are proportional to the severity of the lesion and higher when subclinical cervical radiculopathies are present. Electromyography in these patients may help to the early diagnosis of subclinical cervical radiculopathies.

**Key words:** motor neurons; peripheral entrapment neuropathy; CTS; cervical radiculopathy; repeater F-waves; F-wave persistence.

# RESUM

***Introducció:*** Les ones F repetitives s'observen de vegades en els estudis habituals de la Síndrome del Túnel carpià (STC). Aquestes respostes tardanes són particularment útils per al diagnòstic de polineuropaties i lesions nervioses proximals en un estadi molt primerenc.

***Objectiu:*** El propòsit d'aquest estudi va ser avaluar, comparar i analitzar la incidència i característiques de les ones F repetitives tant en atrapaments nerviosos perifèrics com en radiculopaties cervicals.

***Mètodes:*** Revisem sistemàticament el significat clínic de les ones F repetitives en registres dels nervis mitjà i cubital en pacients consecutius amb síndrome del túnel carpià, mononeuropatia cubital i radiculopaties cervicals, en diferents combinacions. Les polineuropatías perifèriques van ser excloses de l'estudi. Es va estimar el nombre d'ones F idèntiques i les seves repeticions en mostres de 20 estímuls.

***Resultats:*** Es van estudiar un total de 123 pacients (197 extremitats superiors) durant un període de 6 mesos. Les ones F repetitives es van produir amb més freqüència en els nervis dels grups amb radiculopaties que en aquells grups definits per atrapaments nerviosos perifèrics o per subjectes sans. Es va observar una correlació negativa entre la persistència d'ones F repetitives i la d'ones F no repetitives.

***Discussió:*** Els nostres troballes suggereixen que les ones F repetitives mostren diferències entre la patologia radicular i els atrapaments nerviosos perifèrics, encara que no entre diferents nivells de patologia cervical o en el cas de dany axonal molt incipient. Fins i tot en els estudis habituals amb mostres de 20 traces, l'índex de respostes F repetitives respecte al total d'ones F podria ser pres com un signe inespecífic de patologia axonal proximal.

***Conclusions:*** Les ones F repetitives en les síndromes d'atrapament de nervis perifèrics són proporcionals a la gravetat de la lesió, sobretot en presència de radiculopaties cervicals subclíniques. L'electromiografia en aquests pacients pot ajudar al diagnòstic precoç de radiculopaties cervicals subclíniques.

**Paraules clau:** motoneurones; atrapament nerviós perifèric; STC, radiculopatia cervical; ones F repetitives; persistència d'ones F.

# RESUMEN

***Introducción*:** Las ondas F repetitivas se observan a veces en los estudios habituales del Síndrome del Túnel Carpiano (STC). Estas respuestas tardías son particularmente útiles para el diagnóstico de polineuropatías y lesiones nerviosas proximales en un estadío muy temprano.

***Objetivo:*** El propósito de este estudio fue evaluar, comparar y analizar la incidencia y características de las ondas F repetitivas tanto en atrapamientos nerviosos periféricos como en radiculopatías cervicales.

***Métodos*:** Revisamos sistemáticamente el significado clínico de las ondas F repetitivas en registros de los nervios mediano y cubital en pacientes consecutivos con síndrome del túnel carpiano, mononeuropatía cubital y radiculopatías cervicales, en diferentes combinaciones. Las polineuropatías periféricas fueron excluidas del estudio. Se estimó el número de ondas F idénticas y sus repeticiones en muestras de 20 estímulos.

***Resultados*:** Se estudiaron un total de 123 pacientes (197 extremidades superiores) durante un período de 6 meses. Las ondas F repetitivas se produjeron con más frecuencia en los nervios de los grupos con radiculopatías que en aquellos grupos definidos por atrapamientos nerviosos periféricos o por sujetos sanos. Se observó una correlación negativa entre la persistencia de ondas F repetitivas y la de ondas F no repetitivas.

***Discusión*:** Nuestros hallazgos sugieren que las ondas F repetitivas muestran diferencias entre la patología radicular y los atrapamientos nerviosos periféricos, aunque no entre distintos niveles de patología cervical o en el caso de daño axonal muy incipiente. Incluso en los estudios habituales con muestras de 20 trazas, el índice de respuestas F repetitivas con respecto al total de ondas F podría ser tomado como un signo inespecífico de patología axonal proximal.

***Conclusiones:*** Las ondas F repetitivas en los síndromes de atrapamiento de nervios periféricos son proporcionales a la gravedad de la lesión, sobre todo en presencia de radiculopatías cervicales subclínicas. La electromiografía en estos pacientes puede ayudar al diagnóstico precoz de radiculopatías cervicales subclínicas.

**Palabras clave:** motoneuronas; atrapamiento nervioso periférico; STC; radiculopatía cervical; ondas F repetitivas; persistencia de ondas F.

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# 1. INTRODUCTION

## 1.1. NEURAL PATHOLOGIES IN THE UPPER LIMB

Carpal tunnel syndrome (CTS), ulnar mononeuropathy at elbow and wrist, and cervical radiculopathy are common neural pathologies affecting the upper limb. Less frequent pathologies and locations are Pronator Teres Syndrome and Anterior Interosseous Neuropathy in median nerve, metabolic and vasculitic processes affecting ulnar nerve by the forearm or proximal to elbow, brachial plexopathies, and still less common proximal neuropathies of the shoulder and arm, like suprascapular and axillary nerve lesions.
Most prevalent pathologies entail different treatments which depend mostly on their location and severity. Thus, electrodiagnostic methods represent the cornerstone of their respective approaches.

## 1.2. EPIDEMIOLOGY

Carpal Tunnel Syndrome (CTS) is the commonest compressive focal mononeuropathy seen in clinical practice, (1-29) although its prevalence may vary with the population studied. In one population-based study in the Netherlands, clinical carpal tunnel syndrome was present in 3.4 percent of all people, and was likely present, although undiagnosed, in an additional 5.8 percent (30). The disorder is much more common in women; the overall prevalence in the same study was only 0.6 percent in men. In another study from the Mayo Clinic, the female to male ratio of 3:1 (31) with an annual incidence rate of only 99 per 100,000 (0.1 percent).

Ulnar neuropathy at the elbow or “cubital tunnel syndrome” is the second most common compression neuropathy affecting the upper extremities. The elbow is the most common site of compression of the ulnar nerve. Cubital tunnel syndrome affects men more often than women. This is partially due to lesser mechanic protection secondary to anatomical differences. (32)

Cervical radiculopathy is also common. At the Mayo clinic, the average incidence of this disorder between 1976 and 1990 was 83 per 100,000, with higher rates in men than in women (33). The incidence was highest in people 50 to 54 years of age, with C6 and C7 root lesions making up 64 percent of all cases.

Incidence of less frequent pathologies has been poorly reported in most instances. Lesser data are available in median nerve syndromes such as Pronator Teres Syndrome and Anterior Interosseous Neuropathy as well as in those affecting ulnar nerve, mainly metabolic and vasculitic processes by the forearm or proximal to elbow. However, the incidence of brachial plexitis has been studied through the Mayo Clinic records: over a 12-year period, the annual incidence of this disorder was only 1.6 per 100,000 population (34). Similarly, incidence of proximal neuropathies of the shoulder and arm is extremely low. It is likely that these numbers are underestimations of the true incidence. Mild cases of radiculopathy or brachial neuritis may never reach medical attention or may be misdiagnosed as a musculoskeletal injury.

# 1.3. ANATOMY

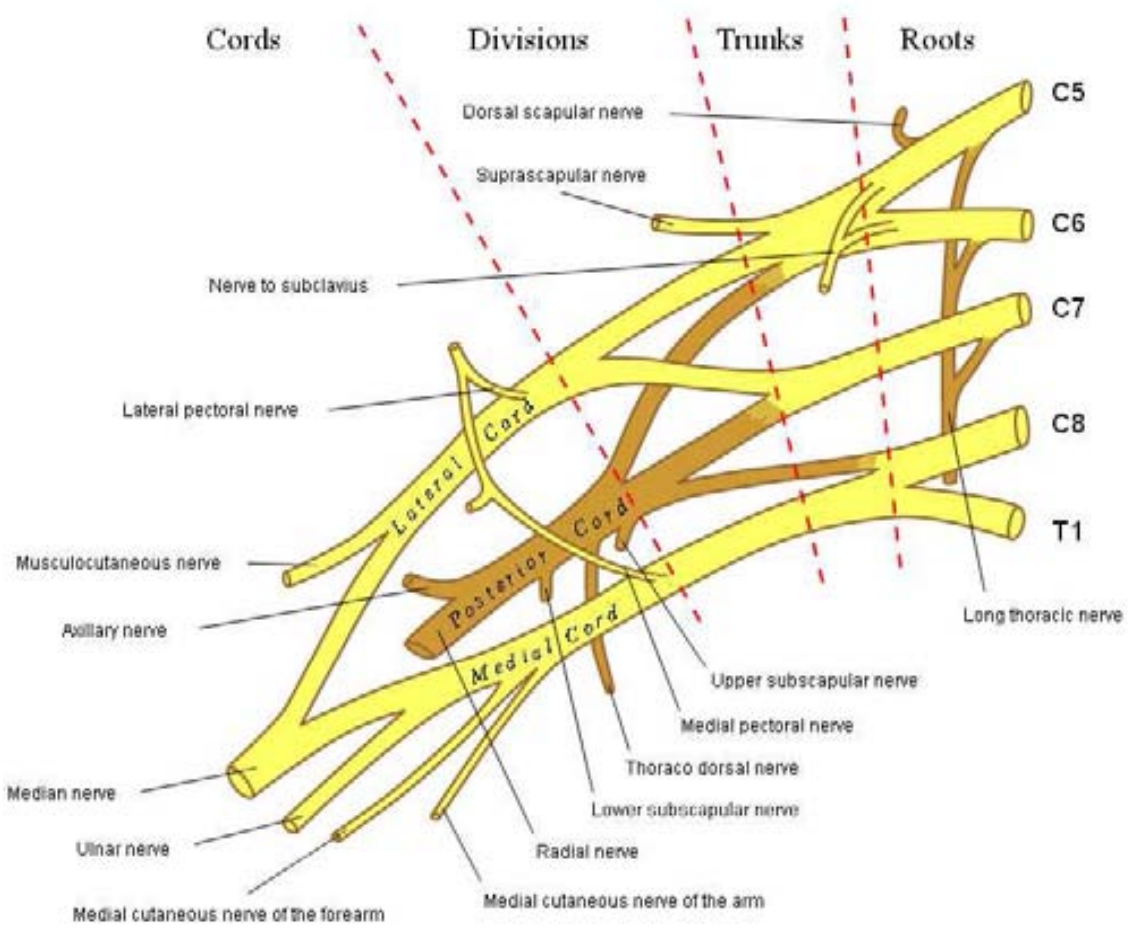
## 1.3.1. Cervical Spine and Intervertebral Foramina

Between the front and back of the vertebrae there is a canal, the spinal canal, within the spinal cord lies. Holes are also formed between the vertebrae, called conjunction, one on each side of the vertebra through which nerve roots exit from the spinal.

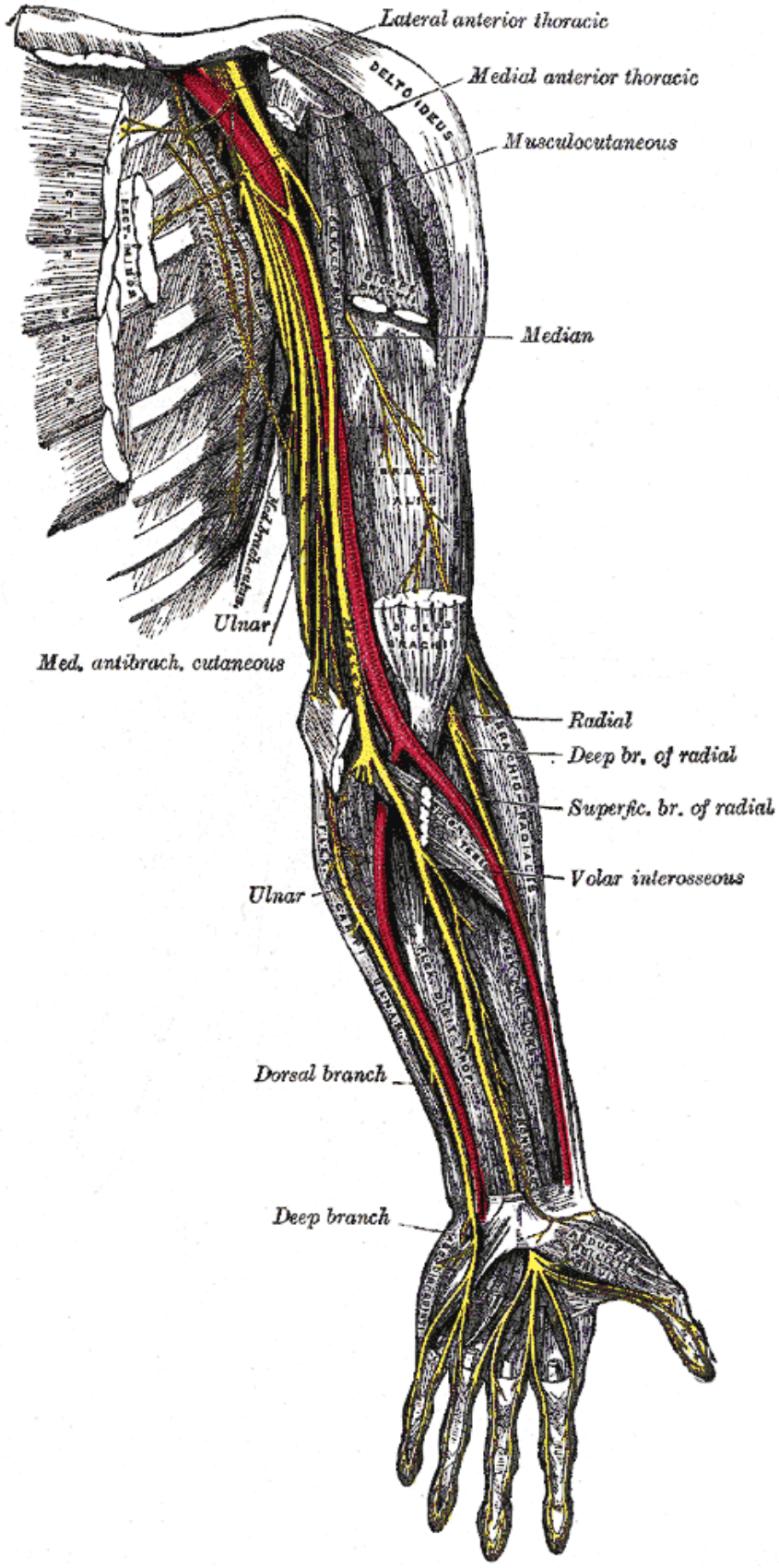
## 1.3.2. Brachial Plexus and Nerves of Upper Limb

The spinal roots C5 to T1 (*Pictures 1-3*) emerge from the column giving off small branches that proximally contribute to form the long thoracic nerve, which innervates the serratus anterior muscle. These roots then merge in a complex region known as the brachial plexus. A number of regions within the plexus have been defined by anatomists, including trunks, divisions, cords, branches, and proximal nerve; however, for practical purposes an understanding of the individual trunks, cords, and nerves is all that is necessary to correctly classify a problem affecting this region (35-37):

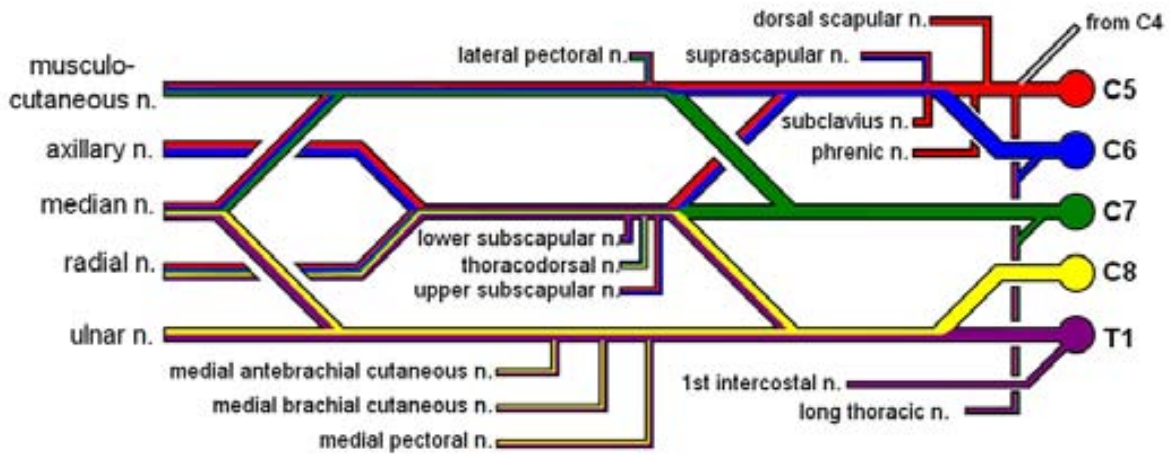
- The C5 and C6 roots merge to form the upper trunk; the C7 root alone makes up the middle trunk; the C8 and T1 roots form the lower trunk.
- The upper trunk becomes the lateral cord after giving off branches that contribute to the posterior cord; the middle trunk becomes the posterior cord after giving off branches which join both the upper and lower trunks; the lower trunk becomes the medial cord after giving off branches that contribute to the posterior cord.
- A number of nerves emerge from the lateral region of the plexus, including, from proximal to distal, the dorsal scapular nerve, the suprascapular nerve, the musculocutaneous nerve, and, in part, the median nerve. The ulnar nerve is the major nerve from the medial region of the plexus, while the posterior cord gives off a number of significant nerves including the axillary, subscapular, thoracodorsal, and most importantly, the radial nerve.
- As the major nerves descend down the arm, the radial and median give off two important branches, the posterior and anterior interosseous nerves, respectively.(35-37)




Picture 1: Anatomical illustration of the brachial plexus. Anterior view of right brachial plexus, modified from the edition of Henry Gray (1825–1861). Anatomy of the Human Body. 1918. *(Source: See Appendix III)*




Picture 2: Anatomical diagram, depicting the peripheral nerves of the left upper extremity, amongst others the median and ulnar nerves. From the edition of Henry Gray: Anatomy of the Human Body. 1918. *(Source: See Appendix III)*




Picture 3: Diagrammatic representation of brachial plexus coloured picture based on an unpublished illustration by JanePhillips-Conroy for the course Principles of Human Anatomy and Development at Washington University in St. Louis. Image shows C5 in median nerve and is missing C6 in subclavius; also, does not show the often-but-not-always contributions of C7 in ulnar nerve and C4 in dorsal scapular and subclavius nerves. *(Source: See Appendix III)*

## 1.3.3. Carpal Tunnel

In the human body, the carpal tunnel or carpal canal is the passageway on the palmar side of the wrist that connects the forearm to the middle compartment of the deep plane of the palm.The tunnel consists of bones and connective tissue. Several tendons and a nerve pass through it (*Pictures 4-5*).

### 1.3.3.1. Contents

A total of nine flexor tendons (not the muscles themselves) pass through the carpal tunnel:

- Flexor digitorum profundus (four tendons)
- Flexor digitorum superficialis (four tendons)
- Flexor pollicis longus (one tendon)
- Flexor carpi radialis (one tendon), considered by some as part of the carpal tunnel although it is more precise to state that it travels in the flexor retinaculum which covers the carpal tunnel, rather than running in the tunnel itself.

A single nerve passes through the tunnel: the median nerve between tendons of flexor digitorum profundus and flexor digitorum superficialis.

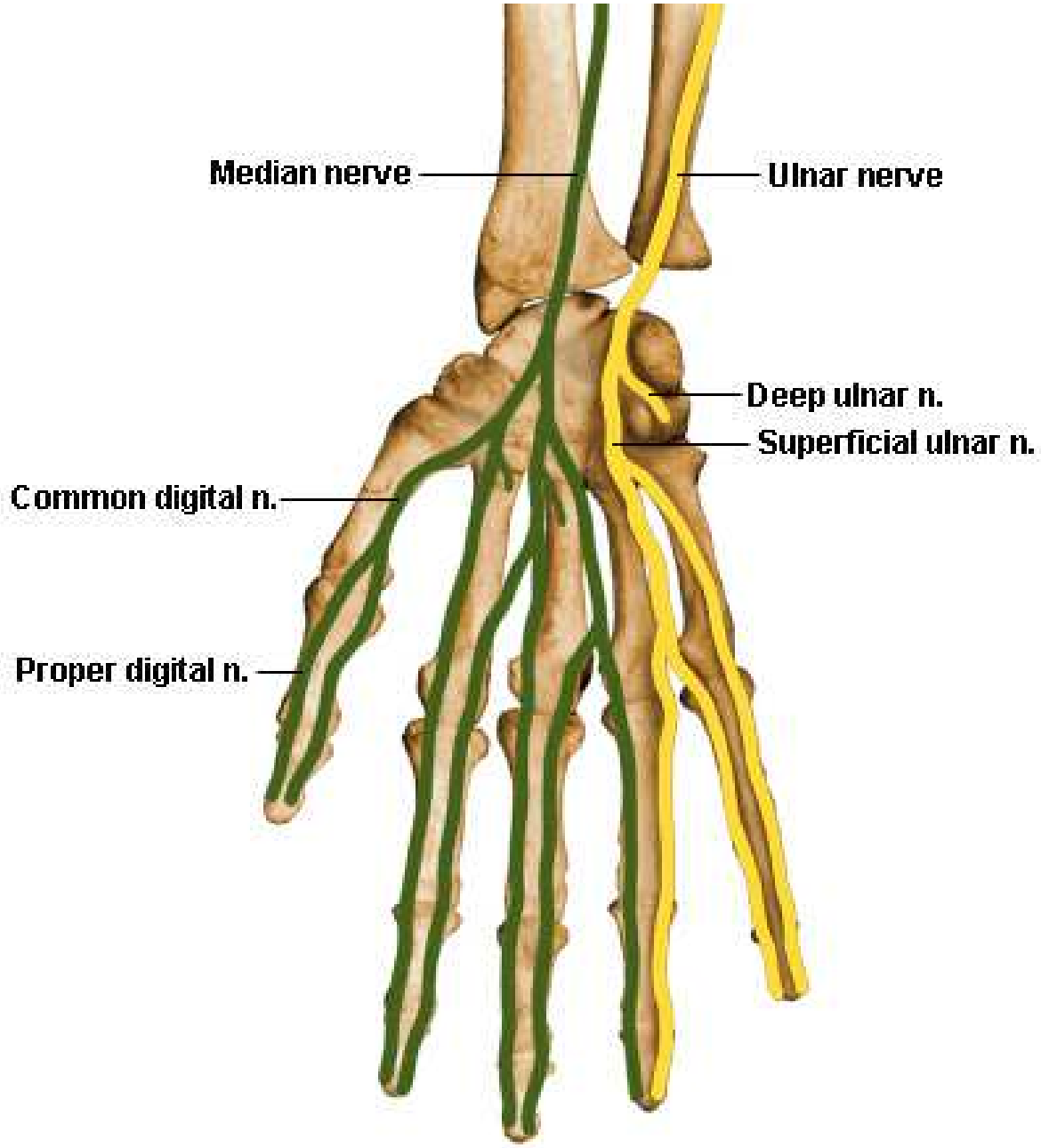
### 1.3.3.2. Structure

The carpus, the bony elements of the wrist, form an arch which is convex on the dorsal side of the hand and concave on the palmar side. The groove on the palmar side, the sulcus carpi, is covered by the flexor retinaculum, a sheath of tough connective tissue, thus forming the carpal tunnel. The flexor retinaculum is attached radially to the scaphoid tubercle and the ridge of trapezium, and on the ulnar side to the pisiform and hook of hamate.

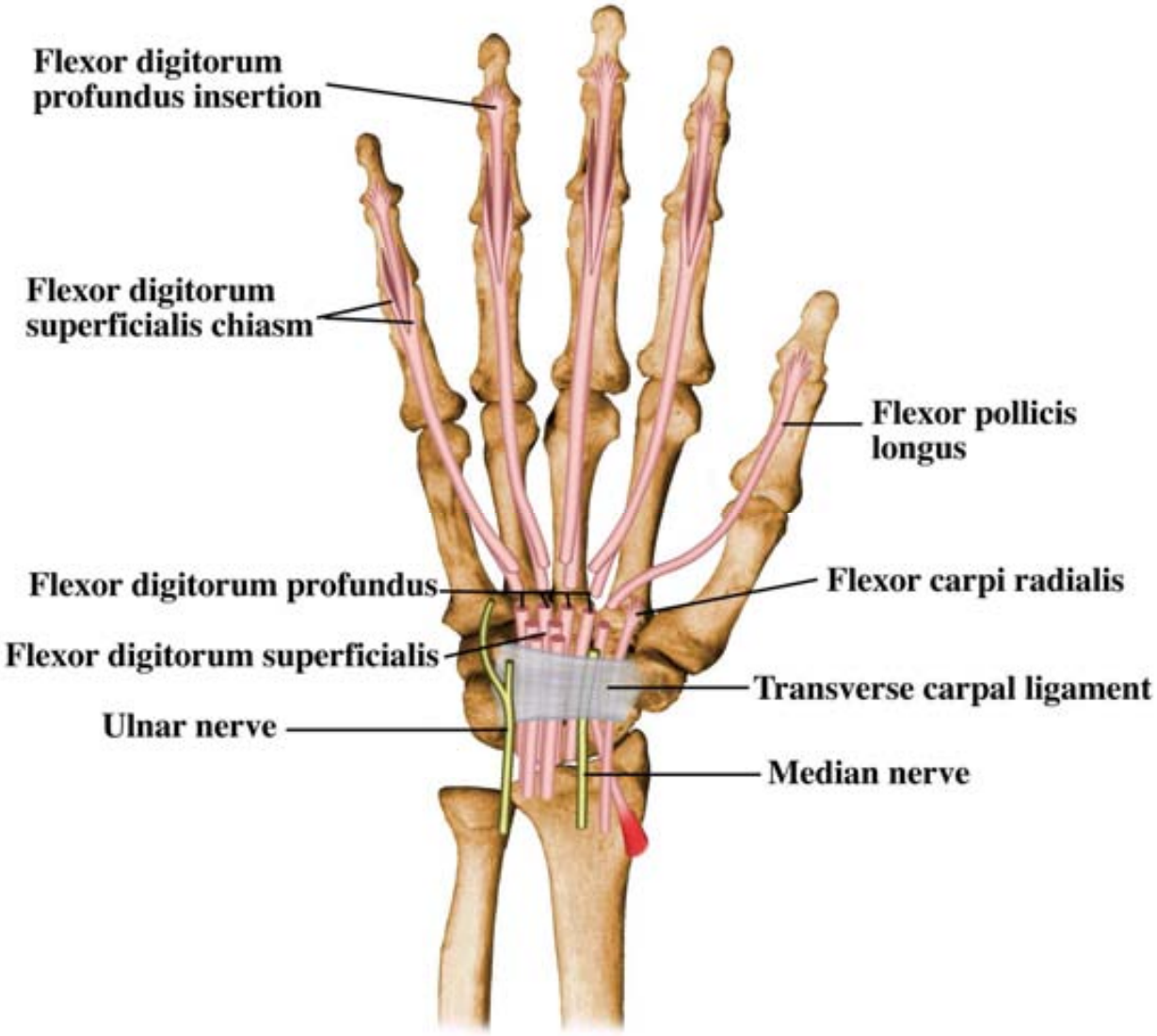
The narrowest section of the tunnel is located a centimetre beyond the mid-line of the distal row of carpal bones where the sectional area is limited to 1.6 $cm^2$.

The tendons of the flexor digitorum superficialis and profundus pass through a common ulnar sheath, while the tendon of the flexor pollicis longus passes through a separate radial sheath. The mesotendon shared by these tendons is attached to the radial and palmar walls of the carpal tunnel.

Superficial to the carpal tunnel and the flexor retinaculum, the ulnar artery and ulnar nerve pass through the ulnar tunnel. (38; 39)




Picture 4: Median and Ulnar nerves and their branches. *(Source: See Appendix III)*




Picture 5: Carpal Tunnel. *(Source: See Appendix III)*

## 1.4. PATHOPHYSIOLOGY

Neural damage at these locations may result either focal or diffuse.

A number of different processes may produce focal nerve disfunction as well as diffuse neuronal disorder. Most common mechanisms are:

- Compression (including neurapraxia and axonotmesis);(40;41)
- Transection (neurotmesis);(42)
- Nerve ischemia/infarct: often related to vasculitis and atherosclerosis;(43)
- Radiation-induced injury (after axillary radiation therapy for breast cancer);(44)
- Inflammation: commonly due to herpes zoster, herpes simplex and Epstein-Barr viruses and sometimes idiopathic as in brachial neuritis (neuralgic amyotrophy);(45)
- Degeneration: monomelic amyotrophy, amyotrophic lateral sclerosis (46;47) ; and
- Metabolic diseases as hypothyroidism and diabetes associated or not with compression and vasculitic-like processes.(48;49)

The present work is mostly aimed to focus on compression. Compression of nerve segments, including neurapraxia and axonotmesis, is the most common problem that affects neuronal structures in the upper extremity. Compression can affect distal nerve segments as in carpal tunnel syndrome, but may also occur very proximally at the root level (e.g., when a herniated cervical disc compresses the spinal root).

The pathologic processes at any site of entrapment are relatively similar. Nerve compression results in damage to the myelin sheath and manifests as delayed distal latencies and slowed conduction velocities. With sustained or more severe compression, axon loss may also occur, resulting in a reduction of the nerve's compound motor or sensory action potential amplitude. A degree of nerve ischemia associated with the direct compression against the nerve plays a role.

- In its most mild form the problem may be intermittent due to positioning; a common situation is that of paresthesias in the hand in a patient with carpal tunnel syndrome when the wrist is flexed, most likely secondary to temporary nerve ischemia.
- Demyelination occurs as compression becomes more consistent and chronic. Symptoms are usually persistent at this point, although often are worsened with certain movement or positions. Pain and weakness, generally minimally noticeable early on, now may become more prominent.
- Distal nerve segments will no longer function as compression progresses and Wallerian degeneration may occur. In severe cases the entire distal segment of nerve can degenerate, similar to what would be seen in a nerve transection.

From a physiologic standpoint, the patient will remain asymptomatic as long as all nerve impulses are transmitted through a region of compression. As ischemia or demyelination occurs, nerve conduction will first be slowed, and then eventually blocked completely. Slowing of nerve conduction has minimal physiological correlate; only the complete conduction block of neuronal impulses produces substantial functional sensory loss or weakness. Conduction block of more and more nerve fibers occurs as compression worsens. Eventually almost no impulses make it through the compressed area, while distal neuronal degeneration simultaneously begins to take place. (50-52)

## 1.5. CLINICAL PRESENTATION

Paresthesia, pain, weakness, clumnsiness and muscle atrophy use to be general symptoms and signs of nerve pathologies in the upper limb. Radiating pain from the neck down the arm leads to the suspicion of proximal pathology. Specific associated features to each pathology are depicted as follows.

### 1.5.1. Carpal Tunnel Syndrome (CTS)

Carpal tunnel syndrome (CTS) refers to the complex of symptoms and signs brought on by compression of the median nerve as it travels through the carpal tunnel. The canal is narrow and when any of the nine long flexor tendons passing through it swells or degenerates, the narrowing of the canal often results in the median nerve becoming entrapped or compressed, a medical condition known as carpal tunnel syndrome. Patients commonly experience pain and paresthesia (numbness and tingling), and less commonly weakness. (1-29) The hallmark of these symptoms in classic CTS is a distribution that includes the median nerve territory, with involvement of the first three digits and the radial half of the fourth digit. The symptoms are typically worse at night and characteristically awaken affected patients from sleep. Bilateral CTS is common.

The symptoms of CTS have a wide range of variability. The pain and paresthesia may be localized to the wrist, involve the entire hand, or radiate proximally to as high as the shoulder.

CTS symptoms are often provoked by activities that involve flexing or extending the wrist or raising the arms. Movements in the wrist affect the shape and width of the carpal tunnel. The width decreases considerably during normal range of motion in the wrist and because the carpal bones move in relation to each other with every motion of the hand the bony walls of the tunnel are not rigid. Both flexion and extension increase compression in the carpal tunnel.

Flexing the wrist causes the flexor retinaculum to move closer to the radius which considerably decreases the cross section of the proximal opening of the tunnel. Additionally, the distal end of the capitate presses into the opening.In extreme extension, the lunate constricts the passage as it is pressed toward the interior of the tunnel.

In more severe CTS, motor involvement leads to complaints of weakness or clumsiness when using the hands. Clinical signs may include weakness of thumb abduction and opposition, and atrophy of the thenar eminence.

### 1.5.2. Ulnar Mononeuropathy at the elbow and the wrist

In mild cases, symptoms of ulnar neuropathy include sensory loss and paresthesias over digits 4 and 5. In more severe cases, weakness of the interosseous muscles of the hand becomes apparent and the patient may complain of worsened grip and clumsiness. Pain in the region of the elbow also is common, although not universal. Because the thinner subcutaneous fat layer as well as the larger size of the tubercle of the coronoid process in men, the ulnar nerve appear less protected against compression-induced ischemia. In this location, the posterior ulnar recurrent artery is covered only by skin, subcutaneous fat, and a very thin aponeurosis of the flexor carpi ulnaris. (53;54) Involvement of ulnar innervated forearm muscles leads to weakness in finger and wrist flexion.

Compression of the ulnar nerve occasionally occurs in the wrist. Like the median nerve, the ulnar nerve travels through its own tunnel into the wrist, known as Guyon's canal. Compression of the nerve can occur in the canal itself or distal, in the proximal hand.

Compression at the wrist may appear clinically similar to that at the elbow: weakness in the interossei muscles and sensory loss and paresthesias affecting digits 4 and 5. However, the ulnar innervated finger flexors are spared in this syndrome, and in some individuals the hypothenar muscles are less affected than some of the other hand muscles, such as the first dorsal interosseous. (55-60)

### 1.5.3. Cervical Radiculopathy

A radiculopathy is a pathologic process affecting the nerve root. Cervical radiculopathy is a common cause of both acute and chronic neck pain.

Most radiculopathies arise from nerve root compression. The two predominant mechanisms of compressive cervical radiculopathy are cervical spondylosis and disc herniation. Lower cervical roots, particularly C7, are more frequently affected by compression than higher cervical roots.

Some causes of noncompressive radiculopathy include infection (especially herpes zoster and Lyme disease), nerve root infarction, infiltration by tumor, infiltration by granulomatous tissue, root avulsion, and demyelination.

Pain in the neck, shoulder, or arm occurs in nearly all patients with cervical radiculopathy, but it is usually not helpful for localizing the precise level of the affected root. The pain may be atypical and present as chest pain (pseudo-angina), breast pain, or pain in the face. Head turning, coughing, or sneezing may exacerbate symptoms.

In patients with suspected cervical radiculopathy, a major goal of the neurologic evaluation is to look for weakness and sensory disturbance in myotomal and dermatomal patterns. Typical clinical findings of solitary root lesions are often summarized in tables.
(55;61-65)

## 1.5.4. Less frequent Median, Ulnar, and Radicular-Plexular syndromes

### 1.5.4.1. Median nerve:

1.5.4.1.1. **Pronator Teres Syndrome:** Patients may present with forearm pain and sensory loss involving the entire lateral palm; sensory loss over the thenar eminence helps to differentiate this disorder from carpal tunnel syndrome, in which sensation in that area is spared. (66 - 70)

1.5.4.1.2. **Anterior Interosseous Neuropathy:** This nerve innervates several muscles including the flexor pollicis longus, the deep flexors of digits 2 and 3, and pronator quadratus. It does not subserve cutaneous sensation; thus, nerve dysfunction is characterized by weakness of this group of muscles only. On examination, the patient cannot make a standard "O" (as in "okay") with the thumb and forefinger. (71 - 76)

1.5.4.1.3. **Other disorders:** More proximal median nerve compression rarely can occur just above the elbow in the ligament of Struthers, where the median nerve is most prone to infarction in patients with a vasculitic process. The clinical and electrophysiological findings such as weakness, fibrillation potentials and positive waves in multiple median and anterior interosseous innervated muscles is helpful. Sensory loss remains confined to the lateral aspect of the hand.

### 1.5.4.2. Ulnar nerve: Ulnar neuropathy

Ulnar neuropathy rarely may occur as the nerve exits the cubital tunnel. In diabetic patients, ulnar neuropathy can occur in the forearm. In vasculitic processes, infarction of the nerve generally occurs just proximal to the elbow. (77;78)

## 1.5.4.3. Radicular-Plexular syndromes:

### 1.5.4.3.1. Brachial plexopathy:

Localizing a problem to a specific region of the brachial plexus is usually the most important first step in patients with brachial plexopathy. Once that is achieved, it is typically relatively straightforward to identify a specific etiology. A few simple rules can lead to accurate localization of problems to the brachial plexus: (79 - 83)

- Weakness generally should involve a "myotomal" pattern: weakness in C8 to T1 muscles suggests the possibility of a lower trunk/medial cord problem; weakness in C5 and C6 muscles raises the possibility of an upper trunk/lateral cord problem; weakness isolated to a single nerve is unlikely to be of plexus origin, except in cases of brachial neuritis.
- Involvement of muscles innervated by the radial or axillary nerves (e.g., deltoid, triceps, brachioradialis, wrist extensors, wrist flexors) is consistent with involvement of the posterior cord.
- Isolated middle trunk plexopathies are almost unheard of; usually some involvement of the lower or upper trunk is also present. A C7 radiculopathy is far more likely.
- Fixed sensory loss extending into the medial forearm is consistent with a lower trunk/medial cord plexopathy; sensory loss extending into the lateral forearm is consistent with an upper trunk/lateral cord plexopathy. The skin in these regions is innervated by nerves that branch off directly from the plexus.
- Weakness of serratus anterior (causing winging of the scapula), the spinati (causing weakness of arm external rotation and initial abduction), or the rhomboids (retraction and elevation of scapula) makes a radiculopathy or component of radiculopathy more likely since all of these muscles are innervated by nerves that branch off at the very proximal plexus or from the spinal nerves themselves. Brachial neuritis is an important exception to this rule since the serratus anterior is often involved.

#### 1.5.4.3.2. Proximal neuropathies of the shoulder and arm: Suprascapular and Axillary neuropathies

These disorders are uncommon. The main causes of injury use to be neuralgic amyotrophy, trauma or compression and stretch or traction from repetitive activities.

Suprascapular neuropathy and axillary neuropathies may present with weakness in arm abduction and external rotation; long thoracic neuropathy usually produces winging of the scapula. Sensory loss and paresthesias occur only with axillary neuropathies. Pain is usually present in all of these disorders. Electromyography and nerve conduction studies identify abnormalities confined to muscles of the affected nerve. (55)

## 1.6. CLINICAL DIAGNOSIS

Common neural pathologies affecting the upper limb are clinically suspected when the above-mentioned characteristic symptoms and signs are present. Provocative maneuvers for the particular case of CTS include the Phalen, Tinel, manual carpal compression, and hand elevation tests for the particular case of CTS. These maneuvers can be helpful when interpreted in the proper clinical context, but the sensitivity and specificity of these tests is moderate at best. (55) In many cases, imaging uses to be the first study to obtain in some patients. As an example, magnetic resonance imaging of the cervical spine is probably the best first test in a patient with radiating neck pain, sensory loss over digits 2 to 4, and weakness in C7 muscles. However, in many situations a patient's complaints are more nondescript. Pain may be nonfocal, weakness minimally present, and no fixed sensory loss identified. In these situations EMG is probably the first test to pursue and, depending upon the results, imaging of the appropriate area can be performed subsequently if needed. In one study, although imaging with MRI was found to be in agreement with EMG findings in 60 percent of cases, it provided different information in 40 percent, suggesting that the two modalities often provide complementary information (84).

Conversely, incidental electrophysiologic findings without related symptoms may be present..Diagnoses of very mild focal abnormalities of the upper extremity nerves are usually incidental findings that are unrelated to the clinical indication for the electrophysiological examination performed. For example, looking for polyneuropathy, ulnar motor conduction velocity slowing across the elbow segment may be consistent with a very mild neuropathy. Similarly, evidence for cervical radiculopathy or polyradiculopathy can be identified in asymptomatic older individuals on electrodiagnostic testing. However, these incidental electrophysiologic findings are not sufficient to diagnose a particular syndrome. Thus, if mild slowing across the wrist in the median nerve is detected without associated symptoms, a diagnosis of mild median neuropathy at the wrist is made, but not the clinical diagnosis of carpal tunnel syndrome.

# 1.7. CLINICAL NEUROPHYSIOLOGICAL TESTS

CLASSIFICATION

ELECTRODIAGNOSTIC STUDIES IN THE UPPER LIMB

- ELECTROMYOGRAPHY (EMG)
- NERVE CONDUCTION STUDIES (NCS)

ELECTRODIAGNOSIS OF CTS AND ULNAR MONONEUROPATHY

OTHER ELECTRONEUROGRAPHIC STUDIES: LATE RESPONSES

- H-REFLEX
- F-WAVE

## 1.7.1. Classification

Neurophysiological tests are an extension of the clinical examination. Thus, a functional anatomic approach to classification makes most sense. Although the term "neurophysiological" may include a variety of tests, the electrophysiological tests are those which shall be particularly discussed in this context.
For the purpose of this categorisation, the nervous system is divided into the somatic and the autonomic nervous systems:

- The somatic nervous system provides motor innervation to the skeletal muscles, and sensory innervation from skin and muscle spindles.
- The autonomic nervous system provides motor innervation to the viscera and other end-organs not under voluntary control (e.g., sweat glands). Its sensory fibres are referred to as visceral afferents. Both systems have central pathways (neurons participating in spinal cord and supraspinal control) and peripheral nerves (those going to and from end-organs).

Thus, electrophysiological tests can be divided into:

1. Somatic motor system tests (EMG, motor nerve conduction studies (MNCS), and motor evoked potentials (MEP));
2. Somatosensory system tests (sensory nerve conduction studies (SNCS), somatosensory evoked potentials (SEP));
3. Reflexes; and
4. Autonomic nervous system tests (for sympathetic or parasympathetic fibres).

Electrophysiological tests may also be categorized technically into those which "passively" record some spontaneous or voluntary bioelectrical activity (for instance: electromyography), and those which record some biological response to an external stimulation (these may be subsumed under the term "conduction tests").

In this study, we will focus mainly on EMG, SNCS, and MNCS including late responses.

### 1.7.2. Electrodiagnostic Studies in the Upper Limb

Electromyography (EMG) and nerve conduction studies (NCS) remain the most effective means of identifying and classifying a disorder affecting the upper extremity. They are useful to support the clinical diagnosis and to rule out other abnormalities.

#### 1.7.2.1. Electromyography (EMG)

Electromyography (EMG) is the clinical study of the electrical activity of muscle fibers individually and collectively. EMG tests the integrity of the entire motor system, which consists of upper and lower motor neurons, the neuromuscular junction, and muscle.
Further subdivision in each category reveals seven possible sites of involvement that may cause muscle weakness. They include: (1) upper motor neuron from the cortex (I) to the spinal cord (II); (2) lower motor neuron with the anterior horn cell (III) and nerve axon (IV); (3) neuromuscular junction (V); and (4) muscle membrane (VI) and contractile elements (VII). (55; 85-87)

##### 1.7.2.1.1. Evaluation of the Motor Unit

The motor unit consists of an anterior horn cell, its axon and terminal branches, and all the individual muscle fibers it innervates. The size of the motor unit, that is the number of muscle fibers innervated by a single anterior horn cell, varies with each muscle. When an anterior horn cell is activated, all muscle fibers belonging to that motor unit are depolarized. The electrical activity from these muscle fibers summates to generate a motor unit action potential (MUAP).

The desired goal of MUAP analysis is the characterization of a disease process as neurogenic or myopathic, or normal. Certain characteristics of MUAP waveform morphology (MUAP amplitude, rise time of the initial spike, MUAP duration, and the number of phases) are particularly important in evaluating the motor unit. In addition, MUAP recruitment and analysis of the interference pattern can determine whether the number of MUAPs that are firing is appropriate for the level of activation.

### 1.7.2.1.2. Stages of the Electromyographic Study

The electromyographic study of each muscle consists of four separate stages, each evaluated at multiple recording sites:

a. Insertional activity
b. Spontaneous activity at complete rest
c. MUAP waveform analysis during minimal voluntary contraction
d. MUAPs analysis during increasing voluntary muscle contraction to maximal levels and determination of the interference pattern

**a. Insertional activity**

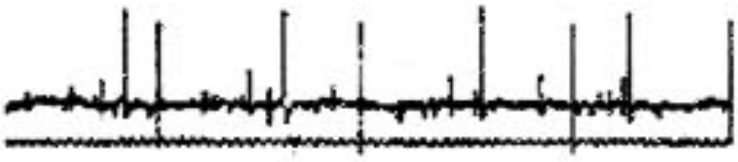
Needle electrode insertion is normally accompanied by brief bursts of electrical activity due to mechanical irritation. Continued burst firing of potentials well after needle movement has ceased is abnormal.

**b. Spontaneous activity at complete rest**

Normal muscle is electrically silent at rest with the exception of potentials that occur in the region of the muscle endplate. Other types of spontaneous electrical activity at rest may be pathologic; these include:

- Fibrillations
- Positive Sharp Waves
- Complex Repetitive Discharges
- Myotonic Discharges
- Fasciculations
- Myokimia
- Cramps

- **Fibrillations**. Produced by denervated muscle fibers. Fibrillation potentials are (<500 µV), short (<5 ms in duration), biphasic or triphasic, fire regularly or sometimes irregularly, and have an initial positive (downward) deflection (whereas the initial deflection of the endplate potential is negative). Their sound has been likened to *"rain on a tin roof" (Picture 6).* If observed, they are scored +1 to +4 according to a semiquantitative grading system.



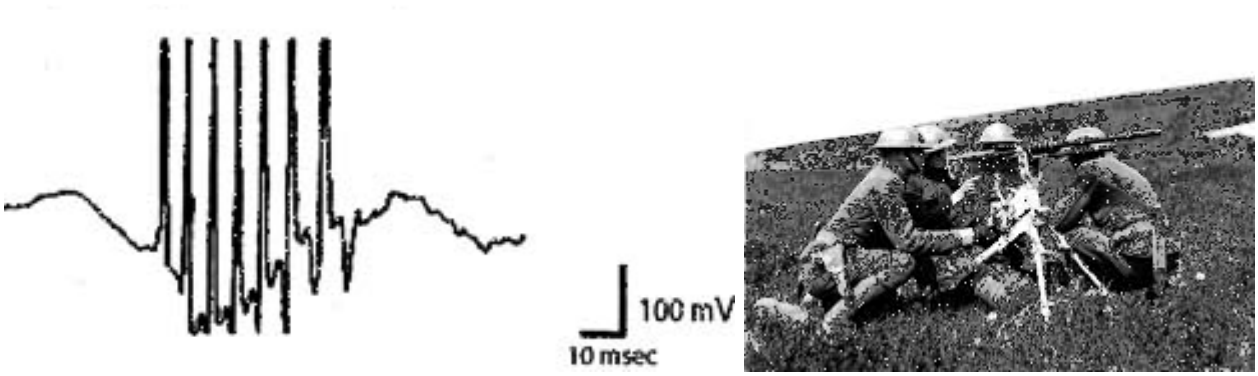
*Picture 6: Fibrillation potentials and rain on a tin roof. (Source: See Appendix III)*

- **Positive sharp waves.** With the same origin and clinical significance as fibrillations. They have a sharp initial positive deflection followed by a longer, lower amplitude negative phase than fibrillation potentials (*Picture 7*).

  Positive sharp waves and fibrillation potentials appear to be dependent upon the electrode's relationship to the muscle fiber membrane; some investigators have observed fibrillation potentials assume the configuration of positive sharp waves, or vice versa, with slight adjustments of the electrode. Presumably, the negative spike of the fibrillation potential becomes manifest as the electrode is moved away from the membrane or disappears with electrode/membrane contact. An alternative view postulates two distinct populations of positive sharp waves: a minority that arise as blocked fibrillation potentials, and a majority (each representing a single muscle-fiber discharge) that arise at the electrode adjacent to a perielectrode-induced zone of crushed muscle membrane and then propagate away from it.

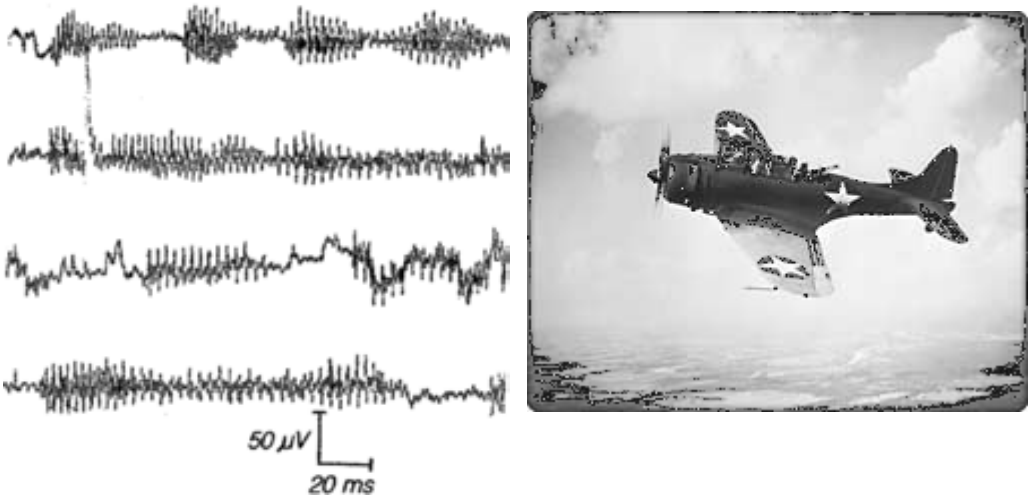
*Picture7: Positive Sharp Waves. (Source: See Appendix III)*

- **Complex repetitive discharges (CRDs).** Bursts of potentials, each having the appearance of grouped fibrillations or positive sharp waves that begin and end suddenly. Each burst is multiphasic and composed of up to 10 spike components representing the firing of individual muscle fibers, and can last for up to 100 ms. One muscle fiber acts as a pacemaker, driving other muscle fibers via ephaptic activation. When many muscle fibers are activated, high-amplitude spikes occur. The bursts end when muscle fibers become fatigued, but can start up again when a new pacemaker starts firing again. The bursts sound "*like a machine gun*" (*Picture 8*). When present, CRDs never occur in isolation. While CRDs occur in both neuropathies and myopathies, the risk of CRDs occurring in myopathies (specially in some muscular dystrophies) is six times that of other diagnoses.




Picture 8: Complex Repetitive Discharges, whose bursts sound "*like a machine gun*". *(Source: See Appendix III)*

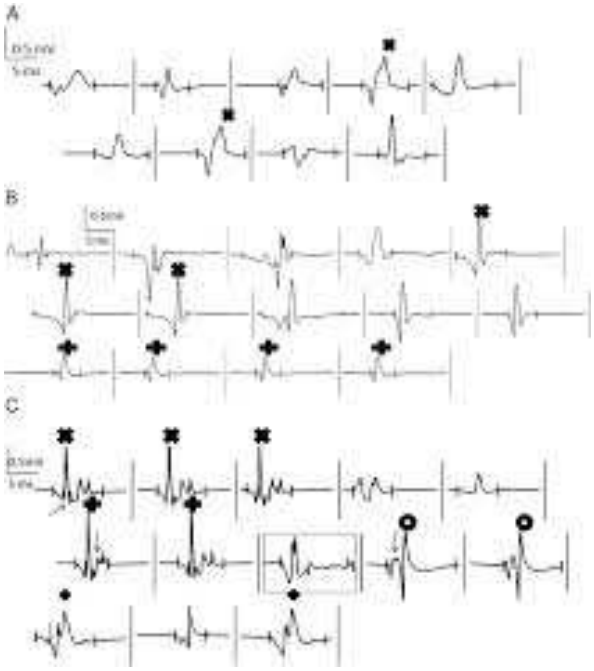
- **Myotonic discharges.** Spontaneous independent repetitive potentials arising from single muscle fibers, evoked by needle insertion, needle movement, or voluntary contraction. While they resemble positive sharp waves or fibrillations, myotonic discharges wax and wane in both amplitude and frequency, and have the whining nature that some have thought "*similar to the sound of World War II dive bombers*" *(Picture 9)*. Myotonic discharges are seen in the various inheritable myotonias (myotonic dystrophy, myotonia congenita, paramyotonia congenita), hyperkalemic periodic paralysis, and glycogen storage diseases (most often glycogen storage disease II or Pompe disease).




Picture 9: Equine myotonic discharges with their typically whining nature, "*similar to the sound of World War II dive bombers*". *(Source: See Appendix III)*

- **Fasciculations.** Single motor unit potentials spontaneously activated. They can look like normal or polyphasic voluntarily activated MUAPs, but fire irregularly. Fasciculation potentials may be a normal –"benign"- finding, but are frequently seen in pathologic conditions. In general, benign fasciculations have faster firing rates and occur in muscles below the knees. Fasciculations are well known to occur in motor neuron disorders such as amyotrophic lateral sclerosis (ALS), *(Picture 10)* but can also be seen in radiculopathies, entrapment neuropathies, and metabolic disorders such as thyrotoxicosis, tetany, and anticholinesterase overdoses. Unlike

other spontaneous potentials, fasciculations can be visible on clinical examination when they occur on the surface of muscles. One advantage to the needle EMG evaluation is the ability to record fasciculations from deep within the muscle body that are not clinically visible.

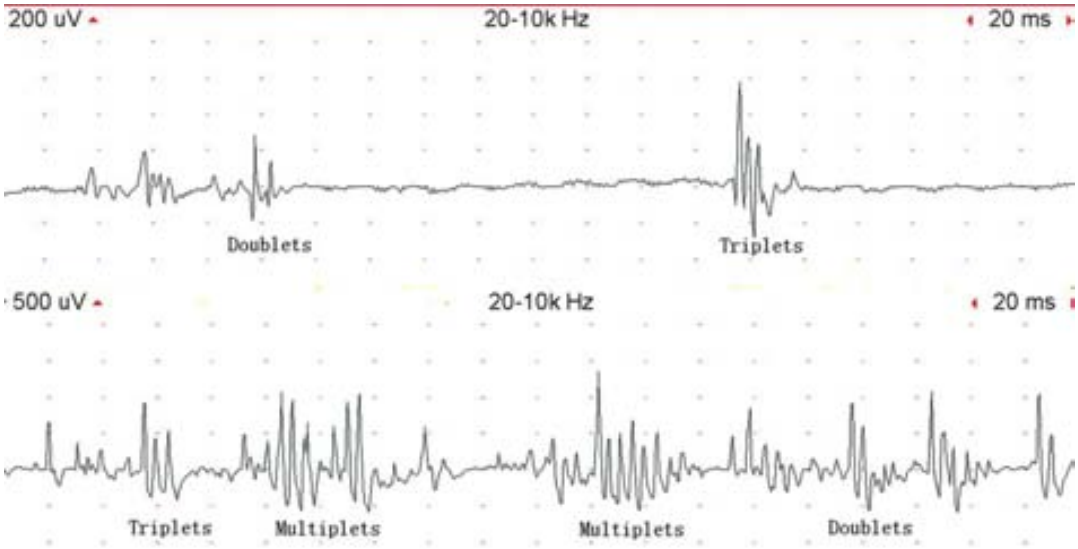


Picture 10: Fasciculation potentials and earliest changes in motor unit physiology in ALS. *(Source: See Appendix III)*

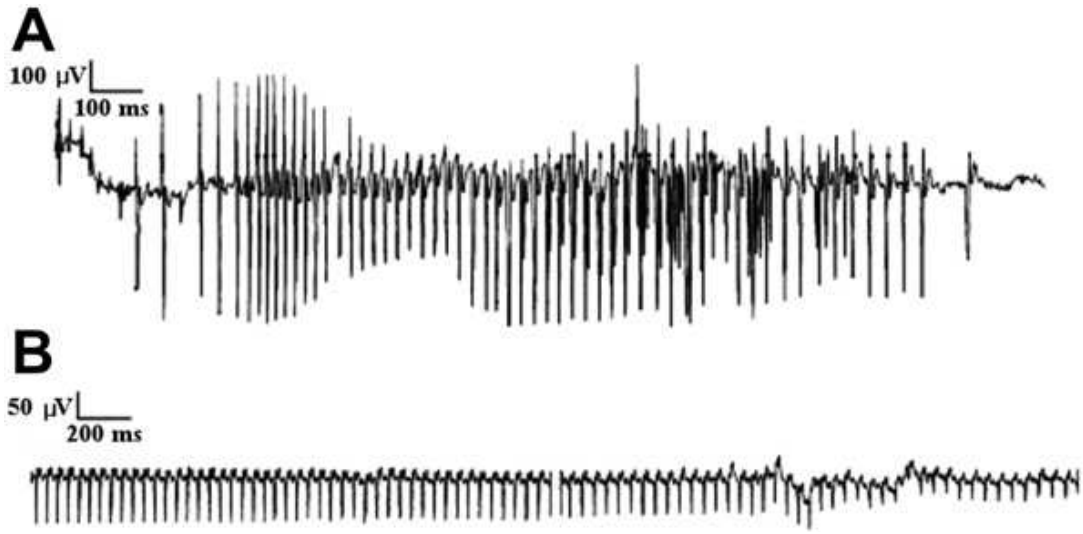
- **Myokymia.** Bursts of MUAPs, usually 2 to 10, firing at rates of 20 to 150 Hz. The bursts consist of regular or irregular doublets, triplets, or multiplets. Between bursts there is electrical silence. The discharge generator is thought to be located along the motor axon. Muscles containing myokymic discharges typically demonstrate vermicular movements on examination that look "*like a bag of worms"*. Myokymia can be differentiated from CRDs in that the spike pattern is not regular from one burst to another, and the bursting does not typically start and stop abruptly (*Picture 11*). Furthermore, myokymic discharges consist of MUAPs, whereas CRDs consist of fibrillations or positive sharp waves. They can present as focal (nerve or nucleus damaged), segmental (roots, plexus, anterior horn damage) or –rarely- generalized (metabolic and inflammatory neuropathies).

Neuromyotonic discharges are similar but fire at higher frequencies (150 to 300 Hz) and may begin and end abruptly with waxing amplitudes (*Picture 12*). They are associated with Isaac's and Morvan's syndromes. These two phenomena -myokymia

and neuromyotonia- probably represent a continuum of an abnormality in voltage-gated K+ channels, with neuromyotonia characterized by more numerous discharges and persistent clinical contractions.



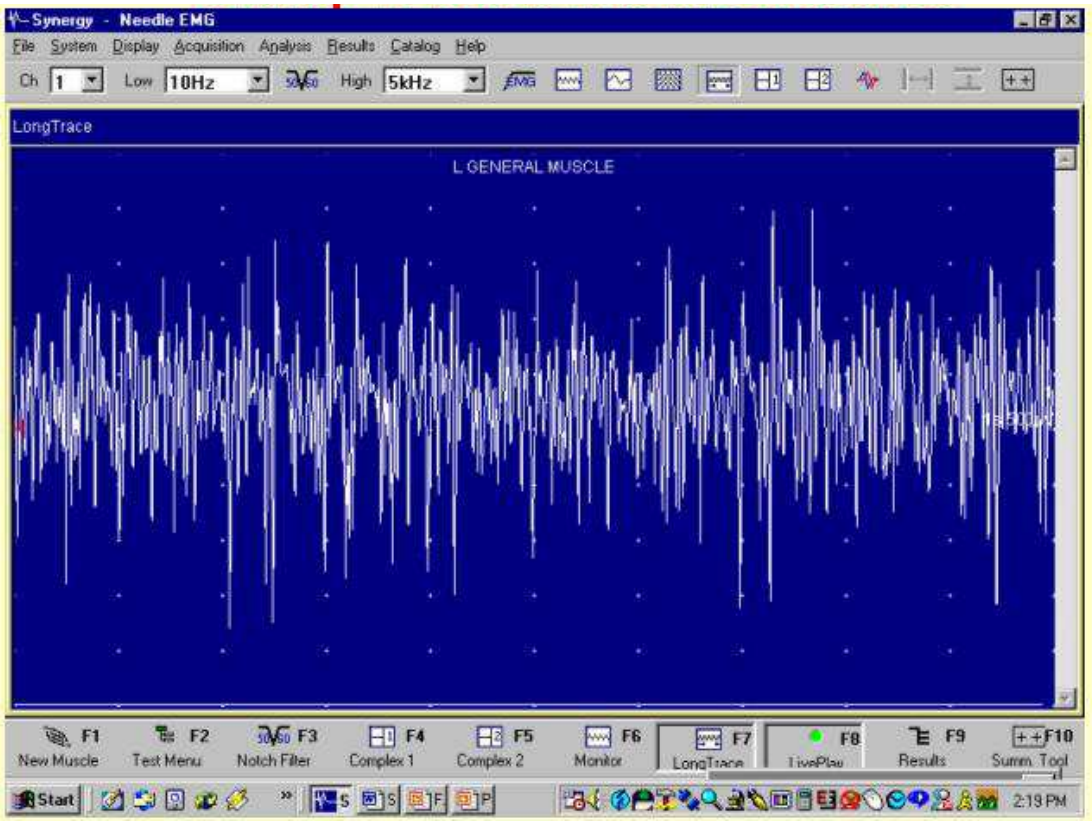

Picture 11: Regional myokimia. Spontaneous continuous irregularly occurring doublet, triplet, and multiplet single and partial motor unit discharges in medial gastrocnemius. *(Source: See Appendix III)*




Picture 12: Electrical myotonia. (A) Two-second myotonic discharge in DM1 patient with typical waxing and waning frequency and amplitude. (B) Four-second waning only myotonic discharge in a DM2 patient in which frequency and amplitude decline gradually with no waxing component. *(Source: See Appendix III)*

- **Cramps.** Cramps are sustained involuntary muscle contractions caused by the activation of multiple motor units (*Picture 13*). They occur in normal subjects, especially in the calves and feet, and disease states such as amyotrophic lateral sclerosis. One small study found an inverse correlation between the cramp

threshold frequency (the minimum electrical stimulation frequency at which a muscle cramps) and a history of cramping. This finding suggests that the cramp threshold frequency might be useful to identify individuals with an increased risk of cramping.




Picture 13: Cramp registered 100 ms/div, 500 uV/div. Note the resemblance to interference pattern. *(Source: See Appendix III)*

- **Contractures.** Muscle contractions associated with **electrical silence**, which occur in McArdle disease and other glycogenoses.

### c. MUAP waveform analysis during minimal voluntary contraction

With minimal voluntary activity, the morphology of individual MUAPs can be analyzed for pathologic evidence of motor unit remodeling:

- Neuropathic MUAPs are characterized by increased amplitude and duration, with an increased incidence of polyphasia and satellite potentials
- Myopathic MUAPs are characterized by decreased amplitude, shorter duration, and polyphasia

### d. MUAPs analysis during increasing voluntary muscle contraction to maximal levels and determination of the interference pattern

In neurogenic disorders, with maximal voluntary activity, the interference pattern itself is reduced due to fewer motor units and less interference of MUAPS with each other, but its amplitude is increased. In myopathic disorders, the interference pattern is normal because the number of motor units activated is normal, but its amplitude is reduced because of reduced numbers of muscle fibers in each motor unit and reduced force.

The electrophysiologic examination is an extension of the clinical investigation and must be interpreted in the proper clinical context. While typical neuropathic and myopathic patterns of EMG abnormalities are recognized, no single abnormality is pathognomonic or diagnostic of a single disease process, and there are always exceptions to the typical examples.

In conjunction with nerve conduction studies, EMG possesses clinical value in the diagnostic work-up of symptoms such as weakness, and for the diagnosis and prognosis of neurogenic disorders and inflammatory myopathies.

In studies evaluating the utility of electrodiagnostic testing, mainly in outpatients with various suspected neurologic complaints (e.g., weakness, nerve complaints, polyneuropathy), new diagnoses were revealed in 31 to 43 percent.
In a report of 98 inpatients, electrodiagnostic studies provided a clinically relevant new diagnosis in 13 percent. Additionally, the electrodiagnostic findings altered treatment in 17 percent.

However, it is no longer sufficient to label a disorder as neuropathic or myopathic, acute, or chronic. Noninvasive genetic studies give greater precision to the diagnosis and often the prognosis of neuromuscular disorders such as the muscular dystrophies. Even in the myotonias, perhaps the most dramatic of abnormalities seen in electrophysiology, genetic studies give greater diagnostic information than EMG. Furthermore, other technologies may supplant the EMG in other diagnostic areas. Nevertheless, EMG continues to be extremely helpful in the neurogenic disorders and inflammatory myopathies. (55; 85)

### 1.7.2.2. Nerve Conduction Studies (NCS)

Focal neuropathic lesions can often be localized using nerve conduction velocities. Measurements of the nerve conduction velocity and the amplitude of the action potential can identify a neuropathic process and also assess whether it is primarily affecting axons or myelin.

Nerve conduction studies are used to:

- Diagnose focal and generalized disorders of peripheral nerves;
- Classify peripheral nerve conduction abnormalities due to axonal degeneration, demyelination, and conduction block; and
- Prognosticate regarding clinical course and efficacy of treatment. (55;85-87)

#### 1.7.2.2.1. Sensory nerve conduction

The cell bodies of sensory neurons are located in the dorsal root ganglia. Each neuron has a central process entering the spinal cord through the dorsal horn and a peripheral process connecting to a sensory receptor in the skin or deep tissues of the limb. The receptors transduce somatosensory stimuli into electrical potentials that eventually give rise to action potentials in the axons; these are transmitted along the peripheral process to the central process. This is called a sensory nerve action potential (SNAPs).

These studies can be done orthodromically (in the physiological direction of conduction) or antidromically in the distal part of major peripheral nerves.

There are a variety of functional types of sensory neurons, each with a characteristic spectrum of axonal diameters. Neurons are myelinated or unmyelinated, but the unmyelinated fibers cannot be routinely measured. Many sensory axons with differing function and size coexist in sensory nerves and with motor axons in mixed nerves.

The two goals of sensory nerve conduction studies are the assessment of:

- The number of functioning axons (estimated by measuring the amplitude of SNAP).
- The state of myelin of these axons (estimated by the conduction velocity of SNAP).

In patients with axonal degeneration neuropathies, the primary feature is reduced sensory action potential amplitudes; this can be observed, for example, in diabetic neuropathy. The conduction velocity may be slightly slowed, but only to the extent that the largest axons are gone; in this setting, the measured conduction velocity reflects the velocity of the largest remaining axons. In addition, slowing of conduction is the primary feature in demyelinating neuropathies, such as Guillain-Barré Syndrome, familial neuropathies, and in compression and entrapment neuropathies, such as carpal tunnel syndrome. In radiculopathies, both the sensory action potential amplitudes and conduction velocities are normal. This is because the lesion is virtually always proximal to the dorsal root ganglion, and the cell body and its peripheral process remain normal. Sensory action potentials similarly remain normal with lesions of the central nervous system.

#### 1.7.2.2.2. Motor nerve conduction

There are significant differences between sensory and motor nerve conduction that depend in large part upon differences of anatomy. Motor neurons have cell bodies in the anterior horn of the spinal cord and send their axons to innervate muscle fibers. Motor axons are always intertwined with sensory axons. Unlike pure sensory nerves (e.g., the sural nerve), there are no pure motor nerves. However, it is possible to study motor nerve axons separate from sensory axons by electrically stimulating the nerve and recording from the muscle fibers it innervates. The amplitude of the compound muscle action potential is very much larger than the nerve action potential since each motor axon typically innervates hundreds of muscle fibers. The amplitude of the muscle action potential is indicative of the number of activated muscle fibers.

However, the amplitude is not indicative of the number of motor axons in the nerve. As an example, the number of axons can be diminished and the action potential can remain normal if the process of collateral reinnervation of muscle fibers by the remaining axons has been complete. Conversely, the number of axons can be normal and the action potential diminished if there is diminished synaptic transmission at the neuromuscular junction or if there is loss of muscle fibers. If a neuropathy progresses and collateral reinnervation fails to keep pace, the size of the muscle action potential declines.

1.7.2.2.2.1. Motor nerve conduction velocity

Synaptic transmission between nerve and muscle is required to produce a muscle action potential. The delay associated with this process, which is referred to as the distal motor latency, prevents direct calculation of the velocity of motor nerve conduction from a single stimulus location. If the nerve is stimulated supramaximally in two places, virtually identical muscle action potentials will result; the major difference is the different latencies from the time of stimulation. In turn, the difference in the latencies is due to the difference in the distances from the sites of stimulation to the muscle. Dividing the distances between the two stimulus sites by the difference in the travel times produces a conduction velocity for the segment of nerve between the two sites of stimulation. As with the sensory action potential, measurements of the muscle action potential are ordinarily made to the time of onset; hence, the calculated conduction velocity refers to the fastest (and largest) axons in the nerve.

With axonal degeneration neuropathies (the most common variety of generalized neuropathies), motor nerve conduction studies are not significantly abnormal until the process is moderately advanced. A focal neurapraxic lesion (e.g., carpal tunnel or other compression or entrapment neuropathies) leads to slowing of conduction and decrement of amplitude across the segment including the lesion. However, studies of the nerve distal to the lesion are fully normal. Studies of nerve segments proximal to the lesion reveal normal conduction velocity with an unchanging reduced action potential amplitude.

Quite dramatic nerve conduction findings are seen with a focal total neurapraxic lesion (e.g., acute trauma or laceration). In this setting, although the nerve is fully normal below the lesion, electrical stimulation proximal to the lesion produces no response (similar to the patients' attempts to activate the muscle). In radiculopathy, motor nerve conduction studies will ordinarily be normal. In central nervous system disease, there will ordinarily be no change in motor nerve conduction unless there is involvement of anterior horn cells. In demyelinating neuropathies, there is slowing of conduction velocity and prolongation of distal motor latency.

## 1.7.3. Electrodiagnosis of CTS and Ulnar Mononeuropathy

### 1.7.3.1. Differential Electrodiagnosis

**Focal entrapments** of the median, radial, or ulnar nerves are generally straightforward to determine using EMG/NCS. The electromyographer looks for evidence of demyelination (conduction velocity slowing and conduction block) across likely affected segments of nerve, such as the median nerve at the wrist in carpal tunnel syndrome. Similar findings may be found across the elbow segment in ulnar neuropathy and across the spiral groove in radial neuropathy. Electromyography tends to be mainly confirmatory and will give some insight into lesion severity.

In **plexopathies**, abnormalities are usually found in several nerves emanating from one region of the plexus, such as the upper trunk. Studying conduction across the plexus is generally not performed for technical reasons; thus, the usual findings of demyelination cannot be sought. Instead, testing is confined to distal segments and a search for axon loss is pursued. As an example, in a patient with an upper trunk lesion, reductions in the amplitude of the median, radial, and musculocutaneous sensory responses are typical.

Since both standard median and ulnar motor testing are confined to lower trunk muscles, results from these studies are usually normal. However, on needle examination, muscles innervated by upper trunk fibers can be studied; in these, fibrillation potentials, positive sharp waves, and chronic reinnervation may be identified. In lower trunk problems, ulnar and medial antebrachial cutaneous sensory responses are reduced while ulnar and median motor studies can both show abnormalities. On electromyography, evidence of denervation and chronic reinnervation may be found in C8 to T1 muscles.

In **radiculopathy**, sensory responses are spared since the lesion is proximal to the dorsal root ganglion. Motor studies are usually also normal, unless the C8 to T1 roots are affected. Abnormalities typically are identified only on needle examination and affect the muscles derived from the involved roots.

### 1.7.3.2. The electrodiagnosis of CTS

The electrodiagnosis of CTS rests upon the demonstration of impaired median nerve conduction across the carpal tunnel in the context of normal conduction elsewhere.

The Nerve Conduction Study (NCS) evaluation for CTS involves measurement of conduction velocity across the carpal tunnel, as well as determination of the amplitude of sensory and motor responses. Mild CTS may not produce any nerve conduction abnormalities. With increased compression of the median nerve, focal demyelination can occur. This may result in local conduction block and/or slowing of motor and sensory conduction across the wrist. With even greater compression, the axons of the median nerve themselves can be damaged, resulting in reduced amplitudes. Sensory fibers seem to be more sensitive to compression than motor fibers. As a result, sensory fibers typically demonstrate changes on nerve conduction studies earlier than do motor fibers.(9;10;13;15;19;21;29;88-90)

Sensory conduction studies may involve branches that innervate any of the first four digits, depending on clinical symptoms. Motor conduction studies most often record from the abductor pollicis brevis muscle, although other muscles can provide added information. Results obtained are compared to age-dependent normal values, as well as to other nerves of the same hand or the contralateral hand. In particular, the ulnar nerve and sometimes the radial nerve are also evaluated to ensure that any abnormalities seen in the median nerve are specific to that nerve and not part of a more widespread disorder, such as a peripheral neuropathy.

Routine NCS for the diagnosis of CTS typically include the following studies:

- Median motor conduction study recording from the abductor pollicis brevis while stimulating at the wrist and elbow
- Ulnar motor conduction study recording from the abductor digiti minimi while stimulating at the wrist and at the elbow above and below the ulnar groove
- Median and ulnar F responses

- Median sensory response recording from digit two or three while stimulating the wrist
- Ulnar sensory response recording from digit five while stimulating the wrist.
- Additional comparison studies should be used for patients who have normal routine NCS in the setting of clinical findings suggestive of CTS. These include the following:
    - Palmar mixed-nerve study, comparing palm-to-wrist peak latencies of median and ulnar nerves, each recorded 8 cm from the stimulating electrodes.
    - Second lumbrical (median) versus interossei (ulnar) distal motor latencies.
    - Digit four sensory latencies stimulating the median and ulnar nerves at the wrist individually at identical distances.

These methods compare the conductions of median fibers directly with ulnar fibers traveling in the same region. In a 2002 systematic review of prospective studies, the sensitivity of various NCS for CTS ranged from 56 to 85 percent, and the specificity ranged from 94 to 99 percent. In a later study of 99 patients meeting clinical criteria for CTS without confounding neurologic disorders, NCS (including median and ulnar palmar mixed-nerve studies) were normal in 25 percent.

Anomalous innervations are not uncommonly seen during electrodiagnostic testing. The one most frequently encountered in the arm is the Martin-Gruber anastomosis, which has a prevalence of 15 to 32 percent. With this median-to-ulnar anastomosis, a subgroup of motor fibers split from the median nerve in the forearm and anastomose with the ulnar nerve as it travels through the forearm into the hand. The median-to-ulnar motor fibers that make up this anastomosis innervate the intrinsic muscles of the hand.
The Martin-Gruber anastomosis is most often identified during ulnar nerve testing. During median nerve motor studies, one may see a pattern where the amplitude of the compound muscle action potential is higher with stimulation at the proximal elbow site than with stimulation at the wrist. In the setting of median nerve entrapment at the wrist (CTS), a surprisingly fast median nerve conduction velocity in the forearm can be seen. These electrodiagnostic findings are intuitive if one keeps in mind that not all median motor

fibers are taking their normal route through the carpal tunnel. Instead, they are bypassing the site of entrapment by taking this circuitous route with the ulnar nerve.

#### 1.7.3.2.1. Electromyography in CTS referrals

As noted above, the electrodiagnosis of CTS depends mainly upon the demonstration of impaired median nerve conduction across the carpal tunnel. EMG is most useful to exclude other conditions, such as polyneuropathy, plexopathy, and radiculopathy. Electrodiagnostic studies are essential if surgical treatment for CTS is being considered.(55)

The EMG portion of the electrophysiologic examination looks for evidence of pathologic changes in the muscles innervated by the median nerve, typically assessing the abductor pollicis brevis muscle. When secondary axonal loss is present, EMG may reveal either active denervation (e.g., spontaneous activity such as fibrillation potentials, positive sharp waves, and fasciculation potentials) or chronic changes that indicate denervation with subsequent reinnervation (e.g., changes in motor unit action potential amplitudes, durations, and recruitment).

Such findings are supportive of the diagnosis of CTS in the context of normal findings in both non-median-innervated muscles and proximal median nerve-innervated muscles.

One suggested protocol for EMG evaluation of CTS involves needle examination of the following muscles:

- Abductor pollicis brevis.
- Two or more C6-C7 innervated muscles (e.g., pronator teres, triceps brachii, extensor digitorum communis) to look for evidence of cervical radiculopathy.

Additional muscles are investigated if the abductor pollicis brevis is abnormal:

- Two or more proximal median-innervated muscles (e.g., flexor carpi radialis, pronator teres, flexor pollicis longus) to rule out a proximal median neuropathy.

- Two or more lower trunk C8-T1 nonmedian-innervated muscles (e.g., first dorsal interosseous, extensor indicis proprius) to rule out brachial plexopathy, polyneuropathy, and C8 to T1 radiculopathy.

### 1.7.3.3. Electrodiagnosis in Ulnar Mononeuropathy

In most cases, the diagnosis of ulnar neuropathy can be confirmed by electrodiagnostic testing or imaging when suspected on the basis of clinical symptoms or signs. There are a number of provocative maneuvers for ulnar neuropathy, but the sensitivity and specificity of these maneuvers appears to be suboptimal.

## 1.7.4. Other Electroneurographic Studies: Late Responses

Nerve conduction studies along with late responses are the main modalities to evaluate the integrity of peripheral nerves. While sensory and motor nerve conduction studies assess the integrity of the peripheral nerves, to study the most proximal segments of nerves is difficult. These nerves are deep and not easily accessible as they leave the spinal column.

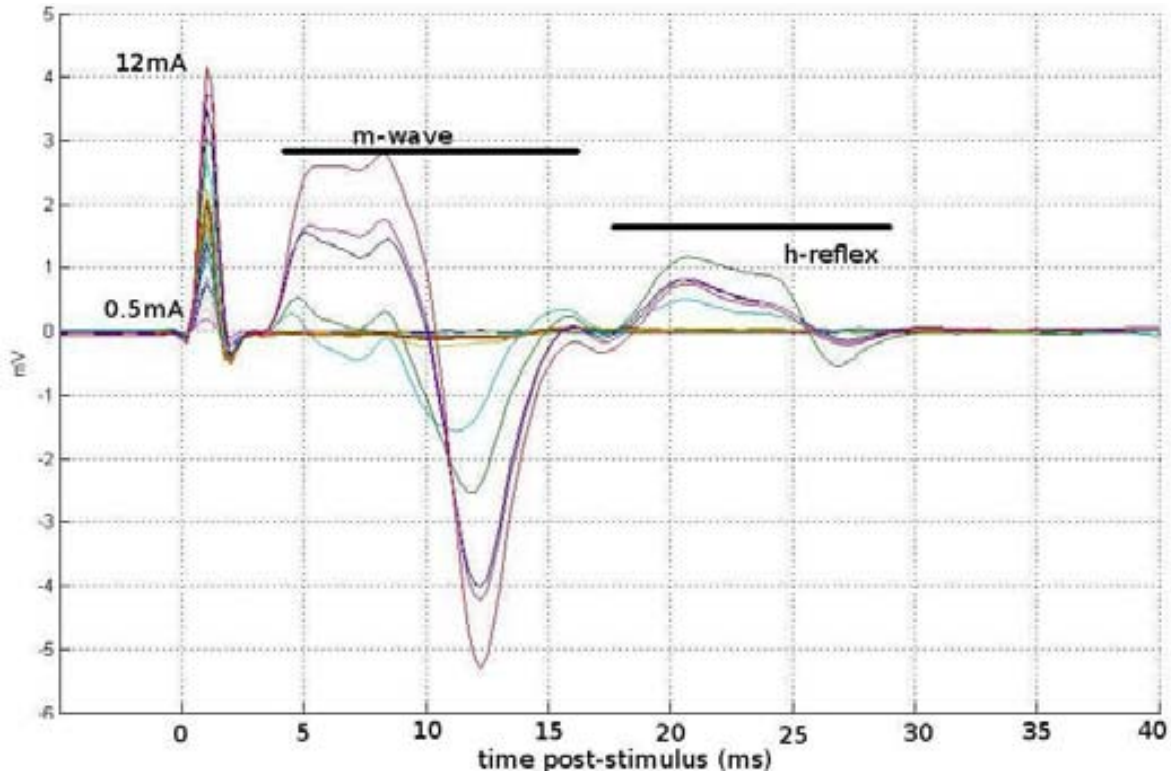
Nevertheless, it is useful to study the proximal segments of a nerve, since processes such as radiculopathies and certain neuropathies such as Guillain-Barré affect this segment predominantly. Late responses (H-reflex and F-response) provide a relatively easy technique for studying proximal segments of nerves, the plexus and nerve roots of the peripheral nervous system that are not accessible to peripheral stimulation. (55;85-87)

The H-reflex and the F-response are produced in certain circumstances after an electrical stimulus to a peripheral nerve. They are so-called late responses because they are "late" with respect to the muscle response (the M-response) produced by the orthodromic volley of action potentials traveling to the muscle directly from the electrical stimulus.(55;85-87)

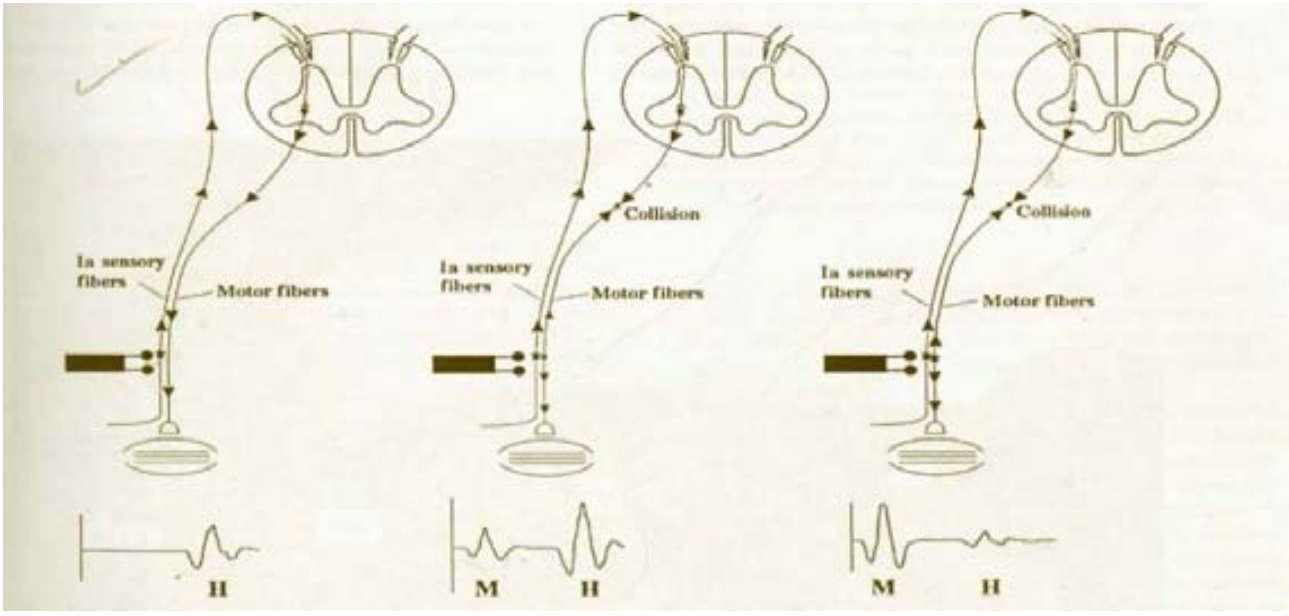
### 1.7.4.1. **H-Reflex**

The H reflex (for "Hoffmann") is a true mono/oligosynaptic reflex with an afferent arc mediated by large, fast-conducting group 1a fibers, and an efferent arc mediated by alpha motor neurons with muscle fiber activation. As such, the neural circuitry is identical to the stretch, or tendon, reflex but bypasses the muscle spindles and gamma-motor system.(55; 85-87) It is visible only with submaximal stimulation (*Picture 14*) and after infancy is most consistently seen with tibial nerve stimulation in the popliteal fossa when recording from the soleus and plantar foot muscles, and less consistently obtained with median nerve stimulation when recording from the flexor carpi radialis. The H reflex is useful for evaluating the S1 nerve root in suspected radiculopathies and proximal conduction in polyneuropathies.

As with tendon reflexes, the H reflex can be enhanced by contraction of the recording muscle and depressed by contraction of antagonist muscles. The soleus H reflex decreases in amplitude with age but can be elicited in 92 percent of healthy people who are age 60 years and older. (91; 92) The typical soleus H reflex latency is approximately 30 msec; the upper limit of normal is 35 msec.




*Picture 14: Electrical stimulation of the median nerve at the elbow. The size & latency of M-waves and H-reflexes are related to the peripheral nerve-spine conduction.(Source: See Appendix III)*




*Picture 15:* ***H reflex circuitry.*** *Diagrammatic picture. (Source: See Appendix III)*

The afferent loop is formed from Ia sensory fibers and the efferent loop from motor axons, with an intervening synapse in the spinal cord (*Picture 15*). At low stimulation intensity (left), the Ia sensory fibers are selectively activated, yielding an H reflex without a direct motor (M) potential. With increasing stimulation (middle), more Ia sensory fibers are activated, as are some of the motor fibers. The motor fiber stimulation results in a small M potential and some collision proximally of the descending H reflex by the antidromic motor volley. At higher stimulation (right), the selective activation of the Ia sensory fibers is lost. Both sensory and motor fibers are stimulated at high levels. The motor stimulation results in an increasingly larger M potential. However, the H reflex decreases in size as there is greater collision proximally of the descending H reflex from the antidromic motor volley.

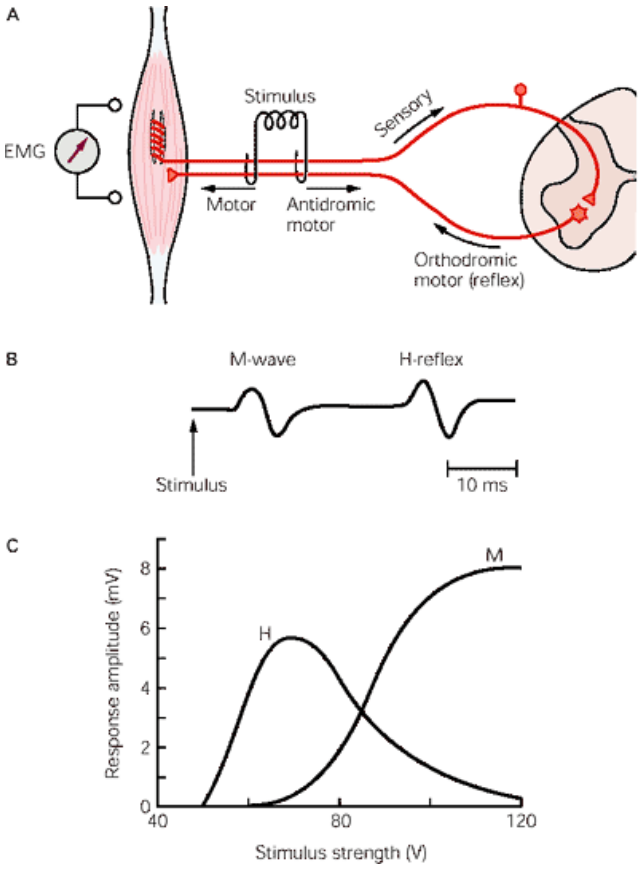
As opposed to the F wave, the H reflex is visible only with submaximal stimulation. With a slow increase in stimulus strength, the H reflex appears as the stimulus changes from subthreshold to submaximal. The amplitude of the H reflex is greatest just below the threshold for the appearance of the compound muscle action potential (CMAP) or M response. With increasing stimulus strength, the H reflex amplitude declines as M response amplitude increases (*Picture 16*). The H reflex disappears with maximal and supramaximal stimulation, replaced by the F wave, which has a slightly longer latency.

Stimulus durations of 0.5 to 1.0 msec are necessary for group 1a afferent fiber activation. As some authors propose with the F wave, to elicit the H reflex the stimulating cathode is proximal to the anode. Several mechanisms may account for the decline and extinction of the H reflex with increasing stimulus strength, including collision of the orthodromic potential from the motor neuron with antidromic activity along the motor axon from the stimulus site, refractoriness of the motor neuron axon hillock, and Renshaw inhibition of the motor neuron pool. (55; 93; 94)

1.7.4.1.1. Clinical utility of H-Reflex

The H reflex is most commonly used to assess the S1 nerve root in suspected radiculopathies and proximal conduction in polyneuropathies.(95)

Unilateral absence of the H reflex or side-to-side differences of >1.5 to 2.0 msec support a focal nerve lesion on the affected side, most commonly at the S1 root, but also at the sacral plexus or sciatic nerve. Because it is a reflex, the H reflex can also be used to study central nervous system functions. (96; 97)



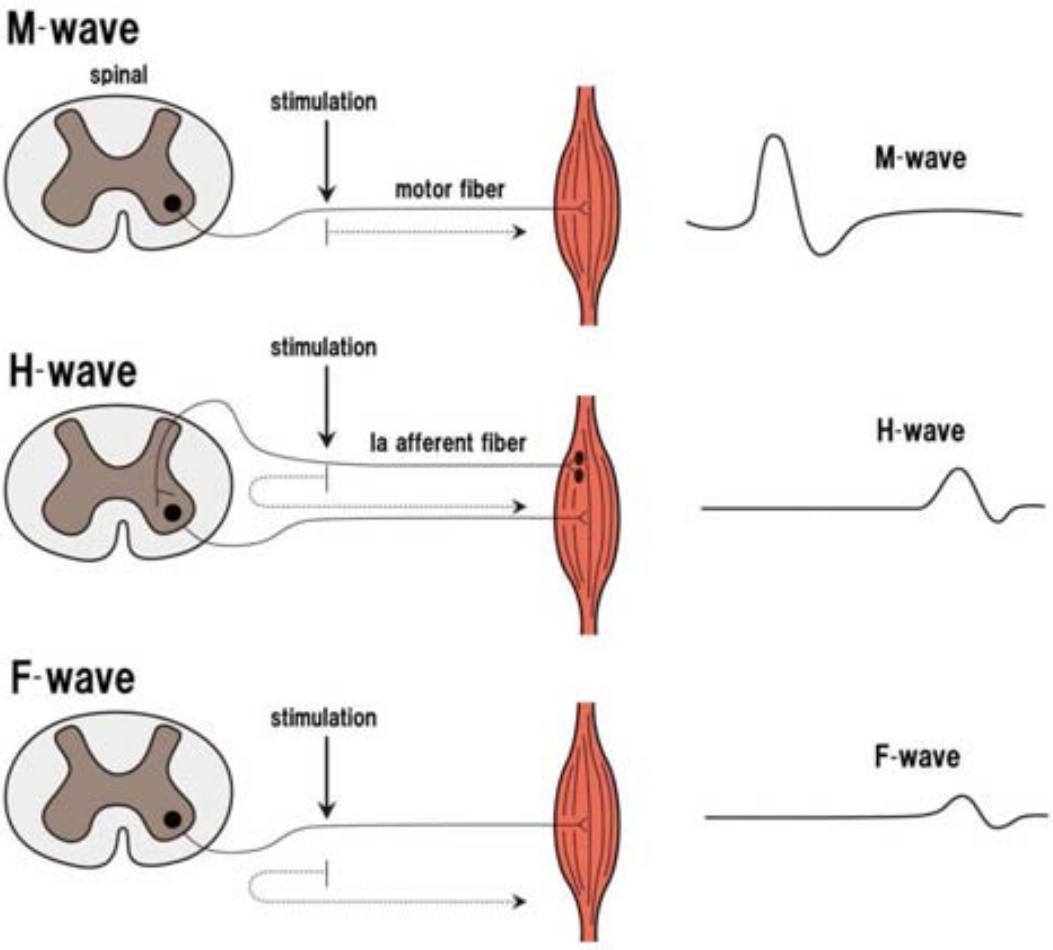

Picture 16: H-Reflex.

A. The H-reflex is evoked by direct electrical stimulation of afferent sensory fibers from primary spindle endings in mixed nerves. The evoked volley in the sensory fibers monosynaptically excites alpha motor neurons, which in turn activate the muscle. Muscle activation is detected by recording the electromyogram (EMG) from the muscles. At very low stimulus strengths a pure H-reflex can be evoked because the axons from the primary spindle endings have a lower threshold for activation than all other axons.
B. As the stimulus strength is increased, motor axons are excited and spindle afferents are activated. The former produces the M-wave that precedes the H-reflex in the EMG.
C. The magnitude of the H-reflex declines at high stimulus strengths because the signals generated reflexively in the motor axon are cancelled by action potentials initiated by the electrical stimulus in the same motor axons. At very high stimulus strengths only an M-wave is evoked.
*(Source: See Appendix III)*

## 1.7.4.2. **F-Responses or F-Waves**

### 1.7.4.2.1. F-Waves: Introduction

F waves are late responses generated by supramaximal nerve stimulation. Electrical activity moving proximally in motor nerves activates or backfires motor neurons, which can generate an orthodromic response known as the F wave that is visible as a low amplitude late potential, following the M wave (*Picture 17*). The F wave, which is a variable response, is seen especially in the distal limb muscles. It is composed of recurrent discharges of the antidromically activated motor neurons. F waves are of particular value in peripheral neuropathies with predominant proximal involvement. (87)




Picture 17: Evoked EMG. M-wave: Excitement is conducted to efferent. H-wave: Excitement is conducted via the monosynaptic reflex. F-wave: Excitement is conducted to antidromic. *(Source: See Appendix III)*

### 1.7.4.2.2. Generation of the F-waves

Depolarizing peripheral nerves with external stimuli evoke potentials that propagate both proximally and distally. With motor nerves, electrical activity moving distally (orthodromically) results in a direct motor response, the compound muscle action potential (CMAP), also known as the M response. Electrical activity propagating proximally (antidromically) activates a small percentage of motor neurons (they "backfire"), which then can generate another wave known as the F wave or F response. The F wave is visible as a low amplitude late potential following the M response.

The pathway of electrical activity along a motor nerve that ultimately results in a recordable F wave is initially antidromic to the motor neuron, and then orthodromic from the motor neuron, traversing the motor nerve axon through terminal nerve branches, synapses, and muscle fibers. The F wave latency incorporates the conduction times through each of these components. Current physiologic evidence supports this concept of an antidromic and then orthodromic motor neuron pathway, although early theories postulated reflex activity. (55; 86)

With SFEMG it is possible to isolate SFAPs with the same latency as the surface recorded F-wave.(98-100) A single fiber F-response is always preceded by a short latency response from the same fiber (corresponding to the M-wave), so that when the M-response is missing on threshold stimulation no F-response is present (*Figure 1*). This indicates that responses of this type are indeed recurrent responses due to antidromic activation of the motor neuron. (101;102)

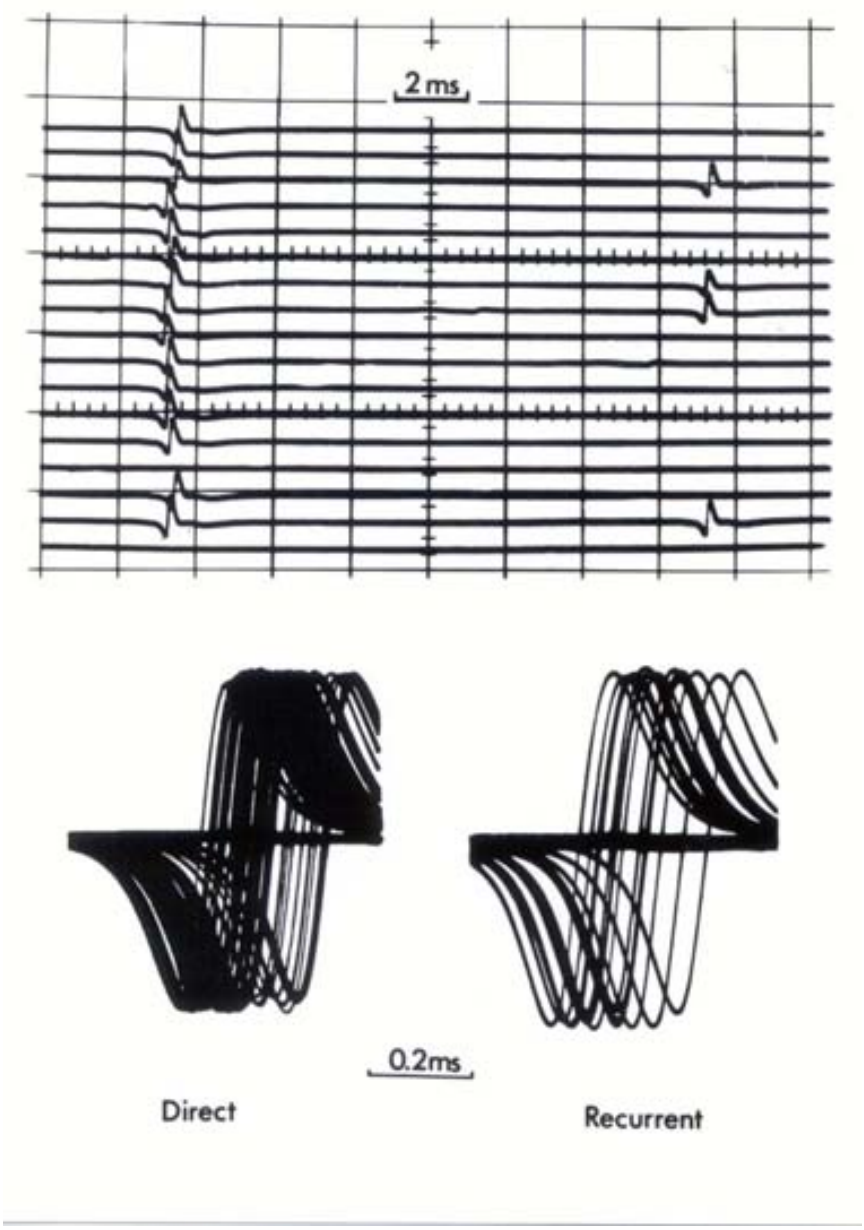



Figure 1: Direct (M) and recurrent (F-) responses of a muscle fiber in abductor pollicis brevis. Top – if at threshold stimulus the direct response is missing, the recurrent response is also missing. Bottom – the direct and recurrent responses of the same muscle fiber superimposed at higher sweep speed. The jitter is similar in both responses. (From the book "Single Fiber EMG"; Stålberg, Trontelj and Sanders 2010; with permission).

## 1.7.4.2.3. Modulating factors. Incidence, morphology, amplitude, latency

On supramaximal stimulation, the F-responses of individual neurons appear randomly, following 0.1 to 20% of M-responses. The frequency of appearance can be increased by a variety of maneuvers (such as Jendrassik's), which presumably produce facilitation of the motor neuron pool. Conversely, it can be decreased by antagonistic muscle movement. (101;102) In some neurons with a high incidence of F-responses at rest, voluntary activity in the recorded muscle may reduce the number of F-responses.

For a recurrent response to occur, at least two events appear to be critical: (1) the antidromically arriving nerve impulse must depolarize the motor neuron cell (so-called antidromic invasion), which does not occur every time, since depolarization of the small membrane of the initial segment ("IS spike") cannot easily spread to depolarize the much larger soma-dendritic membrane ("SD spike"); (2) the initial segment (or the most proximal node of Ranvier) has to recover at least part of its excitability in order to become redepolarized before the SD spike dies down.

There may be a third uncertainty involving transmission of the antidromic impulse from the most proximal node of Ranvier to the initial segment, based on the same reason as the uncertainty of antidromic invasion. The antidromic invasion is facilitated by preceding partial depolarization of the SD membrane, such as produced by the Jendrassik maneuver.

On the other hand, if facilitation is slightly too strong the invasion will be fast and the time will be too short for repolarization of the initial segments. (103-106) There seems to be a relatively narrow range of values of soma-dendritic membrane potential at which both of the later mentioned critical conditions are fulfilled. This explains the sometimes contradictory effects of facilitation maneuvers, and perhaps also the observation that from some motor neurons recurrent responses are not obtained even in long series of stimulation and in spite of attempts to facilitate them.

Another reason suggested for differences in availability of F-responses among motor neurons is the different strength of Renshaw inhibition, favouring large motor neurons. (107)

The latency variation of successive recurrent responses of individual muscle fibers (SFAPs) is usually only slightly larger, up to 15 us, than that of the M-responses of the same fibers (1:1.3 on average).(101;102;108) *(Figure 1)* The additional variation is due to the varying delay at the axon-soma junction, as well as to the irregular rate of appearance of these responses, which introduces firing rate-related changes of the muscle fiber propagation velocity.(109;110) This is also seen in the M-responses of the same unit, which at higher rates of activation usually show supernormal velocity and slight shortening

of the latency for the response after the one that was followed by an F-response *(Figure 2),* which occasionally helps one identify the fiber that is giving the F-response. This low latency variability is in sharp contrast to the markedly variable latency of the surface-recorded F-wave, which is due to activation of different populations of motor neurons by successive stimuli.

The surface-recorded single F waves result, thus, from activation of one to, at most, a few motor neurons, and each F wave results from activation of different subpopulations of motor neurons with each stimulation. This inconsistency in motor neuron activation accounts for the variability in F wave configuration, amplitude, and latency during a series of stimuli. Thus, it is important to record at least 10 to 20 F waves for analysis. (111)

Antidromic neural activity can trigger an orthodromic action potential in the same motor neuron by reactivating its initial segment, or axon hillock. Several physiologic phenomena can prevent all motor neurons from being activated with each nerve stimulus, including prolonged refractory periods at the axon hillock, inhibition of recurrent collaterals from motor neuron to motor neuron, and activation of Renshaw interneurons that inhibit smaller motor neurons. These same phenomena reduce the chance of eliciting an F wave with every nerve stimulus, despite the stimulus being supramaximal. Those neurons that do contribute to the F wave may be the largest and fastest conducting myelinated motor fibers. (111)

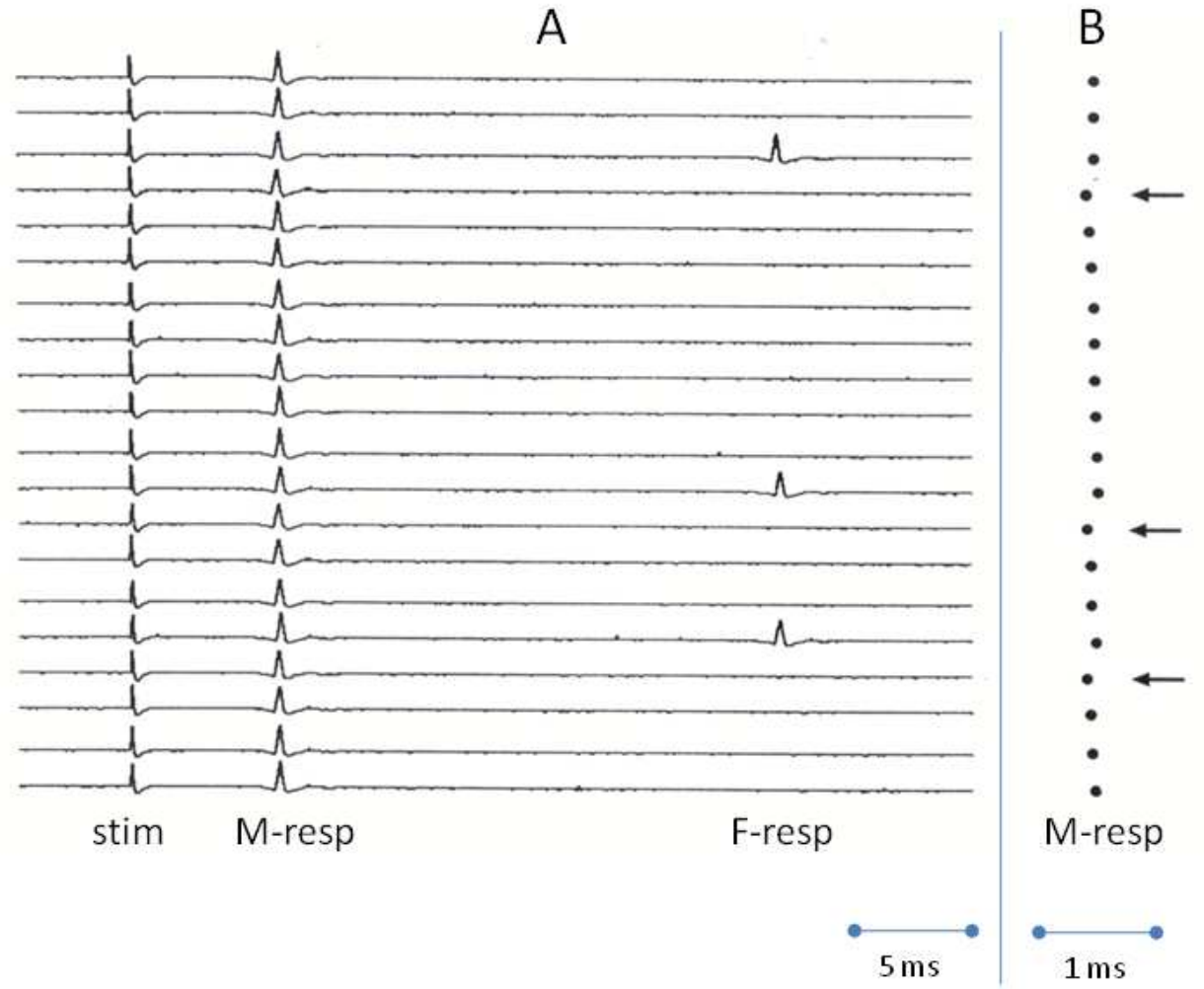



Figure 2: An SFEMG recording of F-responses at a stimulation rate of 10 Hz (A). Dots (B) indicate latency to M response. In traces following those with F-responses, the M-response latency is slightly shorter (arrows), due to supernormal velocity recovery function (VRF). This phenomenon may be helpful in identifying the muscle fiber in the M-response giving the recurrent discharges. (From the book "Single Fiber EMG"; Stålberg, Trontelj and Sanders 2010, with permission).

## 1.7.4.2.4. Clinical utility of F waves

The electrophysiological expression of the excitatory state of the motor neurons is shown to produce repeated back firings, so-called repeater F-waves. In general, these repeater F-waves are related to neurogenic abnormality. (112)

### 1.7.4.2.4.1. Spasticity

In spastic muscles, the motor neurons that give F-responses tend to do so more frequently, apparently due to their increased excitability. In motor neurons that give frequent F-responses, additional facilitation tends to suppress them. In contrast, those with infrequent F-responses will increase their firing rate. (113)

### 1.7.4.2.4.2. Polyradiculoneuropathy

In the acute stage of GBS, the F-response may be absent, even when many motor neurons are still available for voluntary activation. This is likely caused by a block of the orthodromic (i.e., recurrent) impulses due to abnormally prolonged refractoriness of the affected proximal segments of these axons.

F waves are of particular value in peripheral neuropathies with predominant proximal involvement, such as acute and chronic inflammatory demyelinating polyneuropathies, in which distal conduction velocities may be normal early in the disease. (114)

F wave minimal latencies of >120 percent of the upper limit of normal (>150 percent if the distal negative peak CMAP amplitude was <80 percent of the lower limit of normal) in each of two nerves indicate primary demyelination. (115-117)

### 1.7.4.2.4.3. Peripheral Neuropathy and Polyneuropathy

Lesser degrees of F wave slowing may be seen in axonal and mixed polyneuropathies. (111)

Nevertheless, F wave slowing appears to be highly sensitive for nerve pathology in patients with diabetes mellitus. (118)

In demyelinating polyneuropathies, there is decreased persistence of F waves with absent F waves in the presence of relatively preserved M responses. (111)

#### 1.7.4.2.4.4. Radiculopathy

The value of F waves in focal nerve lesions, such as radiculopathy, is controversial. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) concluded that F waves in isolation cannot definitively diagnose radiculopathy. (119)

F wave conduction along longer normal nerve segments may "dilute" any conduction delay across much shorter radicular segments. (55; 120)

Since most peripheral nerves consist of axons from multiple nerve roots, with multiple innervation of the muscles undergoing recording, normal conductivity across unaffected roots may also dilute the abnormalities of the affected root.

### 1.7.4.2.5. Recording and Analysis of the F-waves

F waves are recorded using surface electrodes over distal muscles and supramaximal nerve stimulation in the same manner as motor nerve conduction studies. Some authors defend that the stimulating cathode is proximal to the anode to prevent anodal block of the antidromic potential. However, the value of reversing the orientation of the stimulus for obtaining F waves has been questioned. (121)

Some authors have used the F-response latency to calculate conduction velocity in the proximal portions of the motor axons, allowing 1 ms for the central delay, i.e., the time taken for antidromic invasion and redepolarization of the initial segment. The professors Stålberg, Trontelj and Sanders (122) opinated that the obtained values are underestimated, since in this calculation no allowance is made for the slowing of the orthodromic impulse along the axon, which is, at least in its most proximal portion, profoundly subnormal.

Analysis of the following F wave parameters is clinically useful:

- Mean latency, rather than the shortest latency
- Chronodispersion, the difference between minimal and maximal latencies
- Mean amplitude in relation to the maximum M potential (the mean F/M amplitude ratio)
- Persistence of the F wave, defined as the percentage of stimuli in a series that results in a recordable F wave (normally >50 percent, and usually 80 to 100 percent) (111)

## 1.8. FORMULATION OF THE PROBLEM

F-waves are recorded routinely in clinical neurophysiological practice. F-wave latencies are valuable markers of conduction properties of motor axons that may help in detecting mild or early generalized abnormalities (123), along with the distal motor conduction studies. F-waves also reflect changes in the excitability of motor neurons. (123; 124)

A higher than normal frequency of repeater F-waves has been shown in patients with motor neuron disease and cervical spondylolysis, (125) as well as in patients with carpal tunnel syndrome (CTS). (126) Similarly, in patients with lumbosacral radiculopathy repeater F-waves were found in a higher number when compared to healthy individuals. (127) Further studies have compared healthy subjects and patients with amyotrophic lateral sclerosis and different types of neuropathies. (57; 128)

The clinical significance of repeater F-waves as a sign of proximal root versus nerve pathology and their usefulness in daily electrodiagnostic routines has not been evaluated, since all studies so far have compared individual conditions to normal and not to each other when CTS and cervical radiculopathy appear combined. In addition, a number of sublinical radiculopathies may be easily missed in carpal tunnel syndrome diagnoses using the current standard neurophysiological approach. Thus the Theme that we propose for the present work is to determine the diagnostic role of repeater F-Waves in carpal tunnel syndrome with sublinical radiculopathy by means of a prospective, observational study.

## 1.9. THESIS STATEMENT:

Repeater F-waves have a diagnostic role in carpal tunnel syndrome with subclinical radiculopathy.

## 1.10. RESEARCH QUESTION:

How does the morphology, amplitude and latence of the electroneurographic late responses relate with the location and intensity of the motor axonal pathologies in the upper limb?

## 1.11. OBJECTIVES:

- To assess the frequency and characteristics of repeater F-waves in patients suffering from peripheral nerve entrapment syndromes, i.e., carpal tunnel syndrome, ulnar mononeuropathy or both.

- To assess the frequency and characteristics of repeater F-waves in patients suffering from subclinical cervical radiculopathy, combined or not with peripheral nerve entrapment syndromes.

- To compare the frequency and characteristics of repeater F-waves between both groups of patients with isolated peripheral nerve entrapment syndromes and with additional -or isolated- cervical radiculopathy.

- To analyze the relationship between repeater F-waves and location either proximal or distal of the axonal damage in both groups of patients.

## 1.12. HYPOTHESES:

**HYPOTHESIS I. Research hypothesis (H1) and Null hypothesis (H0):**

**H1:** In peripheral nerve entrapment syndromes, repeater F-Waves frequency and characteristics are related to the severity of the lesion.

**H0:** In peripheral nerve entrapment syndromes, repeater F-Waves frequency and characteristics are not related to the severity of the lesion.

**HYPOTHESIS II. Research hypothesis (H1) and Null hypothesis (H0):**

**H1:** In subclinical cervical radiculopathies combined or not with peripheral nerve entrapment syndromes, frequency and persistence of repeater F-Waves are higher than in isolated peripheral nerve entrapments.

**H0:** In subclinical cervical radiculopathies combined or not with peripheral nerve entrapment syndromes, frequency and persistence of repeater F-Waves are similar than in isolated peripheral nerve entrapments.

**HYPOTHESIS III. Research hypothesis (H1) and Null hypothesis (H0):**

**H1:** Patients with isolated cervical radiculopathies and those with cervical radiculopathy combined with peripheral nerve entrapment can be differentiated by means of frequency and persistence of repeater F-Waves.

**H0:** Repeater F-Waves' frequency and persistence do not show significant differences between isolated cervical radiculopathies and when those present combined with peripheral nerve entrapments.

**HYPOTHESIS IV. Research hypothesis (H1) and Null hypothesis (H0):**

**H1:** In carpal tunnel syndrome (CTS) referrals who are healthy or present mild CTS repeating F-Waves are related to subclinical proximal pathology at plexus or root level.

**H0:** In carpal tunnel syndrome (CTS) referrals who are healthy or present mild CTS repeating F-Waves are not related to subclinical proximal pathology at plexus or root level.

**General Null hypothesis (H0):**

- There is no relationship between the repeating F-waves occurrence and the location and intensity of the motor axonal damage.

# 2. MATERIAL AND METHODS

## 2.1. SCOPE OF RESEARCH

### 2.1.1. Design, Setting, Subjects and Measurements

**Design:** Prospective observational study.

**Setting:** The Clinical Neurophysiology Department of the Lucus Augusti University Hospital, Lugo, Spain. The study was approved by the Institutional Ethics Committee.

**Subjects:** Consecutive patients referred from Orthopedic Surgery, Neurosurgery and Rheumatology consultants under a period of six months (June 01 to November 30, 2012) for differential diagnosis between carpal tunnel syndrome and cervical radiculopathy. Excluded were subjects with neuromuscular disease, diabetes mellitus or other condition known to cause polyneuropathy (including addiction to alcohol or drug abuse).

**Measurements:** Neurophysiological examinations under standardized conditions were performed by the same author (IAST). Four groups were defined according to clinical and electrophysiological criteria:

**I.** Patients with a clinical and electrophysiological supported diagnosis of **both** peripheral nerve entrapment and cervical radiculopathy.

**II.** Patients with a clinical and electrophysiological supported diagnosis of **only peripheral** nerve entrapment without cervical radiculopathy.

**III.** Patients with a clinical and electrophysiological supported diagnosis of **only cervical** radiculopathy without peripheral nerve entrapment.

**IV.** Patients who despite of the clinical symptoms did not fulfill any electrophysiologically supported diagnosis of peripheral nerve entrapment nor cervical radiculopathy.

### 2.1.2. Carpal-Tunnel Syndrome Assessment

In order to assess the Carpal-Tunnel Syndrome, the current protocols for Nerve Conduction Studies from the Department of Clinical Neurophysiology of Uppsala (Sweden) were used:

- Motor Conduction Study (MCS) of median nerve: Distal-latency and CMAP amplitude only.

- Sensory Conduction Studies (SCS) of median and ulnar nerves: Amplitude and Conduction Velocity.
    - Median nerve sensory action potentials were assessed in Digits III-IV;
    - Ulnar nerve was assessed through digits IV-V.

Protocols did not include measurement of the palm-wrist SCS parameters.

Both motor and sensory conduction studies were performed bilaterally.

The grades of severity considered in peripheral nerve entrapments are depicted in Table 3.

For the purposes of this study, the inclusion criteria in the case of ulnar nerve mononeuropathy observe:

• A focal conduction velocity (CV) reduction of 10 m/s or superior in the compound muscle action potential (CMAP) when stimulating distally to elbow joint in comparison with proximal stimulation, reflecting failure of conduction along some of the fibers with or without damage of the motor axons, or

• A significant focal reduction of CV in the sensory nerve potential at the Guyon's channel, or focal amplitude reduction in the compound muscle action potential (CMAP) >20%, reflecting failure of conduction along some motor axons at the wrist level.

## 2.2. ELECTRODIAGNOSTIC TECHNIQUES AND PROTOCOLS

### 2.2.1. Electroneurography: Median and Ulnar nerves. Sensory and Motor potentials.

### 2.2.2. F-Waves: Median and Ulnar nerves.

### 2.2.3. Electromyography: Myotomes C3 to T1.

In the various combinations of Median/Ulnar-neuropathies and C3-T1-radiculopathies, the findings of the affected median and ulnar nerves, respectively were studied.

The ipsilateral ulnar nerve in the CTS patients and ipsilateral median nerve in ulnar-neuropathy patients were explored.

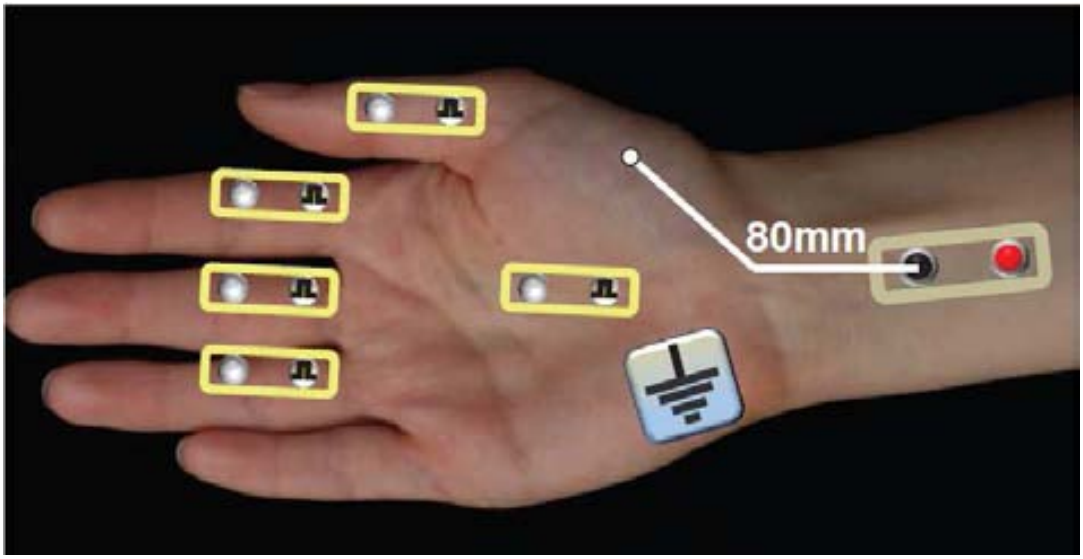
In addition, contralateral upper limbs were examined when the symptoms were related bilaterally.

## 2.2.1. Electroneurography:

## Median and Ulnar nerves. Sensory and Motor Potentials.

### 2.2.1.1. Median Nerve Sensory Conduction Study

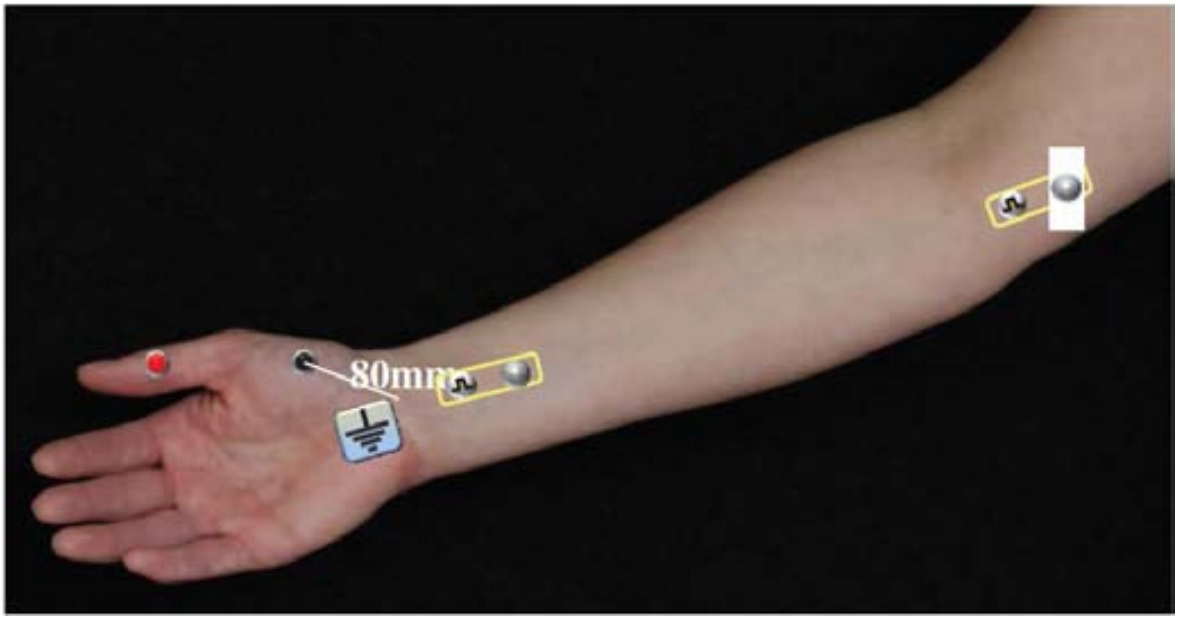
- Type of measurement: Orthodromic.
- Position of the arm: Seated. The elbow stretched or slightly curved. Palm up with fingers in relaxed neutral position with slight flexion.
- Recording electrode: Surface electrode with a fixed distance (23 mm) between the anode and cathode. *(Picture 18)*
- Location of the active electrode: The wrist. There where the median nerve is stimulated for the motor studies.
- Stimulating electrode: Surface electrode with a fixed distance (23 mm) between the anode and cathode.
- Stimulation points:
    - The base of fingers/digits I and II-III-IV laterally;
    - Palm.




*Picture 18: Median Nerve Sensory Conduction Study. Source: Metodbok för Neurografier. Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). (See Appendix III)*

### 2.2.1.2. Median Nerve Motor Conduction Study

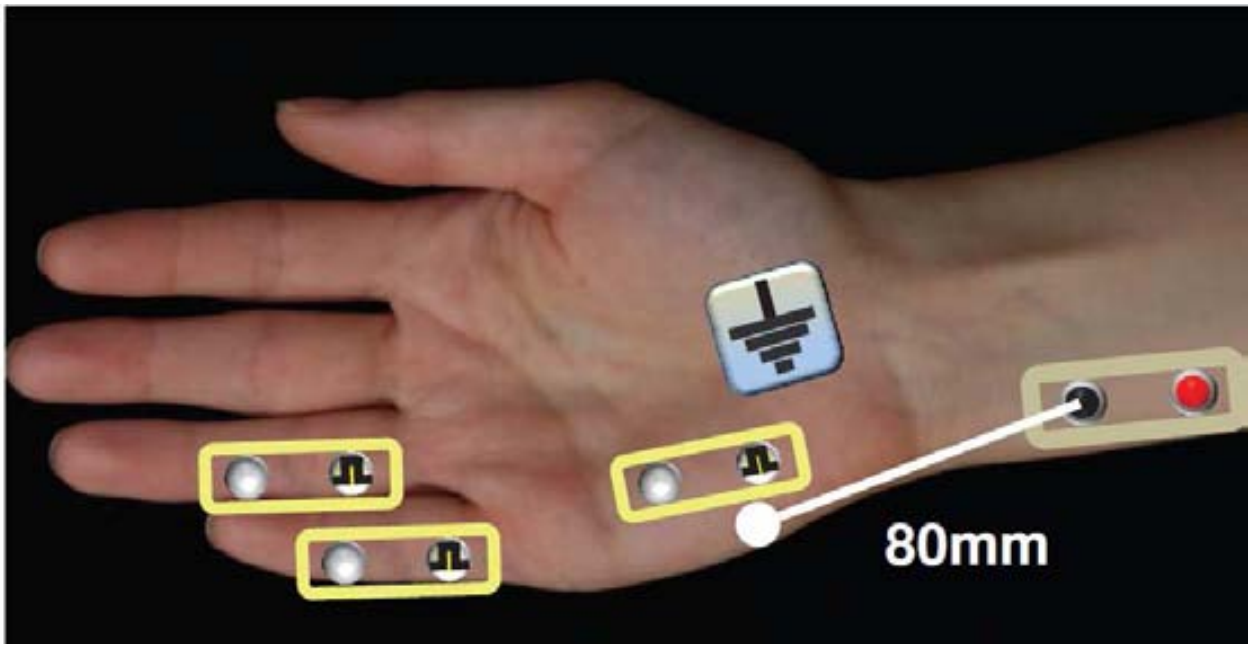
- Patients position: Seated. The elbow stretched or slightly curved. Palm up with fingers in relaxed neutral position with slight flexion.
- Recording electrode: Surface electrodes with 10 mm in diameter. *(Picture 19)*
- Location of the active electrode: Abductor Pollicis Brevis (APB).
- Placement of the reference electrode: Distal interphallangeal joint of the thumb.
- Stimulation electrode: Surface electrode with fixed distance (23 mm) between the anode and cathode.
- Stimulation points:
    - Palm
    - Wrist, 80 mm proximally to the recording electrode (measured according nerve anatomy)
    - Elbow




*Picture 19: Median Nerve Motor Conduction Study. Source: Metodbok för Neurografier. Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). (See Appendix III)*

### 2.2.1.3. Ulnar Nerve Sensory Conduction Study

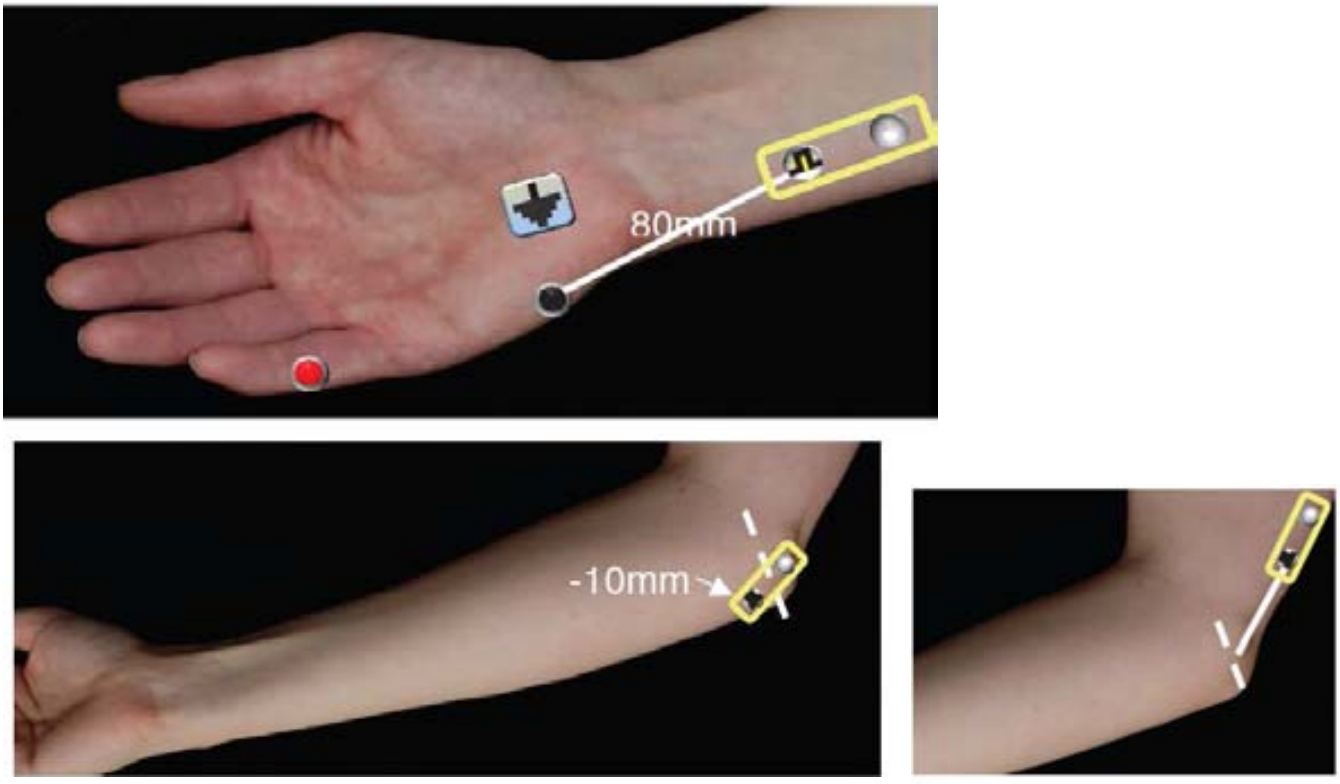
- Type of measurement: Orthodromic.
- Patients position: Seated.
- Recording electrode: Surface electrode with fixed distance (23 mm) between the anode and cathode. *(Picture 20)*
- Location of the active electrode: Wrist. Where the ulnar nerve is stimulated during the motor studies.
- Stimulating electrode: Surface electrode with fixed distance (23 mm) between the anode and cathode.
- Stimulation points:
    - The base of the finger/digit VI medially;
    - The base of the finger/digit V medially;
    - Palm.




*Picture 20: Ulnar Nerve Sensory Conduction Study. Source: Metodbok för Neurografier. Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). (See Appendix III)*

### 2.2.1.4. Ulnar Nerve Motor Conduction Study

- Patient position: Seated. The elbow slightly bent (15º - 30º). Palm up with fingers in a relaxed neutral position with slight flexion.
- Recording electrode: Surface electrodes with 10 mm in diameter. *(Picture 21.a-c)*
- Location of the active electrode: Abductor Digiti Minimi (ADM), on a line between the fifth metacarpo-phalangeal joint and pisiform bone.
- Placement of the reference electrode: Distal interphalangeal joint of the little finger.
- Stimulation electrode: Surface electrode with a fixed distance (23 mm) between the anode and cathode.
- Stimulation points:
    - Wrist, 80 mm proximal to the recording electrode;
    - Below the elbow. Approximately 10-15 mm distal to the medial epicondyle;
    - Above the elbow. Approximately 90-120 mm proximal to the medial epicondyle;
    - Plexus. At Erbs point.




*Pictures 21.a-c: Ulnar Nerve Motor Conduction Study. Source: Metodbok för Neurografier. Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset.Uppsala Universitet (Sweden). (See Appendix III)*

## 2.2.2. F-Waves: Median and Ulnar nerves.

For the obtention of the F-Waves, the following protocol was followed:

Electrodes:

- Active electrodes maintain the same location as in Median and Ulnar motor nerve conduction studies.
- Stimulation points are distal, at the wrist, similar as for the CMAPs obtention. We keep the cathode distal to the anode for this procedure.

Stimulation:

- Stimulus voltage is supramaximal.
- Trains of 20 supramaximal stimuli are respectively delivered on the median and ulnar nerves of each upper limb analyzed.

Display and set-up parameters:

- Sweep speed is set up to 5 ms per division (ms/D); gain was 5 mV/D for M-waves and ten times higher for F-waves (0.5 mV/D).
- Raster and superimposition acquisition modes are implemented during the obtention and edition of the F-waves.

## 2.2.3. Electromyography: Myotomes C3 to T1.

Equipment: Keypoint; concentric needle electrode. Sterile disposable products.

Survey description:

- Preparation: None for adults.
- Program in KP: EMG

Procedure:

- The survey is carried out according to the laboratory's policy and current standards.
- Testing maneuvers by myotomes (at least one muscle by myotome):
  - C3: neck lateral flexion
  - C4: shoulder elevation
  - C5: shoulder abduction
  - C6: elbow flexion/wrist extension
  - C7: elbow extension/wrist flexion
  - C8-T1: thumb/little finger extension
- Typically quantitative analysis should be performed (MultiMUP): Collection of 25 to 30 MUP and editing so that 20 remain. Quality is very important (it is recommended to wait at least 5 seconds with the needle still, light strength).
- Editing seeks to exclude duplicates and bad registrations (jumping of baseline, other interferences). Cursor settings are changed as low as possible in order to avoid subjective elements.

Results and Reporting:

- The results are given as tabular data. Sometimes a muscle diagram can be included.
- Then summarize the whole survey in the form of neurophysiological – pathophysiological diagnosis with other neurophysiological results included, if they are already known (neuro-imaging, etc.).
- Then the investigation in relation to the issue and the clinical situation.
- Anticoagulant drugs: the patient should inform the current INR before EMG investigation undertaken.

# 2.3. ELECTRONIC SYSTEMS AND DATA ANALYSIS

## 2.3.1. *Equipment: Workstation and Data Acquisition Software*

For all neurophysiological studies, a Keypoint.Net EMG machine (Medtronic-Dantec, Skovlunde, Denmark) was used.

## 2.3.2. *Patient preparation*

If skin temperature on the dorsum of the hand was less than 29$^{o}$ C, heating pads, infrared heater or warm water were applied for at least 10 minutes.

## 2.3.3. *Techniques and Protocols:*

### *2.3.3.1. F-wave acquisition in median and ulnar nerves*

Standard nerve conduction studies were performed as previously described. In brief, for F-wave acquisition cathodal electrical pulses of 0.1 ms duration were applied at the distal stimulation sites of the median and ulnar nerves with surface electrode recording from abductor pollicis brevis (APB) and abductor digiti minimi (ADM) respectively.

### *2.3.3.2. F responses' sample size*

A total of 20 supramaximal stimuli were delivered at 1 Hz frequency to each nerve while the examined muscle remained relaxed and no facilitation technique was attempted. Thus, in each upper limb 20-F waves' samples were systematically obtained both in median and ulnar nerves.

Note: Until now, the mention of "sample size" had been related to our patients' study population. But from the Discussion and Results' chapters, the word "sample" will denominate (if not specified as "patient population") the respective F-waves' registers obtained from median and ulnar nerves in each upper limb analyzed.

### *2.3.3.3. Filtering and display settings*

The band pass was set at 20 Hz - 10 kHz; the sweep speed was either 5 or 10 ms/division; and the amplifier gain for F-waves was set to 0.2 or 0.5 mV/division.

#### *2.3.3.4. Data processing*

F-wave latency was measured automatically by software on each trace followed by visual inspection. When needed, manual editing assured correct cursor position.

#### *2.3.3.5. Control nerves*

In order to analyze the parameters of the *"healthy nerves remaining in patients with mononeuropathies"*, healthy control nerves were obtained from the unaffected median or ulnar nerves of group II patients (if only one mononeuropathy per upper limb) and from group IV (where both median and ulnar nerves were healthy). As all patients in group I combine both radicular and neuropathic disorders, any of their nerves was used as control reference.

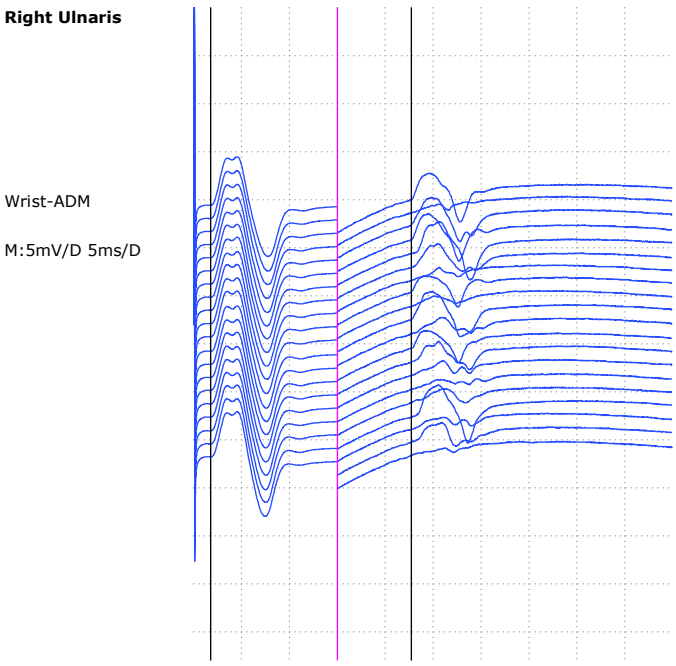
## 2.4. DATA PROCESSING AND VARIABLE DEFINITIONS

The amplitude of the CMAP was measured from baseline to the negative peak. The amplitude of F-waves for each trace was manually measured peak to peak; to eliminate erroneous judgment on the identicality of signal shapes, only those exceeding 40 μV were included in the measurements, which were also the ones recognized by the software program for the automatic latency measurements. Nerves without CMAP or F-waves were excluded from the analysis. A-waves, arbitrarily defined as identical late responses in 8 or more of 20 traces with a constant latency which appeared between the CMAP and the F waves in most cases, but occasionally after the F-waves, were easily identified and excluded from the F-wave measurements. When A-waves occur with the same latency as the F-waves, they may be difficult to separate from repeater F-waves, although the former have typically much higher persistence.

However, outlier results, like subjects presenting identical signals in ≥ 15 traces (75 % of the sample) with latencies within the F-wave latency range, would be excluded from the analysis. These subjects usually represent a very small, not significant, exclusion of data.

F-waves of identical shape in the entire signal, with the same latency and amplitude were defined as repeating F-waves from a given neuron, called a repeating neuron (RN). For identification of repeater F-waves, each recording was visually inspected for RNs. The superimposition of all 20 traces was used to confirm the identical shape of RNs and to ensure that they were indistinguishable from each other. Minor latency deviations due to F-response jitter, which according to single-fiber EMG (SFEMG) studies is expected to be ≤52 μsec, should not be noticeable with the sweep speed used. To be included as a repeater, the entire shape from onset to return to baseline- had to be identical. The presence of a notch or an extra phase disqualified the signal from being considered as a repeater candidate. If other F-responses besides the repeater were present in the same trace, they were not included in the statistics.

*Figures 3a/b and 4* show typical examples of multiple repeating neurons (RNs) in F-wave recordings (explorer: IAST).




| Right Ulnaris FResponse | | | |
|---|---|---|---|
| | F-M Lat | M-Lat | F-Lat |
| | ms | ms | ms |
| Wrist - ADM | 20.9 | 1.79 | 22.7 |

Figure 3a: F-waves recorded in raster and superimposition mode from a 51 year-old woman with cervicobrachial syndrome. She was diagnosed moderate CTS in the ipsilateral median nerve, as well as cervical radiculopathy with signs of chronic mild denervation at the dermatomes C8-T1 in the right side. In the ulnar nerve, 20 stimuli generated 20 F-waves, at least 8 of which were generated by 4 repeating neurons (RNs); in this case each RN presented two repetitions. High and low amplitude RNs are present. Even the low amplitude repeaters depicted can be seen in superimposition as darker lines. Note the different amplitudes in raster and superimposition modes.

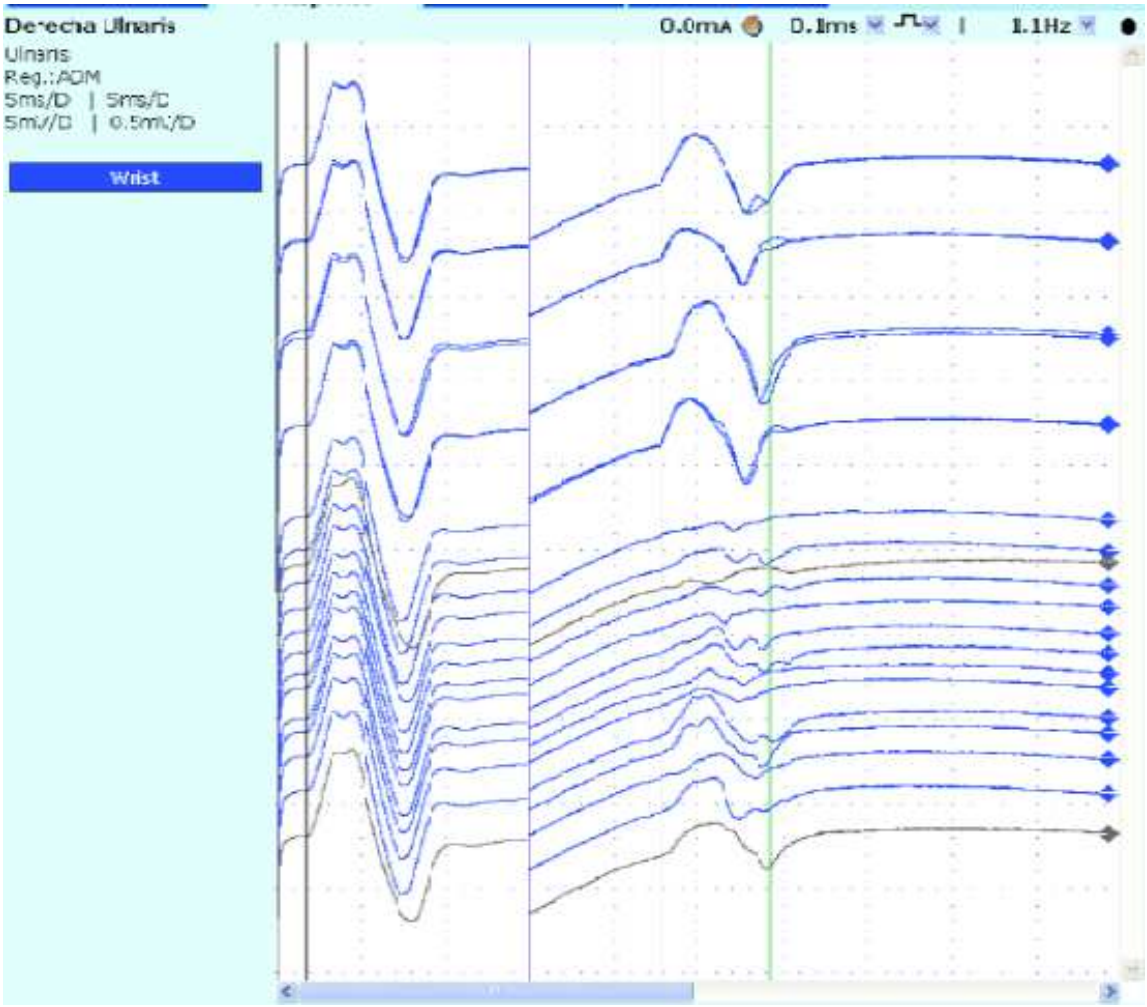



Figure 3b: F-waves recorded in raster and superimposition mode from a 51 year-old woman with cervicobrachial syndrome. She was diagnosed moderate CTS in the ipsilateral median nerve, as well as cervical radiculopathy with signs of chronic mild denervation at the dermatomes C8-T1 in the right side. In the right ulnar nerve, 20 stimuli generated 20 F-waves, at least 8 of which were generated by 4 repeating neurons (RNs); in this case each RN presented two repetitions. High and low amplitude RNs are present. Even the low amplitude repeaters depicted can be seen in superimposition as darker lines. Note the different amplitudes in raster and superimposition modes.

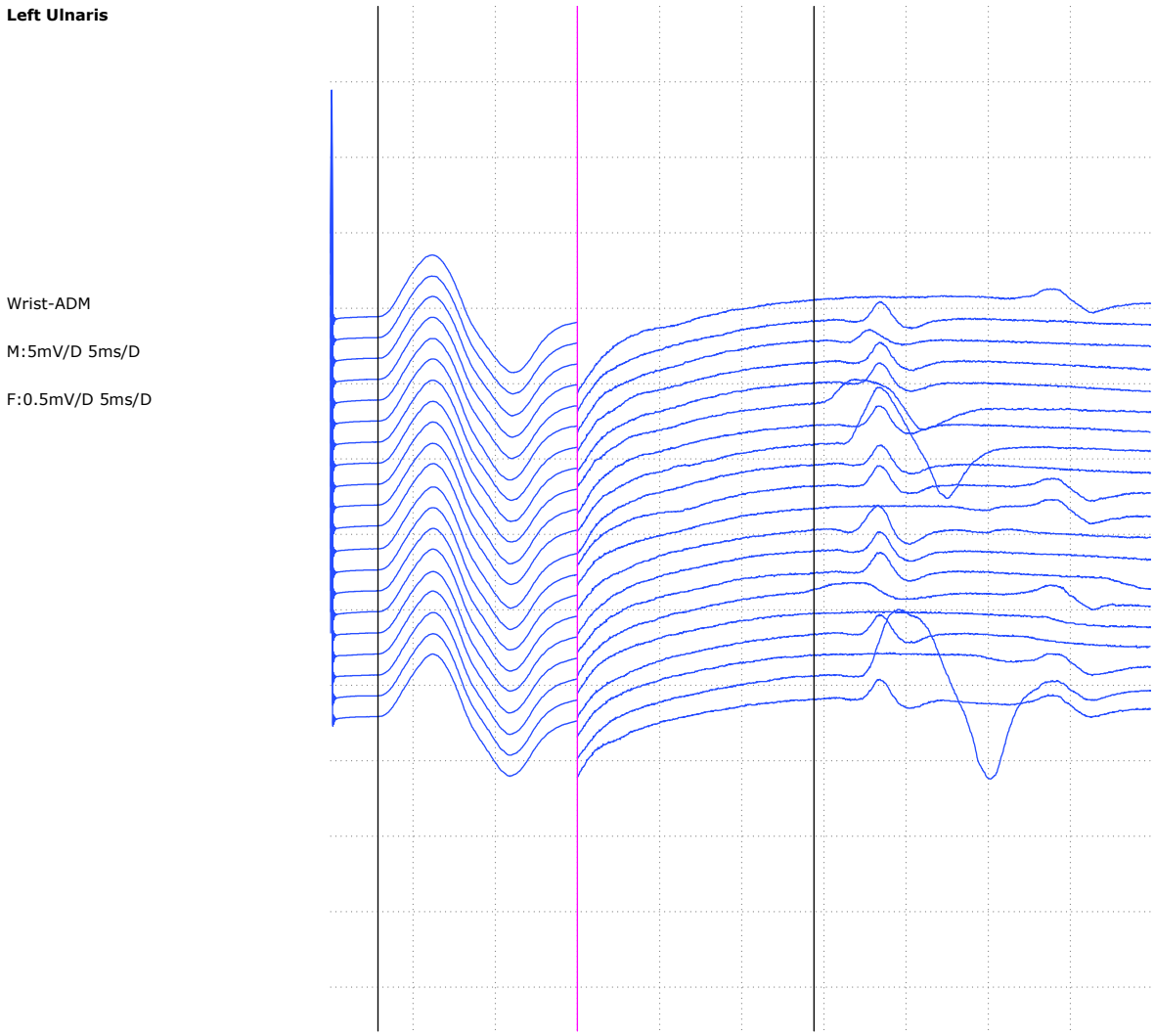



Figure 4: F-waves recorded in raster mode from a 32 year-old woman which referred clinical symptoms such as pain, pins and needles and weakness in both hands. She was diagnosed cervical radiculopathy as the EMG findings showed mild chronic denervation at the cervical dermatomes C3-C6 and C8-T1, as well as moderate chronic denervation at C7. Only normal data were found along the electroneurography of both median and ulnar nerves. In the ulnar nerve, 20 stimuli generated 20 F-waves, 16 of which were generated by 2 RNs, (1 had six repetitions and 1 ten repetitions). The F-wave complex in the nineteenth trace possibly contains another RN which is seen isolated in the right side of the recording (traces 1, 10, 11, 15, 18 and 20) but according to our definition was not identified as RN.

## 2.4.1. Standard neurophysiological parameters used:

Total number of F-waves was defined as follows:

Total number of F-waves = single (non-repeater) F waves + repeating F waves

Persistence of F-waves was defined as:

Persistence of F-waves = % traces with any F-waves in a series of 20 stimuli

or

( Σ F-waves / 20 ) x100

Persistence of F non repeaters was defined as:

Persistence of Fnonreps= % Fnonrepeaters in a series of 20 stimuli

or

( Σ Fnonreps / 20 ) x100 = 100 x (Fwaves – Freps)/20

Persistence of total F repeaters was defined as:

Persistence of total Freps= % traces with any F-repeater in a series of 20 stimuli

or

( Σ Freps / 20 ) x100

In each recording, persistence was noted separately for Freps and for Fnonrepeaters (i.e. all F-waves minus total Freps).

## 2.4.2. RN variables defined (following the Chroni's criteria) (129):

Number of Repeating Neurons (RN): the number of different neurons able to produce repeater F-waves.

Total Freps, total of all repeater F-waves: times that each of the RN is repeating itself in a recording.

These two elements of repeater F-waves were also examined in relation to all F-waves in a recording by the following indices:

Index RN= 100 x number of RN / number of traces with different F-wave shapes in a series of 20 stimuli.
Calculated: Index RN= 100 x RN/(Fwaves – Freps + RN)

Index total Freps=100 x total number of F-wave repeaters / total number of traces with F-waves in the same nerve.
Calculated: Index total Freps= 100 x Freps/Fwaves

*Example: The study of a nerve with 20 stimuli resulted in 12 traces with F-waves identified as follows: one F-wave shape occurred twice, one occurred four times and in the other 6 traces F-wave shapes occurred only once. The number of RN was 2, and the total number of F-wave shapes was 8. Therefore, Index RN =100* x *(2/8), and Index total Freps= 100* x *(6/12).*

The relation of index RN and index total Freps to age was examined in all groups (I-IV). In the different patient groups, the relation of these indices to appropriate parameters of the standard nerve conduction studies was also tested. These parameters included: CMAP amplitude of the corresponding APB or ADM muscle (in groups I-III), CMAP latency of the APB muscle, the SCV of the median nerve (in the groups including CTS) and % of CMAP conduction velocity decay at elbow and SNAP ampltude of ulnar nerve (as markers of severity in the subgroups including ulnar neuropathy).

## 2.5. STATISTICAL ANALYSIS

For measurements distributed as a Gaussian distribution, t tests, F tests and chi-squared tests will be used. In case of not-normally distributed data, non-parametric approaches would be employed. Measurements are presented as median values (5% - 95% percentiles).

For continuous variables, when assuming similar variances, ANOVA followed by a post hoc Bonferroni test will be performed (e.g., mean age analysis). Comparison of frequencies of RN repetitions across groups I to IV can be treated with a chi-square ($\chi^2$) test.

Further RN variables will suppose multiple group comparisons; thus the Kruskal-Wallis one-way analysis of variance will be used, followed by the Mann-Whitney test to define differences between pairs of groups; the p-value of the latter should then be corrected for type 1 error due to multiple (e.g., “four to eight”) comparisons.

The relationship between two variables will be studied by the Spearman rank correlation.
The Wilcoxon test for paired samples can be used to compare our related samples (as latencies and amplitudes between RN and all F-waves in individual nerves) and assess whether their mean ranks differ. Statistical significance will be set at $p<0.05$.

All analyses will be performed using SPSS Statistics for Windows, Version 20.0. Armonk, NY: (IBM Corp. Released 2011).

# 2.6. DATA MANAGEMENT (Tables 1-4)

## DATA COLLECTION FORMS AND VARIABLES

## INCLUDED IN THE MAIN DATABASE

### 2.6.1. Table 1: Data Collection Form of Groups defined based on the sort and intensity of the pathology per root and/or nerve level. Parameters measured in the F Waves and the Repeating Neurons (RN).

| GROUP | PATHOLOGY | ROOT | INTENSITY (EMG CODE) | NERVE | INTENSITY (ENG CODE) | F-WAVE PARAMETERS AND RN VARIABLES |
|---|---|---|---|---|---|---|
| 1 | BOTH PERIPHERAL AND CERVICAL | C3-C4<br>C5<br>C6<br>C7<br>C8-T1 | 1-15 (PER EACH LEVEL) | MEDIAN | 0-5 | MED TOT. NR F-WAVES |
| | | | | | | MED TOT. F-REPS |
| | | | | | | MED N.R.RN |
| | | | | | | MED INDEX RN |
| | | | | | | MED INDEX TOTAL F-REPS |
| | | | | ULNAR | 0-5 | ULN TOT. NR F-WAVES |
| | | | | | | ULN TOT. F-REPS |
| | | | | | | ULN N.R.RN |
| | | | | | | ULN INDEX RN |
| | | | | | | ULN INDEX TOTAL F-REPS |
| 2 | PERIPHERAL ONLY | C3-C4<br>C5<br>C6<br>C7<br>C8-T1 | 0 | MEDIAN | 0-5 | MED TOT. NR F-WAVES |
| | | | | | | MED TOT. F-REPS |
| | | | | | | MED N.R.RN |
| | | | | | | MED INDEX RN |
| | | | | | | MED INDEX TOTAL F-REPS |
| | | | | ULNAR | 0-5 | ULN TOT. NR F-WAVES |
| | | | | | | ULN TOT. F-REPS |
| | | | | | | ULN N.R.RN |
| | | | | | | ULN INDEX RN |
| | | | | | | ULN INDEX TOTAL F-REPS |
| 3 | CERVICAL ONLY | C3-C4<br>C5<br>C6<br>C7<br>C8-T1 | 1-15 (PER EACH LEVEL) | MEDIAN | 0 | MED TOT. NR F-WAVES |
| | | | | | | MED TOT. F-REPS |
| | | | | | | MED N.R.RN |
| | | | | | | MED INDEX RN |
| | | | | | | MED INDEX TOTAL F-REPS |
| | | | | ULNAR | 0 | ULN TOT. NR F-WAVES |
| | | | | | | ULN TOT. F-REPS |
| | | | | | | ULN N.R.RN |
| | | | | | | ULN INDEX RN |
| | | | | | | ULN INDEX TOTAL F-REPS |
| 4 | NONE OF ABOVE | C3-C4<br>C5<br>C6<br>C7<br>C8-T1 | 0 | MEDIAN | 0 | MED TOT. NR F-WAVES |
| | | | | | | MED TOT. F-REPS |
| | | | | | | MED N.R.RN |
| | | | | | | MED INDEX RN |
| | | | | | | MED INDEX TOTAL F-REPS |
| | | | | ULNAR | 0 | ULN TOT. NR F-WAVES |
| | | | | | | ULN TOT. F-REPS |
| | | | | | | ULN N.R.RN |
| | | | | | | ULN INDEX RN |
| | | | | | | ULN INDEX TOTAL F-REPS |

## 2.6.2. Table 2: Data Collection Form of EMG parameters used in cervical radiculopathy

| EMG CODE | EMG DIAGNOSIS | DENERVATION | DEGREE | INSERTION ACTIVITY |
|---|---|---|---|---|
| 0 | NORMAL | 0 | | 0 |
| 1 | INSERTION ACTIVITY + | 0 | IRRITABILITY | 1 |
| 2 | MILD DENERVATION CHRONIC | 1 | MILD | 0 |
| 3 | MILD DENERVATION CHRONIC +INSERTION ACTIVITY | 1 | MILD | 1 |
| 4 | MILD DENERVATION ACTIVE | 1 | MILD | 0 |
| 5 | MILD DENERVATION ACTIVE +INSERTION ACTIVITY | 1 | MILD | 1 |
| 6 | MODERATE DENERVATION CHRONIC | 1 | MODERATE | 0 |
| 7 | MODERATE DENERVATION CHRONIC +INSERTION ACTIVITY | 1 | MODERATE | 1 |
| 8 | MODERATE DENERVATION ACTIVE | 1 | MODERATE | 0 |
| 9 | MODERATE DENERVATION ACTIVE +INSERTION ACTIVITY | 1 | MODERATE | 1 |
| 10 | SEVERE DENERVATION CHRONIC | 1 | SEVERE | 0 |
| 11 | SEVERE DENERVATION CHRONIC +INSERTION ACTIVITY | 1 | SEVERE | 1 |
| 12 | SEVERE DENERVATION ACTIVE | 1 | SEVERE | 0 |
| 13 | SEVERE DENERVATION ACTIVE +INSERTION ACTIVITY | 1 | SEVERE | 1 |
| 14 | NO VOLUNTARY CONTRACTION | 1 | VERY SEVERE | 0 |
| 15 | NO VOLUNTARY CONTRACTION +INSERTION ACTIVITY | 1 | VERY SEVERE | 1 |

## 2.6.3. Table 3: Data Collection Form of ENG parameters used in peripheral nerve entrapment

| ENG CODE | ENG DIAGNOSIS | SENSITIVE ENG | MOTOR ENG |
|---|---|---|---|
| 0 | NORMAL | 0 | 0 |
| 1 | INCIPIENT | 1 | 0 |
| 2 | MILD | 2 | 0 |
| 3 | MODERATE | 2 | 1 |
| 4 | SEVERE | 3 | 2 |
| 5 | VERY SEVERE | 3 | 3 |

### 2.6.4. Table 4: Data Collection Form of F-Wave parameters used in Median and Ulnar nerves

| FIELD NAME | FORMULAE (BASED ON RAW DATA FROM DATABASE) |
|---|---|
| MED TOT.NR.FWAVES | MDNFNUMBER |
| MED PERSIST.FWAVES | MDNFNUMBER*5 |
| MED TOT.FREPS | MDNFREPS |
| MED PERSIST.TOT.FREPS | MDNFREPS *5 |
| MED PERSIST.FNONREPS | (MDNFNUMBER-MDNFREPS)*5 |
| MED NR.RN | MDNNRREPNEUR |
| MED INDEX RN | 100*MDNNRREPNEUR/(MDNFNUMBER-MDNFREPS+MDNNRREPNEUR) |
| MED INDEX TOTAL FREPS | 100*MDNFREPS/MDNFNUMBER |
| | |
| ULN TOT.NR.FWAVES | ULNFNUMBER |
| ULN PERSIST.FWAVES | ULNFNUMBER*5 |
| ULN TOT.FREPS | ULNFREPS |
| ULN PERSIST.TOT.FREPS | ULNFREPS *5 |
| ULN PERSIST.FNONREPS | (ULNFNUMBER-ULNFREPS)*5 |
| ULN NR.RN | ULNNRREPNEUR |
| ULN INDEX RN | 100*ULNNRREPNEUR/(ULNFNUMBER-ULNFREPS+ULNNRREPNEUR) |
| ULN INDEX TOTAL FREPS | 100*ULNFREPS/ULNFNUMBER |

# 3. RESULTS

## 3.1. STUDY POPULATION AND DEMOGRAPHIC ANALYSIS

### 3.1.1. Study Population

The total number of patients recruited was N=137 (221 upper limbs) [N = Number of Patients (Number of electrophysiological recordings in brackets)]. Of them, there were

- N=84 patients with double register (168 upper limbs)
- N=53 patients with single register (53 upper limbs)

The number of withdrawals and exclusions was N=14 (24 upper limbs) by reasons as:

- Consent removal for low tolerance to electrical stimulation: N=3 (5)
- Suboptimal register for voluntary muscle contraction with EMG artifact: N=1 (2)
- Peripheral polyneuropathies: N=10 (17)

  DM-2: N=8 (13)

  DM-1: N=1 (2)

  Idiopatic: N=1 (2)

As a result, the total number of patients who completed the study was N=123 (197 upper limbs).

## 3.1.2. Demographic Analysis

Demographic characteristics

- Age
- Gender
- Side
- Morbidity

Combined analyses

- Age by Gender
- Age by Side
- Gender by Side
- Gender by Bilaterality of symptoms
- Comorbidity analysis: Peripheral neuropathies and Cervical radiculopathies

Patient groups I to IV

- Analysis of Study Groups I to IV

- Comparisons across Groups I to IV:
    - Age
    - Gender
    - Side
    - Comorbidity between CTS and Ulnar-N across groups I and II

### 3.1.2.1. Demographic characteristics

Characteristics of the 123 patients are depicted in Table 5. Characteristics of the 197 electrophysiological recordings are shown in Table 6. Note the different value of N in demographic analysis meaning number of patients and in electrophysiological analyses meaning number of upper limb recordings studied. Frequency distribution of these recordings related to the age and patient's gender is shown in Table 7. Frequency distribution of the laterality of symptomatic upper limbs in relation to patients' age is shown in Table 8. There were no major differences about the side distribution by gender in both male and female patients. Male population occurred to be more symmetrically distributed about the side explored than female population, which presented a slight tendency to describe symptoms on the right side (Table 9). Laterality of symptoms of the whole study group included 89 explorations performed on the left upper limb (45.2%) and 108 explorations on the right side (54.8%) by gender. When unilateral presentation of the symptoms, female patients showed more tendency to present them on right upper limb (proportion 3:1), meanwhile the male patients showed 1:1 proportion between sides (Table 10).

3.1.2.1.1. Study sample population

| | | |
|---|---|---|
| Patients = N | 123 | |
| Age (Range) | 52.23 ± 13.33 | (20 - 84) |
| Gender F/M (%) | 95 / 28 | (77.24 / 22.76) |
| Unilateral / Bilateral Symptoms (%) | 49 / 148 | (24.87 / 75.13) |

Table 5: Study sample population. (Age = mean ± SD)

3.1.2.1.2. Recordings' characteristics

| | | |
|---|---|---|
| Upper limbs studied = N | 197 | |
| Right / Left Side (%) | 108 / 89 | (54.8 /45.2) |
| Morbidity: | | |
| Peripheral Nerve Entrapment (%) | 51* | (25.9) |
| Cervical Radiculopathy C3-T1 (%) | 43† | (21.8) |
| Both: Overlap (%) | 94‡ | (47.7) |
| None of above (%) | 9 | (4.6) |

Table 6: Recording data. * Isolated peripheral nerve entrapments. † Isolated cervical radiculopathies. ‡ Upper limbs where peripheral nerve entrapment and cervical radiculopathy overlap.

## 3.1.2.2. Combined analyses:

### *Age by Gender*

| GENDER (N) | AGE (Average ± S.D.) |
|---|---|
| Female (153) | 50.82 ± 13.047 |
| Male (44) | 57.14 ± 13.292 |

Table 7: Frequency distribution of the recordings related to the age and patient's gender.

### *Age by Side*

| SIDE (N) | AGE (Average ± S.D.) |
|---|---|
| Left (89) | 52.16 ± 13.271 |
| Right (108) | 52.3 ± 13.442 |

Table 8: Frequency distribution of the laterality of symptomatic upper limbs in relation to patients' age. N=197; Median=51.000; p=0.941.

### *Gender by Side*

| | **Male (%)** | **Female (%)** | **SIDE** |
|---|---|---|---|
| **Right (%)** | 22 (11.2) | 86 (43.6) | 108 (54.82) |
| **Left (%)** | 22 (11.2) | 67 (34.0) | 89 (45.18) |
| **GENDER** | 44 (22.33) | 153 (77.66) | **TOTAL N=197 (100%)** |

Table 9: Side distribution by gender.

### *Gender by Bilaterality of symptoms*

| | **Male (%)** | **Female (%)** | **Origin of registers** |
|---|---|---|---|
| **Unilateral (%)** | 12 (6.1) | 37 (18.8) | 49 (24.87) |
| **Bilateral (%)** | 32 (16.2) | 116 (58.9) | 148 (75.13) |
| **GENDER** | 44 (22.33) | 153 (77.66) | **TOTAL N=197 (100%)** |

Table 10: Laterality of symptoms by gender.

***Comorbidity Analysis: Peripheral Neuropathies and Cervical Radiculopathies***

Nearly one half of the studies (47.71%) present an overlap between the proximal and distal pathologies analized, most of them corresponding to female patients. By contrast, both peripheral-only and cervical-only pathologies take almost a fourth of the studies each, while those studies which did not match with none of the above-mentioned pathologies represented a minority (Table 11 and Figures 5a-5b).

| PATHOLOGY | Mean Age | Male [Relative %] (% of N) | Female [Relative %] (% of N) | N (% of 197) |
|---|---|---|---|---|
| OVERLAPPING NEUROPATHY & RADICULOPATHY | 52.85 | 19 [20.21] (9.65) | 75 [79.79] (38.07) | 94 (47.71) |

Table 11: Comorbidity analysis.

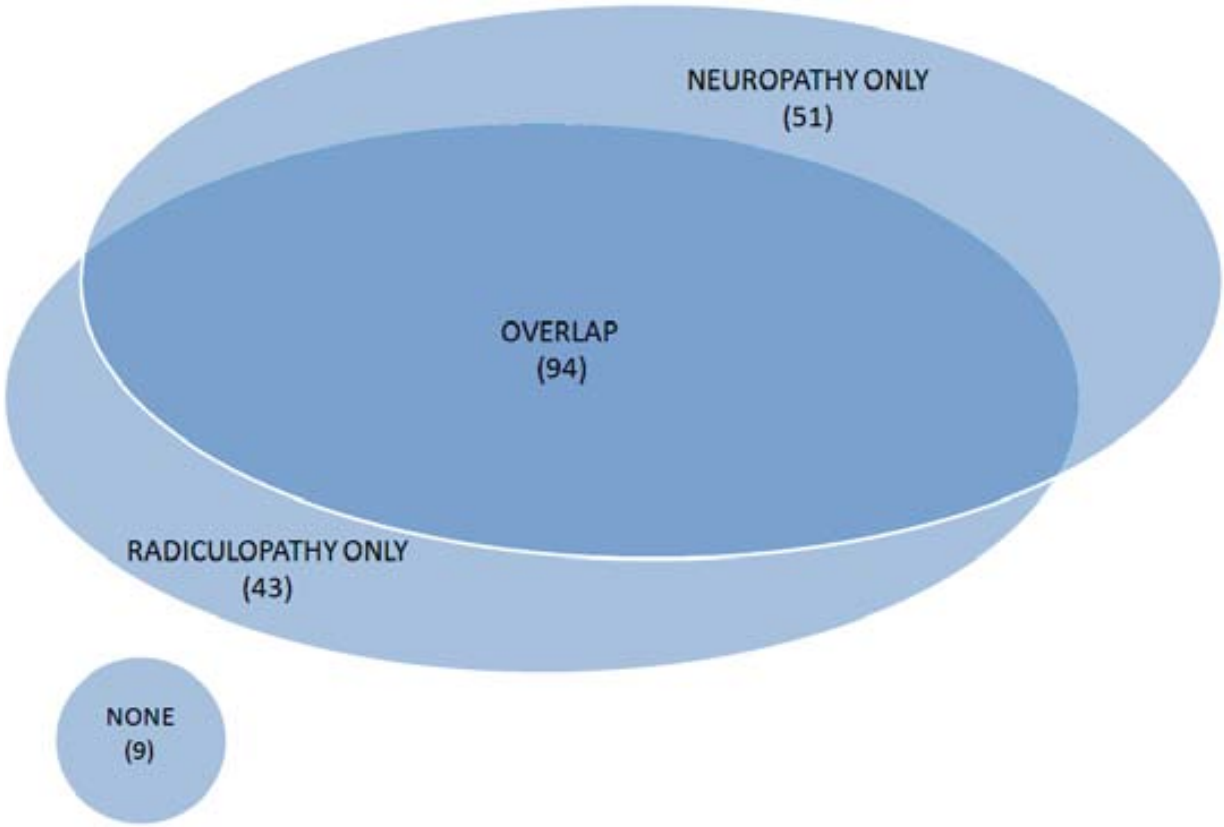



Figure 5.a: Comorbidity analysis.

***Comorbidity Analysis: Peripheral Neuropathies and Cervical Radiculopathies (2)***

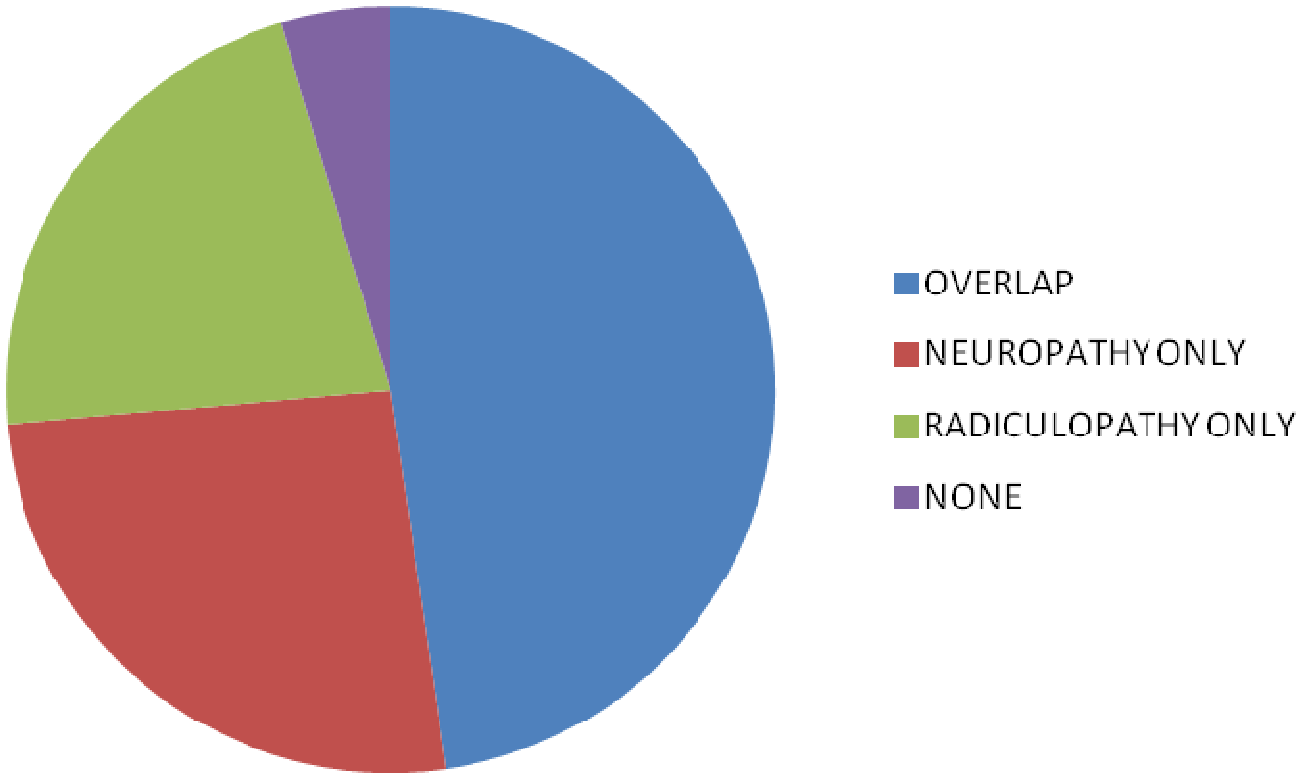



Figure 5.b: Comorbidity analysis.

### 3.1.2.3. Patient groups I to IV

#### 3.1.2.3.1. Analysis of Study Groups I to IV:

According to the design of our study, this comorbidity classification through clinical and electrophysiological criteria will outline the four study groups I to IV depicted in Table 12. Comorbidity analysis shows an overlap of both peripheral (median and ulnar) and proximal pathologies in nearly half of the studies (Figures 5a and 5b).

Study Groups I to IV included:

I. A total of 94 examinations in patients with a clinical and electrophysiological supported diagnosis of both peripheral nerve entrapment and cervical radiculopathy.

II. A total of 51 examinations in patients with a clinical and electrophysiological supported diagnosis of only peripheral nerve entrapment without cervical radiculopathy.

III. A total of 43 examinations in patients with a clinical and electrophysiological supported diagnosis of only cervical radiculopathy without peripheral nerve entrapment.

IV. A total of 9 examinations in healthy subjects which, despite of the clinical symptoms they described, did not fulfill any electrophysiologicaly supported diagnosis of peripheral nerve entrapment nor cervical radiculopathy.

Age, gender and side distributions across the groups I to IV are depicted in Table 12.

***Patient samples according to groups I to IV***

| **Group** | **I** | **II** | **III** | **IV** | **All** |
|---|---|---|---|---|---|
| **Mean Age ± S.D.** | 52.85 ± 11.88 | 58.98 ± 15.41 | 44.21 ± 9.85 | 45.88 ± 5.82 | **52.23** ± **13.33** |
| **Range (min. – Max.)** | (28 - 83) | (28 – 84) | (20 – 71) | (41 – 59) | **(20 – 84)** |
| **Male (%)** | 19 (20.21) | 10 (19.61) | 13 (30.23) | 2 (22.22) | **44 (22.33)** |
| **Female (%)** | 75 (79.79) | 41 (80.39) | 30 (69.77) | 7 (77.78) | **153 (77.66)** |
| **Side ( L : R )** | 41 : 53 | 22 : 29 | 20 : 23 | 6 : 3 | **89 : 108** |
| **N (% of 197)** | 94 (47.71) | 51 (25.89) | 43 (21.83) | 9 (4.57) | **197 (100)** |

Table 12: Age, gender and side distribution across the groups.

### 3.1.2.3.2. Comparisons across Groups I to IV:

***Age across Groups I to IV***

The mean age, 52.23 (median value: 51.00), differed significantly between groups, with the exception of group I which, roughly, worked like a balanced representation of the general sample population. Group II, corresponding to isolated peripheral mononeuropathies, presented the highest mean age. Group III, standing for the isolated radiculopathies, presented the second lowest mean age, just following the healthy group average values. The mean age in the group I, containing the overlap of peripheral and proximal pathologies, is in between the mean ages of the respective "peripheral only" and "proximal only" pathologies ($p<0.05$ in all correlations). *Tool: Median test for independent samples.*

***Gender across Groups I to IV***

Gender distribution resulted to be asymmetrical (F > M) yet since the recruitment period. This asymmetrical distribution remains across the four groups; female represent from 69.77 to 80.39 % of the subjects analyzed, with clear predominance over the isolated peripheral nerve pathology group.

***Side across Groups I to IV***

As in the general sample population, a slight tendency to present symptoms on the right side is observed in groups I-III; the opposite happens in group IV. Group II (only peripheral nerve pathology) shows the biggest tendency towards right side's symptoms.

***Comorbidity between CTS and Ulnar-N across groups I and II***

Group I puts together both radicular and peripheral nerve pathologies, while group II defines the studies with only peripheral nerve entrapments. Thus, the groups I and II include the three types of peripheral nerve entrapments analized: Carpal Tunnel Syndrome (CTS), and focal ulnar mononeuropathy (Ul-N) both at wrist and at elbow levels.

Median and Ulnar mononeuropathies appeared overlapped in 30 of the 94 studies of group I (31.91 %), and in 18 of the 51 studies of group II (35.29 %). Thus, in 48 of the 145 explorations where CTS was present, it appeared to be combined with Ulnar-N in the 33.10 % of the cases.

## *3.2. Validation of the distribution criteria through median nerve sensory conduction velocity and ulnar nerve motor conduction velocity*

A significant difference ($p < 0.001$) between the median nerve sensory conduction velocity was found between the groups including peripheral neuropathies (I, II) versus those without distal pathology (III, IV). The boxplot graph below (Figure 6) depicts the sensory conduction velocity (SCV) in median nerve across the four subject groups. According to the inclusion criteria for groups I and II, containing peripheral nerve entrapments combined with radiculopathies or alone, the SCV in the distal segment of median nerve appears reduced, especially in the isolated peripheral neuropathies' group. Kruskal-Wallis test for K independent samples (N: 191; two-sided asymptotic significance: 0.000; degrees of freedom:3).

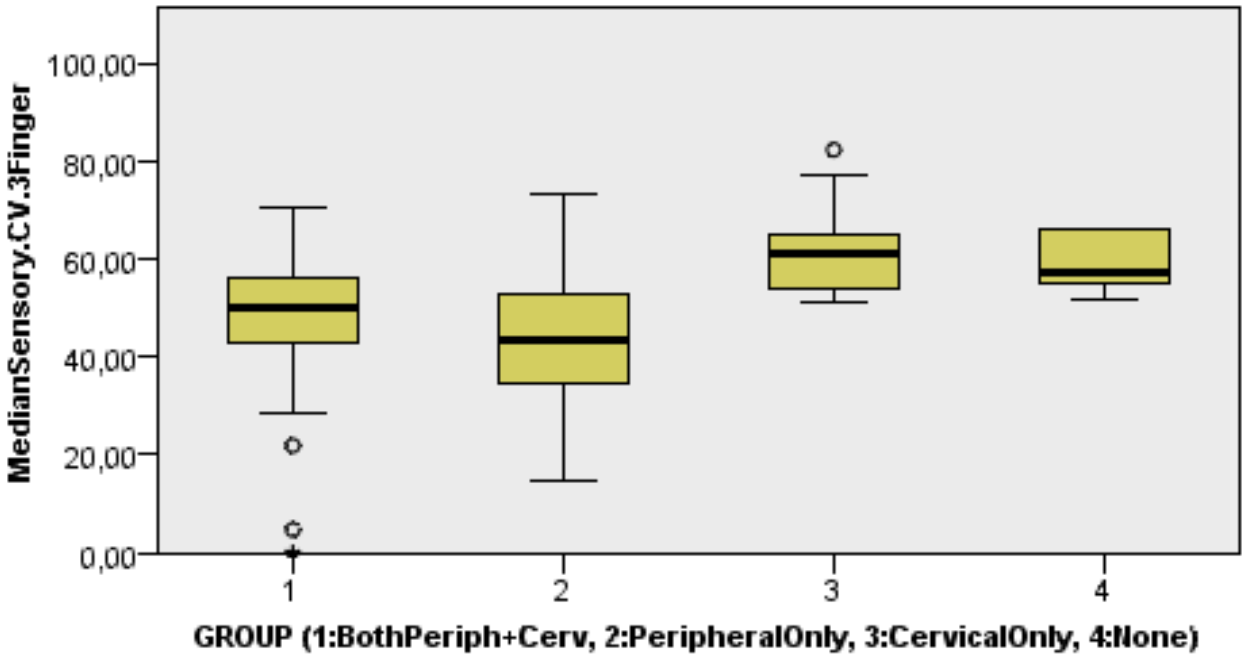



Figure 6: Sensory conduction velocity (SCV) in median nerve across the four subject groups. *The horizontal black line in each box marks the median value, the edges mark the 25$^{th}$ and 75$^{th}$ percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges, and the open circle (○) designates values below or above 1.5 box-length from the box-edges.*

Another significant difference (p = 0.001) was found between the groups including peripheral neuropathies versus the groups with any or only radicular pathology, where the motor conduction velocity decay from forearm to elbow stimulation in the ulnar nerve seems more prominent in the peripheral nerve entrapment groups. The boxplot graph below (Figure 7) represents the motor conduction velocity (MCV) decay in the ulnar nerve from forearm to elbow stimulation across the subject groups. Observe the significantly higher decay (higher median values) in the peripheral nerve entrapment groups, preferentially in group II. Kruskal-Wallis test for K independent samples (N: 195; two-sided asymptotic significance: 0.001; degrees of freedom:3).

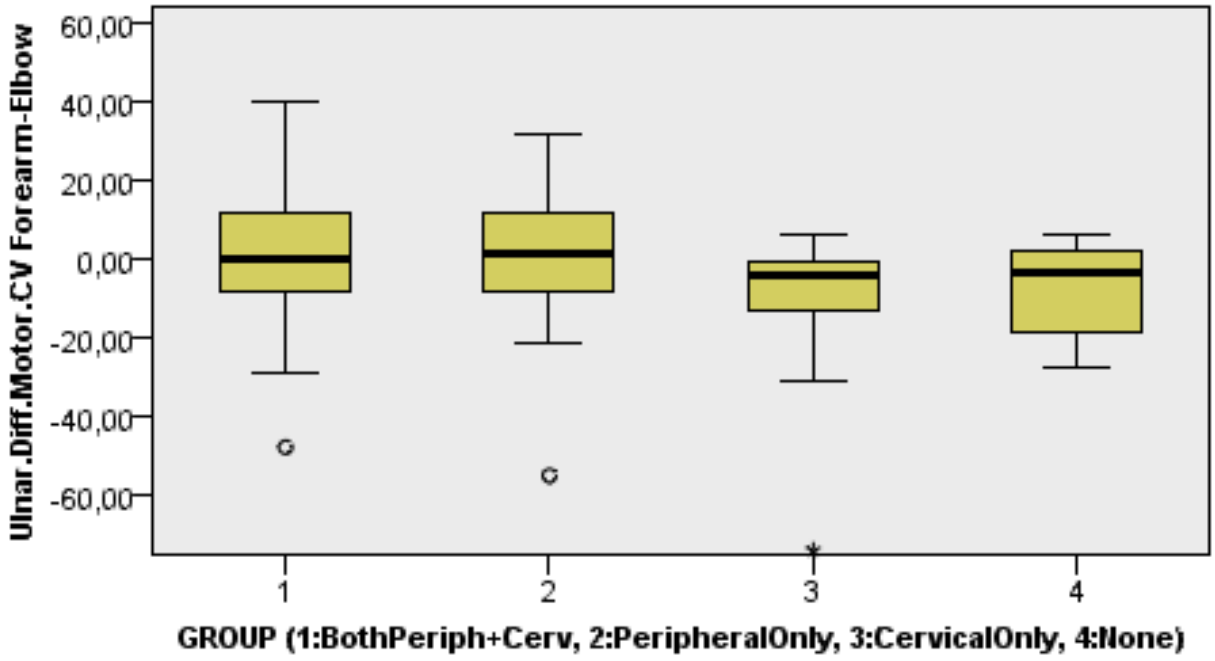



Figure 7: Motor conduction velocity (MCV) decay in the ulnar nerve from forearm to elbow stimulation across the subject groups. *The horizontal black line in each box marks the median value, the edges mark the 25$^{th}$ and 75$^{th}$ percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges, and the open circle (○) designates values below or above 1.5 box-length from the box-edges.*

### *3.3. F-Waves' and Repeating Neurons' (RN) Measurements across Groups I to IV*

Note that in each upper limb are assessed the F-Wave registers of two nerves, median and ulnar, which will be analyzed separately, keeping the N meaning upper limbs or study subjects as common denominator.

## *3.3.1. Comparisons of RN findings between subjects with radiculopathies (groups I and III) and those with isolated peripheral nerve entrapments or without pathology (groups II and IV)*

Repeater F-wave variables were categorized by the nerve studied, Median and Ulnar respectively, allowing comparison between groups I-IV. (Tables 13-14)

Comparative values of indices RN and total Freps across the groups are depicted in the Figures 8-10. Both indices differed significantly between each of the patient groups (specially between proximal versus distal pathologies) in both two nerves (all p-values $\leq$ 0.001).

The groups I and III had significantly higher values of indices RN and total Freps (increased repeater F-waves activity) in the median nerve (both $p = 0.000$) compared to the groups II and IV.

Similar results were observed for ulnar nerve, where both indices showed higher values across the groups I and III, with slightly stronger positive correlation in the case of Index total Freps ($p = 0.000$) than in Index RN ($p = 0.001$).

No other significant difference of the indices values was shown in paired comparison of the patient groups.

In all the groups and both nerves, more than half of the observed RNs were repeated just once. In the healthy group none of the RNs had more than 5 repetitions, whereas in the patient groups repetitions up to 10 times appeared in a small percentage (< 3 %) of cases in any nerve, with predisposition towards the groups I and III.

Table 13: Repeater F-waves' characteristics in the median nerve across the groups I to IV

| Variable | I | II | III | IV |
|---|---|---|---|---|
| Nerves* | 94 | 51 | 43 | 9 |
| Nerves with RN* (%) | 87 (92.55) | 40 (78.43) | 41 (95.35) | 8 (88.88) |
| RN* | 210 | 72 | 108 | 14 |
| Total Freps* | 562 | 173 | 268 | 39 |
| Persistence of F-waves† | 90 (86-93) | 90 (84-96) | 95 (91-99) | 95 (86-104) |
| Persistence of total Freps† | 30 (26-34) | 10 (6-14) | 30 (26-34) | 10 (0-26) |

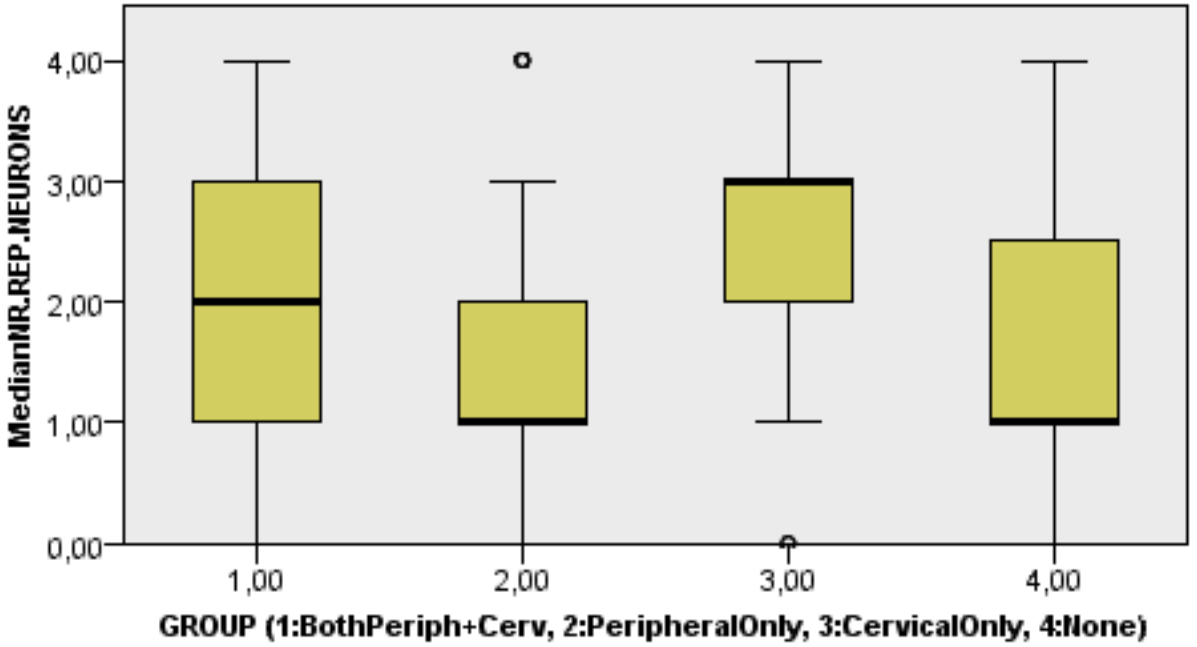
*: variables expressed as number of; †: variables expressed as median values (5 – 95 percentiles)

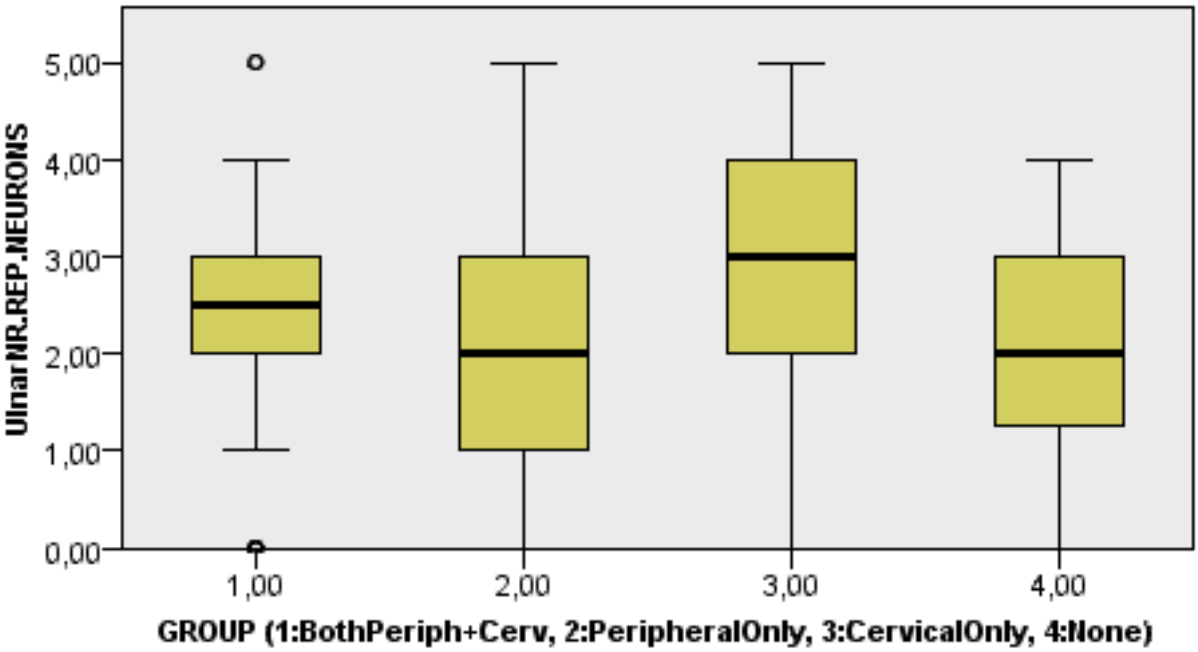
Table 14: Repeater F-waves's characteristics in the ulnar nerve across the groups I to IV

| Variable | I | II | III | IV |
|---|---|---|---|---|
| Nerves* | 94 | 51 | 43 | 9 |
| Nerves with RN* (%) | 87 (92.55) | 44 (86.27) | 41 (95.35) | 8 (88.88) |
| RN* | 220 | 16 | 121 | 17 |
| Total Freps* | 594 | 218 | 318 | 38 |
| Persistence of F-waves† | 100 (97-103) | 100 (96-104) | 100 (97-103) | 100 (75-125) |
| Persistence of total Freps† | 30 (26-34) | 20 (15-25) | 35 (30-40) | 25 (13-37) |

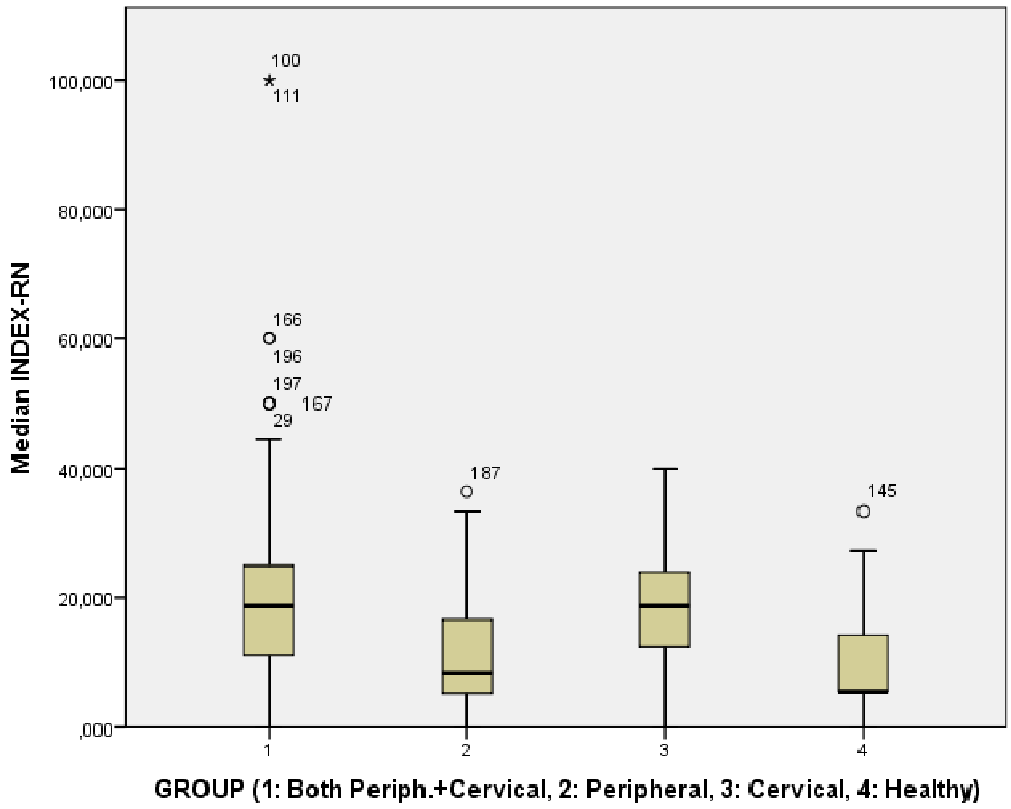
*: variables expressed as number of; †: variables expressed as median values (5 – 95 percentiles)

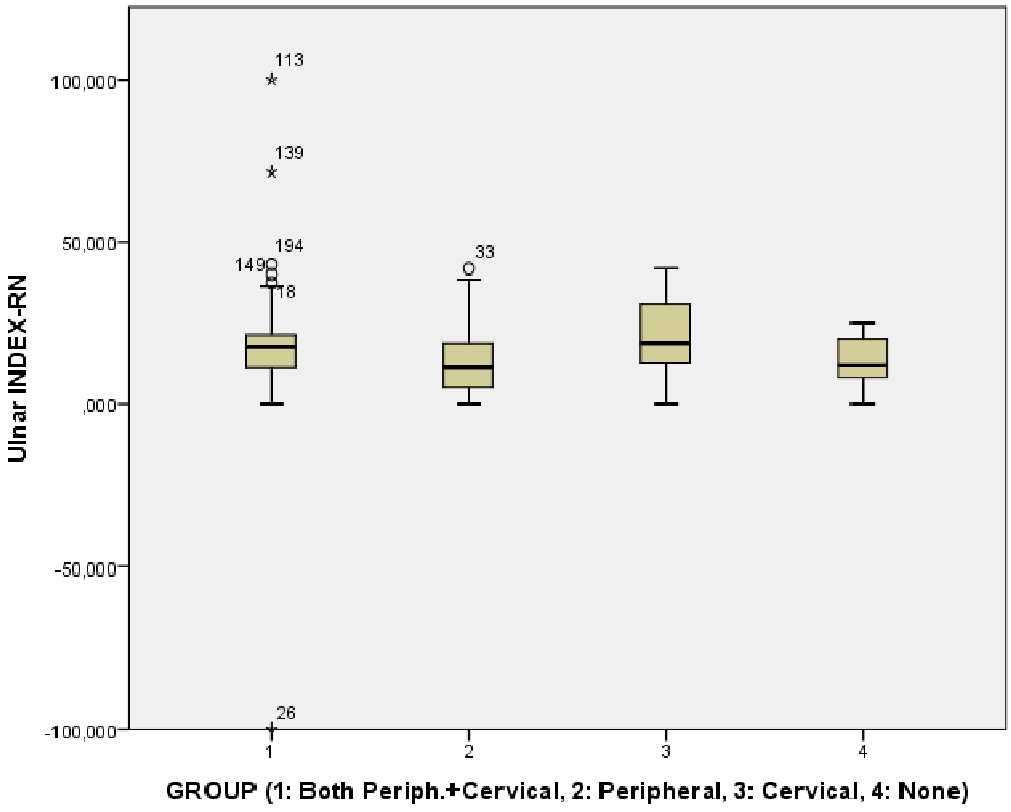
The number of Repeating Neurons (RN), as well as the median values of both indices, RN and Total FReps, appeared to be significantly higher in the groups I and III (both containing proximal pathology, combined or isolated) with dominance of the isolated proximal pathology, while in group II (only distal pathology) these seemed much lower, nearly as in the healthy group (IV). Figures 8-10 depict the number of RN, index RN and index total Freps in the median and ulnar nerve across the subject groups.



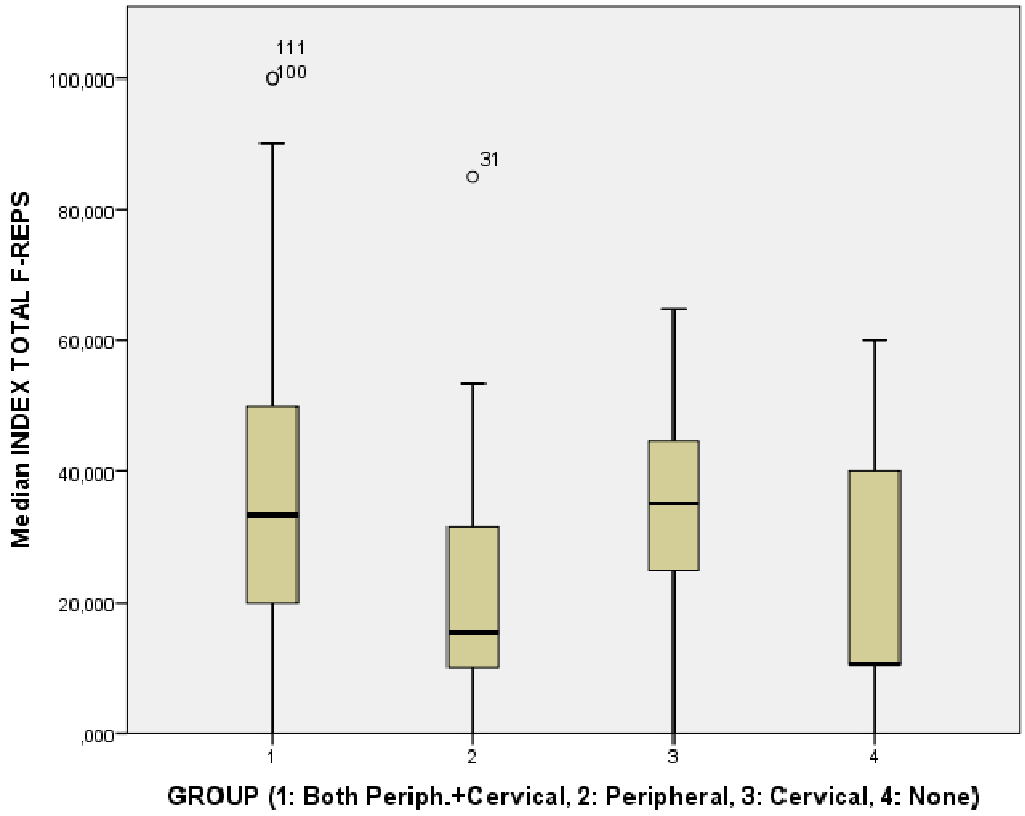



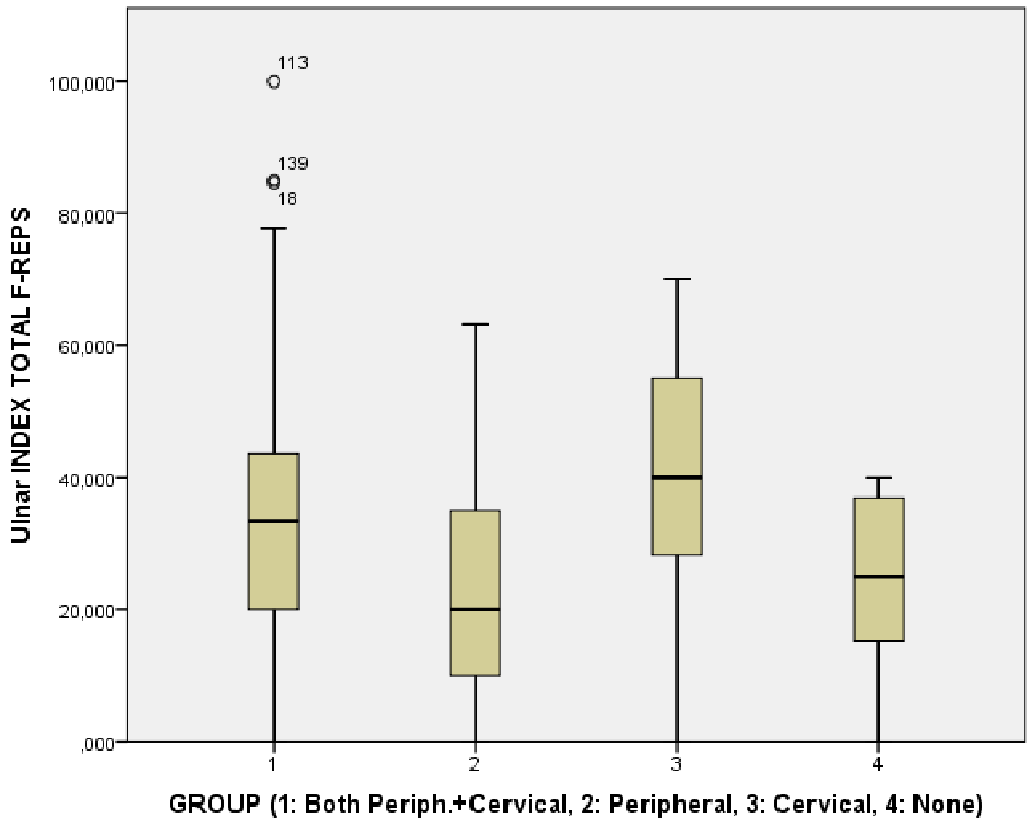

Figures 8.a and 8.b: Boxplot graphs of the number of Repeating Neurons (RN) in the median and ulnar nerves across the subject groups. Kruskal-Wallis test for K independent samples (Median nerve: N: 197; two-sided asymptotic significance: 0.000; degrees of freedom:3; Ulnar nerve: N: 195; two-sided asymptotic significance: 0.005; degrees of freedom:3). *The horizontal black line in each box marks the median value, the edges mark the 25$^{th}$ and 75$^{th}$ percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges,and the open circle (○) designates values below or above 1.5 box-length from the box-edges.*




Figures 9.a and 9.b: Boxplot graphs of the Index-RN in the median and ulnar nerves across the subject groups. Kruskal-Wallis test for K independent samples (Median nerve: N: 196; global Median value: 15,385; two-sided asymptotic significance: 0.000; degrees of freedom:3; Ulnar nerve: N: 194; two-sided asymptotic significance: 0.001; degrees of freedom:3). *The horizontal black line in each box marks the median value, the edges mark the 25$^{th}$ and 75$^{th}$ percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges, the open circle (○) designates values below or above 1.5 box-length from the box-edges and the asterisk (*) designates values below or above 3.0 box-length from box-edges.*




Figures 10.a and 10.b: Boxplot graphs of the index Total FReps in the median and ulnar nerves across the subject groups. *The horizontal black line in each box marks the median value, the edges mark the 25th and 75th percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges, the open circle (○) designates values below or above 1.5 box-length from the box-edges and the asterisk (*) designates values below or above 3.0 box-length from box-edges.*

### *3.3.2. Index RN and Index Total F-Reps in median and ulnar nerves across the groups I-IV. Correlations with comorbidity, pathology location and severity degree*

A multiple positive correlation was found within the three different peripheral nerve entrapments assessed (Table 15). Thus, the presence of one of them is related to further entrapments in the upper limb, in the same nerve or in its vicinity. Concretely, Carpal Tunnel Syndrome patients presented positive correlation with both of the ulnar mononeuropathies, at the elbow ($p=0.036$, $r_s=0.150$) and at Guyon's channel ($p<0.001$, $r_s=0.253$). Besides, the ulnar mononeuropathy itself showed a positive correlation between its two most common entrapment locations, elbow and Guyon's channel ($p<0.001$, $r_s=0.291$).

The indices RN and total Freps appear to be correlated across all the groups between both median and ulnar nerves (Index RN: $p<0.001$, $r_s=0.271$; Index of total Freps: $p=0.002$, $r_s=0.229$), as well as inside the same nerve group (in median nerve: $p<0.001$, $r_s=0.971$; in ulnar nerve: $p<0.001$, $r_s=0.977$).

In the patient groups I to IV, no correlation was found between the indices RN or total Freps and the standard electroneurographical parameters defining the three most common peripheral entrapments (median nerve at carpal tunnel, ulnar nerve at elbow or at Guyon's channel), with the exception of the severity level of the Carpal Tunnel Syndrome, which showed a slightly negative correlation with index RN and index total Freps in ulnar nerve (respectively, $p = 0.046$, $r_s= -0.144$, and $p=0.024$, $r_s= -0.164$).

***Table 15: Correlations between severity degrees of peripheral nerve entrapments and indices of Repeating Neurons and Total F-reps.***

| | | | CTS 0-5 | Ulnar Elbow 0-5 | Ulnar Guyón 0-5 | Median. INDEX.RN | Median. INDEX.TOTAL. F-REPS | Ulnar. INDEX.RN | Ulnar. INDEX.TOTAL. F-REPS |
|---|---|---|---|---|---|---|---|---|---|
| Spearman's Rho | CTS 0-5 | $r_s$ | 1,000 | ,150* | ,253† | -,039 | -,063 | -,144* | -,164* |
| | | Sig. (bilateral) | . | ,036 | ,000 | ,585 | ,380 | ,046 | ,024 |
| | | N | 195 | 194 | 194 | 194 | 194 | 192 | 191 |
| | Ulnar Elbow 0-5 | $r_s$ | ,150* | 1,000 | ,291† | -,103 | -,084 | ,003 | ,003 |
| | | Sig. (bilateral) | ,036 | . | ,000 | ,154 | ,244 | ,962 | ,962 |
| | | N | 194 | 194 | 194 | 193 | 193 | 192 | 191 |
| | Ulnar Guyón 0-5 | $r_s$ | ,253† | ,291† | 1,000 | -,073 | -,061 | ,099 | ,095 |
| | | Sig. (bilateral) | ,000 | ,000 | . | ,312 | ,399 | ,171 | ,191 |
| | | N | 194 | 194 | 194 | 193 | 193 | 192 | 191 |
| | Median. INDEX.RN | $r_s$ | -,039 | -,103 | -,073 | 1,000 | ,971† | ,271† | ,243† |
| | | Sig. (bilateral) | ,585 | ,154 | ,312 | . | ,000 | ,000 | ,001 |
| | | N | 194 | 193 | 193 | 194 | 194 | 191 | 190 |
| | Median. INDEX.TOTAL. F-REPS | $r_s$ | -,063 | -,084 | -,061 | ,971† | 1,000 | ,253† | ,229† |
| | | Sig. (bilateral) | ,380 | ,244 | ,399 | ,000 | . | ,000 | ,002 |
| | | N | 194 | 193 | 193 | 194 | 194 | 191 | 190 |
| | Ulnar. INDEX.RN | $r_s$ | -,144* | ,003 | ,099 | ,271† | ,253† | 1,000 | ,977† |
| | | Sig. (bilateral) | ,046 | ,962 | ,171 | ,000 | ,000 | . | ,000 |
| | | N | 192 | 192 | 192 | 191 | 191 | 192 | 191 |
| | Ulnar. INDEX.TOTAL. F-REPS | $r_s$ | -,164* | ,003 | ,095 | ,243† | ,229† | ,977† | 1,000 |
| | | Sig. (bilateral) | ,024 | ,962 | ,191 | ,001 | ,002 | ,000 | . |
| | | N | 191 | 191 | 191 | 190 | 190 | 191 | 191 |

*: Correlation is significant at the 0.05 level (2-tailed).

†: Correlation is significant at the 0.01 level (2-tailed).

### *3.3.3. Persistence of total Freps across the groups I-IV*

F-wave persistence was not correlated with persistence of total Freps in any nerve nor group of patients, except in the ulnar nerve, only when analised the general pool of patients, where a slight positive correlation was found ($p=0.019$, $r_s=0.167$).

There was a clear negative correlation between persistence of Fnonreps and persistence of total Freps in all nerves of healthy and all patient groups:

$p=0.000$, $r_s= - 0.706$ in the median nerve of peripheral/cervical mixed group;

$p=0.000$, $r_s= - 0.857$ in the ulnar nerve of peripheral/cervical mixed group;

$p=0.000$, $r_s= - 0.555$ in the median nerve of only-peripheral entrapments group;

$p=0.000$, $r_s= - 0.796$ in the ulnar nerve of only-peripheral entrapments group;

$p=0.000$, $r_s= - 0.692$ in the median nerve of only-cervical radiculopathy group;

$p=0.000$, $r_s= - 0.863$ in the ulnar nerve of only-cervical radiculopathy group;

$p=0.002$ and $r_s= - 0.867$ in the median nerve of the healthy group.

One exception to this statistical result was the ulnar nerve of the healthy patients (group IV), where no correlations were found ($p=0.245$, $p>0.05$).

Findings on persistence calculations are presented in Tables 16-25.

| | | | Median PERSIST. F-WAVES | Median PERSIST. TOTAL.F-REPS | Median PERSIST. F-NON.REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Median PERSIST. F-WAVES | $r_s$ | 1,000 | ,093 | ,555* |
| | | Sig. (bilateral) | . | ,192 | ,000 |
| | | N | 197 | 197 | 197 |
| | Median PERSIST. TOTAL.F-REPS | $r_s$ | ,093 | 1,000 | -,685* |
| | | Sig. (bilateral) | ,192 | . | ,000 |
| | | N | 197 | 197 | 197 |
| | Median PERSIST. F-NON.REPS | $r_s$ | ,555* | -,685* | 1,000 |
| | | Sig. (bilateral) | ,000 | ,000 | . |
| | | N | 197 | 197 | 197 |

Table 16: Persistence correlations – General Study Group – Median Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Median PERSIST. F-WAVES | Median PERSIST. TOTAL.F-REPS | Median PERSIST. F-NON.REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Median PERSIST. F-WAVES | $r_s$ | 1,000 | ,131 | ,531* |
| | | Sig. (bilateral) | . | ,203 | ,000 |
| | | N | 96 | 96 | 94 |
| | Median PERSIST. TOTAL.F-REPS | $r_s$ | ,131 | 1,000 | -,706* |
| | | Sig. (bilateral) | ,203 | . | ,000 |
| | | N | 96 | 96 | 94 |
| | Median PERSIST. F-NON.REPS | $r_s$ | ,531* | -,706* | 1,000 |
| | | Sig. (bilateral) | ,000 | ,000 | . |
| | | N | 94 | 94 | 94 |

Table 17: Persistence in Group I – Median Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Median PERSIST. F-WAVES | Median PERSIST. F-NON.REPS | Median PERSIST. TOTAL.F-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Median PERSIST. F-WAVES | $r_s$ | 1,000 | ,731* | ,010 |
| | | Sig. (bilateral) | . | ,000 | ,943 |
| | | N | 52 | 51 | 52 |
| | Median PERSIST. F-NON.REPS | $r_s$ | ,731* | 1,000 | -,555* |
| | | Sig. (bilateral) | ,000 | . | ,000 |
| | | N | 51 | 51 | 51 |
| | Median PERSIST. TOTAL.F-REPS | $r_s$ | ,010 | -,555* | 1,000 |
| | | Sig. (bilateral) | ,943 | ,000 | . |
| | | N | 52 | 51 | 52 |

Table 18: Persistence in Group II – Median Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Median PERSIST. F-WAVES | Median PERSIST. F-NON.REPS | Median PERSIST. TOTAL.F-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Median PERSIST. F-WAVES | $r_s$ | 1,000 | ,499* | ,125 |
| | | Sig. (bilateral) | . | ,001 | ,421 |
| | | N | 44 | 43 | 44 |
| | Median PERSIST. F-NON.REPS | $r_s$ | ,499* | 1,000 | -,692* |
| | | Sig. (bilateral) | ,001 | . | ,000 |
| | | N | 43 | 43 | 43 |
| | Median PERSIST. TOTAL.F-REPS | $r_s$ | ,125 | -,692* | 1,000 |
| | | Sig. (bilateral) | ,421 | ,000 | . |
| | | N | 44 | 43 | 44 |

Table 19: Persistence in Group III – Median Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Median PERSIST. F-WAVES | Median PERSIST. F-NON.REPS | Median PERSIST. TOTAL.F-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Median PERSIST. F-WAVES | $r_s$ | 1,000 | ,394 | ,011 |
| | | Sig. (bilateral) | . | ,294 | ,976 |
| | | N | 10 | 9 | 10 |
| | Median PERSIST. F-NON.REPS | $r_s$ | ,394 | 1,000 | -,867* |
| | | Sig. (bilateral) | ,294 | . | ,002 |
| | | N | 9 | 9 | 9 |
| | Median PERSIST. TOTAL.F-REPS | $r_s$ | ,011 | -,867* | 1,000 |
| | | Sig. (bilateral) | ,976 | ,002 | . |
| | | N | 10 | 9 | 10 |

Table 20: Persistence in Group IV – Median Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Ulnar PERSIST. F-WAVES | Ulnar PERSIST. TOTAL.F-REPS | Ulnar PERSIST. F-NON-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Ulnar PERSIST. F-WAVES | $r_s$ | 1,000 | ,167* | ,282† |
| | | Sig. (bilateral) | . | ,019 | ,000 |
| | | N | 197 | 197 | 197 |
| | Ulnar PERSIST. TOTAL.F-REPS | $r_s$ | ,167* | 1,000 | -,819† |
| | | Sig. (bilateral) | ,019 | . | ,000 |
| | | N | 197 | 197 | 197 |
| | Ulnar PERSIST. F-NON-REPS | $r_s$ | ,282† | -,819† | 1,000 |
| | | Sig. (bilateral) | ,000 | ,000 | . |
| | | N | 197 | 197 | 197 |

Table 21: Persistence correlations – General Study Group – Ulnar Nerve
*: Correlation is significant at the 0.05 level (2-tailed).
†: Correlation is significant at the 0.01 level (2-tailed).

| | | | Ulnar PERSIST. F-WAVES | Ulnar PERSIST. TOTAL.F-REPS | Ulnar PERSIST. F-NON-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Ulnar PERSIST. F-WAVES | $r_s$ | 1,000 | ,158 | ,207* |
| | | Sig. (bilateral) | . | ,127 | ,045 |
| | | N | 95 | 95 | 94 |
| | Ulnar PERSIST. TOTAL.F-REPS | $r_s$ | ,158 | 1,000 | -,857† |
| | | Sig. (bilateral) | ,127 | . | ,000 |
| | | N | 95 | 95 | 94 |
| | Ulnar PERSIST. F-NON-REPS | $r_s$ | ,207* | -,857† | 1,000 |
| | | Sig. (bilateral) | ,045 | ,000 | . |
| | | N | 94 | 94 | 94 |

Table 22: Persistence in Group I – Ulnar Nerve
*: Correlation is significant at the 0.05 level (2-tailed).
†: Correlation is significant at the 0.01 level (2-tailed).

| | | | Ulnar PERSIST. F-WAVES | Ulnar PERSIST. TOTAL.F-REPS | Ulnar PERSIST. F-NON-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Ulnar PERSIST. F-WAVES | $r_s$ | 1,000 | ,085 | ,399* |
| | | Sig. (bilateral) | . | ,549 | ,004 |
| | | N | 52 | 52 | 51 |
| | Ulnar PERSIST. TOTAL.F-REPS | $r_s$ | ,085 | 1,000 | -,796* |
| | | Sig. (bilateral) | ,549 | . | ,000 |
| | | N | 52 | 52 | 51 |
| | Ulnar PERSIST. F-NON-REPS | $r_s$ | ,399* | -,796* | 1,000 |
| | | Sig. (bilateral) | ,004 | ,000 | . |
| | | N | 51 | 51 | 51 |

Table 23: Persistence in Group II – Ulnar Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Ulnar PERSIST. F-WAVES | Ulnar PERSIST. TOTAL.F-REPS | Ulnar PERSIST. F-NON-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Ulnar PERSIST. F-WAVES | $r_s$ | 1,000 | ,209 | ,207 |
| | | Sig. (bilateral) | . | ,173 | ,183 |
| | | N | 44 | 44 | 43 |
| | Ulnar PERSIST. TOTAL.F-REPS | $r_s$ | ,209 | 1,000 | -,863* |
| | | Sig. (bilateral) | ,173 | . | ,000 |
| | | N | 44 | 44 | 43 |
| | Ulnar PERSIST. F-NON-REPS | $r_s$ | ,207 | -,863* | 1,000 |
| | | Sig. (bilateral) | ,183 | ,000 | . |
| | | N | 43 | 43 | 43 |

Table 24: Persistence in Group III – Ulnar Nerve
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | Ulnar PERSIST. F-WAVES | Ulnar PERSIST. TOTAL.F-REPS | Ulnar PERSIST. F-NON-REPS |
|---|---|---|---|---|---|
| Spearman's Rho | Ulnar PERSIST. F-WAVES | $r_s$ | 1,000 | ,496 | ,267 |
| | | Sig. (bilateral) | . | ,145 | ,487 |
| | | N | 10 | 10 | 9 |
| | Ulnar PERSIST. TOTAL.F-REPS | $r_s$ | ,496 | 1,000 | -,432 |
| | | Sig. (bilateral) | ,145 | . | ,245 |
| | | N | 10 | 10 | 9 |
| | Ulnar PERSIST. F-NON-REPS | $r_s$ | ,267 | -,432 | 1,000 |
| | | Sig. (bilateral) | ,487 | ,245 | . |
| | | N | 9 | 9 | 9 |

Table 25: Persistence in Group IV – Ulnar Nerve

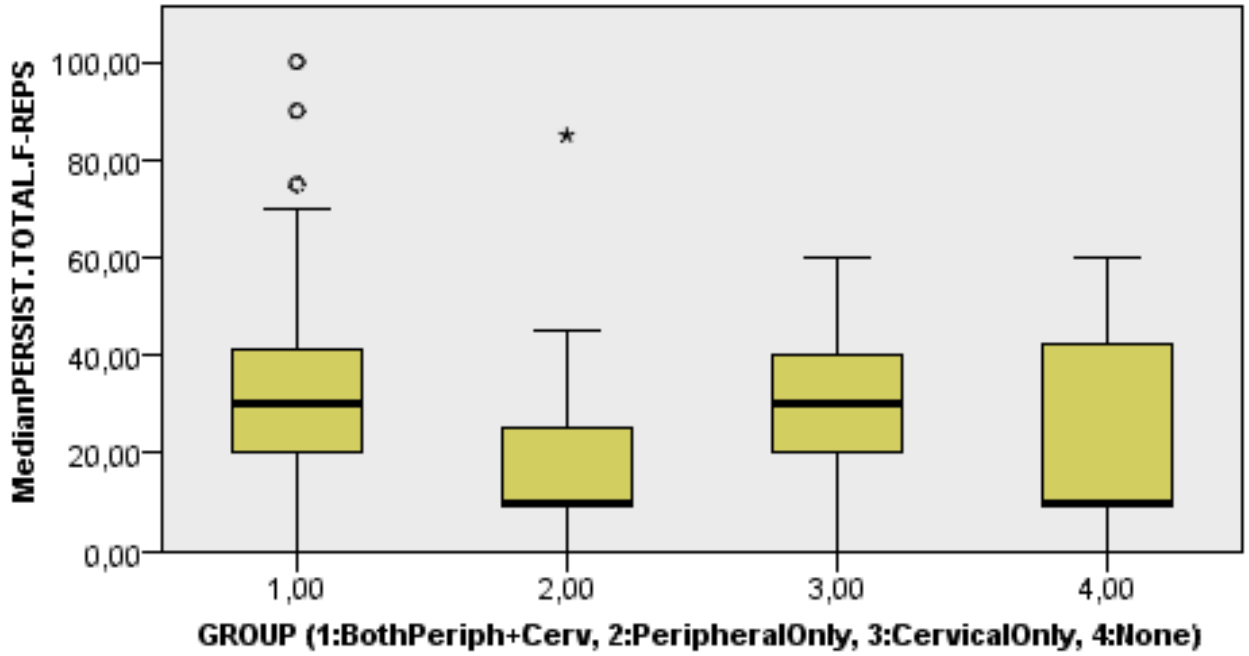
### *3.3.4. Persistence of Total F-Reps and proximal upper limb pathology*

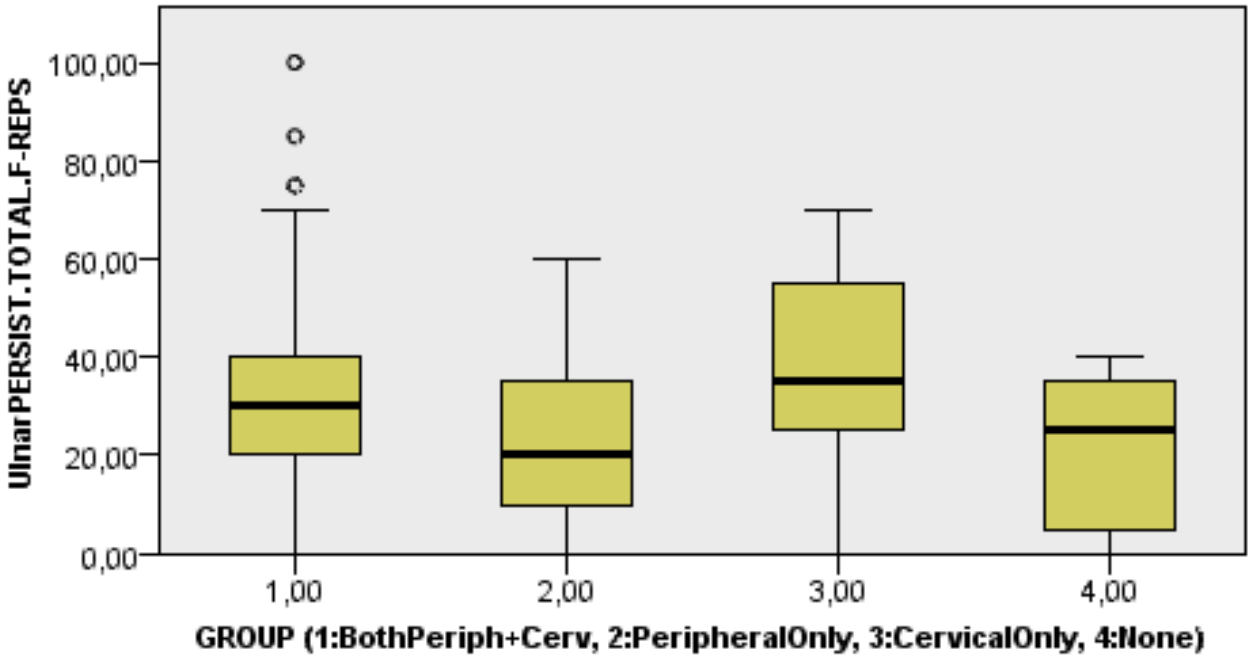
There was found a positive significative correlation between the persistence of Total F-Reps and the proximal location of the lesion (p-value < 0.001), both isolated and in combination with distal pathology (Table 26). Thus, in the groups I and III, where cervical radiculopathy patients are included, mixed with peripheral nerve entrapments or isolated, it is possible to observe significantly higher median values of F-Reps persistence (Figures 11.a and 11.b) in comparison with the groups II (only peripheral nerve entrapments) and IV (healthy).

The persistence of total F-Waves (both repeaters and non-repeaters together) did not show correlation with any of the groups. Tool: *Kruskal-Wallis test for K independent samples*; N: 197; two-sided asymptotic significance: 0.030 for median nerve and 0.774 for ulnar nerve; degrees of freedom:3.

| Nerve / Group | I | II | III | IV |
|---|---|---|---|---|
| Median | | | | |
| ρ | -.706 | -.555 | -.692 | -.867 |
| p-value | .000 | .000 | .000 | .002 |
| Ulnar | | | | |
| ρ | -.857 | -.796 | -.863 | -.432* |
| p-value | .000 | .000 | .000 | .245 |

Table 26: Correlation between F-wave persistence and persistence of total Freps. Rho (Spearman's rank correlation coefficient) and p-values across the groups. *: There is no significant negative correlation.




Figures 11.a and 11.b: Boxplot graphs describing the persistence of total Freps in the median (above) and in the ulnar (below) nerves across the subject groups. Kruskal-Wallis test for K independent samples (N: 197; two-sided asymptotic significance: 0.000; degrees of freedom:3). *The horizontal black line in each box marks the median value, the edges mark the 25$^{th}$ and 75$^{th}$ percentiles, the vertical lines extending up and down show the range of values within 1.5 box-length from the box edges, the open circle (○) designates values below or above 1.5 box-length from the box-edges and the asterisk (*) designates values below or above 3.0 box-length from box-edges.*

### *3.3.5. RN findings in the unaffected nerves of patients with mononeuropathies*

Motor and sensory conduction studies of the ulnar nerve in the CTS sub-group and the median nerve in the Ul-N sub-group revealed no abnormalities.

The "normal" ulnar nerve in the CTS sub-group (Figure 12) had an index RN of 5.55 (5%-95% percentiles: 0 - 38.4; SD: 10.60) and index of total Freps of 15 (0 – 60.71; SD: 17.30), which differed significantly from the corresponding values of the ulnar nerve in the healthy subject group (for both indices p=0.000) and in Ul-N sub-group (p=0.001).

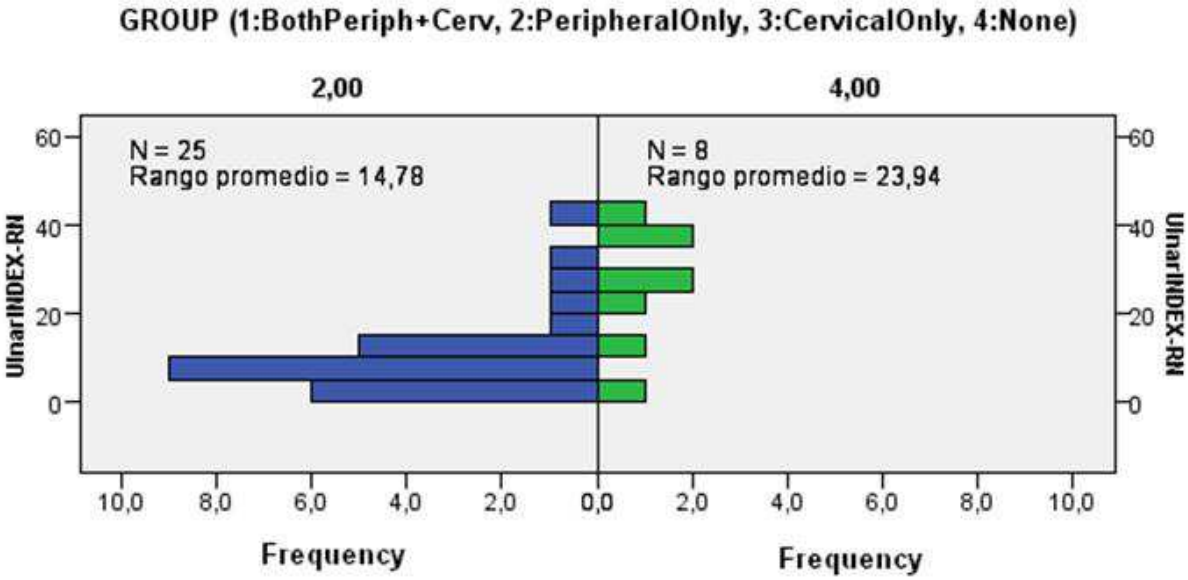
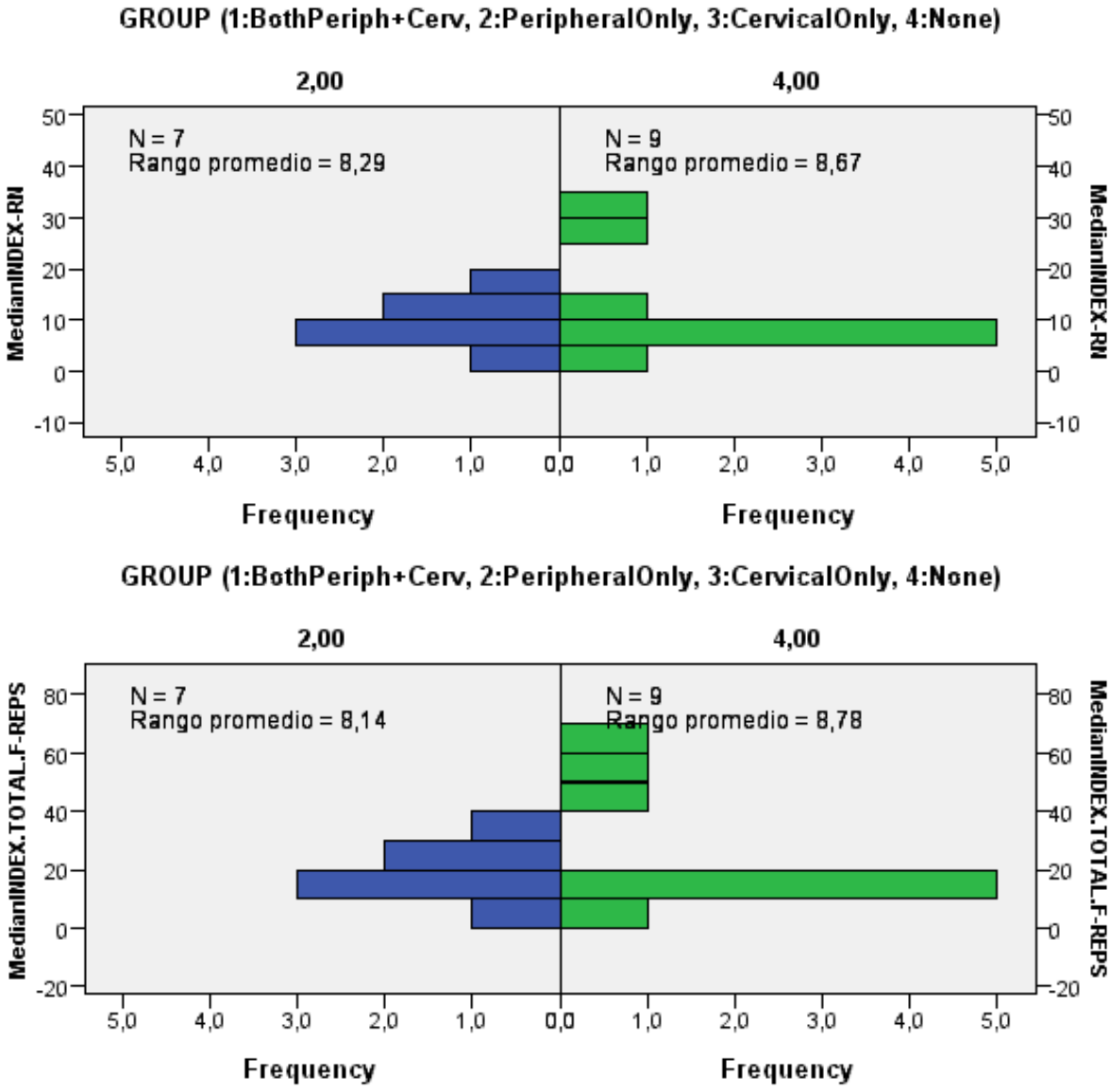



Figure 12: Index-RN of ulnar nerve in the subgroup"only-CTS" (selected from group II), and in the healthy (group IV). Tool: Mann-Whitney U test (for two independent samples). N: 33; Mann–Whitney U test: 155,500; Wilcoxon's W: 191,500; Typical error: 23,657; two-sided asymptotic significance: 0.019; two-sided exact significance: 0,017.

The “normal” median nerve in the UL-N sub-group (Figures 13.a and 13.b) had an index RN of 8.33 (SD: 5.81) and an index of total Freps of 15.38 (SD: 11.19), which were significant different from the corresponding values of the median nerve in the CTS sub-group (for both indices $p<0.05$) but not significantly different from those of the median nerve in the healthy subject group ($p>0.500$).




Figures 13.a and 13.b: Index-RN and Index-Total F-Reps of median nerve in the subgroup“only-Ulnar Neuropathy” (selected from group II), compared with the healthy (group IV). Tool: Mann-Whitney U test (for two independent samples). For Index-RN: N: 16; Mann–Whitney U test: 33,000; Wilcoxon’s W: 78,000; Typical error: 9,356; two-sided asymptotic significance: 0.873; two-sided exact significance: 0,918. For Index-Total F-Reps: N: 16; Mann–Whitney U test: 34,000; Wilcoxon’s W: 79,000; Typical error: 9,356; two-sided asymptotic significance: 0.789; two-sided exact significance: 0,837.

No significant correlations were found, in the healthy group (IV), between the median and ulnar nerve indices; meanwhile, it remains a significant positive correlation between both indices for each nerve separately. (Table 27)

| | | | Median INDEX. TOTAL.F-REPS | Median INDEX-RN | Ulnar INDEX. TOTAL.F-REPS | Ulnar INDEX-RN |
|---|---|---|---|---|---|---|
| Spearman's Rho | Median INDEX. TOTAL.F-REPS | $r_s$ | 1,000 | ,983* | ,160 | ,160 |
| | | Sig. (bilateral) | . | ,000 | ,706 | ,706 |
| | | N | 9 | 9 | 8 | 8 |
| | Median INDEX-RN | $r_s$ | ,983* | 1,000 | ,160 | ,160 |
| | | Sig. (bilateral) | ,000 | . | ,706 | ,706 |
| | | N | 9 | 9 | 8 | 8 |
| | Ulnar INDEX. TOTAL.F-REPS | $r_s$ | ,160 | ,160 | 1,000 | 1,000* |
| | | Sig. (bilateral) | ,706 | ,706 | . | . |
| | | N | 8 | 8 | 8 | 8 |
| | Ulnar INDEX-RN | $r_s$ | ,160 | ,160 | 1,000* | 1,000 |
| | | Sig. (bilateral) | ,706 | ,706 | . | . |
| | | N | 8 | 8 | 8 | 8 |

Table 27: Correlations between Median and Ulnar Indices in Group IV

*: Correlation is significant at the 0.01 level (2-tailed).

## *3.3.6. FURTHER ANALYSES*

### *3.3.6.1. Latency and Amplitude of Repeating Neurons (RNs) across the groups I-IV*

The latency and amplitude of Repeating Neurons (RNs) were assessed in three ways:

- The number of RNs, and subsequently, the Index RN, showed significant differences between groups I-III and II-IV, happening to be higher in the groups I and III both in median and ulnar nerves, with a stronger positive correlation in the case of median nerve ($p=0.000$ for number and index RN) than in ulnar nerve (number of RN, $p=0.005$; Index RN, $p=0.001$).
- Comparison between RNs and all F-waves in each nerve and subject group:
    (i) Latency-wise, there were no significant differences in any nerve and group except for the ulnar nerve in Ul-N subgroup and the median nerve in CTS subgroup –both extracted from group II, isolated nerve entrapments-, where RNs had significantly longer latency values.
    (ii) Amplitude-wise, with the exception of the ulnar nerve in the healthy subject group where the sample size was too small to obtain meaningful statistical results, in the two nerves and for all subject groups a statistically lower value of max amp was found for the RNs as compared to all F-waves.
- The ratio of latency and amplitude values of RNs over those of all F-waves in a given nerve was compared between the healthy subjects and the three patient groups; no significant inter-group difference was found, all p-values resulting $>0.05$.

### *3.3.6.2. Correlation of RN and total Freps indices to age and standard neurophysiological parameters*

There was no significant correlation ($r_s \neq 0$ so that $0 < r_s < 1$, or $-1 < r_s < 0$; $p < 0.05$) between age and indices RN or total Freps in any nerve and for any patient groups (Tables 28-32). Testing for such correlation among healthy subjects did not seem relevant due to the smaller number of patients as well as the shorter range of ages inside this group.

When testing the general pool of subjects (Table 28), index RN in the median nerve correlated positively with index RN and total Freps in the ulnar nerve ($p<0.001$, $r_s=0.272$ and $p=0.001$, $r_s=0.240$ respectively).

The index of Total F-Reps in the ulnar nerve also correlated positively with index RN and total Freps in the median nerve ($p=0.001$, $r_s=0.240$ and $p=0.002$, $r_s=0.223$ respectively).

Median and ulnar indices RN and total Freps correlated positively between themselves in each nerve separately ($p<0.001$, $r_s=0.971$ for median nerve, and $p<0.001$, $r_s=0.977$ for ulnar nerve).

| | | | AGE | Median INDEX-RN | Median INDEX.TOTAL F-REPS | Ulnar INDEX-RN | Ulnar INDEX.TOTAL F-REPS |
|---|---|---|---|---|---|---|---|
| Spearman's Rho | AGE | $r_s$ | 1,000 | -,045 | -,074 | -,020 | -,041 |
| | | Sig. (bilateral) | . | ,529 | ,299 | ,777 | ,572 |
| | | N | 197 | 196 | 196 | 194 | 193 |
| | Median INDEX-RN | $r_s$ | -,045 | 1,000 | ,971* | ,272* | ,240* |
| | | Sig. (bilateral) | ,529 | . | ,000 | ,000 | ,001 |
| | | N | 196 | 196 | 196 | 193 | 192 |
| | Median INDEX.TOTAL F-REPS | $r_s$ | -,074 | ,971* | 1,000 | ,251* | ,223* |
| | | Sig. (bilateral) | ,299 | ,000 | . | ,000 | ,002 |
| | | N | 196 | 196 | 196 | 193 | 192 |
| | Ulnar INDEX-RN | $r_s$ | -,020 | ,272* | ,251* | 1,000 | ,977* |
| | | Sig. (bilateral) | ,777 | ,000 | ,000 | . | ,000 |
| | | N | 194 | 193 | 193 | 194 | 193 |
| | Ulnar INDEX.TOTAL F-REPS | $r_s$ | -,041 | ,240* | ,223* | ,977* | 1,000 |
| | | Sig. (bilateral) | ,572 | ,001 | ,002 | ,000 | . |
| | | N | 193 | 192 | 192 | 193 | 193 |

Table 28. Correlations of RN and total Freps indices to age – General Group
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | AGE | Median INDEX-RN | Median INDEX.TOTAL. F-REPS | Ulnar INDEX-RN | Ulnar INDEX.TOTAL .F-REPS |
|---|---|---|---|---|---|---|---|
| **Spearman's Rho** | AGE | $r_s$ | 1,000 | ,098 | ,079 | ,047 | ,035 |
| | | Sig. (bilateral) | . | ,346 | ,447 | ,656 | ,738 |
| | | N | 102 | 94 | 94 | 93 | 92 |
| | Median INDEX-RN | $r_s$ | ,098 | 1,000 | ,966* | ,137 | ,116 |
| | | Sig. (bilateral) | ,346 | . | ,000 | ,190 | ,269 |
| | | N | 94 | 94 | 94 | 93 | 92 |
| | Median INDEX.TOTAL .F-REPS | $r_s$ | ,079 | ,966* | 1,000 | ,100 | ,077 |
| | | Sig. (bilateral) | ,447 | ,000 | . | ,341 | ,467 |
| | | N | 94 | 94 | 94 | 93 | 92 |
| | Ulnar INDEX-RN | $r_s$ | ,047 | ,137 | ,100 | 1,000 | ,976* |
| | | Sig. (bilateral) | ,656 | ,190 | ,341 | . | ,000 |
| | | N | 93 | 93 | 93 | 93 | 92 |
| | Ulnar INDEX.TOTAL .F-REPS | $r_s$ | ,035 | ,116 | ,077 | ,976* | 1,000 |
| | | Sig. (bilateral) | ,738 | ,269 | ,467 | ,000 | . |
| | | N | 92 | 92 | 92 | 92 | 92 |

Table 29. Correlations of RN and total Freps indices to age – Group I.
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | AGE | Median INDEX-RN | Median INDEX.TOTAL. F-REPS | Ulnar INDEX-RN | Ulnar INDEX.TOTAL. F-REPS |
|---|---|---|---|---|---|---|---|
| Spearman's Rho | AGE | $r_s$ | 1,000 | -,036 | -,067 | ,149 | ,119 |
| | | Sig. (bilateral) | . | ,802 | ,646 | ,302 | ,412 |
| | | N | 55 | 50 | 50 | 50 | 50 |
| | Median INDEX-RN | $r_s$ | -,036 | 1,000 | ,991* | ,306† | ,292† |
| | | Sig. (bilateral) | ,802 | . | ,000 | ,032 | ,042 |
| | | N | 50 | 50 | 50 | 49 | 49 |
| | Median INDEX.TOTAL. F-REPS | $r_s$ | -,067 | ,991* | 1,000 | ,298† | ,285† |
| | | Sig. (bilateral) | ,646 | ,000 | . | ,038 | ,047 |
| | | N | 50 | 50 | 50 | 49 | 49 |
| | Ulnar INDEX-RN | $r_s$ | ,149 | ,306† | ,298† | 1,000 | ,989* |
| | | Sig. (bilateral) | ,302 | ,032 | ,038 | . | ,000 |
| | | N | 50 | 49 | 49 | 50 | 50 |
| | Ulnar INDEX.TOTAL. F-REPS | $r_s$ | ,119 | ,292† | ,285† | ,989* | 1,000 |
| | | Sig. (bilateral) | ,412 | ,042 | ,047 | ,000 | . |
| | | N | 50 | 49 | 49 | 50 | 50 |

Table 30. Correlations of RN and total Freps indices to age – Group II
*: Correlation is significant at the 0.01 level (2-tailed).
†: Correlation is significant at the 0.05 level (2-tailed).

| | | | AGE | Median INDEX-RN | Median INDEX.TOTAL. F-REPS | Ulnar INDEX-RN | Ulnar INDEX.TOTAL. F-REPS |
|---|---|---|---|---|---|---|---|
| Spearman's Rho | AGE | $r_s$ | 1,000 | -,140 | -,156 | ,195 | ,225 |
| | | Sig. (bilateral) | . | ,371 | ,318 | ,209 | ,146 |
| | | N | 47 | 43 | 43 | 43 | 43 |
| | Median INDEX-RN | $r_s$ | -,140 | 1,000 | ,915* | ,240 | ,081 |
| | | Sig. (bilateral) | ,371 | . | ,000 | ,121 | ,607 |
| | | N | 43 | 43 | 43 | 43 | 43 |
| | Median INDEX.TOTAL. F-REPS | $r_s$ | -,156 | ,915* | 1,000 | ,191 | ,073 |
| | | Sig. (bilateral) | ,318 | ,000 | . | ,219 | ,641 |
| | | N | 43 | 43 | 43 | 43 | 43 |
| | Ulnar INDEX-RN | $r_s$ | ,195 | ,240 | ,191 | 1,000 | ,947* |
| | | Sig. (bilateral) | ,209 | ,121 | ,219 | . | ,000 |
| | | N | 43 | 43 | 43 | 43 | 43 |
| | Ulnar INDEX.TOTAL. F-REPS | $r_s$ | ,225 | ,081 | ,073 | ,947* | 1,000 |
| | | Sig. (bilateral) | ,146 | ,607 | ,641 | ,000 | . |
| | | N | 43 | 43 | 43 | 43 | 43 |

Table 31. Correlations of RN and total Freps indices to age – Group III
*: Correlation is significant at the 0.01 level (2-tailed).

| | | | AGE | Median INDEX-RN | Median INDEX.TOTAL. F-REPS | Ulnar INDEX-RN | Ulnar INDEX.TOTAL. F-REPS |
|---|---|---|---|---|---|---|---|
| Spearman's Rho | AGE | $r_s$ | 1,000 | ,017 | -,113 | -,186 | -,186 |
| | | Sig. (bilateral) | . | ,965 | ,772 | ,658 | ,658 |
| | | N | 13 | 9 | 9 | 8 | 8 |
| | Median INDEX-RN | $r_s$ | ,017 | 1,000 | ,983* | ,160 | ,160 |
| | | Sig. (bilateral) | ,965 | . | ,000 | ,706 | ,706 |
| | | N | 9 | 9 | 9 | 8 | 8 |
| | Median INDEX.TOTAL. F-REPS | $r_s$ | -,113 | ,983* | 1,000 | ,160 | ,160 |
| | | Sig. (bilateral) | ,772 | ,000 | . | ,706 | ,706 |
| | | N | 9 | 9 | 9 | 8 | 8 |
| | Ulnar INDEX-RN | $r_s$ | -,186 | ,160 | ,160 | 1,000 | 1,000* |
| | | Sig. (bilateral) | ,658 | ,706 | ,706 | . | . |
| | | N | 8 | 8 | 8 | 8 | 8 |
| | Ulnar INDEX.TOTAL. F-REPS | $r_s$ | -,186 | ,160 | ,160 | 1,000* | 1,000 |
| | | Sig. (bilateral) | ,658 | ,706 | ,706 | . | . |
| | | N | 8 | 8 | 8 | 8 | 8 |

Table 32. Correlations of RN and total Freps indices to age – Group IV
*: Correlation is significant at the 0.01 level (2-tailed).

# 4. DISCUSSION

The aim of our study was to identify patients complaining from peripheral symptoms who are actually suffering from cervical root pathology –either isolated or in combination with very mild peripheral mononeuropathies.

We evaluated F-wave recordings in the median and ulnar nerves in patients with primary suspicion of peripheral mononeuropathies of the upper limb, such as Carpal Tunnel Syndrome (CTS), ulnar neuropathy, or both. In a significant number of cases, electroneurographical findings were compatible with a proximal pathology, isolated or overlapping with the suspected peripheral mononeuropathy.

Thus, we studied a population of patients with cervical root lesions at different levels and severities, isolated or in combination with distal nerve pathology.

Demographically, our patients are comparable in number and characteristics with those from similar studies, designed according to the incidence of the pathologies and the items analyzed in their electrodiagnostic tests. (130-137)

In our study men showed higher mean age than women. Age did not influence whether or not the right or the left side was involved or either one or both sides were affected. Naves et al. studied incidence of mild CTS in otherwise healthy elderly patients, finding that women presented symptoms since earlier in life and more than double as frequently than men did. (138) The higher incidence in women since earlier ages than in men may have relationship with the pregnancy at older ages, as Klemetti and coworkers have demonstrated, as older women seem to present a higher tendency to persistant symptoms after pregnancy than younger women, who usually reported different pathologies like depression.(139)

The one-side pathology occurs more often in our patients related to peripheral pathology being right-side-the predominant. In our opinion, this is probably related to laterality of the patients, who were mostly right-handed, as long as this hand usually accomplishes most of the everyday tasks and efforts. Mondelli et cols. have also observed that thenar motor neuropathy –an "only motor" variant of carpal tunnel syndrome- presents more likely related to chronic direct compression of the motor branch of median nerve, because it preferentially affected dominant hand and persons doing manual work. (140)

In the last years, several studies about CTS and ulnar neuropathy have been developed, mostly focusing on epidemiology,(141;142) risk factors,(143-145) diagnosis,(146) treatment and outcomes. (147-149;149-162) In addition, a valuable amount of previous work has focused on combinations of peripheral and proximal pathologies, although under perspectives different from the present study.

Sohn and co-workers studied the epidemiological conditions causing symptoms in the upper extremity in some groups –workers, diabetics, cancer patients and others. (61; 163-166)

The electrodiagnostic findings in each of the possible combinations have been reported,(167-169) especially those aimed to support the "double-crash hypothesis" (DCH). This hypothesis was formulated in 1973 by Upton and McComas, (170) suggesting that nonsymptomatic impairment of axoplasmic flow at more than one site along one single nerve might contribute to cause symptomatic neuropathy as carpal tunnel syndrome. Since then, further series of patients supporting the frequent association of a proximal and distal nerve compression syndrome have been reported, (168; 171-173) highlighting the poorer surgical outcome of carpal tunnel release in these double crush patients and suggesting the need of double-treatment of both entrapments for optimal results. (174)

However, other anatomic and pathophysiologic studies have found limitations DCH as an explanation for coexisting cervical root lesions and carpal tunnel syndrome or ulnar neuropathy at the elbow. According to these authors, Double-Crash Syndrome (DCS) evaluation would require both structural and functional diagnosis of peripheral neurones using MRI and electrophysiological examination. (167-169)

A study group from Bethesda surveyed retrospectively 12,736 limbs with CTS or UN-E, with results suggesting that a cervical root lesion can seldom serve as the proximal lesion with these entrapment neuropathies in the double-crash hypothesis.(173) Several studies have demonstrated that severe Carpal Tunnel Syndrome, various polyneuropathies, metabolic or autoimmune diseases, as well as cervical radiculopathic injuries –even subclinical-, are related to motor axonal damage, turned into higher number of repeater neurons, detectable in the motor electroneurographic studies. (118;127;129;175-177)

In our study, the number and morphology of identical F-waves, along with their repetitions in samples of 20 stimuli, were estimated. Other authors have also assessed the F-waves' characteristics, as amplitude, latency and duration, as well as their relationship to the motor unit size.(178-182)

The F responses' sample size may vary; some authors have used up to 200 stimuli per nerve to demonstrate that the recurrent patterns of F-waves are formed by determined sequences in a complex but not random way, settled by physiological factors which may operate altered under disease processes of the nervous system. (181;183)

Nevertheless, most works are based on clinical findings retrospectively analyzed, thus following the most extended protocol which is based in samples of 20 stimuli.(57; 127; 184-186)

Significantly, in our study the repeater F-waves occurred more frequently in the nerves of the groups including radiculopathies than in isolated peripheral nerve entrapments or

healthy individuals. Their persistence was negatively correlated with that of non-repeaters F-waves.

Persistence was assessed in further studies (121; 187-191) but minimal F-wave latency rather than persistence was considered the most sensitive measure for detection of nerve pathology in diabetic patients. (118; 192)

Other research groups have assessed how reflex activity may influence the F-waves' chronodispersion and even prevent F waves in low-threshold motor units. (193) More recent studies tested systematically how F-waves' persistence and amplitude were lower when using submaximal stimulation for their acquisition. Anyway, the latency and duration of these F-waves were statistically equivalent to those obtained under supramaximal stimulation.(194)

In our case, we evaluated F-waves' persistence in relationship with proximal versus distal motor axonal damage, using supramaximal stimulation in every patient, and discarding the suboptimal registers as well as polyneuropathic patients in order to meet the inclusion criteria. Our findings suggest that repeater F-waves may differentiate between proximal motor axonal lesions –as in radiculopathy- and peripheral nerve entrapment pathologies, although the indices of RN and total Freps are not significantly bounded to concrete cervical levels nor related to the etiology of the proximal pathologies.

Other authors have validated the relationship between radicular pathology and repeater F-waves' parameters, as relative amplitude, latencies and percentage. These parameters showed to be consistent and significatively higher in patients with lumbosacral root injury.(127) Chroni et al. analyzed the electroneurographic studies of 300 patients concluding that repeater F-waves differentiate between health and disease but not between different types of pathology of motor neurons or their axons. (57; 195) We have validated this observation in our study, and share the opinion that repeater F-waves constitute a more sensitive than specific sign of motor axonal pathology.

In our study design we hypothesized that isolated cervical radiculopathies and cervical radiculopathy combined with peripheral nerve entrapment could be differentiated by means of F-Waves. Surprisingly, our results have shown that frequency and persistence of repeater F-Waves do not differentiate between them. We can suggest to explain these findings that, when mild axonal damage at any level is present, i.e., incipient radiculopathy or mild to moderate peripheral nerve entrapment, F-waves could not present any specific feature related to the location of the lesion.

The degree of axonal injury also plays an important role. In peripheral nerve entrapments seen in our work, repeater F-waves showed a frequency and persistence proportional to the severity of the lesion. Accordingly, healthy subjects from group IV revealed a small number of RNs and a low number of repetitions (≤5 in 20 stimuli).

We can speculate that distal entrapment neuropathies from moderate to severe intensity could also produce a secondary axonal degeneration in proximal segments of the nerve. This secondary proximal degeneration may lead to more frequent repeating F-waves when no primary radicular pathology is present. Thus, if keeping a limited diagnostic approach, incomplete and confusing findings may lead to misleading conclusions and subsequently suboptimal treatment.
Summarizing, proximal location of the damage and moderate to severe degrees of severity, seem to play a major role in the amount and morphology of the repeater F-waves generated. Therefore, the combination of two or more electrodiagnostic methods (as electroneurography and electromyography) to widen and delve into the study of a "suspected mononeuropathy", is very important in order to keep a good praxis.

Other authors also advocate for complete electrodiagnostic studies as useful adjuncts to the clinical examination of the peripheral nervous system. The main reason is because nerve traumas -like peripheral nerve entrapment, radiculopathy or nerve root compression-, in opposition to polyneuropathy, show marked differences in their effect on the results of electrodiagnostic studies.(196)

On the basis of our results, repeater F-Waves found either in healthy carpal tunnel syndrome (CTS) referrals or in those with mild CTS are mostly related to subclinical proximal pathology at plexus or root level. Ulnar nerve demonstrated larger values of these repeater variables among the nerves studied. Conversely, repeater variables values were smaller in the median nerve. Interestingly, our estimates were anyhow slightly lower than previously reported.

Thus, Macleod (126) examined the median nerve using 100 stimuli in 125 healthy subjects and found a group mean value of index total Freps of 14.9±12.2 as compared to ours of 10.53±21.73, using 20 stimuli (126). For the ulnar nerve, using 100 stimuli in 11 healthy volunteers Guiloff and Modarres-Sadeghi (182; 197) reported a mean value of index RN of 11.2±4.9, which was reduced to 5.7±6.0 when samples of 20 stimuli were assessed; similarly using 200 stimuli in 21 subjects Peioglou-Harmoussi et al. (125) estimated the median value of RN to be 3.3 (min-max: 1.1-5.4) as compared to our median value of RN of 2.0 ± 1.307.

In our opinion, these studies are reflecting that F-waves sample size keeps a direct proportion with the absolute numerical values of the indices of repeating neurons and repeating F-waves.

However, these comparisons should be treated with caution due to different statistical variables employed in the above mentioned studies. In any case, inter-study variations should mainly be attributed to:

i) criteria to define RNs,
ii) number of stimuli, and
iii) number of subjects.

In our patient population, RN occurrence expressed by different indices and ratios was found to be significantly higher in patients with radiculopathies than in CTS, Ulnar-N and healthy subjects.

Accordingly, even subclinical cervical radiculopathies, combined or not with peripheral nerve entrapment syndromes, repeater F-waves frequency and persistence showed in our study to be higher than in isolated peripheral nerve entrapments only.

When comparing F-waves' parameters in both median and ulnar nerves among our patient groups, no correlation was found between increased total Freps and some specific root level in cervical pathology.

Irrespective of the absolute values of the repeater F-waves, the mean differences between healthy controls, patients with CTS or Uln-N and cervical (C3-C8/T1) root lesion found here were proportionally similar to those previously reported (112; 125-127). Thus, we agree that the index of repeater to all F-waves is a reliable sign of nerve pathology, as well as a comparison tool with other studies. Furthermore, even in routinely recorded samples of 20 traces, the index of repeater to all F-waves could be used as a nonspecific sign of proximal axonal pathology, when none or very mild distal pathology is present.

Although the mechanism for generating F-repeaters remains unclear, pathology and clinic may correlate through the analysis of the derived events of these late responses' generation, like how persistently they do appear. It has been shown that under normal conditions the size of motor unit, linked to the persistence of F-waves, varies from one nerve to another; thus the persistence is high in the ulnar (70-100%), less in the median (60-100%) and much lower in other nerves as the fibular (30%). (198) We addressed in our work the question whether physiological factors of a certain motor neuron pool or simply technical issues of F-wave analysis can be held responsible for an enhanced total Freps.

Thus, we hypothesized that repeater F-waves should be seen more often in nerves with a general increase in persistence. However, with the exception of ulnar nerve, no correlation was found in our study between persistence of total Freps and persistence of F-waves in the same nerve.

Conversely, a consistent finding in all patient groups I to IV was the inverse relationship between the persistence of total Freps and Fnonreps, i.e. the lower the persistence of Fnonreps, the higher the persistence of total Freps. Interestingly, RNs appeared more often when other neurons did not generate F-waves.

This reverse association between total Freps and Fnonreps could be explained by technical reasons. F-waves are fewer in series of traces where it is easier to identify RNs, since the latter are not hidden in complex F-waveforms. Although this possibility cannot be ruled out, the fundamental principles of low frequency of back firing of individual motor neurons makes it rather unlikely. Thus, we also hypothesize for future work that RNs activity is enhanced in a motor neuron population that has low tendency for F-wave generation, as in the fibular/peroneal nerve, compared to a nerve with a large number of neurons able to produce F-waves, such as the ulnar nerve.

A SFEMG study of F-responses elicited by 200 stimuli in the ulnar nerve in healthy subjects showed that only 6% of the individual motor neurons are able to generate 5-15 F-responses, whereas the majority of neurons seldom or never backfire.(113) Thus, considering that these F-responses are unevenly distributed in time, RNs might only occasionally be seen during recordings of 20 traces.(199) In our patient groups –especially in those including radiculopathies-, the amount of total Freps exceed by many times the frequency expected only by unmasking of RNs due to reduced persistence of Fnonreps. We therefore suggest that increased indices RN and total Freps observed in our study constitute an abnormal phenomenon.

To explain our results, we considered the increased amount of total Freps observed in our patients was due to loss of motor neurons as well as changes in their excitability as part of the aging process. As already mentioned elsewhere, the persistence of F-waves depends on the size of the motor unit, which in practice is related to the anatomical location of each nerve.

Loss of motor neurons with age resulting in alterations of their corresponding motor unit size is a well-known process (200-202). In our study, there was found no correlation between age and the indices RN and total Freps.

We measured latency and amplitude parameters to detect any particular characteristic of RNs. RNs latencies in the vast majority of our comparisons were found within the range of all F-wave latencies in the same nerves. These results agreed with previous findings. Guiloff et al. in 30 healthy controls (197), found that F-repeaters had similar latency and duration, than F wave shapes that did not repeat, suggesting that the former have a larger number of component motor units (MUs) responding to each threshold stimulation.
With regard to the amplitude of RNs, the maximum value in our study was chosen over mean or median value to examine the common impression that RNs are high amplitude F-waves. The same authors (197) reported that repeater F-waves were of higher amplitude than ordinary F-waves and concluded that they were more likely to be generated by a greater number of neurons each rather than by single larger motorneurons.

This view is also supported by our findings in the isolated peripheral nerve entrapments group (Group II). In this group, the maximum amplitude of RNs was not as high as the maximum F-wave amplitude in the same recording. As a result, the RNs were not different in terms of amplitude from other F-waves in our study.

Conversely, the proximal pathology groups in our study (Groups I and III) gave findings according to earlier publications. These studies support the higher-amplitude-than-ordinary repeater F-waves when related to anterior horn pathology, thus fitting the criteria of F-waves modulated by newly formed distal (or proximal or both) axonal branching (179; 203).

As generally accepted, taking into account the infrequent backfiring of each neuron, the statistical change of two or more neurons backfiring together twice or more times in a sample of 20 stimuli is close to zero. Therefore, we suggest that each individual F-wave occurring repeatedly is generated by backfiring of a single neuron, justifying the term “RNs”.

In order to adjust for the overall F-wave abnormalities documented, we searched for latency and amplitude changes between subject groups. RNs values were expressed as ratios to the corresponding values of all F-waves in a given nerve. These ratios remained stable in all groups and were unaffected by the diverse pathologies examined, particularly in the radiculopathy groups.

Pastore-Olmedo, Kohara, Argyriou and coworkers (127; 204-205) assessed such F-wave characteristics in other pathology groups, as lumbosacral root injury,(127) diabetic polyneuropathies,(204) and ALS.(205) Due to our exclusion criteria, taking out of the study those patients with Diabetes Mellitus and other conditions leading to the lesion of multiple nerves, our study did not assess repeater F-waves in polyneuropathies. To our knowledge, only one single report has described increased frequency of RNs in 3 patients with diabetic polyneuropathy. (178) Thus, if peripheral polyneuropathies (206) would have been included in our study, the findings would have affected by selection bias, making less likely to get significative and reliable results when comparing the groups.

Our study has several limitations. First of all, the study is limited both to one single institution and to one single electrodiagnostician. This may have influenced the population sample size. The same diagnostician for all the registers may also influence some type of bias (observer knows that the researcher hypothesized) different from biases that could come up among different explorers (inter-observer variation).

Second, the sample size of F-waves analyzed in each recording has been of 20, as in common practice. More accurate measurements of the amount of repeater F-waves can be obtained by sampling higher number of F-waves, but reliable comparisons can be made through the Indices RN and TotalFreps. Our overly strict definition of RN used here in order to standardize the method, could have led to underestimation of their repetition numbers. By contrast, RNs could have been relatively overestimated due to the methodological tactic of not to include in the analysis any other signals in a trace where an RN was identified.

And third, a follow-up of the patients and their evolution is lacking. If this were a follow-up study other factors, such as the medical history and the prolonged exposition to metabolic axonal damage (e.g. if comorbility with DM and other variables as time or treatments) prior to the study would have been considered. Our current approach was not intended as a case-control study, but as a prospective observational diagnostic study based on the electroneurographical and electromyographical parameters of three case series, their electrophysiological analysis and correlations. This "one-intervention, one-diagnosis" management is the current approach to the neurophysiologists' everyday practice.

Our work has several clinical implications. First of all, finding repeater F-waves in patients without or with very mild peripheral neuropathies may suggest to expand the electroneurographic diagnostic protocol towards EMG, and thus finding a significant percentage of patients suffering from subclinical mild to moderate cervical radiculopathies who are currently missed. Second, as future clinical approaches we recommend the careful observation of the morphology and amplitude of F-waves when looking for a suspected CTS in otherwise healthy patients -even without proximal/cervical symptoms. And third, it has been demonstrated that more accurate measurements of the amount of repeater F-waves can be obtained by sampling 40, 60 or more F-waves. (180; 197; 207) We propose the future inspection of repeater F-waves were made in routinely recorded samples of 100 stimuli, as an add-on to the detection of abnormalities of motor neurons or their axons.
Instead of using absolute numbers of repeater F-waves, the relative RN activity to all F waves in a recording is advised for reasons of comparison. In our study no superiority between index RN and index total Freps was found, though the latter is simpler to estimate in a clinical setting. This strategy may improve the efficiency and diagnostic yield of each electrophysiologic performance, optimizing the approach to full-diagnosis and the subsequent needs of treatment of our patients.

As future perspectives for research we propose that F-waves characteristics have a role to study suppression or enhancement of the spinal excitability and also to detect early signs of proximal pathology. Recent research has shown that spinal excitability, as measured by F-waves, is suppressed after 3 hours of voluntary relaxation, and this was prevented by mentally simulating the corresponding motor task. (208) Thus, the assessment through the

F-waves characteristics of effects such as suppression or enhancement of the spinal excitability could represent future electrophysiological strategies within a widened realm of study. In addition, our work has also examined “normal” nerves in patients with mononeuropathies. We have found that in these nerves RNs occurrence was higher than in the nerves of healthy subjects but lower than in the clinically and electrophysiologically damaged nerves. We hypothesize for future work that subtle changes in presumed “normal” nerves in co-existence of cervical radiculopathy in the nerves of the affected limb could have accounted for enhanced RNs occurrence, as well as in the case of patients with chronic lumbosciatic pain where EMG tests often report non-significant findings. Thus, in our perspective, increased repeater F-wave activity is an early sign of proximal pathology that deserves further research as well as implementation in the everyday practice.

# 5. CONCLUSIONS

- Repeater F-Waves are present in peripheral nerve entrapment syndromes, with a frequency and persistence proportional to the severity of the lesion.

- Repeater F-Waves' frequency and persistence in subclinical cervical radiculopathies, combined or not with peripheral nerve entrapment syndromes, are higher than in isolated peripheral nerve entrapments only.

- Repeater F-Waves' frequency and persistence in cervical radiculopathies do not differentiate between isolated proximal pathology and when combined with peripheral nerve entrapments.

- Repeater F-Waves found either in healthy carpal tunnel syndrome (CTS) referrals (five or less repetitions per repeating neuron) or in those with mild CTS, are mostly related to subclinical proximal pathology at plexus or root level.

# 6. GLOSSARY

**ADM:** Abductor Digiti Minimi

**Amp decay:** 100 x [(amplitude at distal stimulation - amplitude at proximal stimulation) / (amplitude at distal stimulation)]

**APB:** Abductor Pollicis Brevis

**CMAP:** Compound Muscle Action Potential

**CMAP amp:** Negative amplitude of the CMAP

**CMAP lat:** Distal motor latency of the CMAP

**CTS:** Carpal Tunnel Syndrome

**Fnon-repeaters:** All F-waves minus total Freps

**F-wave max amp:** The maximum peak to peak amplitude of the largest F-wave in a series of 20 stimuli

**F-wave mean lat:** The mean latency of F-waves in a series of 20 stimuli minus CMAP lat

**Index RN:** 100 x number of RN / number of traces with different F-wave shapes in a series of 20 stimuli

**Index total Freps:** 100 x total number of F-wave repeaters / total number of traces with F-waves in the same nerve

**MCV:** Motor Conduction Velocity

**Persistence of F-waves:** % traces with any F-waves in a series of 20 stimuli

**Persistence of Fnonreps:** % Fnonrepeaters in a series of 20 stimuli

**Persistence of total Freps:** % total Freps in a series of 20 stimuli

**RN:** Repeating Neuron

| | |
|---|---|
| **RN max amp:** | The maximum peak to peak amplitude of the largest RN appearing in a series of 20 stimuli |
| **RN mean lat:** | The mean latency of RNs in a series of 20 stimuli |
| **SCV:** | Sensory Conduction Velocity |
| **SFEMG:** | Single-Fiber EMG |
| **SNAP amp:** | Amplitude of Sensory Nerve Action Potential |
| **Total Freps:** | Total F-wave repeaters |
| **Uln-N:** | Ulnar Mononeuropathy |

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**Picture 2:** Peripheral nerves of the left upper extremity. Reproduced with permission from <http://www.bartleby.com/107> (original unmodified image) and <http://commons.wikimedia.org/wiki/Category:Brachial_plexus>. Last Accessed 3 October 2013.

**Picture 3:** Diagrammatic representation of brachial plexus. Reproduced with permission from <http://commons.wikimedia.org/wiki/Category:Brachial_plexus>. Last Accessed 3 October 2013.

**Picture 4:** Median and Ulnar nerves and their branches. Reproduced with permission from <http://depts.washington.edu/msatlas/content.html#102>. "Copyright 2003-2004 University of Washington. All rights reserved including all photographs and images. No re-use, re-distribution or commercial use without prior written permission of the authors and the University of Washington." Last Accessed 3 October 2013.

**Picture 5:** Carpal Tunnel. Reproduced with permission from <http://depts.washington.edu/msatlas/content.html#102>. "Copyright 2003-2004 University of Washington. All rights reserved including all photographs and images. No re-use, re-distribution or commercial use without prior written permission of the authors and the University of Washington." Last Accessed 3 October 2013.

**Picture 6:** Fibrillation potentials and rain on a tin roof. Image and photograph. Reproduced with permission from <http://www.glowm.com/section_view/heading/Neurophysiologic%20Testing%20of%20the%20Pelvic%20Floor/item/57>, and <http://likethedew.com/2012/12/27/listening-to-the-rain/>. Last Accessed 3 October 2013.

**Picture 7:** Positive Sharp Waves. Reproduced with permission from <http://www.glowm.com/section_view/heading/Neurophysiologic%20Testing%20of%20the%20Pelvic%20Floor/item/57>. Last Accessed 3 October 2013.

**Picture 8:** Complex Repetitive Discharges and machine gun. Image and photograph. Reproduced with permission from <http://www.glowm.com/section_view/heading/Neurophysiologic%20Testing%20of%20the%20Pelvic%20Floor/item/57>, and <http://www.weaponsofthemilitary.com/machine-guns-in-the-ww1/>. Last Accessed 3 October 2013.

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**Picture 14:** Electrical stimulation of the median nerve at the elbow. M-waves and H-reflexes. Reproduced with permission from <http://neurobiography.info/teaching.php?lectureid=125&mode=handout>. Last Accessed 3 October 2013.

**Picture 15:** H reflex circuitry. Diagrammatic picture. Reproduced with permission from <http://www.intechopen.com/books/>. Last Accessed 3 October 2013.

**Picture 16:** H-Reflex. Reproduced with permission from the book "Principles of Neural Science", E.Kandel. (Adapted from Schieppati 1987) <http://www.ib.cnea.gov.ar/~redneu/2013/BOOKS/Principles%20of%20Neural%20Science%20-%20Kandel/gateway.ut.ovid.com/gw2/ovidweb.cgisidnjhkoalgmeho00dbookimagebookdb_7c_2fc~43.htm>. Last Accessed 3 October 2013.

**Picture 17:** Evoked EMG. M-wave. H-wave. F-wave. Reproduced with permission from <http://www.intechopen.com/books/electrodiagnosis-in-new-frontiers-of-clinical-research/evoked-emg-makes-measurement-of-muscle-tone-possible-by-analysis-of-the-h-m-ratio>. Last Accessed 3 October 2013.

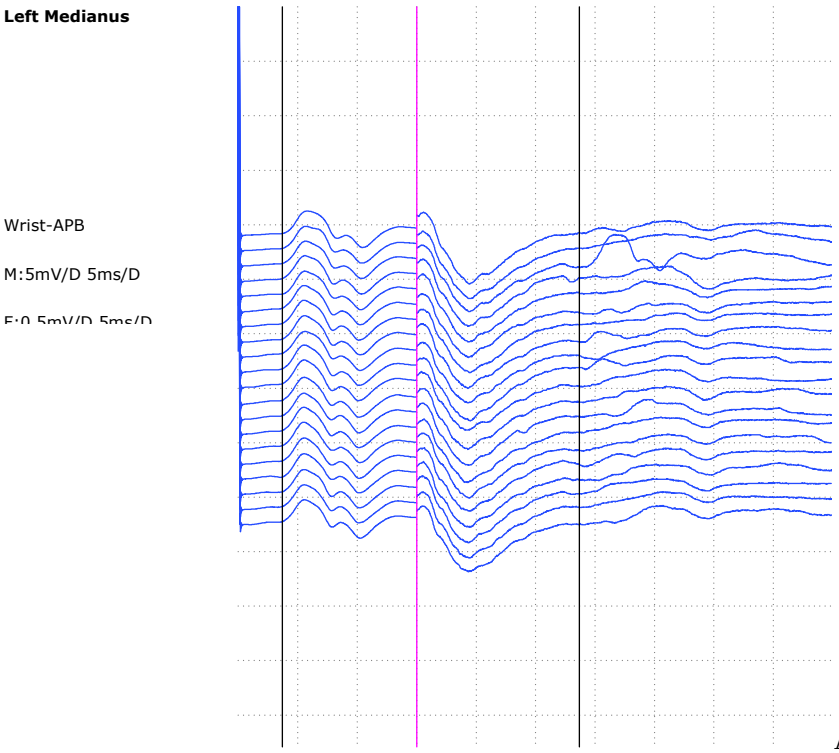
**Picture 18:** Median Nerve Sensory Conduction Study. *Source: Metodbok för Neurografier.Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). Photograph-Diagram.* Reproduced with permission from <http://www.neurofys.uu.se/v2/docs/metod/index.php>. Last Accessed 3 October 2013.

**Picture 19:** Median Nerve Motor Conduction Study. *Source: Metodbok för Neurografier.Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). Photograph-Diagram.* Reproduced with permission from <http://www.neurofys.uu.se/v2/docs/metod/index.php>. Last Accessed 3 October 2013.

**Picture 20:** Ulnar Nerve Sensory Conduction Study. *Source: Metodbok för Neurografier.Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). Photograph-Diagram.* Reproduced with permission from <http://www.neurofys.uu.se/v2/docs/metod/index.php>. Last Accessed 3 October 2013.

**Pictures 21.a-c:** Ulnar Nerve Motor Conduction Study.*Source: Metodbok för Neurografier.Avdelningen för klinisk neurofysiologi. Akademiska Sjukhuset. Uppsala Universitet (Sweden). Photograph-Diagram.* Reproduced with permission from <http://www.neurofys.uu.se/v2/docs/metod/index.php>. Last Accessed 3 October 2013.

# 11. Appendix IV: F-WAVE SAMPLES



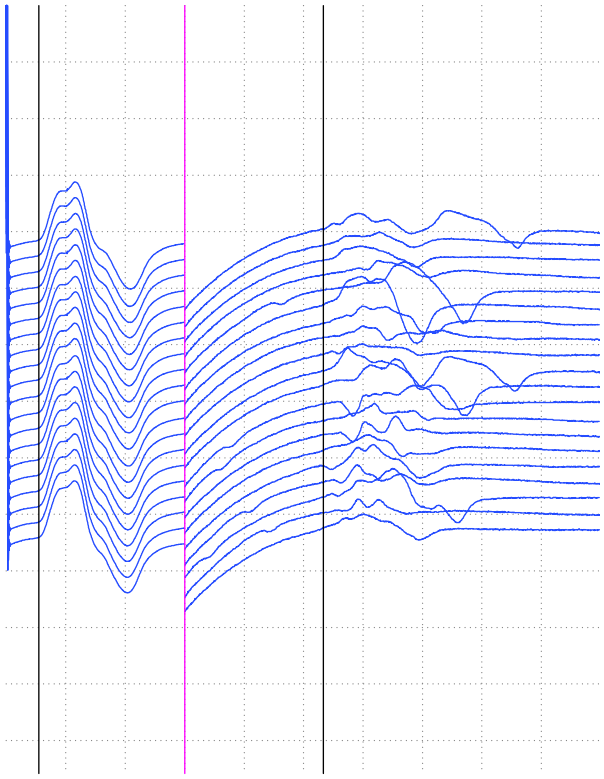

A-Waves and F-Waves

**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

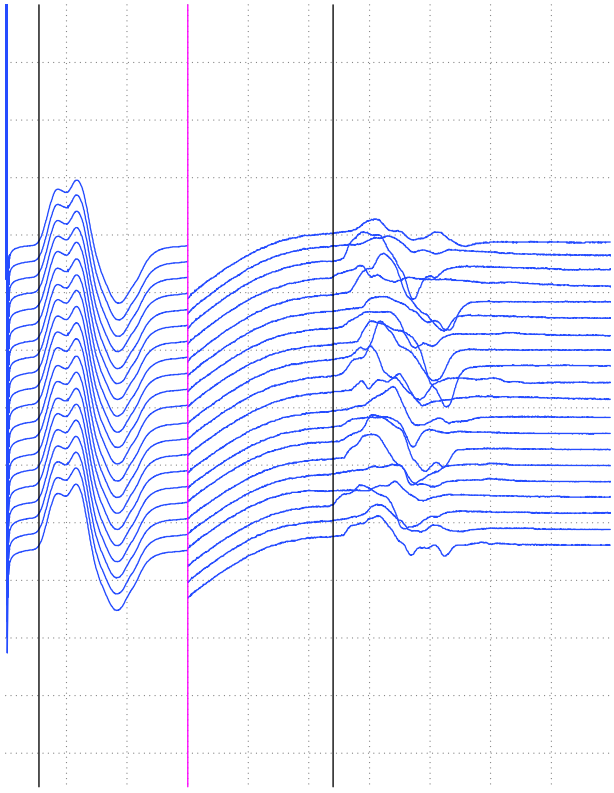


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

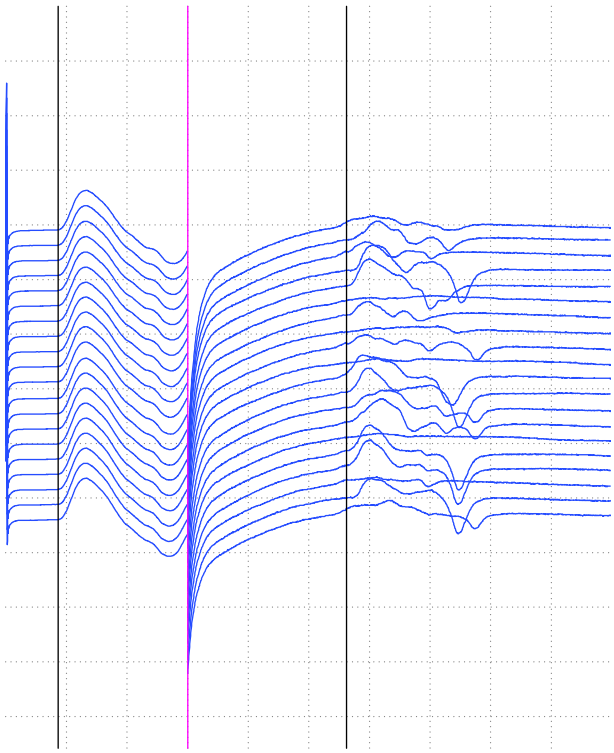
F:0.5mV/D 5ms/D



**Right Medianus**

Wrist-APB

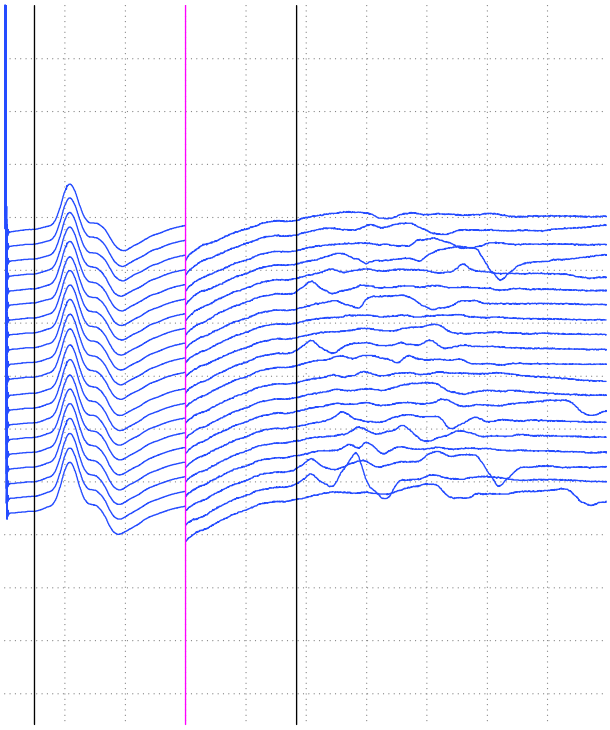
M:5mV/D 5ms/D



**Left Ulnaris**

Wrist-ADM

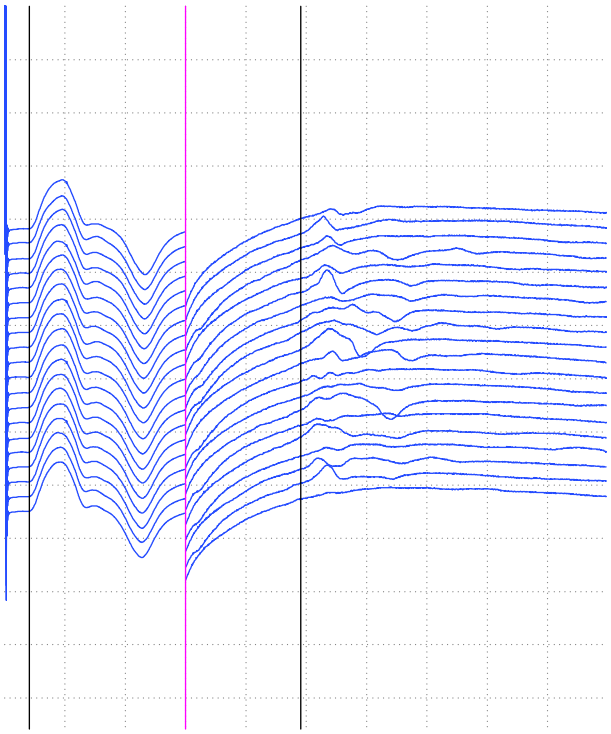
M:5mV/D 5ms/D



**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

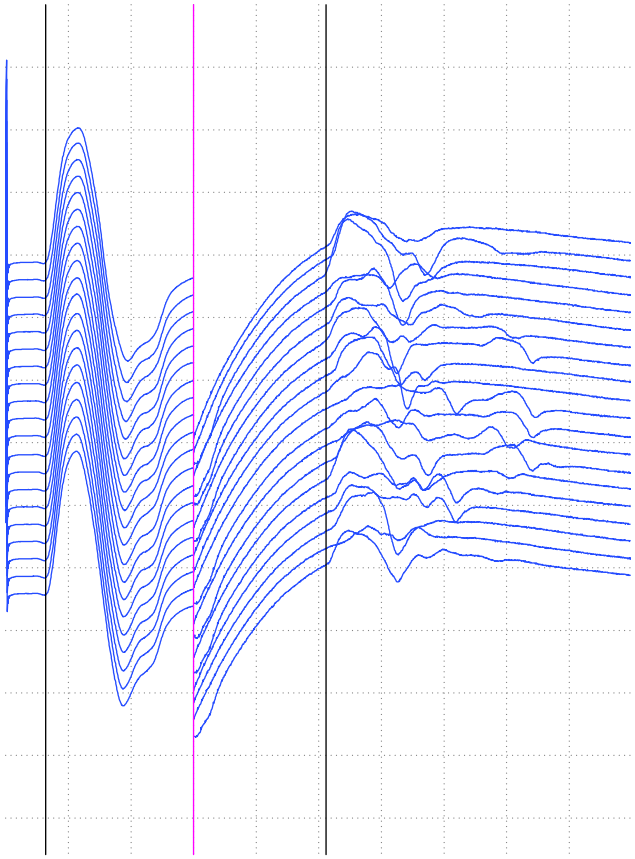


**Left Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

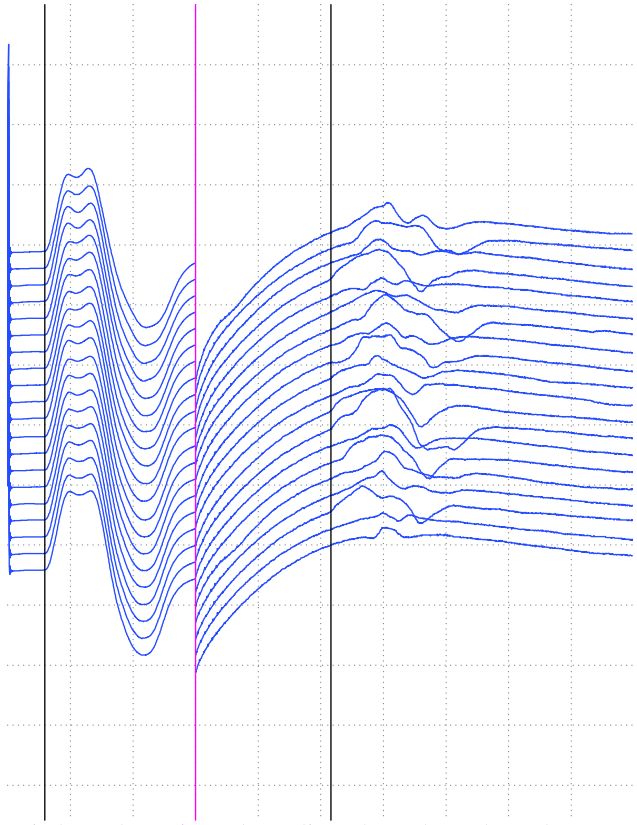


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

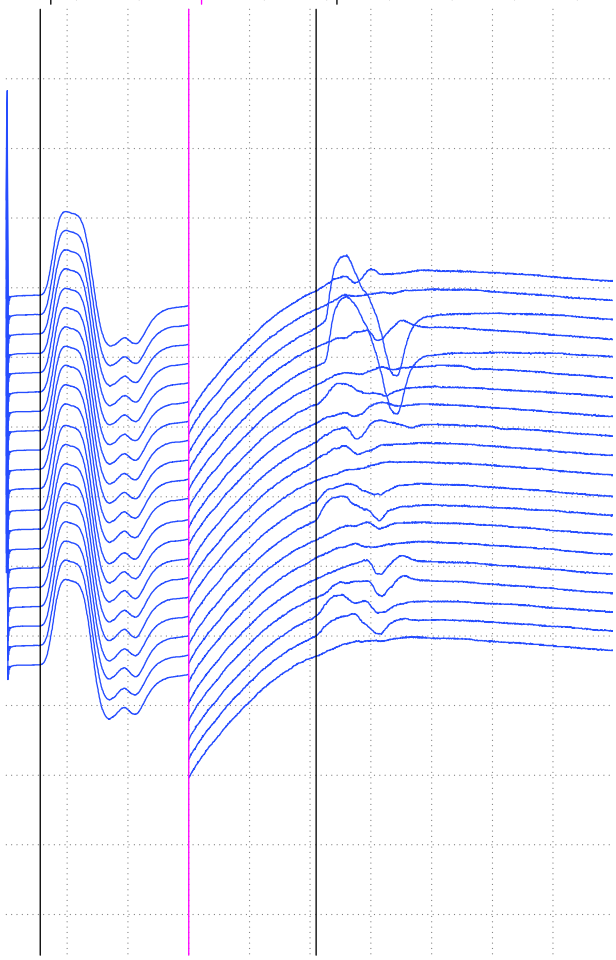


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D



**Right Ulnaris**

Wrist-ADM

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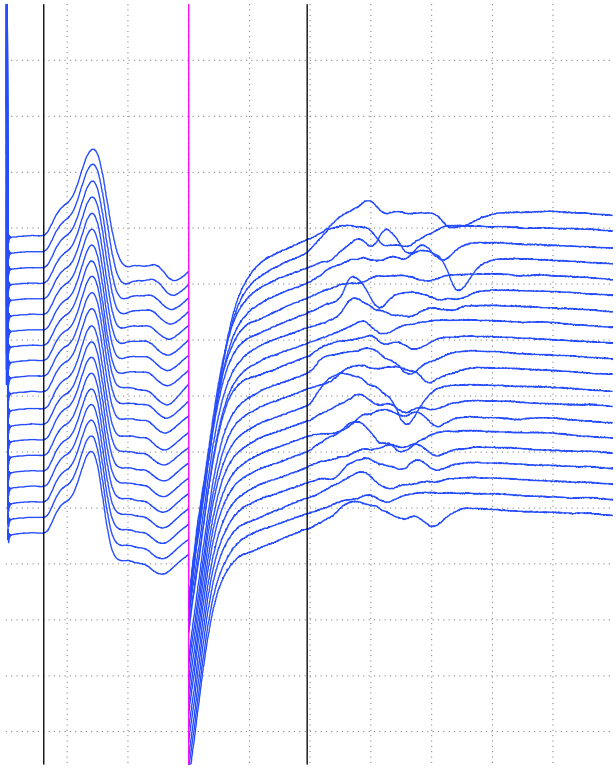
F:0.5mV/D 5ms/D

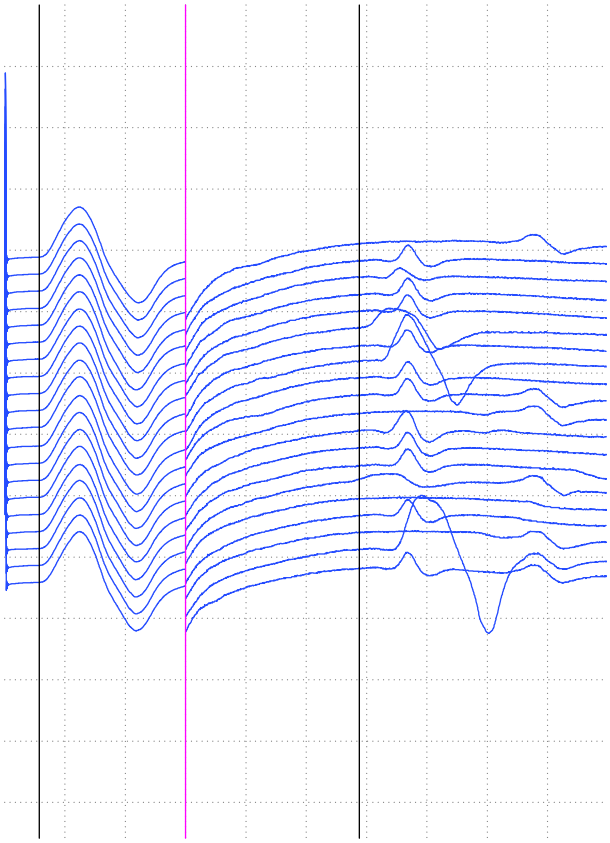


**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

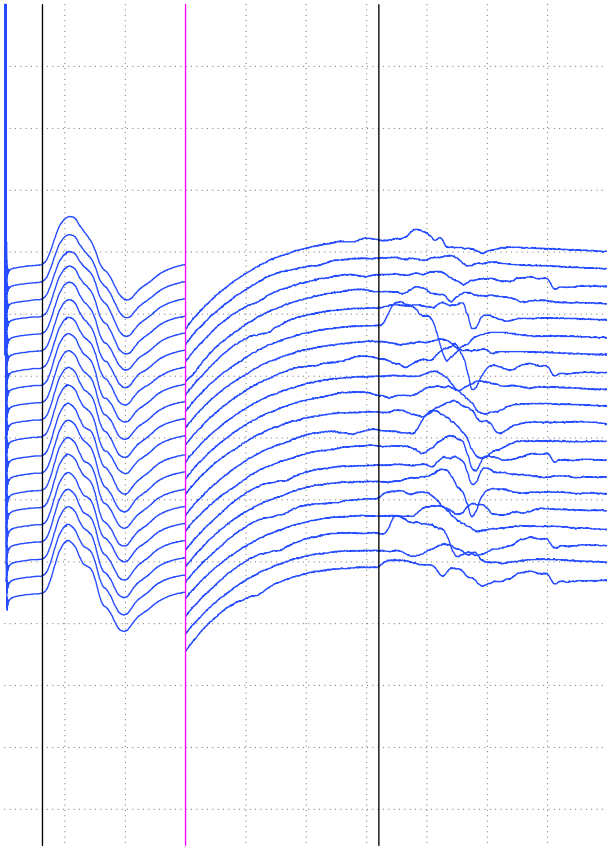


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

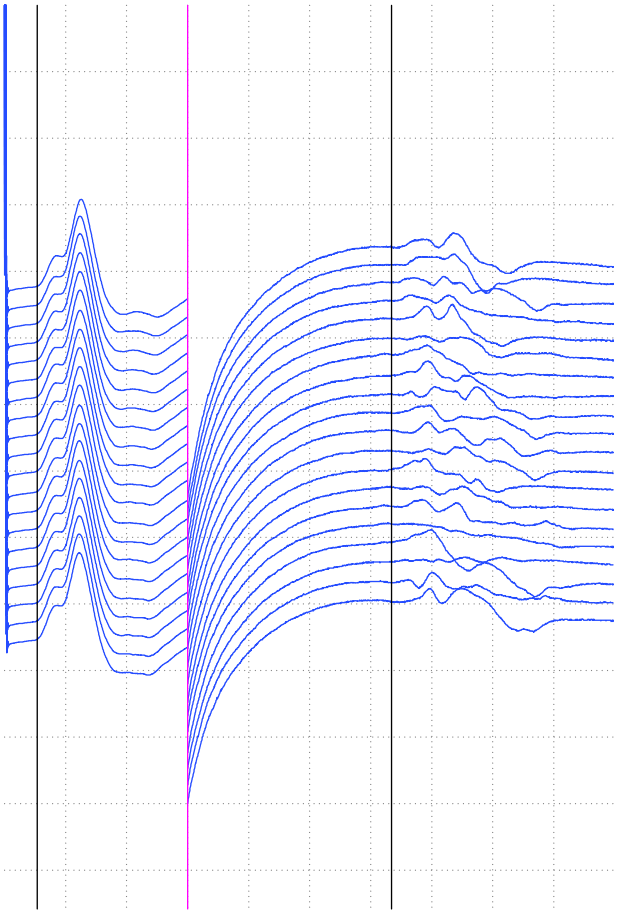


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

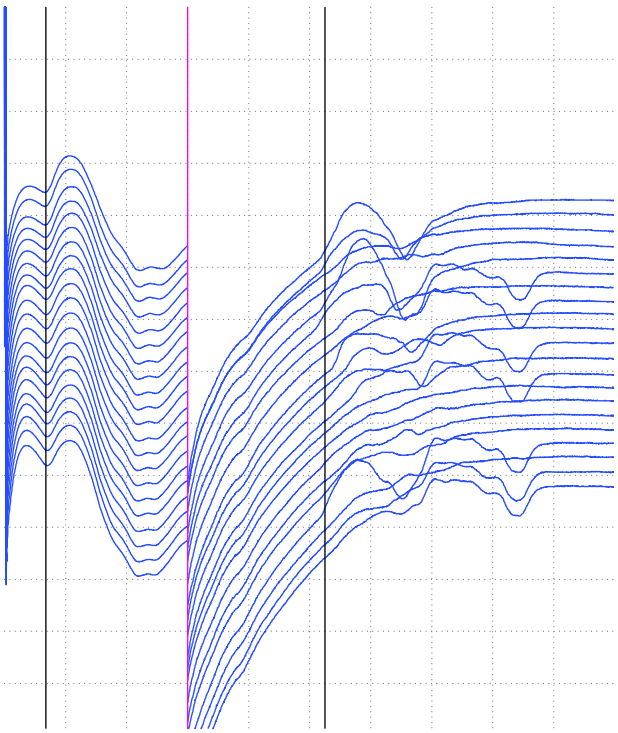
F:0.5mV/D 5ms/D



**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

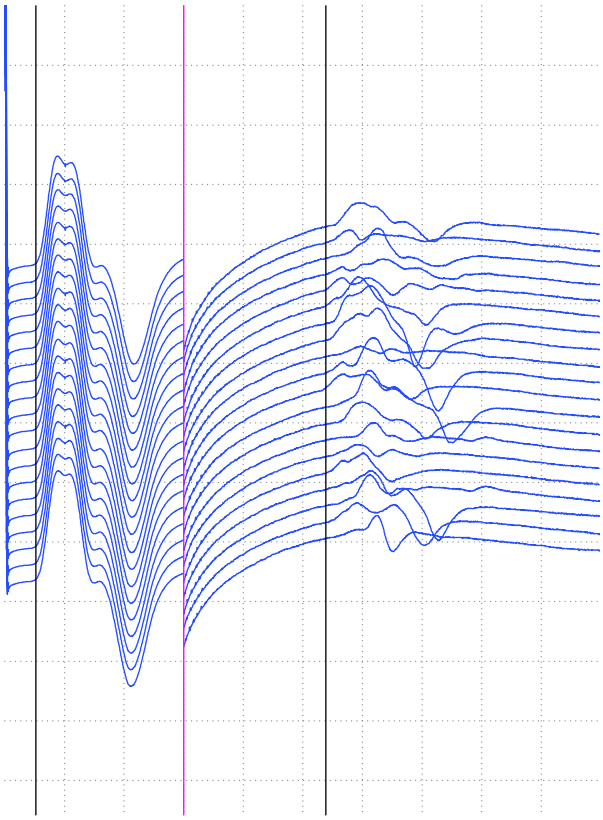


**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

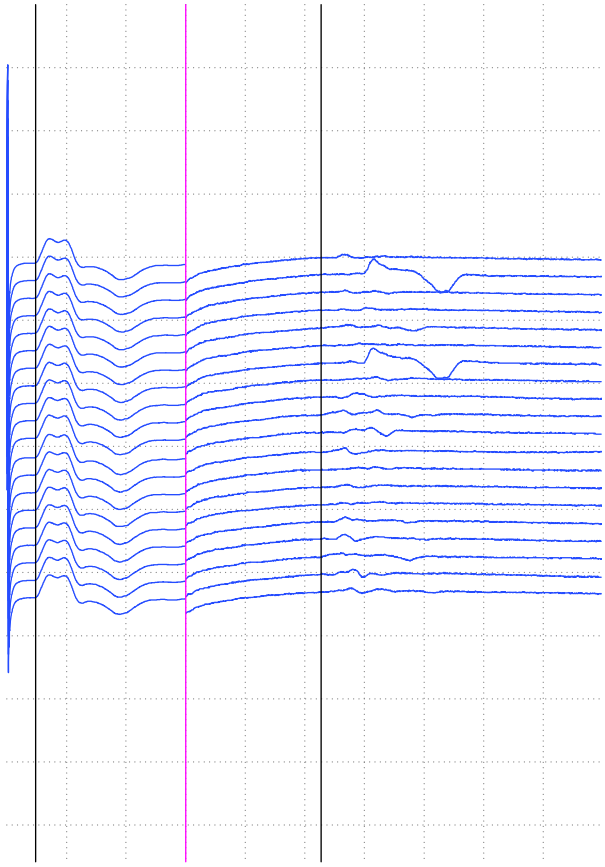


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

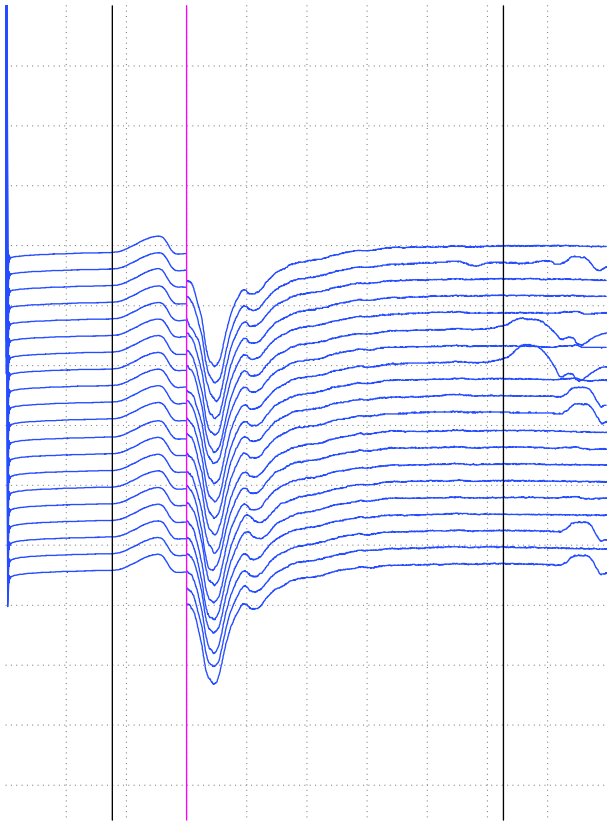


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

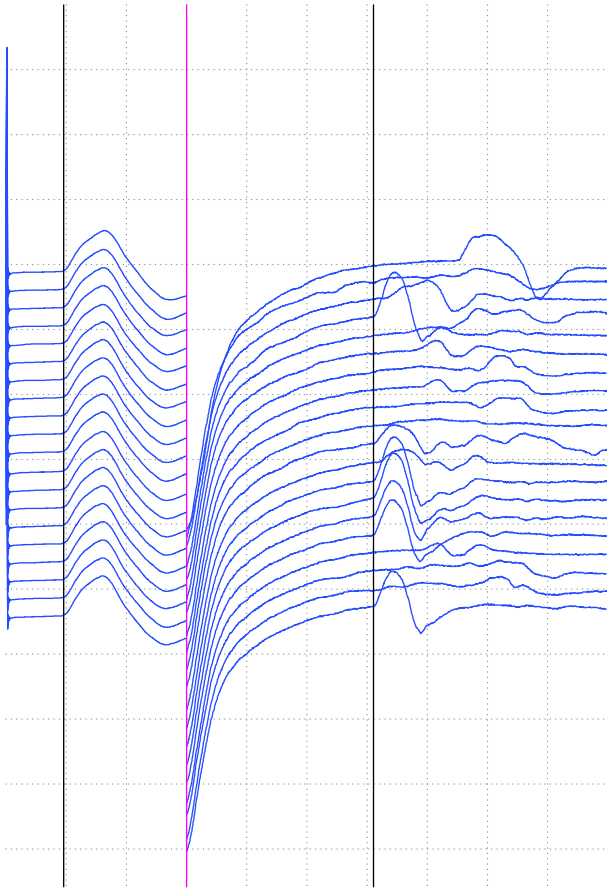


**Left Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

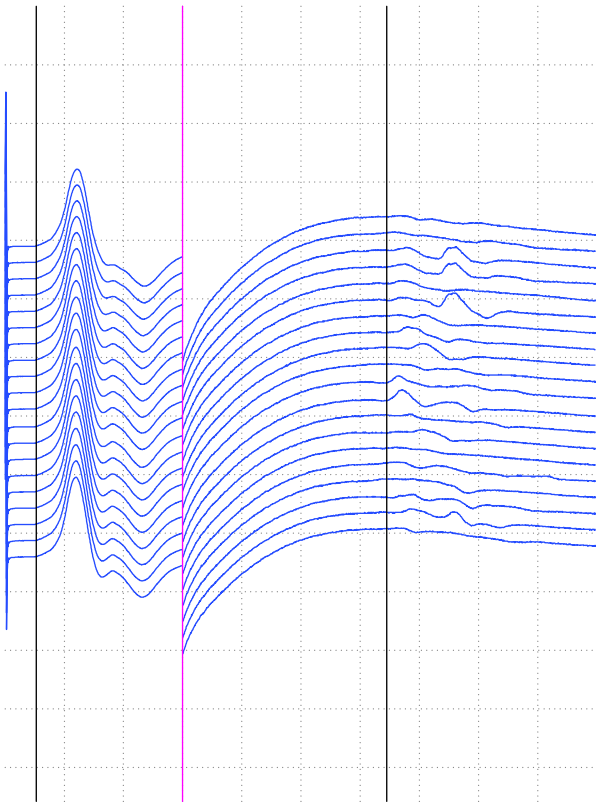


**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

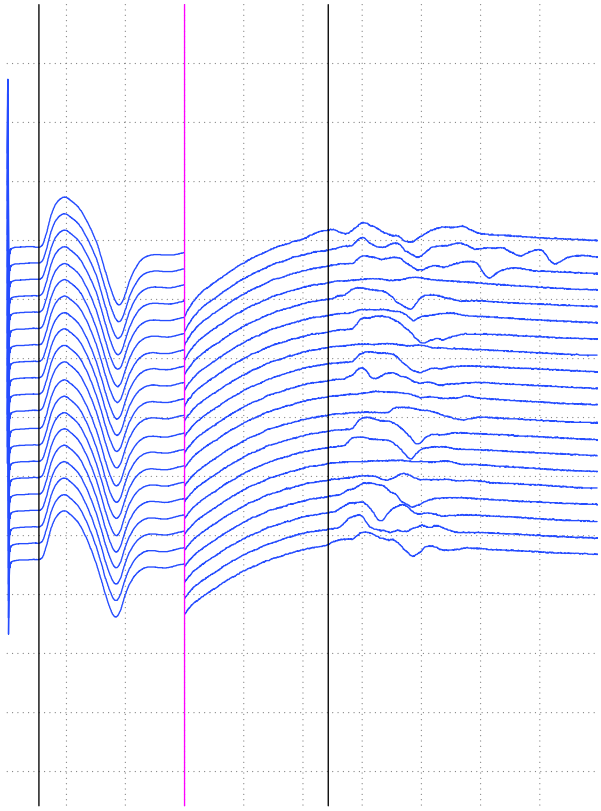


**Left Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

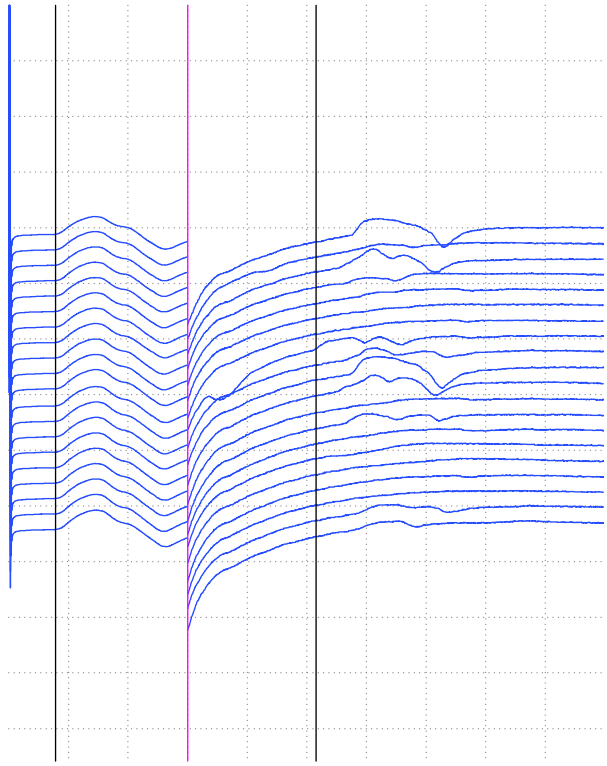


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

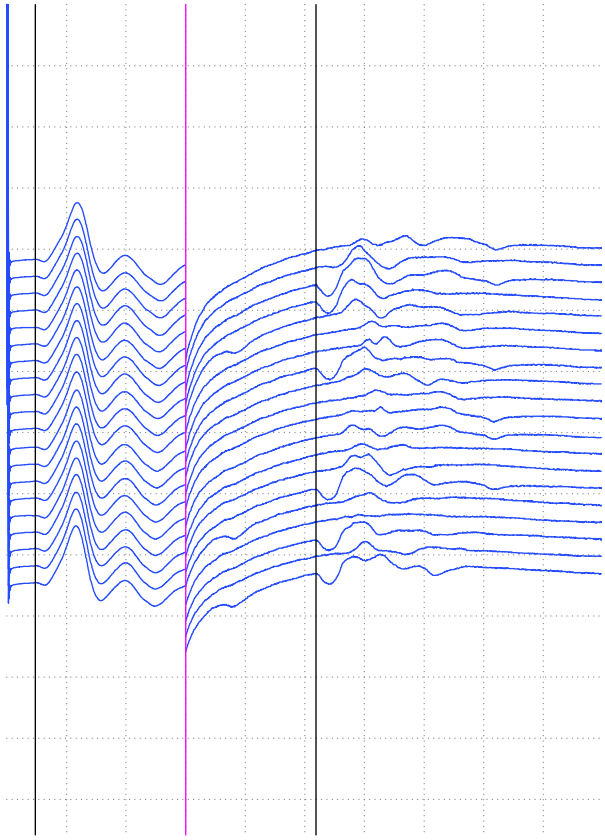


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

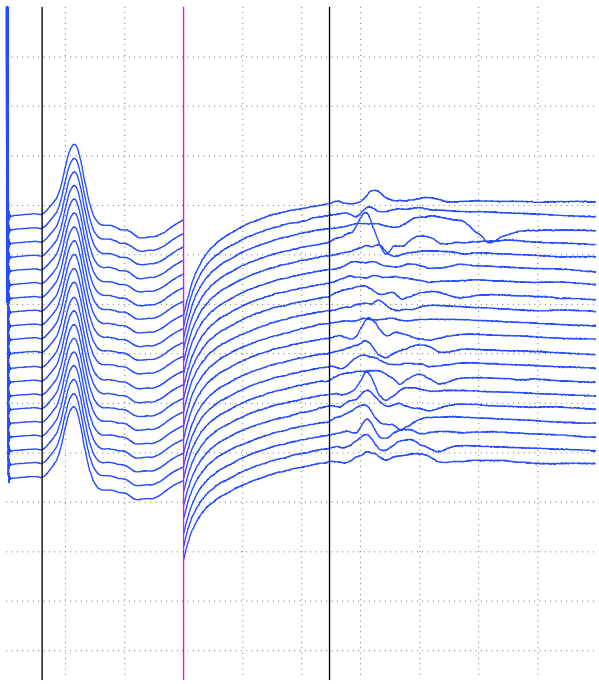
F:0.5mV/D 5ms/D



**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

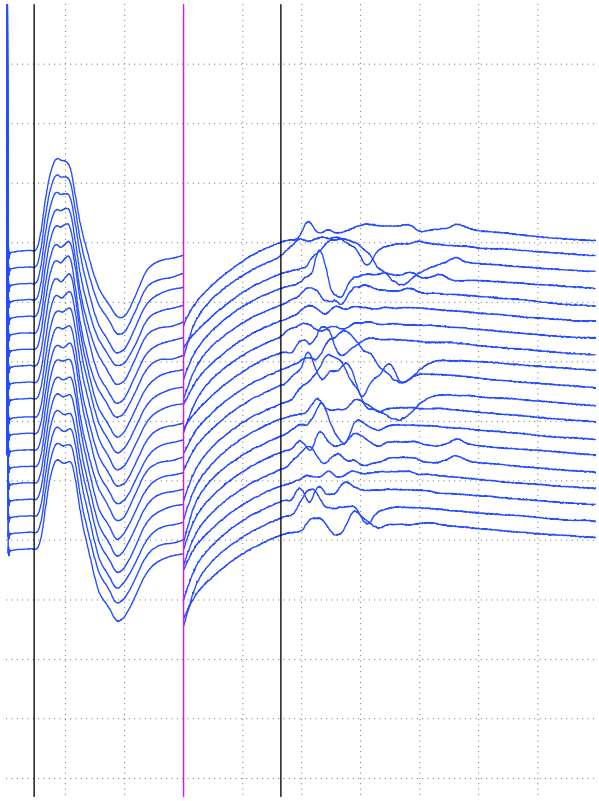


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

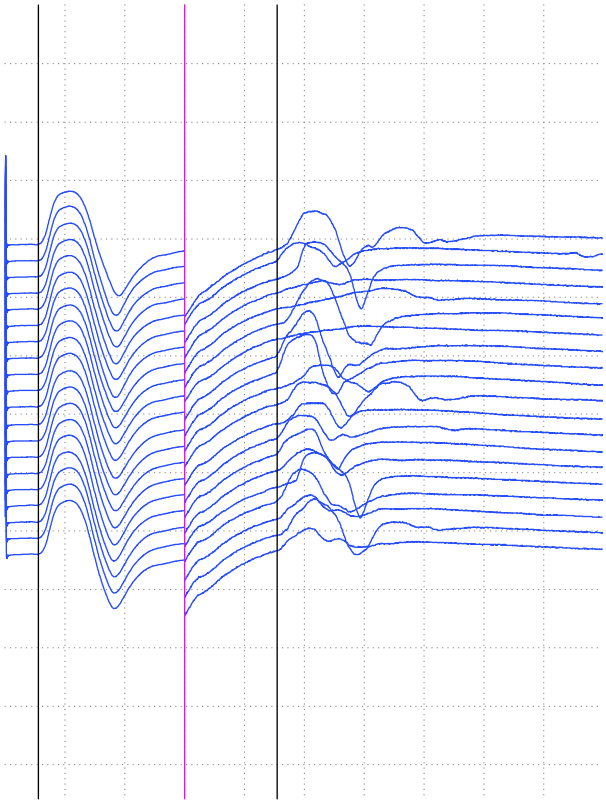


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

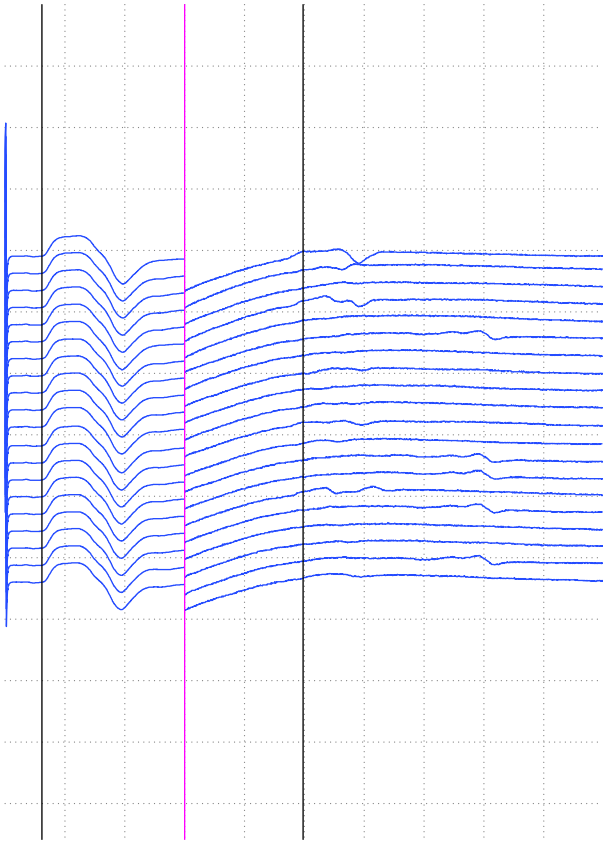


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

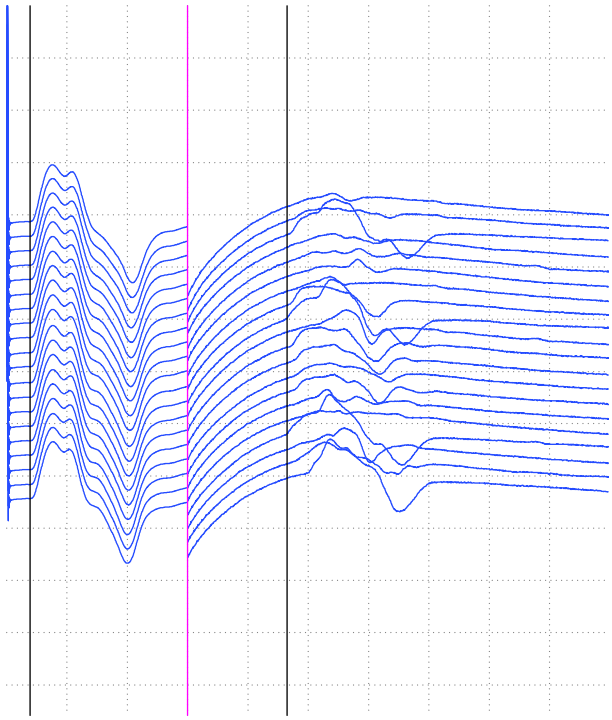
F:0.5mV/D 5ms/D



**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

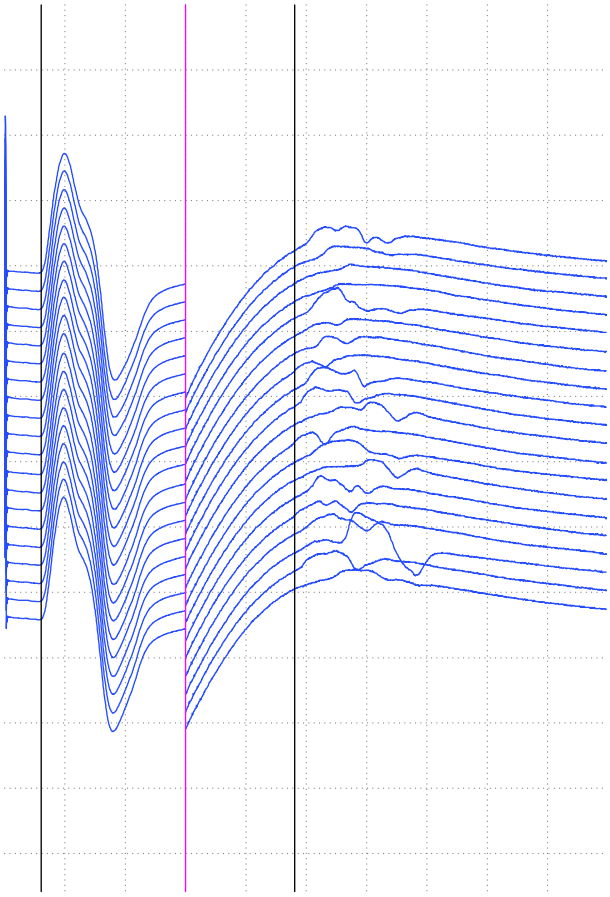


**Left Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

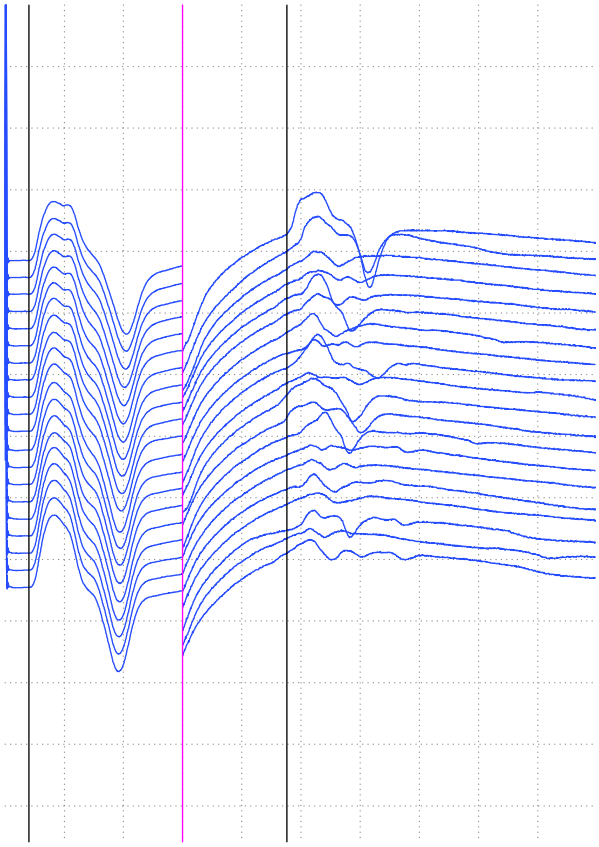


**Left Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

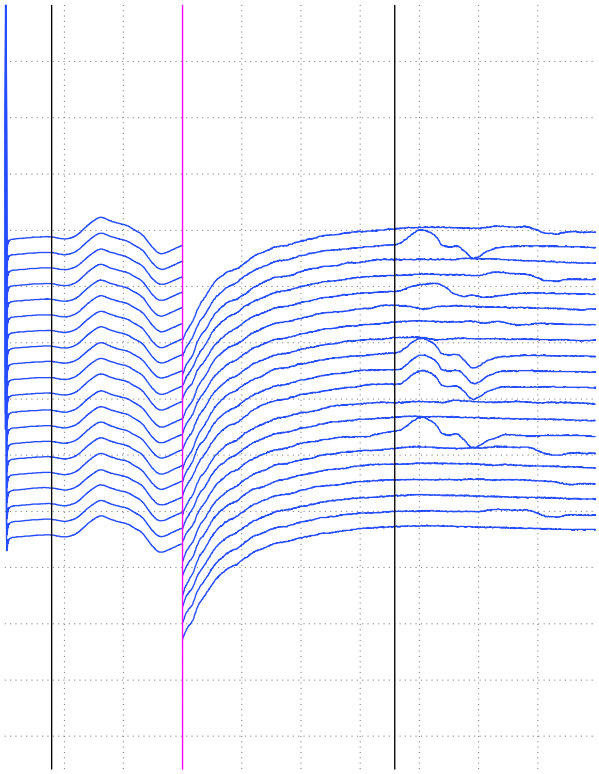


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

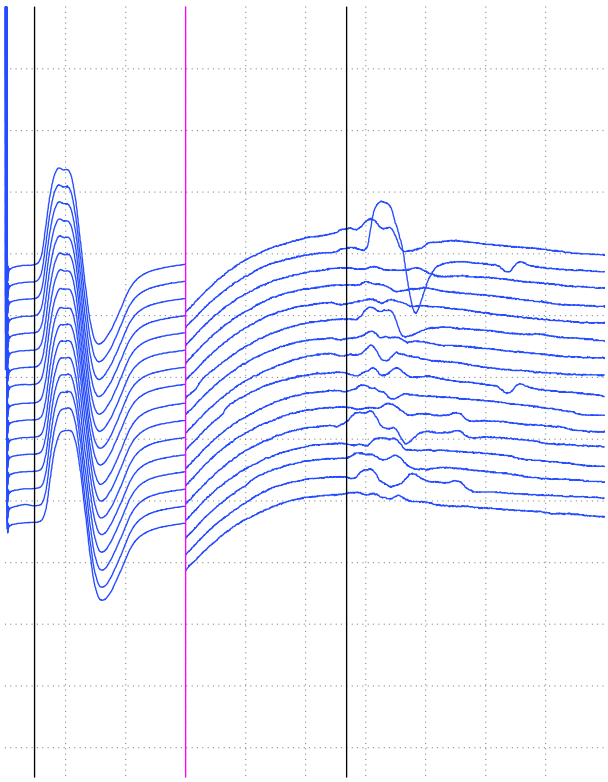


**Right Ulnaris**

Wrist-ADM

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

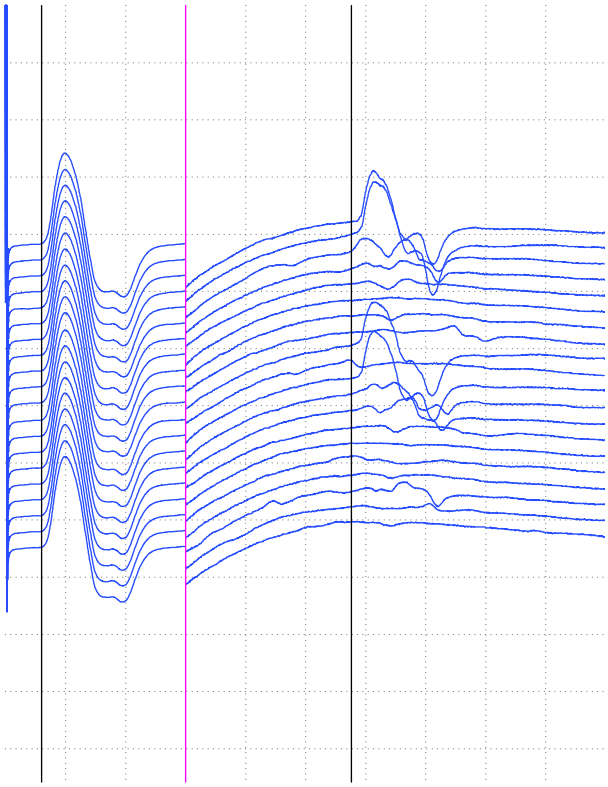


**Right Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

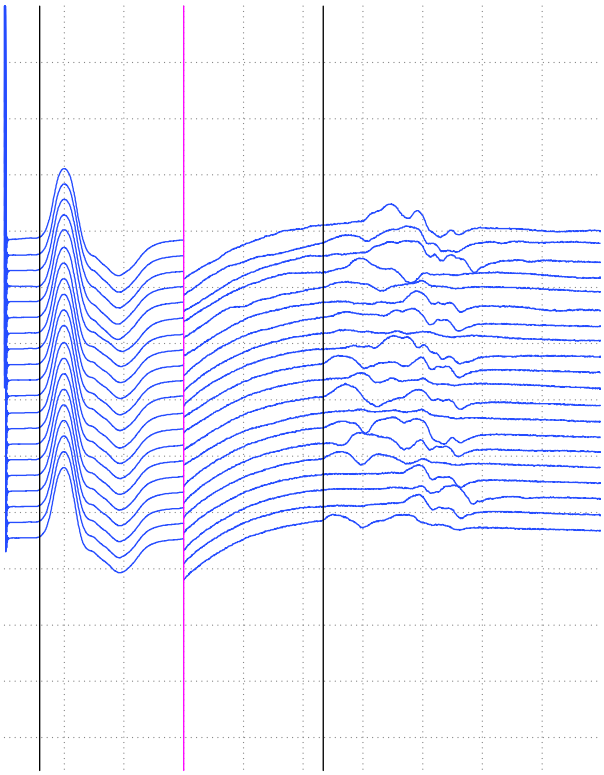


**Left Medianus**

Wrist-APB

M:5mV/D 5ms/D

F:0.5mV/D 5ms/D

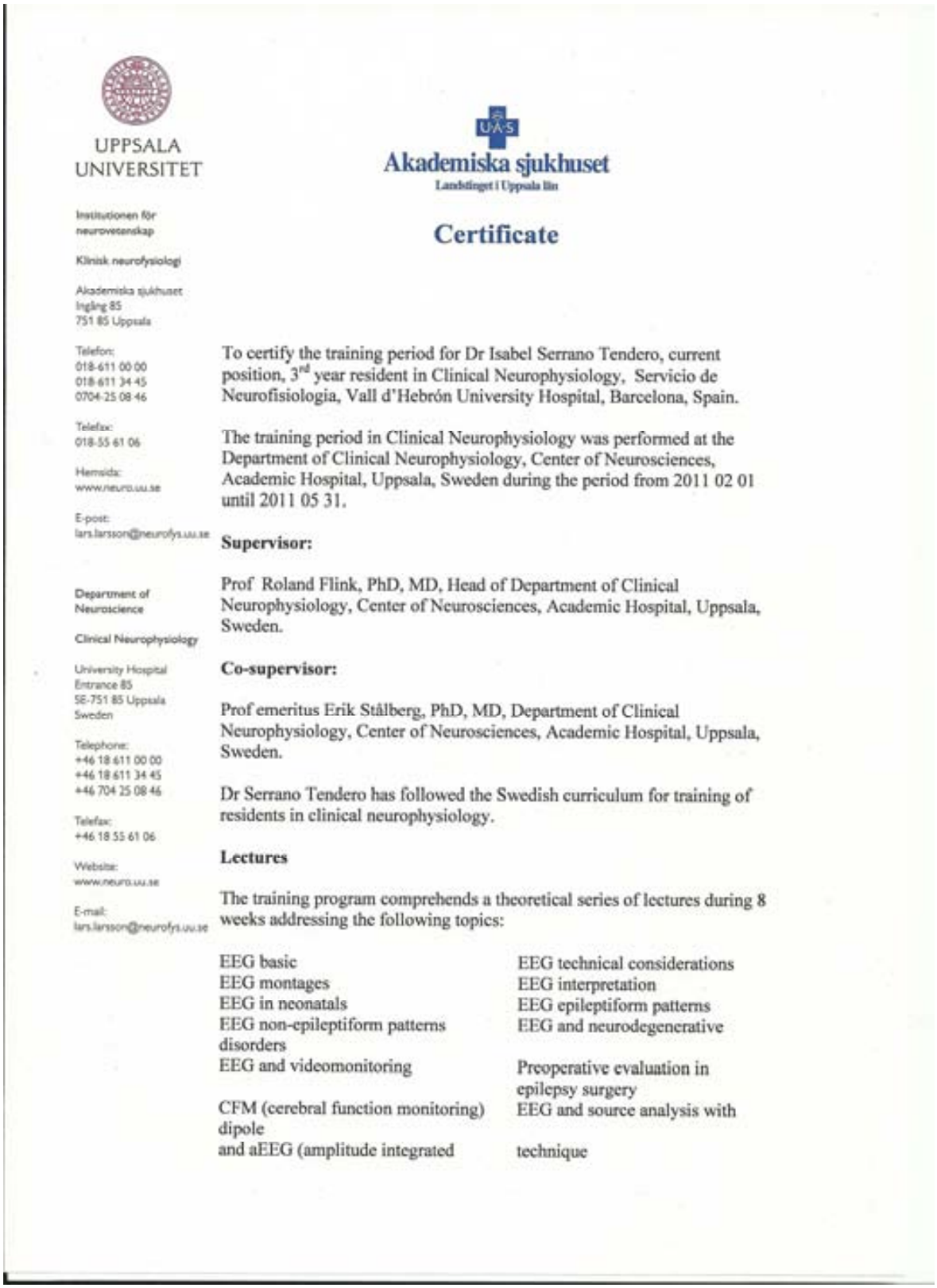


# 12. Appendix V : TRAINING PERIOD AND DIRECTION

## 12.1. AKADEMISKA SJUKHUSET / UNIVERSITY HOSPITAL (UPPSALA, SWEDEN)

## 12.2. DOCTORAL THESIS REPORT FORM: CERTIFICATE OF DIRECTION

## 12.1. AKADEMISKA SJUKHUSET / UNIVERSITY HOSPITAL (UPPSALA, SWEDEN)



UPPSALA UNIVERSITET

Institutionen för neurovetenskap

Klinisk neurofysiologi

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751 85 Uppsala

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018-611 34 45
0704-25 08 46

Telefax:
018-55 61 06

Hemsida:
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E-post:
lars.larsson@neurofys.uu.se

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Clinical Neurophysiology

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Akademiska sjukhuset
Landstinget i Uppsala län

# Certificate

To certify the training period for Dr Isabel Serrano Tendero, current position, 3rd year resident in Clinical Neurophysiology, Servicio de Neurofisiologia, Vall d'Hebrón University Hospital, Barcelona, Spain.

The training period in Clinical Neurophysiology was performed at the Department of Clinical Neurophysiology, Center of Neurosciences, Academic Hospital, Uppsala, Sweden during the period from 2011 02 01 until 2011 05 31.

**Supervisor:**

Prof Roland Flink, PhD, MD, Head of Department of Clinical Neurophysiology, Center of Neurosciences, Academic Hospital, Uppsala, Sweden.

**Co-supervisor:**

Prof emeritus Erik Stålberg, PhD, MD, Department of Clinical Neurophysiology, Center of Neurosciences, Academic Hospital, Uppsala, Sweden.

Dr Serrano Tendero has followed the Swedish curriculum for training of residents in clinical neurophysiology.

**Lectures**

The training program comprehends a theoretical series of lectures during 8 weeks addressing the following topics:

EEG basic
EEG montages
EEG in neonatals
EEG non-epileptiform patterns
EEG and videomonitoring

CFM (cerebral function monitoring)
and aEEG (amplitude integrated

EEG technical considerations
EEG interpretation
EEG epileptiform patterns
EEG and neurodegenerative disorders

Preoperative evaluation in epilepsy surgery
EEG and source analysis with dipole technique

EEG)
Ambulatory EEG
Basic neurography
F latencies, late components
QEMG
Macro EMG
Single fiber EMG
Intraoperative monitoring
Plexus lesions
Polyneuropathies
Motor neuron diseases
EMG in myopathies and myotonia
Autonomic testing
measurements
Clinical neurophysiology in evaluation of chronic pain patients
Motor and sensor neurography
Basic EMG
Motor unit analysis
Post polio syndrome
Evoked potentials
Entrapments
Rizopathies
AIDP, CIDP
Myastenia gravis
Critical illness
Quantitative sensibility

*Senior lecturers:*
Prof em Erik Stålberg
Prof Lars Larsson
Ass prof Tomas Winkler
Senior consultant Hans Axelson
Prof Roland Flink
Ass prof Karin Edebol Eeg-Olofsson
Senior consultant Arne Sandberg

Dr Serrano Tendero has participated in the clinical conferences discussing patient investigations and presenting her own cases. These conferences are held on a daily, weekly and monthly basis.

- Internal conferences (Mon, Tue and Friday) 3 x 0,5 hrs / week
- Conference with neurologists 0,5 hrs / week
- Conference with pediatric neurologists 1 hrs / week
- Epilepsy surgery conference 1 hrs / week
- Epilepsy surgery conference, consulting doctors
- from Karolinska Hospital, Stockholm 3 hrs / month
- Conference with hand surgeons 1 hrs / month
- CME (continous medical education) in the department 1 hrs / week

**Autonomous work**

Dr Serrano Tendero has analysed routine EEG . The EEG analysis has been summarized in clinical reports in Swedish by dr Serrano Tendero. During the period dr Serrano Tendero has analyzed 64 recordings including EEG with video, hyperventilation and photic stimulation. Some of the recordings were acute EEG performed in the intensive care unit.

In the diagnostic routines of peripheral nervous system dr Serrano Tendero has analyzed and reported 26 neurographies including carpal

tunnel diagnosis, polyneuropathies and autonomic tests such as RR intervall.

Dr Serrano Tendero has worked with and masters the following recording systems:

- Nervus™ - digital EEG system
- Keypoint™ - digital system for neurography and electromyography

Dr Serrano Tendero has worked with the following administrative systems:

- Cosmic™ - digital system for patient charts
- Remisse™ - digital system for handling referrals and reports

Apart from her autonomous work she has participated under supervision in the following investigations:

- EMG recordings in patients
- SFEMG (single fiber EMG) recordings during voluntary contraction and with electrical stimulation
- Navigated transcranial magnetic stimulation in preoperative evaluation of patients with cerebral tumours
- Muscle biopsies
- Technical support of medical equipment during the supervison of our chief engineer Peo Fällmar
- Attending EMG clinics together with senior consultant at our satellite laboratories, prof em Erik Stålberg and assistant prof Karin Edebol Eeg-Olofsson
- Attended the international course: " Training Course in EMG and Neurography – Clinical Neurophysiology of the Peripheral Nervous System", May 23-27, 2011 and during the demonstrations she has been assisting the faculty.

**Scientific projects**

Dr Serrano Tendero has participated in a study of late CMAP responses after peripheral nerve stimulation:
"Usefulness of assessing repeater F-waves in routine studies". E Chroni, I Serrano Tendero, A Rostedt Punga, E. Stålberg. Muscle & Nerve 2011, submitted manuscript.

Furthermore she is currently working on a study entitled:
"Diagnostic yield of sphenoidal electrodes in EEG recordings in the diagnosis of epilepsy", under the supervision of prof Roland Flink.

**Final impression**

Dr Serrano Tendero has performed an excellent achievement during her stay at the department. She has enhanced her basic knowledge of clinical neurophysiology and has on her own made patient investigations following our strategies, analysed the recordings and made the final reports.

Dr Serrano Tendero is very receptive and most efficient in her way to work keeping a very tidy office. She handles stress well and is also able to keep to the strategy in the investigations even under a tight time schedule. Hence, we have been able to put her on a work load that exceeds what we normally do with residents.

She has my unconditional admiration for the way she has accomplished her training period in Uppsala. Apart from her excellent knowledge, she has a most pleasant behaviour towards both patients and staff and I can only give her the best recommendations and congratulations in her future career

Uppsala 30th of May 2011

Roland Flink
Prof PhD MD, Head of the Dept of Clinical Neurophysiology
Center of Neurosciences
Academic Hospital
Uppsala Sweden

Inst. för Neurovetenskap
Klinisk neurofysiologi
Akademiska sjukhuset
751 85 Uppsala

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

## 12.2. DOCTORAL THESIS REPORT FORM: CERTIFICATE OF DIRECTION

UAB
Universitat Autònoma de Barcelona

**Ph.D. THESIS - CERTIFICATE OF DIRECTION**

**Doctors Josep Maria Espadaler Gamissans, Associate Professor, and Jose Alvarez-Sabin, Full Professor at the Autonomous University of Barcelona, in our capacity as Director and Tutor of this thesis,**

**DECLARE:**

**That the work entitled: "DIAGNOSTIC ROLE OF REPEATER F-WAVES IN CARPAL TUNNEL SYNDROME WITH SUBCLINICAL RADICULOPATHY", developed by Isabel Asunción Serrano-Tendero for obtaining the degree of Doctor of Philosophy (Ph.D.), has been performed under our direction and supervision, and meets the requirements to qualify for the European Doctorate Mention.**

**Signatures:**

**Barcelona, October 28, 2013**

UAB
Universitat Autònoma de Barcelona

## CERTIFICAT DE DIRECCIÓ DE TESI DOCTORAL

**Els Doctors Josep Maria Espadaler Gamissans i José Álvarez-Sabín, adscrits a la Universitat Autònoma de Barcelona, en la nostra condició de director i tutor de tesi,**

**DECLAREM:**

**Que el treball titulat: "DIAGNOSTIC ROLE OF REPEATER F-WAVES IN CARPAL TUNNEL SYNDROME WITH SUBCLINICAL RADICULOPATHY", que presenta Isabel Asunción Serrano-Tendero per a l'obtenció del títol de Doctor/a, s'ha realitzat sota la nostra direcció i tutela, i compleix els requisits per poder optar a la Menció Doctor Europeu.**

**I perquè així consti i tingui els efectes oportuns, signem el present document.**

**Signatures:**

**Barcelona, 28 octubre 2013**

UAB
Universitat Autònoma de Barcelona

## CERTIFICADO DE DIRECCIÓN DE TESIS DOCTORAL

**Los Doctores Don Josep Maria Espadaler Gamissans y Don José Álvarez-Sabín, adscritos a la Universidad Autónoma de Barcelona, en nuestra condición de Director y Tutor de tesis,**

**DECLARAMOS:**

**Que el trabajo titulado: "DIAGNOSTIC ROLE OF REPEATER F-WAVES IN CARPAL TUNNEL SYNDROME WITH SUBCLINICAL RADICULOPATHY", que presenta Doña Isabel Asunción Serrano-Tendero para la obtención del título de Doctor/a, se ha realizado bajo nuestra dirección y tutela, y cumple los requisitos para poder optar a la Mención Doctor Europeo.**

**Y para que así conste y tenga los efectos oportunos, firmamos el presente documento.**

**Firmas:**

**Barcelona, 28 de octubre de 2013**