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# 神經鬆動術對腕隧道症候群患者正中神經機械性特質與臨床症狀之影響

# Effect of median nerve mobilization in subjects with carpal tunnel syndrome: nerve mechanical properties and clinical symptoms

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本論文係黃建穎君（學號 R01428013）在國立臺灣大學物理治療學系研究所完成之碩士學位論文，於民國105年1月11日承下列考試委員審查通過及口試及格，特此證明

指導教授：林居正 （簽名）

口試委員：

系主任、所長 （簽名）

## 致謝

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# 中文摘要

**背景與目的：**正中神經的機械性特質被廣泛應用在解釋腕隧道症候群的成因及診斷依據，但鮮有文獻探討正中神經機械性特質對患者臨床症狀的影響。本研究目的為探討正中神經機械性特質和臨床症狀表現的關聯性，並探討神經鬆動術對此類患者之正中神經機械性特質的影響及臨床效果。**方法：**本研究共徵召 30 位腕隧道症候群患者，利用波士頓腕隧道症候群量表量測受試者臨床症狀程度，使用超音波影像量測正中神經橫切面截面積(cross-sectional area)、長寬比(aspect ratio)、圓周性(circularity)、平均灰階(mean grey scale)、橫向活動度(transverse mobility)，使用手持式肌張力測量儀(myotonometer)、痛覺計(algometry)量測腕隧道順應性(compliance)與壓痛閾值，並使用 VAS 紀錄疼痛程度。接著隨機分為治療組及控制組各 15 人，治療組接受肌筋膜放鬆術及正中神經鬆動術，控制組接受肌筋膜放鬆術及假神經鬆動術，於接受治療後再次量測受試者正中神經橫切面截面積(cross-sectional area)、長寬比(aspect ratio)、圓周性(circularity)、平均灰階(mean grey scale)、橫向活動度(transverse mobility)、腕隧道順應性(compliance)、壓痛閾值(pressure-pain thresholds)及疼痛程度變化。以皮爾森相關係數探討臨床症狀程度和正中神經機械性特質的相關聯性，由於兩組間年齡存在差距(治療組：29±12；控制組：41±10)，因此利用重複測量雙因子共變數分析(Two-way repeated measure ANCOVA)控制年齡並檢定接受治療後兩組在壓痛閾值與疼痛程度的變化，接著利用重複測量單因子共變數分析(One-way repeated measure ANCOVA)控制年齡後檢定在接受介入後兩組臨床症狀和正中神經機械性特質變化量上的差異，最後探討症狀改變與機械性特質變化的相關性。**結果：**皮爾森相關係數顯示，波士頓

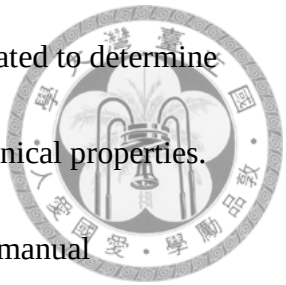
腕隧道症候群量表和正中神經截面積(r=.231)、平均灰階(r=-.316)存在低度相關性。重複測量雙因子共變數分析顯示患者在接受介入後疼痛程度將下降(Time effect, p<.0005, 治療組：4.6±1.1→1.9±1.1；控制組：5.2±0.8→2.8±1.5)，但兩組間沒有顯著差異，壓痛閾值則出現上升趨勢(治療組：2.9±2.3→3.0±2.2；控制組：1.5±0.5→1.7±0.6)，但統計上皆未達顯著差異。重複因子測量共變數分析結果顯示正中神經橫向活動度在接受神經鬆動術後有較大的改變(控制組:4%;對照組:34%, p<.0005)，其他正中神經機械性特質改變量在兩組間沒有顯著差異。在接受神經鬆動術的組別，正中神經橫向活動度和壓痛閾值的上升僅有低度相關(r=.162)。**結論：**腕隧道症候群患者的正中神經機械性特質與臨床症狀存在相關性,肌筋膜放鬆術合併正中神經鬆動術可以增加正中神經橫向活動度並降低疼痛程度，但臨床症狀改善與神經機械性特質轉變的機制尚需進一步研究。

關鍵字：神經鬆動術、腕隧道症候群、機械性特質、超音波影像

# ABSTRACT

**Background and Purpose**：Carpal tunnel syndrome (CTS) is one of the most common compression neuropathy in clinical practice. The compression of median nerve within carpal tunnel can result in sensorimotor dysfunction and distortion in nerve morphology, physiology and mechanical properties. Clinically, nerve mobilization technique is believed to relief the clinical symptoms and alter the compliance, circulation of nerve itself as well as the surrounding soft tissue in respond to mechanical stress. The first purpose of the study was to investigate whether the severity of carpal tunnel syndrome can be predicted by the features of median nerve mechanical properties. Second, we want to investigate the effect of manual intervention in patients with carpal tunnel syndrome. The clinical effects like current pain intensity, pressure pain threshold and mechanical properties of median nerve like cross-sectional area, aspect ratio, circularity, transverse mobility and, compliance of carpal tunnel were investigated. Third, the correlation between changes in clinical symptoms and mechanical properties after mobilization were investigated.

**Methods**：This was a randomized control trial with 30 subjects randomized assigned to 2 groups with and without nerve mobilization treatment. All subjects were tested on the mechanical properties of median nerve by Sonography imagine system and clinical symptoms before and after the median nerve mobilization and sham



mobilization. Separated Pearson correlation coefficients were calculated to determine the relationships between severities of clinical symptoms and mechanical properties. Paired sample t-test were performed to examine the difference after manual intervention. Separated ANCOVA were used to test the group effects (mobilization versus sham-mobilization) for measures of clinical symptoms and mechanical properties with control the influence of age between groups. Correlation coefficients between changes in clinical symptoms and mechanical properties were conducted. Alpha level was set at 0.05 and adjusted accordingly to achieve significant difference. Results：Low correlations were found between clinical symptoms (Boston carpal tunnel syndrome questionnaire), and nerve properties (cross sectional area, r=.231; mean grey scale, r=-.316). After manual intervention (myofascial release with and without nerve mobilization), significant change were presented in pain (pre: 4.9±1→post: 2.4±1, p<.0005), compliance of carpal tunnel (pre: 4.9±1.0→post: 5.4±1.0, p<.0005), cross sectional area (pre: 11.0±3.2→post: 11.8±4.1, p=.007), circularity (pre: 0.57±0.09→post: 0.59±0.08, p=.029), mean grey scale (pre: 42.14±16.67→post: 45.34±18.12, p=.038) and transverse mobility (pre: 2.1±1.0→post: 2.4±1.3, p=.012). Results of ANCOVA indicated that there were significant difference in median nerve mechanical properties between groups. Transverse mobility of median nerve increased 34% in mobilization group compared

to 4% in sham-mobilization group ($p<.0005$). The correlations, however, between changes in clinical symptoms and mechanical properties were less than 0.17.

Conclusion：In patients with carpal tunnel syndrome, the clinical severities were correlated with the enlarged cross section area and diminished echodensity. After receiving manual intervention, both clinical symptoms and mechanical properties of median nerve can be altered while the transverse mobility of median nerve only improved in nerve mobilization group. However, the changes in clinical symptoms cannot be explained by the changes in mechanical properties alone. In order to further understand the behind mechanism of symptom relief, long term follow-up was suggested.

Key words：Nerve mobilization, carpal tunnel syndrome, mechanical properties, ultrasound

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# Nature of the Study

## Background

Carpal tunnel syndrome (CTS) is one of the most common entrapment neuropathy in clinical practice with the prevalence of 2.7-5.8% in general population [1, 2]. Patients' median nerve is suffered from long term compression which attributed to increased pressure within the carpal tunnel [3]. The typical symptoms in patients with CTS include pain over wrists and hands which can sometimes radiate to forearm, paresthesia (numbness) in the thumb, index finger, middle finger and radial half of the ring finger [4]. Thenar muscle weakness is also noted in those with advanced CTS.

Mechanical properties of median nerve may play a role in management of carpal tunnel syndrome. Experimental evidence suggests that anatomic compression in the carpal tunnel can injure the nerve directly, impair axonal transport, or compress vessels in the perineurium and cause median nerve ischemia [5]. The edema, thickening of vessel walls within the endoneurium and perineurium, noninflammatory synovial fibrosis, vascular proliferation, fibrosis, myelin thinning, nerve fiber degeneration and regeneration can occur [6, 7]. CTS is an entrapment syndrome which may cause the morphological changes in the median nerve. Deformity in the nerve physiology and morphology may reflect relative thickening of the nerve

beneath the transverse carpal tunnel ligament and increasing stiffness. The associations between deformity of physiological function, morphology, mechanical properties of median nerve, and clinical symptoms have not been investigated yet. Theoretically, median nerve hardness and enlargement may be affected by possible fibrosis or edema secondary to compression and reflect the severity of CTS.

Nerve tissues are under combination of strain, compression and gliding in response to body movements [8, 9]. With regards to biomechanical stresses placed on a nerve as an individual assumes a posture or movement, the nerve follows the path of least resistance to disperse the mechanical stress and maintain normal nerve function [10, 11]. In patients with carpal tunnel syndrome, stiffer and enlarged median nerve is constricted in the narrow bony tunnel along with reduction in neural excursion and consistent compression [12, 13]. The reduction in neural excursion and distortion in tissue stiffness would interfere nerve's potential to disperse pressure and imply additional stress on local segments as "friction fibrosis" descripted by Sunderland in 1976 [9, 11, 12]. As a result, nerve tissue loses its ability to corporate with mechanical stress and maintain its normal function/blood supply which developed into ischemia or hypoxia and result in production of the symptoms and limitation of movement [14].

Mechanical properties of median nerve such as deformation under muscle contraction, mobility in response to joint motion could be measured by high-

resolution sonography which may reveal the dynamic interaction between flexor tendons and median nerve within the narrow carpal tunnel [15-17]. Through the conventional B-mode sonography, mechanical properties of median nerve can be descripted by morphology include circularity, aspect ratio, cross-sectional area and the movement of median nerve can be expressed as radial-ulnar, palmar-dorsal direction under transverse view of sonogram.

Treatment of carpal tunnel syndrome includes surgical release, neural/tendon gliding exercise, nerve mobilization, cortical injection, therapeutic ultrasound and splinting [18-21]. Treatment option depends on the severity of the disease and proposed rationales. Generally, the surgical intervention is advocated in severe case who are failed in conservative treatment and the conservative treatments are suitable for patients with mild to moderate syndrome [22]. The pathological conditions of the median nerve in both physiological and biomechanical aspects are proposed to explain the symptoms and signs of carpal tunnel syndrome [3, 12, 23-26]. Physiologically, inflammation, trophic change and formation of adhesion/intraneural fibrosis have been observed in these patients. Biomechanically, enlargement of cross sectional area/aspect ratio, decreasing of the excursion/circularity, and increasing stiffness of median nerve have be presented. Thus, different conservative treatments had been proposed to manage the condition like therapeutic ultrasound/cortical

injection for decreasing inflammation related symptoms [20, 27], nerve mobilization for releasing adhesion, intraneural fibrosis, intraneural swelling and stiffness [25, 28], splinting for avoiding inappropriate stress or strain to the nerve [29]. Park et al. had serially evaluated the stiffness, conduction velocity and cross sectional area of the median nerve in a case with carpal tunnel syndrome after conservative treatment [30]. The distortion in nerve cross sectional area, stiffness and conduction velocity was gradually restored along with symptom relieved which indicated conservative treatment could both affect mechanical properties, physiological function and clinical symptoms of median nerve.

Within above mentioned conservative treatments, only nerve mobilization targeting on the distorted stiffness, intraneural swelling and restricted motion of the affected nerve at the same time. Median nerve mobilization is suggested in management of CTS especially in patients with distortion in median nerve stiffness by implying longitudinal tensile force on median nerve from wrist to proximal nerve roots [25, 31]. The concept of nerve mobilization is to position the extremities passively in different positions to imply mechanical stress on target nerve segments. Through repetitive lengthening/shortening of the nerve, neural excursion and elongation are expected to restore the natural elasticity and intraneural circulation [32, 33]. Grewel et al. suggested that nerve tissues are viscoelastic bodies and the creep

phenomena could be observed when the tissue is under external stress [34]. In other words, the nerve tissue might deform in a linear trend when encounter an external tensile force and these properties indicate the stiffness of nerve tissue can be managed by manual stretch or mobilization to restore the appropriate stiffness [35-37].

**Statement of the problem**

In clinical practice, nerve mobilization is one of the most common manual therapy in management of carpal tunnel syndrome. Previous studies had been published to investigate the clinical benefits for nerve mobilization in treatment of carpal tunnel syndrome [19, 38, 39]. Theoretically, nerve mobilization target on the impaired neural excursion, intraneural circulation and mechanical properties. To author's knowledge, most studies only apply the clinical outcomes such as pain, numbness, sensory recovery and ADL related questionnaire to investigate the effect of mobilization while no study investigates the possible mechanism behind of symptom relief. Generally, the median nerve of CTS patients would present enlarged cross sectional area and stiffness, reduced aspect ratio and circularity, reduced in neural excursion, reduced echo-density under transverse sonogram and associated with clinical signs. Moderate correlations can be expected between the improvements of clinical symptom and change of median nerve mechanical properties. In order to understand the underlying mechanism, the effect of nerve mobilization in subjects

with carpal tunnel syndrome were investigated based on changes of median nerve mechanical properties in this study.

**Purposes of the study**

The purposes of this study were (1) to investigate whether the severity of CTS can be predicted by the features of median nerve mechanical properties; (2) to investigate the effect of manual intervention in subjects with CTS. The clinical effects like current pain intensity, pressure pain threshold and median nerve mechanical characteristics like cross-sectional area, stiffness, compliance of carpal tunnel were investigated; (3) to investigate the correlations between changes in clinical severity and median nerve mechanical properties after nerve mobilization.

**Hypotheses**

Hypotheses of this study are in the following. For the first purpose, the null hypothesis was that the severity of CTS cannot be predicted by mechanical properties of median nerve. The alternative hypothesis was that the severity of CTS can be predicted by mechanical properties of median nerve. For the second purpose, the null hypothesis was that there were no differences in clinical symptoms or median nerve mechanical characteristics after manual intervention. The alternative hypothesis was that there were differences in clinical symptoms or median nerve mechanical

characteristics after manual intervention. For the third purpose, the null hypothesis was that the correlation between changes in clinical symptoms and median nerve mechanical properties were lower than moderate. The alternative hypothesis was that the correlation between changes in clinical symptoms and median nerve mechanical properties were higher than moderate.

# Literature review

## Carpal tunnel syndrome

Carpal tunnel syndrome is one of the most common entrapment neuropathy in clinical practice with the prevalence of 2.7-5.8% in general population [1, 2]. Previous study had suggested that in certain population such as worker, motorcyclist, women and pregnancy the prevalence of carpal tunnel syndrome could be exaggerate to 24% or higher due to exposure under certain risk factors [40-42]. Patients' median nerve were suffered from long term compression which attributed to increased pressure within the carpal tunnel[3].The most typical symptom in patients with carpal tunnel syndromes include pain over wrist and hands which can sometimes radiate to forearm, paresthesia (numbness) in the thumb, index finger, middle finger and radial half of the ring finger [4]. Thenar muscle weakness has been found to occur in those with advanced CTS. Besides, distortion in nerve morphology and mechanical properties are also been observed which may play a role in detecting progress or diagnosis of the carpal tunnel syndrome [24, 43]. Additionally, carpal tunnel syndrome also caused the workdays lost for mean 84 days/year and a heavy medial cost for $4,941.7 per case [44].

The treatment of carpal tunnel syndrome includes surgical release, exercise,

mobilization, cortical injection, therapeutic ultrasound and splinting [18-21]. Each treatment had its own theoretical basis, for example, the currently standard surgical procedure of carpal tunnel syndrome are open carpal tunnel release (OCTR) with a long curvilinear palmar incision [45]. Though there are many other modification of surgical procedure, the core concept is still aim to reduce the pressure within carpal tunnel through release surrounding tissue [21, 46]. In exercise intervention, for instance, the tendon or nerve-gliding exercise are believed to change the dynamic interaction between tendons and median nerve within the carpal tunnel through maximizing the relative excursion [26, 47]. Splinting is advocated in patients who developed carpal tunnel syndrome overuse, through maintaining the wrist in a neutral position, the wrist could rest under the lowest intra-canal pressure and therefore the least pressure on the median nerve[48].

Generally, the surgical intervention is advocated in severe case who are failed in conservative treatment and the conservative treatments are suit for patients with mild to moderate syndrome or who are waiting for the surgery [22]. The effect of the mobilization intervention was reviewed by Cochrane in 2012, the result has suggested the limited and very low quality evidence of benefit for all of a diverse collection of mobilization interventions for CTS [19]. In compared with no treatment, patients with carpal tunnel syndrome showed relief of symptoms after received mobilization and no

any improvements was observed in patients with no treatment [39, 49]. Though it seems not so effective, the feasibility of the mobilization still make it as a satisfactory approach in clinical practice. In the other hand, nerve mobilization is the only approach to put an emphasis on the mechanical properties of the nerve itself which may be neglected in the past. The effect of nerve mobilization maybe response better in patients with carpal tunnel syndrome and showed distortion in mechanical properties.

**Upper limb tension test and nerve mobilization**

The concepts of nerve mobilization are the application of upper limb tension test (ULTT) proposed by Elvey et al. on 1985. Through the observation of peripheral nervous system continuum on cadaver, Elvey suggest that may have the potential to apply mechanical loads to the nervous system by changing the dimensions of the targeted nerve bed through extremities motion to test the nerve tension. The application of upper limb tension test as a treatment was proposed by Kaltenbon in 1991 to treatment abnormal nerve tension and restore normal neurodynamics. There are two main kinds of nerve mobilization which is named sliders and tensioners. Sliders are aimed to produce movement in nerve without generating much tension or compression. And may have the potential to reduce pain and improve excursion. Tensioners are used to activate viscoelastic, movement related and physiological

functions in the nervous system. Tension is applied to the neural tissues by increasing the distance between each end of the nerve tract. That is, elongating the telescope in which the nerves are contained and attached at each end. A key feature of the tensioner is that, in addition to the joints being moved, the innervated tissue is used to apply tension to the nerve [26, 32].

There are three standard positions to separately target the median, ulnar and radial nerve in the upper limb. The median nerve was under most tension in the following combination of the movements：(1) Wrist extension/supination (2) elbow extension (3) Glenohumeral abduction (4) glenohumeral external rotation. The tension travelled through the distal part of median nerve to the proximal segments of brachial plexus [31]. In order to differentiate the affected nerve segments, the sequence of neurodynamics are suggested to be modified for individuals [50]. Zorn et al. had reported the difference of sequence would change that different sequences of a median nerve biased test (ULTT1) changed the distribution of sensory responses reported by asymptomatic participants. The potential explanation is that strain in a targeted nerve segment is believed to be greatest when the joint nearest that nerve segment is moved first in the neurodynamics test sequence [32, 51]. For example, ULTT1 may be more sensitive for detecting carpal tunnel syndrome if it is performed in a distal-to-proximal sequence where wrist extension is the first movement. Despite

the difference of sensory distribution, the expected larger strain and excursion nearest the first moved joint was not been observed in cadaver study[52]. In other words, the distal to proximal sequence of ULTT1 would not produce larger excursion and strain in the carpal tunnel than the proximal to distal sequence and this is in conflicting with the previous study. The possible reason may due to the impact of different ranges of joint motions during the tests rather than a specific effect from the order of movement. As a result, in this study we still choose the distal to proximal sequence to test the appearance of carpal tunnel syndrome since it's in a clinical setting and the in-vivo study.

Some people may doubt that it is hard to quantify the dosage of the nerve mobilization or the intensity of upper limb tension test. The dosage or the intensity of the mobilization and upper limb tension test may include many components, such as frequency, joint angle, tension of the end feel and the repetition times. Studies investigates the effect of exercise based self-mobilization usually quantified the dosage of nerve mobilization the by the repetition times and joint angle[53]. In studies to investigate the strain or excursion on the targeted nerve tissue which caused by nerve mobilization usually quantified the dosage of the nerve mobilization in the forms of joint angle [52, 54, 55]. In clinical trials to investigate the effect of nerve mobilization on symptom relief, the dosage of the nerve mobilization are mostly

decided by the therapist with limitation of the sets and duration of the mobilization, but is only based on author's suggestion or text book without providing the rationale [53, 56-59]. The aim of the tensioner of the nerve mobilization is to stimulate an improvement in the ability of neural tissue to withstand the tension and improve its viscoelastic behavior. Grewel et al. had suggested that the blood flow and the conduction velocity of the peripheral nerve would be compromised over a strain value over 6 % within short periods [34]. As a result, nerve mobilization should not be performed as a stretch and each movement is performed several times. The amplitude, duration and joint angel are determined through monitoring patient's response. Naturally, acceptable symptoms will be evoked during the mobilization and the therapist would only perceived small tension during the practice. There are no studies to support appropriate dosage in the application of nerve mobilization, which leaves it up to the clinician to determine these parameters.

Recently, Orman et al. had reported that in patients with carpal tunnel syndrome the stiffness of their median nerve are higher than normal control[23]. Since nerve mobilization are designed to improve the viscoelasticity of the targeted nerve, it may response better in patients showed problems in nerve mechanical properties.

## Basic anatomy of human nerve tissue

### Anatomical structure of peripheral nerve

The nervous system possesses a natural ability to move and withstand mechanical forces that are generated by daily movements. For the nervous system to move normally, it should be capable of executing three primary mechanical functions：(1) Withstand tension (2) slide in its container, and be (3) compressible (Figure 1-3) [32]。Above mentioned three biomechanical properties of nerve are contributed by its special multi-membrane structures. Perineurium, mesoneurium and epineurium serves the above three mechanical properties respectively (Figure 5). The perineurium is the primary guardian against excessive tension and is effectively the cabling in the peripheral nerve and densely packed connective tissue and forming each fascicle.

The perineurium possesses considerable longitudinal strength and elasticity which allows peripheral nerves to withstand approximately 18-22% strain before failure. It comprises 7 or 8 layers that are dense with fibroblast cells. The main function of perineuriun are (1) protect its contents the endoneurial tubes (2) provide a diffusion barrier to guard against foreign substances (3) provide resistance to external forces. Besides, the perineurium is the last connective tissue layer to break when a

nerve is subjected to extreme traction.

The mesoneurium allows the sliding of peripheral nerves in their nerve bed. In cadavers, the mesoneurium has been observed to be a thin multilayered membrane made of loose connective tissue that has distinct boundaries and behaves in a fashion similar to the synovial membrane around tendon.

The epineurium is the continuum of dura mater and connect to the end of the peripheral nerve which serves as a padding of the nerve to protect the axons from excessive compression. As an interfascicular connective tissue surrounding the secondary fascicles and forming the peripheral nerve trunks, it consists of finer and less densely packed connective tissue than the perineurium, a feature that gives the nerve spongy qualities and enables the nerve to spring back when pressure is removed. It also functioned as the path way of the blood vessels, consisted the vasa nervorum to maintain the microcirculation within the nerve tissue.

**Blood supply**

In macro observations, peripheral travelled with the parallel artery and viens and got the blood supply from its branch. If we observe in a more detail perspective such as under microscope, we could find that the blood supply of human nerve tissues are coming from the complex micro-vessels anastomoses between the epineurium and endoneurium. In the perineurium of nerve exist extensively plexus of capillaries

which is also serve as an important source of nerve's blood supply [8](Figure 4).

**Mechanical properties of nerve tissue**

The value of the above mentioned three biomechanical properties are to maintain the blood flow and prevent is from compromised under the mechanical stress associated with complex body movements [8]. In activities of daily living, the movements may bring some mechanical stress as well as tension, shearing and compression force to the nerve tissue pass through the moving joint. For instance, during the wrist extension the median nerve locate in the ventral sides of carpal tunnel is being stretched. And the flexor tendon in the narrow carpal tunnel may impinge the carpal tunnel and bring some compression force and transverse gliding to the nerve tissue (Figure 6) [9]. Owning to the simultaneously multiple mechanical stress occurred in the carpal tunnel, the within tunnel stress would increase along with changed wrist flexion angle.

Previous studies had shown the viscoelasticity properties of nerve segments (Figures 7)[34]. The slope of stress strain curve indicated the stiffness of nerve tissue. Once there are increasing in the stiffness, may reduce the compliance of the nerve. As a viscoelastic material, nerve tissue have its own stress-relaxation curve (Figure 8) which may provide a possible solution to correct the abnormal nerve tension.

In brief summary, when nerve tissue encountered mechanical stress, in order to

reduce interfere of blood flow the nerve tissue would deform and gliding between the surrounding tissue forming a pressure gradients to redistribute pressure from high to low area. However, when the mechanical properties of the nerve tissue impaired (such as increased in stiffness) and it travelled along narrow osteo-tunnel (i.e. carpal tunnel, cubital tunnel, cervical foramen etc.), the nerve are surrounded by the stiff environments and limit its potential to redistribute the abnormal stress. As a consequence, increase the risk of being compression-induced neuropathy.

**Entrapment neuropathy**

Animal studies have shown that chronic nerve compression initially leads to nerve ischemia and oedema at the site of compression due to the compromised circulation. Immediately after nerve being compression, the endoneural fluid pressure elevated and arrest the endoneural micro-circulation[60]. Along with the consistent compression, the nerve segments would enlarge at the site of compression[61]. The clear mechanisms of nerve enlargement which is observed in chronic entrapment neuropathy are not clear. However, the enlargement of nerve segments may increase the risk of secondary impingement when nerve travelled through the tight osteo-tunnel.

As the compression condition is not solved, the nerve tissue would experience further morphological changes and neovascularization [43]. The enlargements of the

nerve segments cross sectional area and the appearance of neovascularization would associate with severe symptoms. The reason of the changed morphological appearance may be a compensatory approach to the arrest blood flow in patients with chronic entrapment neuropathy. Unfortunately, these neovascularization may not successful to compensate the chronic dysfunction of nerve tissue (Figure 9).

**Ultrasonography of median nerve**

**Static ultrasonography**

Ultrasonography had been applied in observation of median nerve changes and the flexor retinaculum in patients with carpal tunnel syndrome since 1990s. The patients is usually imaged in a sitting position with the wrist resting on a hard surface in a supinated position [12, 15, 62, 63]. The median nerve is echogenic when the beam is perpendicular to the surface. The fibrotic epineurium is seen as a thin hyperechoic rim surrounding the nerve. Increased of cross-sectional area of the median nerve is presented at the level of distal radio-ulnar, pisiform and the hook of hamate. The nerve will be most easily identified in the level of pisiform as a result of its superficial location. In patients with carpal tunnel, reported findings include increased cross-sectional area of the median nerve, flattening of the nerve under flexor retinaculum and bowing of the flexor retinaculum [64]. An additional findings

is an abrupt contour change of the median nerve when visualized longitudinally. This finding is found in severe cases [65].

The increased cross-sectional area and flattening of nerve can be measured by manual tracking at the border of the hypoechoic fascicles and the hyperechoic perineurium. This method improves accuracy because the border of the perineurium may be difficult to distinguish from the adjacent perineural fat, which is also hyperechoic. Measurement of cross-sectional area through ultrasonography had shown its value for the early detection and diagnosis of carpal tunnel syndrome [24, 66-68]. Previous studies had concluded that when a threshold value of 10mm$^2$ was used at the level of the pisiform, results included 89% sensitivity and 83% specificity for carpal tunnel syndrome [67, 68]. The enlarged of cross-sectional area in patients with carpal tunnel syndrome are highly correlated with the severity syndrome which is improved by nerve conduction [69].

In patients with CTS, changes in median nerve echotexture consistent with loss of the fascicular pattern due to intraneural edema have been considered signs of pathology under transverse view ultrasonography [70]. Evidence of nerve swelling in patients with CTS also noted in MRI study, the T2 signal value are higher in proximal and distal carpal tunnel, indicated the presence of intraneural swelling. At the same time, there are low correlation between enlarged CSA and hyperintense T2 signal

[71]. The fascicular pattern of peripheral nerves based on the ratio between fascicles, which are hypoechoic and total number of pixels. The median nerve would become relatively hypoechoic than normal control under transverse view of ultrasonography. Tagliafico et al. had presented that the echo-density of median nerve is capable of discriminating between normal and pathologic nerves of patients affected by CTS [72]. Moreover, the results had suggested that the value of echo-density is correlated with severity of CTS.

Besides the value in early detection or diagnosis of carpal tunnel, the altered median nerve configures or signal intensity had been applied as an outcome measure in management of carpal tunnel syndrome. Cudlip et al. had presented that 3 months after carpal tunnel decompression surgery, the cross-sectional area, flattening ratio and T2 signal intensity toward that of controls was seen in the median nerve in the carpal tunnel [73]. Similar results had been presented by Abicalaf et al. in 2013, the cross-sectional area of median nerve tends to increase 4 weeks after surgery for carpal tunnel syndrome. Then, the cross-sectional area were gradually reduced in 4, 8, 12, 96 weeks after transverse carpal ligament [74]. In respect of conservative treatment, Schmid et al. had presented that following 1 week of intervention but not immediately after 10 min of splinting or exercise the signal intensity of median nerve reduced 7.8 ~ 16% at level of distal radio-ulnar joint ($p < 0.03$). This was accompanied by a mild

improvement in symptoms and function ($p < 0.004$) [75].

**Dynamic ultrasonography**

Reduced longitudinal and transverse gliding of the median nerve at the wrist has been demonstrated in patients with CTS [15, 63, 76, 77]. The three-dimensional movement of the tendons and nerve in response to upper quarter motion had been detailed described in previous studies. As a results, Coppieters et al. had advocated neurodynamic approach such as nerve gliding exercise to restore the restricted motion of median nerve [52, 54, 55]. Although these findings may distinguish patients with carpal tunnel syndrome from normal subjects, there have been no attempts to utilize the changes in nerve gliding in the carpal tunnel as an outcome in management of CTS.

**Boston carpal tunnel questionnaire**

The BCTQ evaluates two domains of CTS, namely ‘symptoms’, assessed with an 11-item scale (pain, paresthesia, numbness, weakness, and nocturnal symptoms) and ‘functional status’ assessed with an eight-item scale (writing, buttoning, holding, ripping, bathing, dressing) [78]. The questionnaire was presented in multiple-choice format, and scores were assigned from 1 point (mildest) to 5 points (most severe). No response to a certain question was given 0 points. Each score is calculated as the mean

of the responses of the individual items. Patients were divided into five groups according to their mean score: extreme (4.1–5 points), severe (3.1–4 points), moderate (2.1–3 points), mild (1.1–2 points) and minimal (0.1–1 point). Previous study had suggested moderate to high correlation between BCTQS and patient symptoms (r = 0.51), clinical motor tests (r = 0.38-0.87), patient-based questionnaire (r = 0.71-0.9), quality of life (r = 0.41-0.5) [79].

# Methods

## Study design

This study was a randomized controlled trial designed to investigate the effect on median nerve mobilization in subjects with carpal tunnel syndrome. Specifically, mechanical prosperities of median nerve was investigated by ultrasonography.

## Participants

### Sample size estimation

Sample size estimate was calculated by G*power 3.1.7 package. In order to detect the effect of mobilization on subjects with CTS, sample size estimation was based on change in cross-sectional area (effect size = 0.26), pressure-pain thresholds (effect size = 0.20), compliance of carpal tunnel (effect size = 2), aspect ratio (effect size = 0.34), circularity (effect size = 0.23), echo-density (effect size = 0.75) and transverse mobility (effect size = 0.265) with mobilization by using effect sizes from our pilot study (Table 1). A sample of 15 subjects for each group can provide greater than 80% power to detect the effect of mobilization on median nerve mechanical properties in the proposed analysis of covariance (ANCOVA) model. Totally 30 subjects were recruited in this study.

**Inclusion criterion**

Subjects were included if (1) they were beyond the ages of 20 years and (2) had signs or symptoms associated with CTS based on the American Academy of Neurology clinical diagnostic criterion as defined by sensory (pain, paresthesia, swelling or sensory deficit) or motor changes (thenar muscle atrophy ,weakness or clumsiness of the hand) in the median nerve distribution [80] and (3) at least 2/4 clinical examinations for CTS should be positive. The clinical examinations include ULTT, Phalen's test, reverse Phalens' test and compression test. Additionally, participants were required to have a rating of their CTS pain intensity or symptom intensity of at least 4/10 on a numeric rating scale (range of 0 to 10, with 0 indicating no pain at all and 10 indicating the worst pain imaginable over the past 24 hours).

**Exclusion criterion**

Subjects were excluded from participation for the following reasons: acute trauma involving in the region of the wrist, brachial plexus injury, history of polyneuropathy and other conditions associated with increased incidence of carpal tunnel syndrome. Additionally, bifid median nerve detected by ultrasound images were excluded from analysis.

**Instrumentations**

An ultrasonographic instrument (Terason t3000 system, Teratech Corporation, MA, USA) with a 5.12 MHz, 38-mm linear transducer were used to obtain B-mode imagine of median nerve and contents of carpal tunnel. A hand-held Myotonometer (neurogenic technologies, INC.) were used to access the compliance of carpal tunnel. A hand-held pressure algometer (Force TEN$^{TM}$ FDX Compact digital force gage, Wagner Instruments.) were used to test the pressure-pain thresholds.

**Procedures**

The experimental procedure was illustrated in Figure 10. Participants were recruited from National Taiwan University Hospital and also through open advertisements. Subjects who meet the criterion of the study were included in the study. After appropriate explanation of the purpose and procedure of the study, patients were asked to sign the inform consent agreement. In patients with consentient, the following basic data were collected：(1) Age (2) Gender (3) Height (4) Weight (5) Involved sides (6) Symptom duration (7) Current pain intensity (8) Boston carpal tunnel questionnaire. After completing the basic information, subjects were sited in a comfortable position facing the sonographer with their arms resting on the knees (90 degree flexion) and their forearms supine. The forearm of the subjects

were rested on the knee and placed on a custom-made splint with the wrist maintain in neutral position and their fingers semi-flexed (Figure 11). The full course of median nerve in the carpal tunnel were assessed in longitudinal and transverse planes. The probe was held in vertical to avoid the artifact caused by angulation between nerve and probe. To avoid a compression effect of the transducer, the sonographer placed the transducer onto the skin surface with light contact using ample coupling gel and keep the transducer stationary during acquisitions. This is to make sure that no additional force is applied other than the weight of the probe.

The cross-sectional area of the median nerve were measured at the proximal inlet of the carpal tunnel using pisiform as landmark by manual tracing a continuous line within the hyperechogenicity boundary of the nerve under the transverse US images. At the same time, other sonography based outcome measurements include transverse mobility, echo-density, aspect ratio and circularity were calculated by Image J package and the contrast of sonography image were enhanced through adjustment of thresholds. Every sonography-based outcomes were measured three times, and the mean value had been used for further analysis.

The transverse mobility of median nerve were defined as the displacement of nerve centroid from full four fingers extension (0° at index, middle, ring and little finger joints) to full four fingers flexion (i.e., until each finger tips touched the palm)

which can be divided into palmar-dorsal and radial-ulnar direction. Before the data collection, participants were asked to practice the finger motions under examiner supervision. During the data collection, participants were asked to flex their fingers continuously at a pace of 3 seconds/cycle repeatedly. The full course of the finger motions were recorded as avi. file and the initial and final frame of the motion for the extension and flexion positions were chosen for analysis. The eco-density was defined as the average gray value within the selection area. The aspect ratio was defined as the major axis divided by the minor axis of minimum enclosing rectangle which can be used to describe the flattening of nerve. The higher value indicated more flattening of selected area. The circularity was calculated from following formula: Circularity = $4\pi \times Area/(Perimeter)^2$. Value equal to 1 indicated perfect circle in the selected area.

In mobilization group, participants were received myofascial release before median nerve mobilization. The myofascial release included the soft tissue manipulation of pronator teres, general kneading of forearm muscles and stretching of transverse carpal ligament [59]. Then, the mobilization procedure were followed the procedure presented by Shaclock in 2005. Patients were lying down with shoulder depression, shoulder abduction and external rotation to 90°, full elbow extension, forearm supination and extend wrist several times. Grade of treatment, amplitude of mobilization, and the progression of treatment were decided according to the

irritability and severity of the individual patient's symptoms [32, 57]. In the sham mobilization group, the patients would receive the same myofascial release as mobilization group. Then, the mobilization procedure were modified from the procedure presented by Bialosky et al. in 2009 with the emphasis on minimized anatomical stress across the median nerve [57]. Patients will lie down with no shoulder depression, shoulder abduction and shoulder external rotation to 45°, elbow full extension, forearm pronation and flex wrist with several time (Figure 12). Immediately after intervention, the mechanical properties of median nerve were measured again in the sitting position.

**Other Outcomes**

**Clinical Ratings of Pain Intensity**

Pain intensity were assessed for changes from pre-mobilization to post-mobilization using a 100-mm visual analogue scale (VAS) to rate associated pain.

**Pressure Pain Threshold**

A pressure algometer were used to determine changing of pressure pain threshold from pre-mobilization to post-mobilization. Subjects were positioned in a seated position and the force was apply gradually at a rate of 1 kg/s through the application probe on tip at the thenar eminence, and the participants were asked to rate the

associated pain from 0 to 10..

**Compliance of Carpal Tunnel**

A hand held myotonometer (neurogenic technologies, INC.) were used to test the compliance of carpal tunnel [81]. Subjects were sit in a comfortable position facing the examiner with their arms resting on the knees and their hands palmar side facing upward. The indentation probe of myotonometer has a flat end with a diameter of 10 mm. To standardize identification location on the skin overlying the transverse carpal ligament, a line was drawn to connect the palpable pisiform and scaphoid. A point 10 mm distal from the connection line on the bisector was marked as the center of indentation. Then, the probe was manually pressed down perpendicular to the skin surface. The device takes measurements from 0.25 to 2.00 kg at an increment of 0.25 kg and provide the value of tissue displacement under the probe.

**Boston carpal tunnel syndrome Questionnaires (BCTSQ)**

The BCTQ evaluated two domains of CTS, symptom domains assessed with an 11-item scale (pain, paresthesia, numbness, weakness, and nocturnal symptoms) and functional status domains assessed with an eight-item scale (writing, buttoning, holding, gripping, bathing, and dressing) [78]. The questionnaire was presented in multiple-choice format, and scores were assigned from 1 point (mildest) to 5 points

(most severe). No response to a certain question was given 0 points. Each score is calculated as the mean of the responses of the individual items. The patients who have bilateral symptoms were asked to answer two questionnaires, one for each hand separately.

**Statistical Analysis**

SPSS statistical package, Version 19.0 (SPSS Inc., Chicago, IL) was used for data analysis. Descriptive statistics including means and standard deviations were calculated to describe demographic characteristics of the sample. The Shapiro-Wilk test were used to test the normal distribution of the data and Levene's test were used to test the homogeneity of variance.

The intra-rater reliability of ultrasonographic measurements of median nerve were calculated by intra-class correlation coefficients with model (2,k).

To determine the relationships between severities of clinical symptoms (BCTSQ) and mechanical properties of median nerve (CCT, CSA, AR, Cir, MGS and Mob), separated Pearson correlation coefficients were calculated.

To investigate whether manual intervention can change the clinical symptoms and mechanical properties of median nerve, paired sample t-test were performed to examine the difference after intervention.

Because the age between groups were significant different which could affect the

mechanical properties of median nerve and the effects of intervention, separated mixed model two-way repeated measures analysis of covariance (ANCOVA) were used to control the influence of age and test for an interaction of group (mobilization versus sham-mobilization) for measures of clinical symptoms includes changes in current pain intensity, pressure pain threshold. To investigate the influence on mechanical properties like compliance of carpal tunnel, cross sectional area, echo-density, aspect ratio, circularity and mobility of median nerve, one-way repeated measure ANCOVA were used to test the difference of percent changes for mechanical properties between groups. Bonferroni post-hoc tests were performed to find the significant effect in ANCOVA.

To investigate the relationships between changes of clinical symptoms and mechanical properties after median nerve mobilization, the data were split by group. The correlation coefficients between changes in clinical symptom and variables improved after median nerve mobilization were calculated.

# Results

Thirty subjects with carpal tunnel syndrome were recruited in this study and randomized allocated to sham mobilization or mobilization group.

**Basic Data**

The demographic data were showed in Table 2. The BCTSQ, symptom duration, current pain intensity, CCT and USD measured outcomes between sham mobilization and mobilization groups were similar ($p>0.05$) except age, BMI, and pressure pain thresholds ($p<.05$).

**Reliability**

The ICC (2,k) value for the thirty paired measurements was 0.99. The 95% confident interval of intrarater reliability ranged from 0.98 to 0.99. The results were showed in Table 3.

**Whether Severity of Clinical Symptoms Is Associated with Mechanical**

**Properties of Median Nerve**

The results of Pearson correlation coefficients between BCTSQ and mechanical properties were showed in Table 4. Low correlations existed between BCTSQ and

mechanical properties (CSA, r=.231; MGS, r=-.316).

**Whether Manual Therapy Can Change The Clinical Symptoms and Mechanical Properties of Median Nerve**

The results of paired-t-test (N=30) were showed in table 5 and table 6. There were significant difference in pain (pre: 4.9±1→post: 2.4±1, p<.0005), CCT (pre: 4.9±1.0→post: 5.4±1.0, p<.0005), CSA (pre: 11.0±3.2→post: 11.8±4.1, p=.007), Cir (pre: 0.57±0.09→post: 0.59±0.08, p=.029), MGS (pre: 42.14±16.67→post: 45.34±18.12, p=.038) and mob (pre: 2.1±1.0→post: 2.4±1.3, p=.012) after manual intervention.

**Effect of Median Nerve Mobilization in Patients with Carpal Tunnel Syndrome**

Results of two-way ANCOVA analysis were showed in table 7. The results showed there were no difference in symptom reduction between sham-mobilization and mobilization group. Results of one-way ANCOVA were showed in table 8. The results showed there were significant differences between groups in changes of median nerve mobility after intervention. Estimated of marginal means indicated that the transverse mobility of median nerve increased 34 % in mobilization group and 4% in sham-mobilization group (p<.0005).

## Correlations between Changes in Symptom Severity and Median Nerve Mechanical Properties after Mobilization

In order to understand the correlation between changes in clinical symptoms and mechanical properties of median nerve after mobilization treatment. The data were split by group. Results were showed in table 9. Since there were no significant difference between group in changes of mechanical properties except transverse mobility. The transverse mobility improved significantly only in mobilization group. Thus the transverse mobility was chosen to calculate the correlation with change of symptoms. In mobilization group, low correlation between the improvement of PPT and the improvement of mobility was presented (r=.17, p=.58).

# Discussion

This is the first trial to investigate the effect of manual intervention in patients with carpal tunnel syndrome on both clinical symptoms and mechanical properties of median nerve. Present study revealed that combination of manual intervention and nerve mobilization can influence patients' symptoms and mechanical properties including current pain intensity, CCT, CSA, Cir and MGS.

Mechanical properties of median nerve are associated with the clinical severity of CTS. In the present study, the BCTSQ were used to determine the clinical severity of CTS. The mechanical properties of median nerve were descripted by the morphology of median nerve, compliance of carpal tunnel and the transverse mobility during fisting. The score of BCTSQ was correlated with CSA (r=.231) and MGS (r=-.316) of median nerve. The results were consistent with study hypothesis. The higher BCTSQ were correspond to larger median nerve CSA and lower MGS. Enlargement of median nerve were possibly the consequence of long-period compression which leaded to fibrotic accumulation and swelling. Previous studies had also suggested the enlargement of CSA were correlated with longer duration of symptoms and higher clinical severity in patients with CTS [82-84]. Reduction in MGS were possibly the consequence of intraneural swelling. The negative correlation

indicates that severity of symptoms reflected the lower MGS with possibility of the presence of water signal and the intraneural swelling [70, 72]. Above mentioned correlations suggested that the mechanical properties of median nerve were associated with the clinical severity of CTS.

Both routine myofascial release combined with sham-mobilization or median nerve mobilization can alter the clinical symptoms and mechanical properties of median nerve in patients with CTS. The trend of reduction in current pain intensity was consistent with previous studies [39, 56, 57, 59, 85]. In the current study, pain intensity improved from 4.9 to 2.4 with the effect size of 0.78, which was better than previous studies from 0.2 to 0.6. This comparison was showed in Table 10. Compared to the treatment from previous studies, we modified the mobilization treatment by combining the myofascial release with sham-mobilization or nerve mobilization. These treatments can focus on the release of transverse carpal ligament and associated muscles along forearm [39, 57, 59, 86]. Additionally, the characteristics of our subjects including VAS score higher than 4, younger age and shorter symptom duration may be the criteria for clinicians to judge patients with CTS who can be responded to mobilization treatments.

After manual intervention, the CCT increased which might be the consequence of myofascial release especially the stretching of transverse carpal ligament.

Stretching of transverse carpal ligament might permit the elongation of ligament which decrease the mechanical constraint of carpal tunnel and the intra-tunnel pressure [87]. In our finding, the increase of both CSA and Cir after manual intervention might be the consequence of transverse carpal ligament elongation which decrease the possible compression of median nerve. Similar median nerve CSA enlargement had also been presented in patients with carpal tunnel syndrome who received surgical release of transverse carpal ligament [88, 89]. The increase of MGS might indicate the decreased of intraneural swelling of median nerve.

In addition to improvements in clinical symptoms with manual therapy, mobilization can have additional effect on nerve transverse mobility. The results of ANCOVA indicated that there was no difference in changes of clinical symptoms and mechanical properties between groups except the improvement of transverse mobilization in mobilization group after intervention. Presumably, the appropriate mobility of median nerve in response to finger motion can prevent kinking or stretching, and facilitate the re-establishment of equilibrium in tensile force occurring during joint motions [32, 63]. This effect can reduce clinical symptoms. However, the correlations between changes in clinical symptoms and mobility are low. The unexpected low correlation may due to lack of long-term follow up and the lack of measuring longitudinal gliding. The decrease of longitudinal nerve gliding in patients

with CTS had been highly emphasized in previous studies [52, 54, 55, 90-92]. The mechanical distortion of median nerve are the consequence of long-term compression. Thus, the temporary changes in mechanical properties and reliefs in clinical symptoms might not be proportional as our low correlation finding. Further investigation was needed to validate this assumption.

Limitations of the study should be noted. Carpal tunnel syndrome can be diagnosed clinically with a high degree of confidence by expert physicians or surgeons, but instrumental confirmation is usually required. Traditionally, electrodiagnosis such as nerve conduction velocity (NCV) study was the ancillary method. However, electrodiagnosis had its share of false-negative and false positive results, and it was usually expensive and uncomfortable. To avoid those problems, four provocative physical examination and the presence of clinical symptoms were chosen as the diagnostic criterion of CTS. Previous studies had highly recommended Phalen's and compression test for its good resultant mean positive likelihood ratio (>2.0), or the negative likelihood ratio (<0.5) [93]. Since nerve mobilization were more responsive in patients with positive upper limb tension test, the ULTT was chosen as ancillary test.

Lack of NCV in this trial may not influence the diagnostic accuracy of CTS in this trial. The mean CSA of the median nerve in the present study was 11.0±3.2mm

which was bigger than normative value 7.2±1mm from 100 healthy Asian reported by Bathala et al. in 2014 [94]. Substantial enlargement of median nerve in our subjects was noted. According to previous study, the enlargement of CSA was correlated with delayed NCV, positive provocative test, sensory loss and severe clinical symptoms in patients with CTS [95-97]. At the same time, about half of clinically defined CTS with normal NCV can be detected by enlarged CSA. Thus, validity of our samples should be adequate in terms of diagnosis as CTS in our subjects.

Limitation of image acquisition was noted. First, applying ultrasonographic measurements in the investigation of the median nerve, the transverse and longitudinal image cannot be acquired at the same time. In the longitudinal plane, the nerve can be accessed through the entire track and identified the location of entrapment as the enlargement presence. In the transverse plane, we can access the presence of compression through flattening of median nerve and enlarged in the cross sectional area. In the aspect of mobility, the longitudinal gliding was more clinical significant than the transverse gliding which had been reported with higher correlation with clinical symptoms. However, the transverse gliding can reflect the interaction between median nerve and the surrounding soft tissues such as flexor tendons or subsynovial connective tissues during the joint motion. The purpose of this trial was to investigate the effect of median nerve mobilization in both clinical symptoms and

mechanical properties, since the transverse plain can reflect more domains of mechanical properties than the longitudinal plane. We choose to examine the transverse plane of median nerve in this trial. Second, one previous study indicated that the deformation of median nerve immediately following physical activities would return to its original size within 10 minutes [98]. In the present study, no resting time was provided between the manual interventions, the accumulated effect of myofascial release and mobilization/sham-mobilization cannot be neglected. Further, we only investigated the immediate effect of intervention on median nerve morphology and mobility, the long term influence of median nerve mobilization on median nerve morphology and mobility was still unknown.

# Conclusion

In this study, we first investigated the correlation between clinical symptoms and distorted mechanical properties in patients with CTS. Results suggest the clinical severity is correlated with enlarged CSA and echo-density of median nerve. Second, we investigated the effect of manual intervention on clinical symptoms and mechanical properties of median nerve. The results suggest that manual treatment could significant influence the pain intensity, CSA, CCT, Cir, MGS and Mob immediately after intervention. In addition, we investigated the further clinical

benefits brought by median nerve mobilization. The results suggest that median nerve mobilization improve transverse mobility of the median nerve. However, the association between changes in mechanical properties and clinical symptoms were unexpected low which suggest that the changes in clinical symptoms cannot be fully explained by mechanical properties alone and may need long term follow-up to investigate the correlation.

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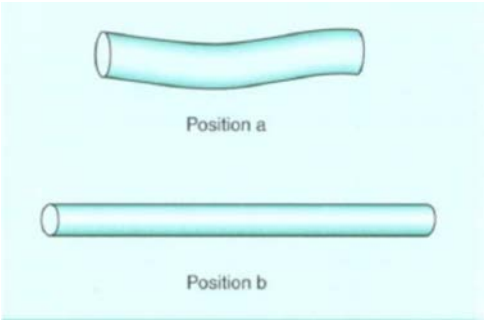


Figure 1. Nerve elongate during tensile force

Position a indicated neutral position without any tension applied
Position b indicated tensile force applied on nerve tissue and subsequent elongation.

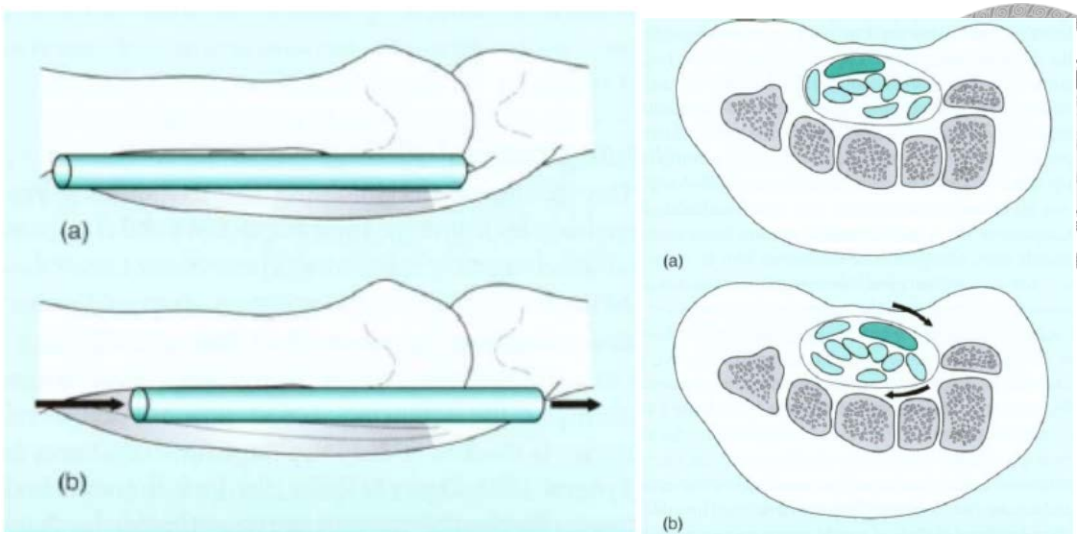


Figure 2. Sliding of nerve segments

Left = longitudinal gliding, right = transverse gliding.
(a) indicated start position and (b) indicated end position.

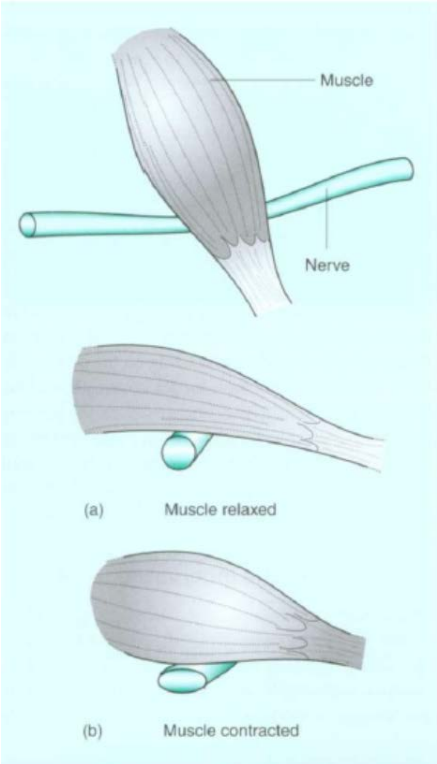


Figure 3. Nerve being compression

As nerve track passed through muscle tissue, it can be compressed during muscle contraction.

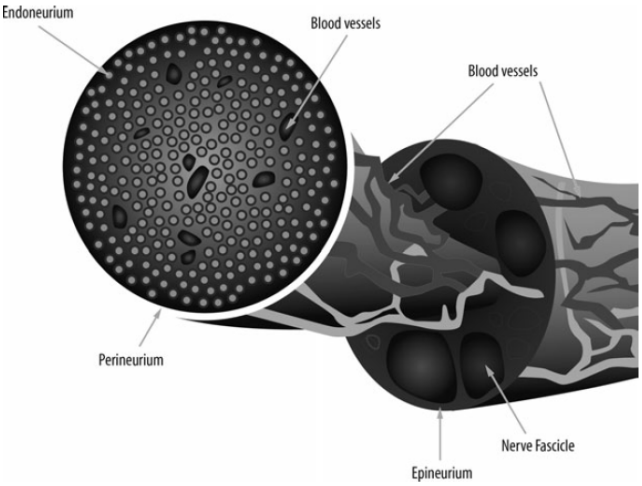


Figure 4. Blood supply of nerve tissue

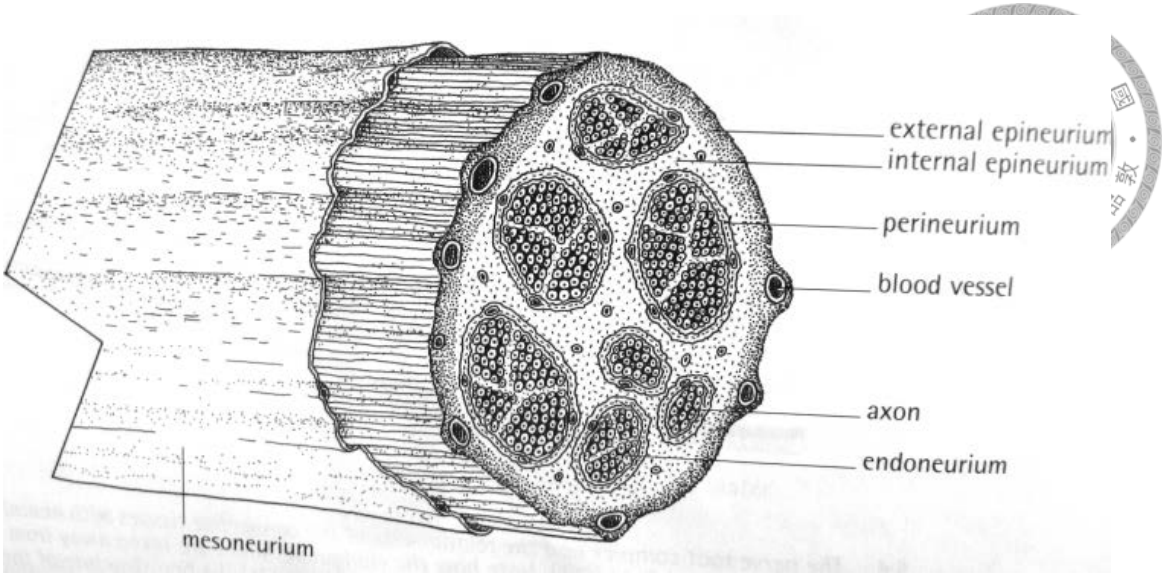


Figure 5. Multi-membrane structure of nerve tissue

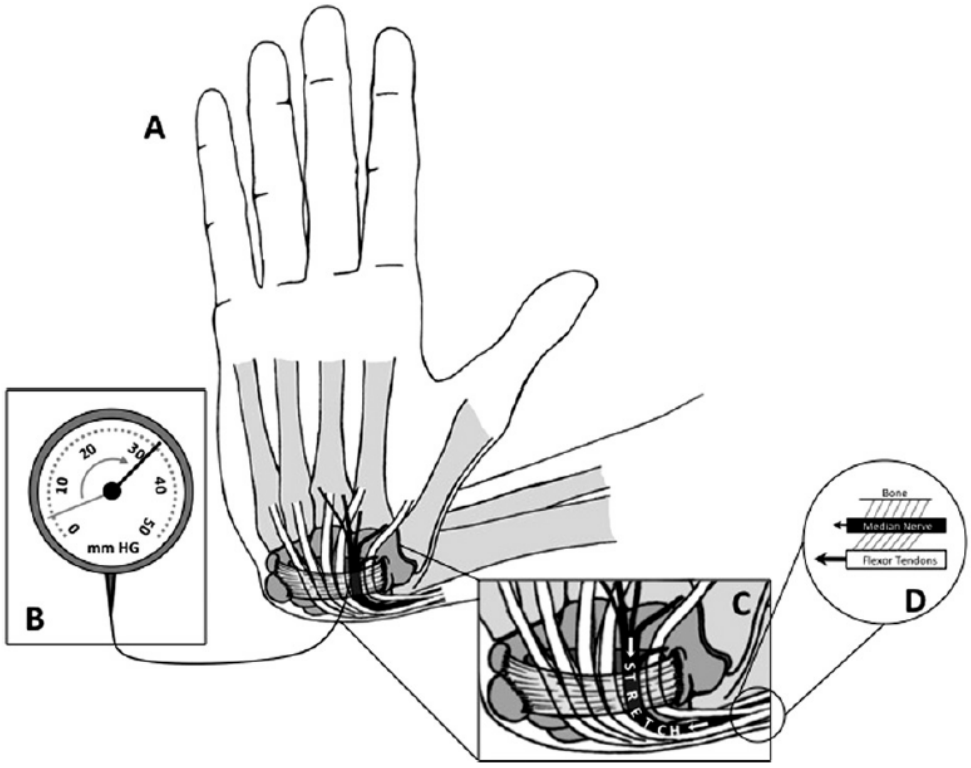


Figure 6. The mechanical stress in carpal tunnel correspond to wrist extension

A indicated full wrist extension
B indicated elevated intra-carpal tunnel pressure
C indicated stretch of median nerve in response to joint motion
D indicated gliding of median nerve between surrounding soft tissue

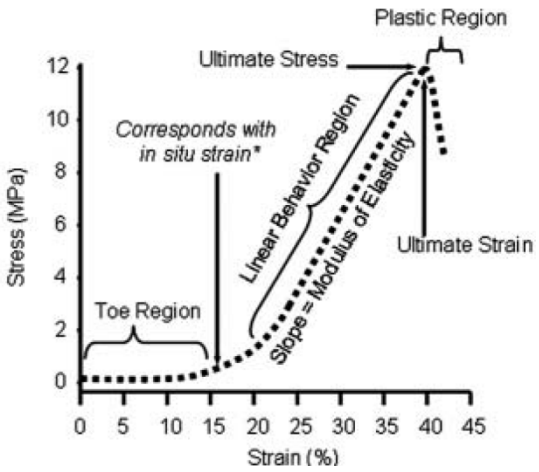


Figure 7. Stress-strain curve of peripheral nerve

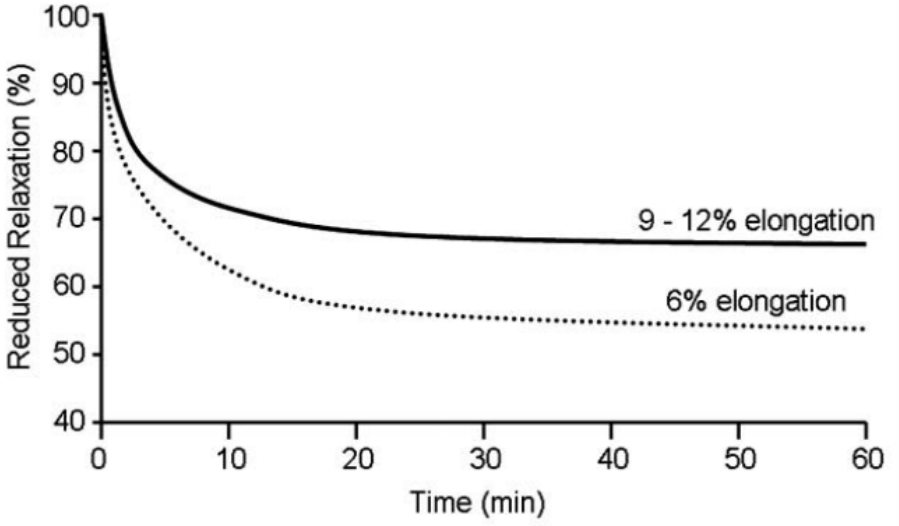


Figure 8. The stress-relaxation curve of nerve tissue

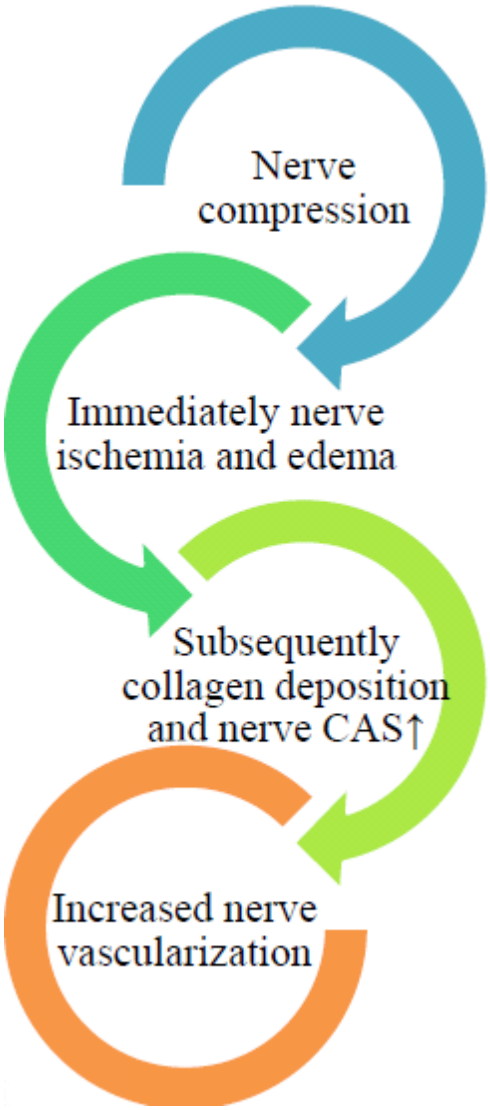


Figure 9. The response after nerve compression

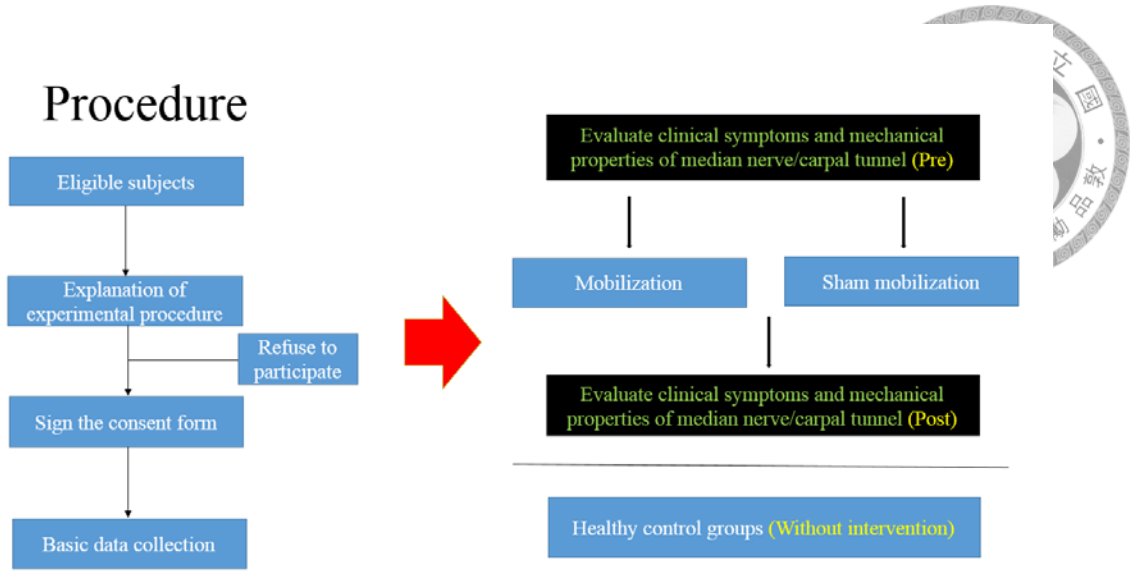


Figure 10. Experiment procedures

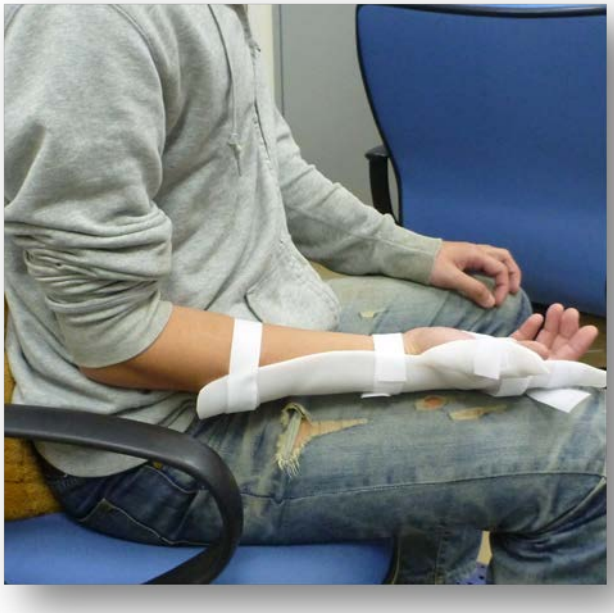

Figure 11. Positioning of subjects

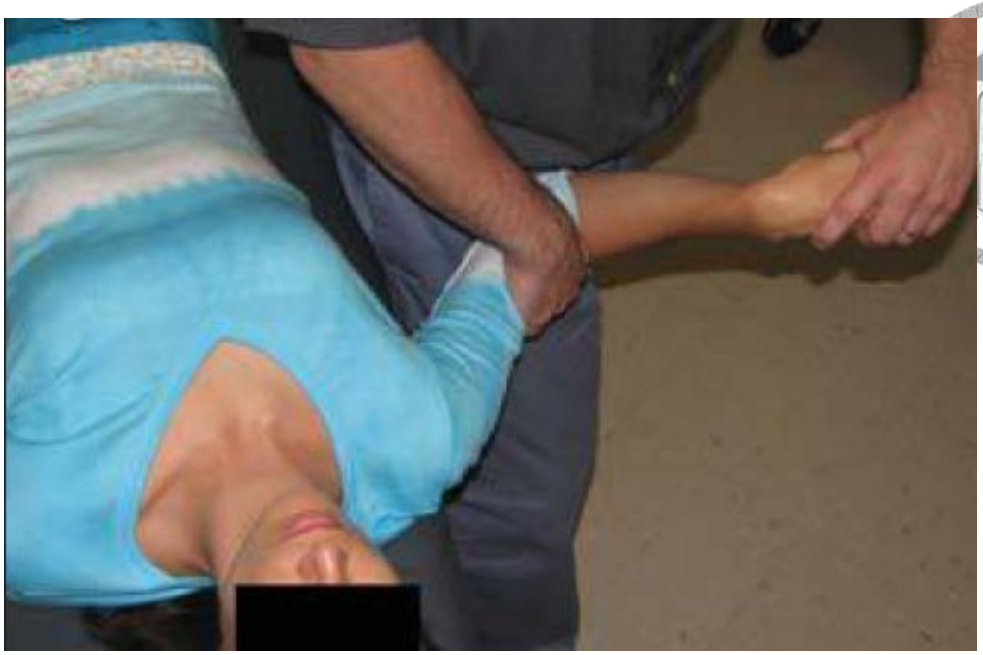

Figure 12. Sham median nerve mobilization

Table 1. Total sample size to achieve 80% power in each outcome measures

| Outcome measure | Partial-eta squared | Effect size (f) | Sample size |
|---|---|---|---|
| Compliance of carpal tunnel | 0.801 | 2.006 | 4 |
| Echo-density | 0.365 | 0.758 | 8 |
| Cross-sectional area | 0.063 | 0.259 | 16 |
| Aspect ratio | 0.101 | 0.335 | 20 |
| Transverse mobility | 0.066 | 0.266 | 30 |
| Circularity | | 0.227 | 41 |
| Pressure-pain thresholds [99] | 0.04 | 0.204 (0.21~0.56) | 50 (43~246) |

Table 2. Demographic data

| | Sham mobilization group (N=15; 9 males) | Mobilization group (N=15; 6 males) | P-value |
|---|---|---|---|
| Age (years) | 41±10 | 29±12 | .007* |
| BMI | 25±3 | 22±3 | .025* |
| BCTSQ | 27±6 | 23±6 | .069 |
| Symptom Duration (months) | 52±44 | 29±50 | .199 |
| Pain | 5±1 | 5±1 | .116 |
| PPT | 1.5±0.5 | 2.9±2.3 | .049* |
| CCT | 4.6±0.9 | 5.2±1.1 | .102 |
| CSA | 11.0±2.6 | 11.0±3.8 | .97 |
| AR | 3.2±0.7 | 3.2±1.3 | .861 |
| Cir | 0.59±0.08 | 0.55±0.1 | .23 |
| MGS | 42±14 | 43±20 | .867 |
| Mob | 2.1±1.1 | 2.1±1.0 | .971 |

Values shown are mean ± standard deviation.

BMI, body mass index; BCTSQ, Boston carpal tunnel syndrome questionnaire; PPT, pressure pain threshold; CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity; MGS, Mean grey scale; Mob, transverse mobility.

*. P value < .05

Table 3. Intraclass Correlation Coefficients

| | Intraclass Correlation | 95% C.I. |
|---|---|---|
| Single Measures | 0.964 | 0.934-0.983 |
| Average Measures | 0.988 | 0.977-0.994 |

Table 4. Correlations between BCTSQ and mechanical properties of median nerve

| | BCTSQ | |
|---|---|---|
| | r | P |
| CCT | -.13 | .493 |
| CSA | .231 | .257 |
| AR | .025 | .897 |
| Cir | .194 | .305 |
| MGS | -.316 | .089 |
| Mob | .028 | .881 |

BCTSQ, Boston carpal tunnel syndrome questionnaire; CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity;
MGS, Mean grey scale; Mob, transverse mobility.
* Indicated p <.05, ** indicated p <.005;

Table 5. Effects of manual intervention (N=30)

| | Pre. | Post. | P-value |
|---|---|---|---|
| Pain | 4.9±1 | 2.4±1 | <.0005 |
| PPT | 2.1±1.8 | 2.3±1.7 | .073 |
| CCT | 4.9±1.0 | 5.4±1.0 | <.0005 |
| CSA | 11.0±3.2 | 11.8±4.1 | .007 |
| AR | 3.2±1.0 | 3.1±1.0 | .204 |
| Cir | 0.57±0.09 | 0.59±0.08 | .029 |
| MGS | 42.14±16.67 | 45.34±18.12 | .038 |
| Mob | 2.1±1.0 | 2.4±1.3 | .012 |

Values shown are mean ± standard deviation.

PPT, pressure pain threshold; CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity; MGS, Mean grey scale; Mob, transverse mobility.

Table 6. Mean change (SD) from baseline to post-intervention for each variable

| | Sham-mobilization | | Mobilization | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| Pain | 4.94±0.27 | 2.28±0.32* | 4.68±0.26 | 1.25±0.30* |
| PPT | 1.54±0.35 | 1.78±0.33 | 3.00±0.34 | 3.07±0.33 |
| CCT | 4.70±0.25 | 5.30±0.25* | 5.19±0.26 | 5.80±0.27* |
| CSA | 10.24±0.67 | 10.60±0.64* | 10.85±0.69 | 10.85±11.15 |
| AR | 3.00±0.23 | 2.99±0.23 | 3.32±0.24 | 3.14±0.23 |
| Cir | 0.59±0.02 | 0.60±0.02 | 0.54±0.02 | 0.56±0.02* |
| MGS | 42.05±4.17 | 48.36±4.80* | 46.80±4.30 | 52.42±4.93 |
| Mob | 2.14±0.17 | 2.36±0.33 | 2.19±0.27 | 3.02±0.34* |

Values shown are mean ± standard deviation.

PPT, pressure pain threshold; CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity; MGS, Mean grey scale; Mob, transverse mobility.

*. P value < .05

Table 7. Results from separated repeated 2 way ANCOVA

| Factors | Sham-mobilization | | Mobilization | | Covariance (Age) | |
|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | f | P value |
| Pain | 4.94±0.27 | 2.28±0.32* | 4.68±0.26 | 1.25±0.30* | 5.18 | .031✯✦ |
| PPT | 1.54±0.35 | 1.78±0.33 | 3.00±0.34 | 3.07±0.33 | 5.27 | .030✦ |

Values shown are mean ± standard deviation.

PPT, pressure pain thresholds.

* Indicated time effect, p<.05

✯ Indicated interaction between time and age, p<.05

✦ Indicated p value of age <.05

Table 8. Results from separated one-way ANCOVA

| Factors | Sham-mobilization | Mobilization | Covariance (Age) | |
|---|---|---|---|---|
| | | | f | P value |
| CCT | 0.11±0.09 | 0.09±0.08 | 0.13 | 0.72 |
| CSA | 0.06±0.20 | 0.07±0.13 | 0.78 | 0.39 |
| AR | -0.01±0.12 | -0.03±0.14 | 0.12 | 0.73 |
| Cir | 0.24±0.94 | 0.06±0.10 | 0.07 | 0.80 |
| MGS | 0.11±0.22 | 0.08±0.26 | 1.123 | 0.30 |
| Mob | -0.04±0.15* | 0.34±0.34* | 1.17 | 0.29 |

Values shown are mean ± standard deviation of percent change, indicated as (Post − Pre)/Pre.

CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity; MGS, Mean grey scale; Mob, transverse mobility.

* Significant difference between group, $p<.05$

Table 9. Correlations of changes in clinical symptoms and mechanical properties of median nerve

| | Pain | | PPT | |
|---|---|---|---|---|
| | Sham. | Mob. | Sham. | Mob. |
| CCT | .01 | -.378 | -.047 | -.023 |
| CSA | .252 | .549* | -.556* | .047 |
| AR | .195 | .263 | -.138 | .310 |
| Cir | -.315 | -.057 | .222 | .317 |
| MGS | -.454* | .041 | .360 | .016 |
| Mob | .461* | -.062 | -.168 | .032 |

Values shown are correlation coefficients.

PPT, pressure pain threshold; CCT, compliance of carpal tunnel; CSA, cross sectional area; AR, aspect ratio; Cir, circularity; MGS, Mean grey scale; Mob, transverse mobility.

*. P value < .05

Table 10. Comparison of pain reduction

| | Intervention | Participant | Current Pain intensity | Effect Size |
|---|---|---|---|---|
| Tal-Akabi et al.2000 | NDT | 7 patients with CTS Age:47.1±14.8 | 2.42±1.4 (Range: 0-4) | 0.3 |
| Bialosky et al.2009 | NDT | 19 patients with CTS Age: 46.9±10.25 | 2.3±1.6 (VAS at least> 4) | 0.21 |
| De-la-Llave-Rincon et al.2012 | Soft tissue mobilization + NDT | 18 patients with CTS Age: 44±10 | 5.4 ± 1.8 (95% CI, 4.5-6.3) | 0.56 |
| Oskouei et al.2014 | Soft tissue mobilization + NDT | 16 patients with CTS Age: 46.7±11 | 5.56±1.9 (Not provided) | 0.63 |

NDT, neurodynamic technique; CTS, carpal tunnel syndrome. VAS, visual analogue scale.