EFFECT OF WRIST POSTURE AND FORCE ON MEDIAN NERVE BLOOD FLOW

EFFECT OF WRIST POSTURE AND FINGERTIP FORCE ON MEDIAN NERVE BLOOD FLOW VELOCITY

By

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TITLE: Effect of Wrist Posture and Fingertip Force on Median Nerve Blood FlowVelocity

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ABSTRACT

Carpal tunnel syndrome (CTS) is one of the most prevalent work-related musculoskeletal disorders of the upper extremity yet its etiology remains elusive. Nerve hypervascularization has been proposed as a pathophysiological change in CTS and can be measured using high resolution sonography of intraneural blood flow. The purpose of this study was to determine the effects of deviated wrist postures and fingertip force on the intraneural blood flow velocity of the median nerve proximal to the wrist crease. Ten participants experiencing the classic symptoms of CTS and nine healthy volunteers were recruited and underwent qualitative assessments (Phalen's test, Katz hand diagram, Levine's CTS questionnaire). Intraneural blood flow velocity was measured in five wrist postures (flexion 30°, flexion 15°, neutral, extension 15°, extension 30°) with and without a middle digit fingertip press (0N, 6N). A control (N=9) group and a CTS symptomatic (N=9) group were determined, in addition to a CTS individual (N=1) that required a separate analysis. A significant main effect of force was found ($F_{1,16} = 28.039$, $p < 0.0005$) with the mean peak velocity being greater with force (3.56 cm/s) than without force (2.81 cm/s). Wrist posture had a main effect ($F_{4,64} = 3.163$, $p < 0.020$) with flow velocity as neutral (2.87 cm/s) was significantly lower than flexion 30° (3.37 cm/s), flexion 15°(3.27 cm/s) and extension 30° (3.29 cm/s). There was no significant difference in peak blood flow velocity between the two experimental groups, CTS symptomatic (3.34 cm/s) and control (3.03 cm/s) ($F_{1,16} = 4.121$, $p < 0.059$). The results suggest that both force and non-neutral wrist postures may acutely induce vascular changes previously associated with CTS. The quantification of reactive median nerve hypervascularity should be investigated further as it has potential to be both a reliable diagnostic technique and a non-invasive assessment of CTS risk.

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CHAPTER 1 - INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy of the upper extremity (Van Rijn et al., 2009; Peer and Bodner, 2008). CTS is caused by the compression of the median nerve as it passes through the carpal tunnel, a canal formed by the flexor retinaculum and the carpal bones. The median nerve innervates the sensory neurons of the first, second, third and radial half of the fourth digit and the motor neurons of the thenar muscles. Common symptoms of CTS include radiating pain from the wrist, stiffness in the hand, and paresthesia, numbness and tingling in the digits innervated by the median nerve (Aroori and Spence, 2008). Early diagnosis and treatment of CTS is important to avoid more severe symptoms such as permanent sensory loss, persistent pain and thenar muscle atrophy, which greatly affect quality of life (Peer and Bodner, 2008; Werner and Andary, 2002).

Work-related CTS is the most frequently reported work-related musculoskeletal disorder of the upper extremity in Ontario and imposes a significant economic burden (Manktelow et al., 2004). Distal upper extremity musculoskeletal disorders are more expensive and have greater work disability associated with them than other upper extremity disorders. In 1996, the cost per patient was approximately $8330 in unilateral CTS and $15,450 in bilateral CTS; the average cost of upper extremity disorders was $1000 per patient (Manktelow et al., 2004). As a result of work-related CTS, many Ontario workers experience permanent pain and suffering and employers experience a large loss of work productivity and sustain a considerable financial deficit with over $13 million per year in total costs (Manktelow et al., 2004). Injury prevention through

ergonomic interventions and more reliable CTS diagnostic measures to facilitate early intervention can reduce these costs on our society.

Establishing a non-invasive assessment tool to predict CTS risk has been the focus of recent studies aiming to improve ergonomic assessments. Carpal tunnel pressure (CTP) models have been proposed as a tool to measure CTS risk; however, CTP is an indirect measurement of pathological changes that are occurring in the blood vessels. It is more ideal to measure blood flow changes directly as the mechanism of altered nerve function is directly related to ischemia of the capillaries that supply the median nerve (Lundborg, 1975). Currently, there are a limited number of imaging studies that have measured blood flow in the median nerve (Evans et al., 2012; Joy et al., 2011; Mallouhi et al., 2006). Evaluating the changes in blood flow throughout various work tasks may be an effective method to identify hazardous tasks in the workplace. Measuring changes in blood flow within the median nerve in response to occupational risk factors, proposed to aggravate symptoms in CTS is a novel application of this technique. Establishing this new technique will provide insight into how wrist posture and fingertip force can affect the vascular mechanisms and has potential to provide a non-invasive assessment tool for CTS risk in the workplace.

Sonography is an imaging technique that can be used to detect any changes in the nerve's echotexture, including the flattening of the nerve at the site of compression and the enlargement and hypervascular state of the nerve proximal to the entrapment (Walker et al., 2004). High-resolution sonography has become a valuable tool for evaluating peripheral nerve compression. Recent advances in sonographic equipment

including higher frequency transducers (up to 18 MHz) have enhanced the capability of sonography for examining and diagnosing peripheral neuropathies (Peer and Bodner, 2008). High-resolution ultrasound technology provides detailed depictions of superficial soft-tissue structures, including peripheral nerves (Walker et al., 2004). In nerve compression syndromes, pathophysiological reactions occur from the chronic irritation of a nerve due to the persistent compression. The interference of the local intraneural microvasculature results in ischemia to the distal tissue, venous congestion that produces perineural and endoneural edema and fibrotic reactions that further compromise the nerve fascicles. Doppler ultrasound has the unique ability to provide blood flow measures from arteries, veins and even intraneural blood vessels (Wilder-Smith, 2012) and may therefore provide reliable measures to diagnose and determine the severity of CTS.

Ideally, to predict risk of development of CTS, blood flow changes in different work postures would be evaluated in healthy subjects. The low intraneural flow rate in healthy individuals makes this challenging to measure and even if the low flow rate can be successfully observed in healthy subjects, the likelihood of measuring pulsatile flow is uncertain. Pulsatile flow allows for consistent and reliable analysis of the signal. The blood vessels of those with severe CTS increase in size to adapt to the disruption of blood flow caused by the nerve compression, which has been observed as a larger pulsatile signal that is not observed in healthy individuals. The first step to develop this technique is to establish the appropriate ultrasound parameters for low velocities assessment and then, use these ultrasound parameters to evaluate blood flow in CTS patients. The elevated and pulsatile blood flow in CTS patients will then be compared to the flow

signal observed in healthy individuals. Very few previous studies have measured median nerve blood flow directly (Evans et al., 2012; Joy et al., 2011; Mallouhi et al., 2006). Evaluating blood flow in CTS patients and comparing it to the flow rate of healthy subjects is a step towards using ultrasound to accurately assess CTS risk in asymptomatic, apparently healthy individuals.

CHAPTER 2 – REVIEW OF LITERATURE

2.1 Work-Related Musculoskeletal Disorders

Work-related musculoskeletal disorders (WMSD) consist of a wide range of injuries, affecting the muscles, tendons, ligaments, joints, nerves and supporting blood vessels (Punnett and Wegman, 2004). Representing the largest category of work-related illness, these types of disorders have been extensively reviewed, specifically for their relationship with work exposure (Van Rijn et al., 2009; NIOSH, 1997; Gerr et al., 1991; Silverstein et al., 1986). A strong relationship exists between many types of WMSD and work exposures such as high force (Silverstein et al., 1986), high repetition (Tanaka et al., 1995) and awkward postures (Rempel et al., 1998). In addition, non-neutral postures of the hand, wrist and forearm have been shown to alter grip force, affect muscle loading of the forearm (Mogk and Keir, 2003), increase carpal tunnel pressure and subsequent median nerve compression (Keir et al., 2007). Identifying work exposures that compress the structures in the carpal tunnel is an important step in the prevention of WMSD.

Preventing WMSD has been a primary goal of ergonomics based research around the world and requires recognition, assessment and control of the hazards that cause them. Since all work has the potential to be hazardous, the distinction between hazard and risk is important to consider. Hazards are conditions that may cause injury. The risk of injury is related to the hazard as well as the conditions under which the person is exposed to the hazard (Dellman et al., 2004). Mechanical exposure to the body has three dimensions: amplitude, frequency and duration of exposure. Therefore, even extreme postures can have low risk if the motion is infrequent. The interactions between

these three dimensions are important when evaluating tasks in the workplace. The initial step in preventing WMSD is recognition, which requires extensive research of the key risk factors for WMSD during specific work tasks. The risk factors of particular WMSD, such as CTS, are difficult to predict in the workplace.

2.2 Occupational Risk Factors

The majority of CTS cases are considered idiopathic leaving the exact cause of the syndrome unknown. Several occupational risk factors increase the probability of developing CTS through mechanical compression of the median nerve. Occupational risk factors include high repetition, high forces, deviated wrist postures, grip or pinch, the use of vibrating tools, and direct external compression (Van Rijn et al., 2009; Keir et al., 1998; Rempel et al., 1998; Keir et al., 1997; Silverstein et al., 1986). Repetitive tasks, especially in conjunction with vibration, lead to the thickening of the synovial lining of the flexor tendons, increasing the pressure in the carpal tunnel and compressing the median nerve (Werner and Andary, 2002). Aroori and Spence (2008) noted a five-fold greater risk of CTS amongst workers who were required to engage in repetitive use of hands/wrists than in the general population. Fingertip loading, pinching or gripping tasks contract the finger flexor muscles causing increase tension in the tendons that transverse the carpal tunnel (Keir et al., 1998; Rempel et al., 1997). The combination of high force and high repetition increases the risk of damage to the tendon, its surrounding sheath and/or possible median nerve trauma in the carpal tunnel (Silverstein et al., 1986). With 574 workers, Silverstein et al. (1986) found an odds ratio of 30.3 for high force-high

repetition in contrast to 4.9 for high force-low repetition and 3.6 or low force-high repetition. These risk factors can be reduced by further evaluating wrist posture guidelines, restricting force levels, limiting repetitive work and investigating how these exposures interact to produce higher CTS risk.

2.3 Carpal Tunnel Syndrome

2.3.1 Anatomy of the Carpal Tunnel

The carpal tunnel is a narrow canal on the palmar side of the wrist, formed by four rigid carpal bones, the hamate, capitate, trapezoid and trapezium, and the flexor retinaculum (Figure 2.1) (D'Arcy and McGee 2000). Wrist and finger postures can alter the size and shape of the tunnel with the narrowing or expanding of the flexor retinaculum, which composes the palmar side of the tunnel (Rempel and Diao, 2004). The median nerve and the tendons of the flexor digitorum profundus (4), flexor digitorum superficialis (4) and flexor pollicis longus (1), traverse the tunnel. If any of the tendons or their sheaths swell or degenerate, the median nerve, lying anterior to the second flexor digitorum superficialis tendon, can become compressed or entrapped. CTS is a neuropathy caused by compression of the median nerve within the carpal tunnel and manifests with symptoms in the distribution of the median nerve. The sensory branch of the median nerve innervates the skin on the palmar aspect of the first, second, third and radial half of the fourth digit. The motor branch innervates the thenar muscles, which include the opponens pollicis, flexor pollicis brevis and abductor pollicis brevis. The compression of the median nerve can cause symptoms such as paresthesia, numbness,

tingling, burning sensations, nocturnal pain, and if severe, atrophy of the thenar muscles (Aroori and Spence, 2008; Werner and Andary, 2002).

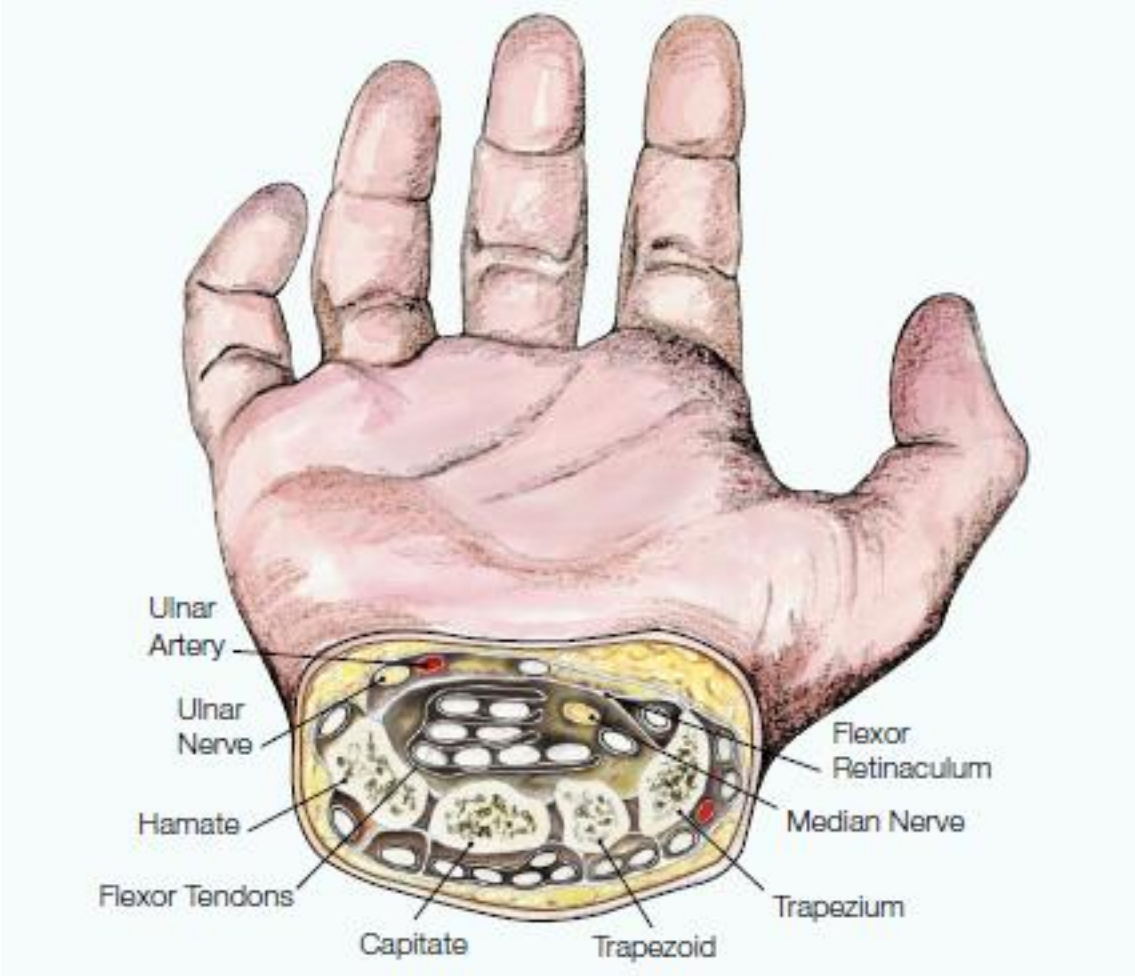

Figure 2.1. Anatomy of the carpal tunnel in a healthy individual (D'Arcy and McGee, 2000).

2.3.2 Peripheral Nerve Blood Supply

The vascular system of the median nerve at the wrist is primarily supplied by the superficial palmar arch (distal) and the ulnar artery (proximal) but several branches exist from the median and radial arteries (Blunt, 1959). The median nerve requires continuous supply of oxygen from the surrounding blood vessels in order to function properly. The

peripheral nerves have two functionally independent vascular systems: an extrinsic and an intrinsic system. The extrinsic system is composed of vessels that originate from nearby arteries and veins and is responsible for supplying blood and nutrients to the outer layer of the intrinsic system in the epineurium of the nerve. The intrinsic system consists of the epineurial, perineurial and endoneurial plexuses (Figure 2.2) (Topp and Boyd, 2006). If the intrinsic system is obstructed by a direct compression of the nerve, the extrinsic system must compensate to preserve the blood supply (Lundborg, 1975). The extrinsic system requires a greater change in nerve structure before blood flow can be impaired as the vessels have a coiled appearance that allows them to be stretched. The intrinsic system is more susceptible to damage but has a system of anastomoses to compensate. All the intrinsic vessels are attached through anastomoses, where no specific direction of flow is dominant. Empty capillaries exist that will start to function when the blood flow requires an alternate pathway if the nerve is damaged. However, once the disruption of blood flow exceeds the critical limit, microcirculation within the intraneural vascular system will be impaired. Deterioration of nerve function can occur within 30-90 minutes of complete ischemia (Lundborg, 1975). However, this damage can be reversible because nerve function can return if blood supply to the nerve is quickly restored and no demyelination has occurred (Lundborg et al., 1982).

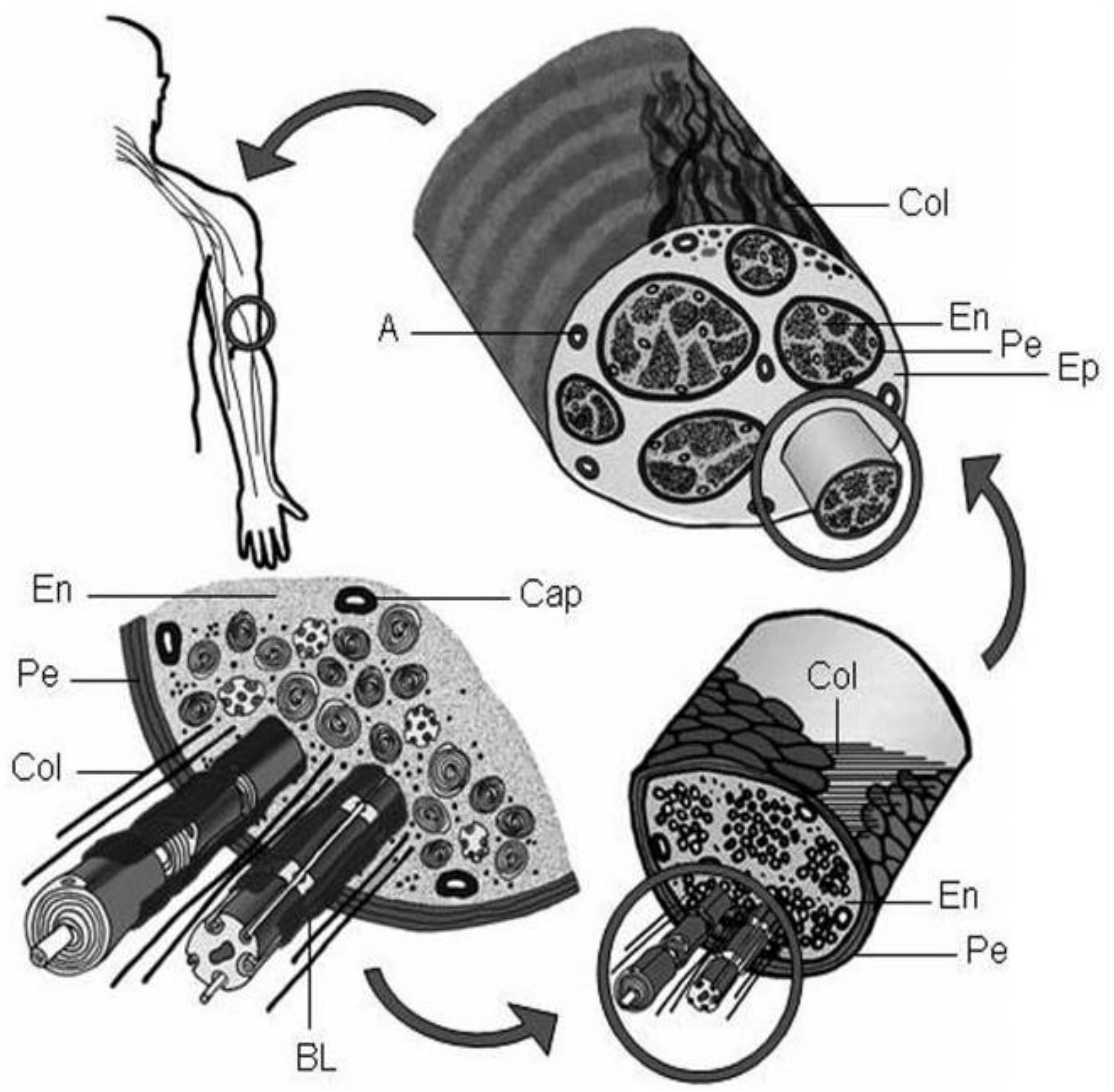

Figure 2.2. The anatomy of peripheral nerves. The three layers consist of the endoneurial compartment (En), perineurium (Pe) and the epineurium (Ep). The endoneurial compartment contains capillaries (Cap), axons, Schwann cells covered with basal lamina (BL), collagen (Col) and endoneurial fluid. These structures are bundled into fascicles by the perineurium (Pe). These fascicles are bundled by the epineurium to form a nerve. The epineurium consists primarily of collagen fibers, fibroblasts and elastic fibers. Arterioles (A) and veins run longitudinally within the epineurium. (Topp and Boyd, 2006).

2.4 Pathophysiology

The underlying pathophysiology of CTS is not well understood due to complexity of cause, risk factors and presentation of symptoms, resulting in most cases of CTS to be considered idiopathic. Several mechanisms have been shown to be possible causes including (i) mechanical trauma due to contact stresses on the nerve, (ii) elevated pressure within the carpal tunnel, and (iii) vascular changes in the nerve (Ibrahim et al., 2012). All of these mechanisms are interrelated and will result in damage to the nerve and blood supply, leading to pain, numbness and tingling in the areas innervated by the median nerve. *In vivo* studies that provide further insight into these mechanisms are still needed to better understand the etiology and track the progression of CTS (Viikari-Juntura and Silverstein, 1999).

2.4.1 Mechanical Trauma

Any compression in the carpal tunnel will compromise the conductivity of the median nerve by interrupting the blood supply, reducing axonal transport and physically damaging the nerve sheath. The extent and reversibility of the injury is dependent on the level and duration of compression (Viikari-Juntura and Silverstein, 1999). A large body of research on animal studies has provided information about the mild to severe pathological changes that occur with peripheral nerve entrapment. Rydevik et al. (1981) used a rabbit model to show the retardation of blood flow with externally applied compression. After the application of pressure (20-30 mmHg), the venular flow in the epineurium was almost immediately interrupted. The greater the pressure applied, the

larger the observed reduction in blood flow. The endoneurial capillary flow and epineurial arteriolar flow decreased and complete ischemia occurred with pressure of 60-80 mmHg (Rydevik et al., 1981). In a rat model, Powell and Myers (1986) found damage to the nerve sheath followed a similar trend following damage to the blood vessels. Nerve edema and axonal lesions had demonstrated a positive correlation with the severity of the compression, with high external pressures of 80 mmHg resulting in greater axonal damage. The application of pressure (both 30 and 80 mmHg) induced some level of Schwann cell destruction with a subsequent disintegration of the myelin sheath (Powell and Myers, 1986). Changes in the nerve sheath after long periods of mechanical compression were studied by Dahlin and McLean (1986) in a rabbit vagus nerve model. A low pressure of 20-30 mmHg for 8 hours led to a decrease in both slow and fast axonal transport. This impairment caused reduced cytoskeletal elements in the distal axons, causing axonal degeneration and altering the function of the nerve (Dahlin and McLean, 1986). Therefore, both severe acute compression and chronic mild constriction will damage the nerve fiber and eventually lead to axonal damage, with the most vulnerable cell being the Schwann cell (Powell and Myers, 1986). Necrosis of Schwann cells emphasizes the role of ischemia as the most probable pathogenic mechanism during nerve compression as the death of the Schwann cell consequently leads to disintegration of the myelin sheath (Figure 2.3) (Viikari-Juntura and Silverstein, 1999; Powell and Myers, 1986). Demyelination disrupts the nerve signals and causes the various symptoms associated with entrapment neuropathies. As such, contact stresses may be a mediator in

damage to the nerve by decreasing axonal transport (Viikari-Juntura and Silverstein, 1999).

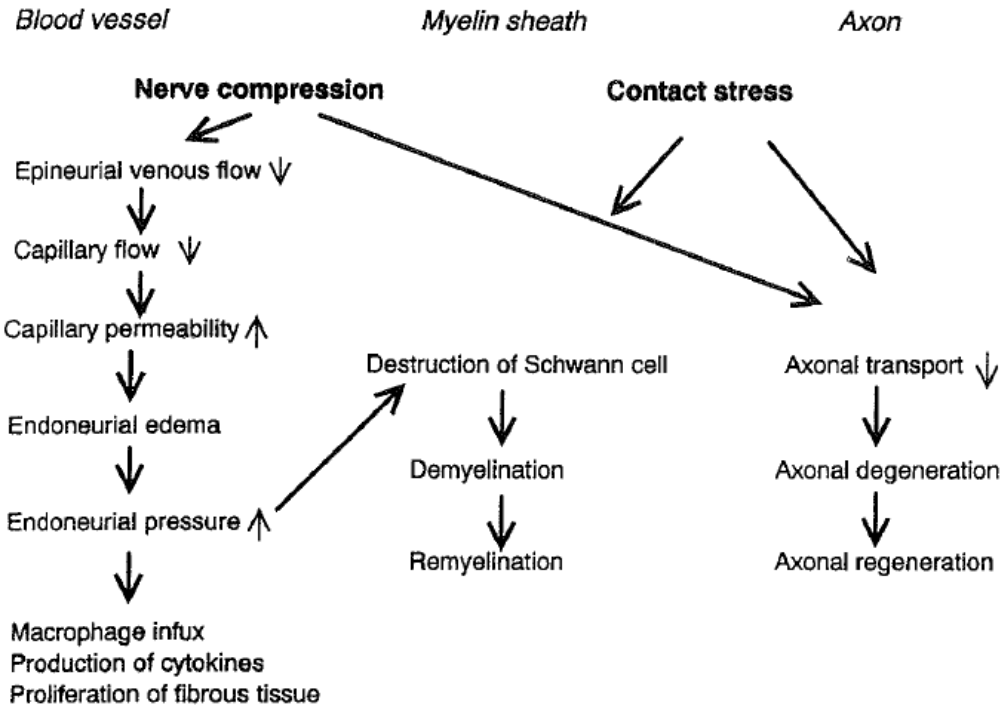

Figure 2.3. Pathomechanical pathways of CTS (Viikari-Juntura and Silverstein, 1999).

2.4.2 Elevated Carpal Tunnel Pressure

Recent studies have found carpal tunnel pressure (CTP) to be an appropriate predictor of CTS risk since elevated pressure within the carpal tunnel has been linked to a decrease in nerve function (Coppieters et al, 2012; Keir et al, 2007). High interstitial fluid pressure causes the capillaries to collapse and limits blood flow to the nerve, resulting in the symptoms of numbness, tingling and weakness. Lundborg et al. (1982) were able to reproduce the symptoms of CTS by applying an external compression to the distal end of the carpal tunnel, and manually increasing the CTP in participants. These

findings support the knowledge that elevated CTP is a mechanism of the development and further aggravation of CTS symptoms. Furthermore, the changes in pressure are influenced by hand, wrist and forearm posture (Keir et al., 2007; Werner et al., 1997; Gelberman et al., 1981) and fingertip loading (Rempel and Diao, 2004).

2.4.2.1 Hand, Wrist and Forearm Posture

The exact pathophysiology of how wrist posture contributes to the onset of CTS remains unclear. Wrist posture has been shown to have a direct relationship to changes in CTP (Keir et al., 2007). Both flexion and extension can dramatically increase the fluid pressure in the carpal tunnel as a change in posture alters the shape and width of the carpal tunnel. In healthy subjects, CTP is 3-9 mmHg in a neutral posture and this can increase as high as 60 mmHg with fully extended wrist and fingers (Werner et al., 1997). The carpal bones are not a rigid wall but move in relation to each other with every motion of the hand. Wrist extension causes the elements of the volar side to stretch and the dorsal side to compress as the lunate moves towards the interior of the tunnel (Werner and Andary, 2002). As a result, an extended wrist has been found to have the smallest carpal tunnel to content volume ratio (Bower et al., 2006) and the smallest carpal tunnel CSA (Mogk and Keir, 2008). The narrow dimensions result in greater hydrostatic pressures within the tunnel (Keir and Rempel, 2005). With wrist flexion, the flexor tendons move towards the transverse carpal ligament, placing contact stress on the median nerve and creating areas of elevated pressure within the carpal tunnel (Keir and Wells, 1999). Both postures significantly increase compression on the structures that lie

in the carpal tunnel with contact stress playing a greater role in flexion and pressure from the narrowed tunnel in extension. Keir et al. (1997) measured CTP with a catheter inserted into cadaveric specimens at different wrist postures, nine positions in the flexion/extension plane and six in the radial/ulnar deviation plane. The results showed significant increases in CTP (>30 mmHg) with non-neutral postures that include radial/ulnar deviation and flexion/extension (Keir et al., 1997). With increasing wrist angle, the CTP for flexion and extension elicit a different pattern, with higher pressures seen with wrist extension (Keir et al., 2007).

2.4.2.2 Fingertip Loading

The level of force exerted at the fingertips has a significant effect on the development of carpal tunnel syndrome through changes in carpal tunnel pressure (Figure 2.4) (Rempel et al., 1997; Keir et al., 1998). Rempel et al. (1997) found an increase in CTP with active, static loading of the fingertip, independent of wrist angle. Keir et al. (1998) found greater pressures with a pinching task but still found an increase in CTP with a fingertip pressing task. The magnitude of the CTP varied significantly between the two studies. Relatively low fingertip loads (1-12 N) are capable of increasing CTP, with evidence that sustaining these postures may initiate pathological changes in the nerve such as ischemia and trigger symptoms in carpal tunnel syndrome patients (Rempel et al., 1997). Furthermore, the combination of varying wrist postures with a gripping task led to higher CTPs than a relaxed hand, with even higher pressures in CTS patients (Luchetti et al., 1998). Therefore, wrist and finger postures that deviate from neutral can alter the

interaction within the carpal tunnel between the flexor tendons and the median nerve, leading to compression and obstruction of their motion.

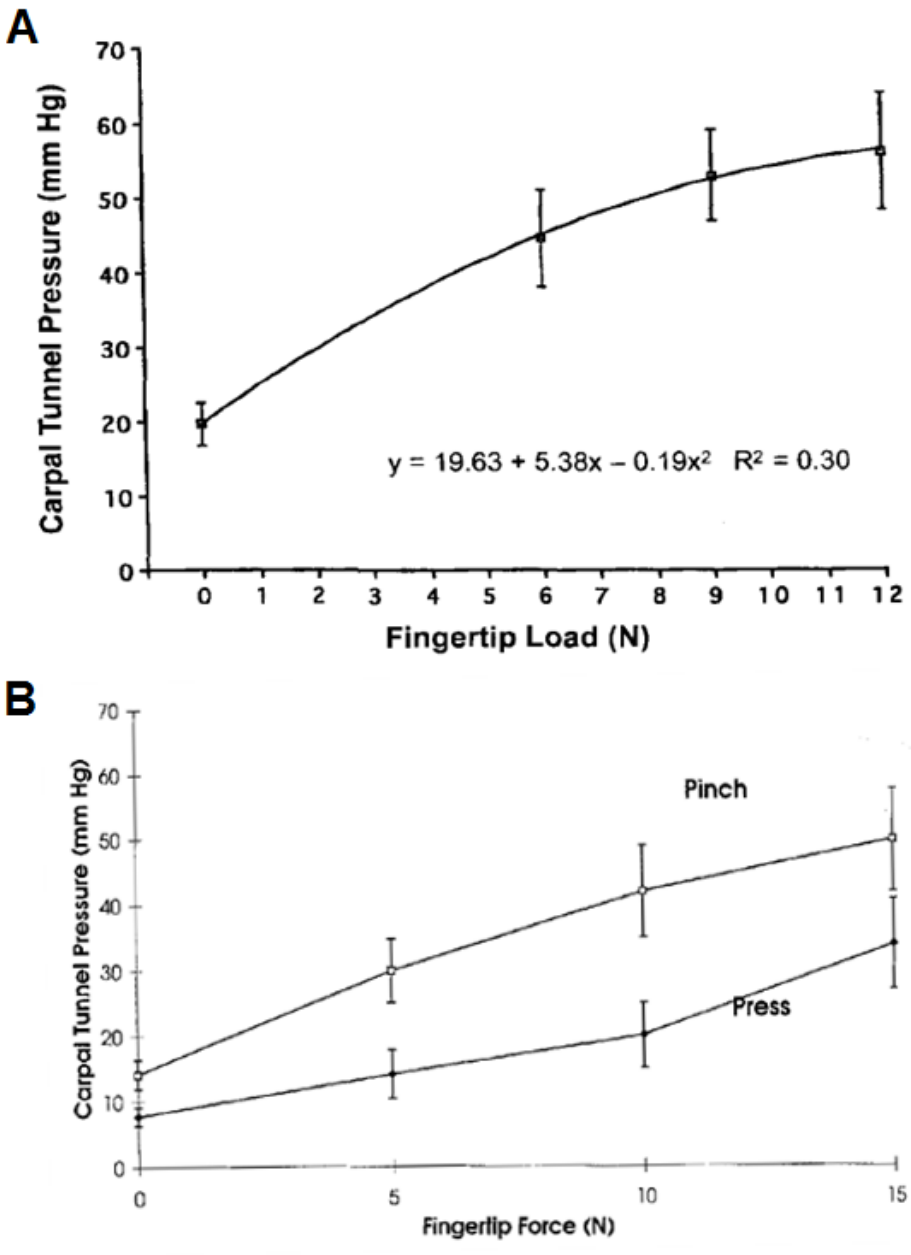

Figure 2.4. (A) The relationship between fingertip load and carpal tunnel pressure with a neutral wrist posture (Rempel et al., 1997). (B) The relationship between pinch grip, fingertip press and carpal tunnel pressure with a neutral wrist posture (Keir et al., 1998).

2.4.3 Vascular Changes

Although CTP is an important measure, researchers hypothesized that the mechanism of the altered nerve function is directly related to ischemia of the capillaries that supply the median nerve. This theory was determined from the removal of the external compression when nerve function returned to normal and the CTS-like symptoms dissipated (Lundborg et al., 1982). With laser Doppler flowmetry, Seiler et al. (1989) evaluated median nerve blood flow at the time of surgical release. After transecting the transverse carpal ligament, a pulsatile signal returned within 1 minute and was positively correlated with relief of CTS symptoms. This suggests that rapid reversible vascular changes are a significant factor in the pathogenesis of CTS (Seiler et al., 1989). By inflating a sphygmomanometer cuff around the upper arm to induce an increase in hand and forearm volume, Boland and Adams (2002) reproduced CTS symptoms, further establishing that CTS is a vascular phenomenon. In early compression, venous outflow is blocked, causing the nerve to be hypervascularized and edematous (Werner and Andary, 2002). With the development of high-resolution sonography, Mallouhi et al. (2006) were able to image the presence of median nerve edema and nerve hypervascularization. In addition, they showed that nerve hypervascularization was the sole variable to independently predict CTS, proving to be a more valuable measure than nerve swelling, nerve edema and flattening or increased bowing of the flexor retinaculum (Table 2.1) (Mallouhi et al., 2006).

Table 2.1. Sonographic criteria and its accuracy in detecting CTS in comparison with nerve conduction studies (from Mallouhi et al., 2006).

Criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Nerve edema	80 (137/172)	65 (22/34)	77 (159/206)	92 (137/149)	39 (22/57)
Nerve swelling	91 (157/172)	47 (16/34)	89 (183/206)	90 (157/175)	52 (16/31)
Nerve flattening	60 (103/172)	76 (26/34)	63 (129/206)	93 (103/111)	27 (26/95)
Bowing of flexor retinaculum	65 (111/172)	68 (23/34)	65 (134/206)	91 (111/122)	27 (23/84)
Nerve hypervascularization	95 (164/172)	71 (24/34)	91 (187/206)	94 (164/174)	75 (24/32)

Note—Numbers in parentheses are numbers of wrists.

2.5 Diagnostic Techniques

The diagnosis of CTS can be complicated and is typically established through provocative tests and nerve conduction studies (NCS) (Cartwright et al., 2013). Screening for CTS and determining at-risk populations proves to be just as challenging. Qualitative methods (surveys, interviews) have overpredicted the rates of CTS while quantitative methods such as NCS can be technically challenging (Cartwright et al., 2013). Often it is necessary to use several diagnostic tests in combination for the most sensitive results. Sensitivity is an index describing the power to detect CTS in individuals with very few falsely negative results. Specificity is an index describing the power to detect healthy individuals with very few falsely positive results. Techniques with sensitivity and specificity greater than 50% are deemed potentially reliable and are used to diagnose CTS (Georgiew, 2007). Nerve conduction studies (NCS) and nerve cross-sectional area (CSA) are often used to diagnose CTS based on their sensitivity and specificity; however, both tests have been shown to have significant false negative rates

(16-34%) (Joy et al., 2011). Magnetic resonance imaging (MRI) and high-resolution sonography are able to identify and map pathological changes in peripheral nerves, with high-resolution sonography being significantly more accessible and cost-effective than MRI. Recent studies have shown that detecting changes in blood flow using sonography may be a superior method for diagnosing CTS (Wilder-Smith, 2012; Joy et al., 2011; Mallouhi et al., 2006).

2.5.1 Electrodiagnostic Tests

Clinicians use electrodiagnosis frequently to confirm the diagnosis of CTS; this includes nerve conduction studies (NCS) and electromyography (EMG). EMG consists of a fine needle inserted into a muscle and impairments in the electrical activity are observed. NCS have a more direct association with the pathophysiology of focal demyelination in CTS than EMG studies (Wang, 2013). Mechanical pressure and ischemic changes damage the myelin sheath and reduce the conductivity of the nerve. NCS can detect these neurophysiological changes occurring in the median nerve (Werner and Andary, 2002). The median nerve at the carpal tunnel is stimulated by a pulse of electricity and the action potential is recorded by a surface electrode. The latency and amplitude of the signal is compared to other sections of the nerve to determine the severity of the nerve damage (Werner and Andary, 2002). Both prolonged motor and sensory latencies and reduced motor and sensory conduction velocities are considered criteria for the diagnosis of CTS; however, the optimal diagnostic criteria is still unknown (Ibrahim et al., 2012).

As an objective test, NCS are thought to be the most sensitive and accurate techniques and are considered the 'gold standard' for diagnosis of CTS (Ibrahim et al., 2012; Evans et al., 2012; Georgiew, 2007; D'Arcy and McGee, 2000). However, the relationship between NCS and symptoms of CTS has been found to be unpredictable and highly variable (Werner and Andary, 2002). The characteristic symptoms such as pain, tingling and numbness are sometimes reported in the ulnar nerve digits, forearm, elbow and/or shoulder or not present at all (Stevens et al., 1999). In addition, other factors can result in the misdiagnosis of CTS such as electrode placement, stimulation intensity, temperature and distance measurements (Wang, 2013). Another disadvantage is that NCS are unable to assess the small unmyelinated fibers that mediate pain (Werner and Andary, 2002). Thus, without the classic presentation of symptoms, a positive NCS cannot stand alone to confirm the diagnosis of CTS.

2.5.2 Hand Diagrams

The Katz hand diagram (Appendix B) has been frequently used to assess the location and type of CTS symptom (Dale et al., 2008). The subjects draw patterns representing four types of symptoms (pain, numbness, tingling and decreased sensation) over the area they are felt with the option of dorsal or palmar views of both left and right hands and arms. The diagrams are self-administered by the subject, reducing experimenter bias, and scored on a four point ordinal scale (unlikely, possible, probable or classic). Scoring criteria varies slightly between studies (Calfee et al., 2012; Franzblau et al., 1994; Katz et al. 1990). Both Calfee et al. (2012) and Franzblau et al. (1994)

modified the original scoring criteria by Katz et al. (1990) to include additional criteria for individual digits (Appendix B). The hand diagram score indicates the likelihood of CTS and can be used as a diagnostic technique.

In the clinical setting, hand diagrams have a high sensitivity of 80% and a high specificity of 90%, indicating that they can be a valid method for classifying CTS (Katz and Stirrat, 1990). However, a sensitivity rate of 50% was shown in the industrial setting when compared to NCS. This may be due to the subjective nature of the test as most workers reported false positive results when comparing the hand diagrams with the NCS (Franzblau et al., 1994). When evaluating the reliability of the hand diagram, high intraclass correlation coefficients of 0.83 (right hand) and 0.88 (left hand) were found (Dale et al., 2008). These highly reliable results were reported in a working population from a large, diverse group of industries and personal factors, job type and other disorders had no impact of the results (Dale et al., 2008).

2.5.3 Provocative Tests

Provocative tests are physical manoeuvers that deliberately provoke symptoms of the abnormality. Two common tests are the Phalen's test and the Tinel's sign. The Phalen's test has been commonly used to detect CTS by increasing the compression on the nerve, which stresses the circulation and increases the pressure within the carpal tunnel (Georgiew, 2007). The Phalen's test is performed by holding the wrist in flexion for one minute. Variations of the maneuver include letting the wrist passively fall into flexion, patients actively but without excessive force positioning the wrist into flexion,

the examiner flexing the patient's wrist, and using the dorsal part of both hands to press the wrist into flexion (Georgiew, 2007). A positive test requires a report of pain, tingling or numbness in the areas distal to the carpal tunnel and innervated by the median nerve. The Tinel's sign induces CTS symptoms by direct mechanical pressure on the median nerve (Georgiew, 2007). Tinel's sign requires the clinician to tap on the distal wrist crease, approximately where the median nerve lies. A positive test requires a report of pain, tingling or numbness in the distribution of the median nerve (D'Arcy and McGee, 2000). Both of these provocative tests are easily performed, non-invasive and cost efficient. Unfortunately, both tests have shown a wide range of sensitivity and specificity values. The Phalen's test has been reported to have between 43-93% sensitivity and 40-95% specificity and Tinel's sign has shown a 43-75% sensitivity and 40-99% specificity (Georgiew, 2007), indicating that the Phalen's test may be the superior of the two methods. Homan et al. (1999) showed less than half of cases with positive NCS proved to have a positive provocative test. This inconsistency may be due to the lack of reliability of these tests with a large variability in how the tests are performed (Werner and Andary, 2002). For example, the wrist position and level of force will affect the outcome of the Tinel's sign with a greater percussion force increasing the sensitivity while decreasing the specificity (Mossman and Blau., 1987). Evans et al. (2012) stressed the lack of accuracy that exists with provocative testing and the need to explore alternative techniques.

2.5.4 Magnetic Resonance Imaging (MRI)

MRI provides a detailed visualization of the anatomical structures within the carpal tunnel as opposed to information on the pathophysiological changes. As a result, it is commonly used before surgical treatment to rule out other pathological causes of CTS such as ganglions, haemangioma and bone growths (Ibrahim et al., 2012). Transverse images of the median nerve can determine the cross-sectional area (CSA) of the nerve at the level of the carpal tunnel. The CSA measurement is used to assess the severity of CTS with a sensitivity of 96% but a specificity of 33-38% (Ibrahim et al., 2012). The high cost and inaccessibility can deter clinicians from using MRI over other diagnostic techniques; nevertheless, it is the preferred technique by patients (Ibrahim et al., 2012).

2.5.5 High-Resolution Sonography

Ultrasound is an inexpensive, non-invasive, portable and easy to use diagnostic tool (Walker et al., 2004). When compared to MRI, ultrasound imaging is not only more convenient and less expensive but excels at fine measurements of small structures such as nerves and blood vessels. Ultrasound imaging has evolved from the ability to create an echo. Sound-wave pulses are emitted by an ultrasound transducer through biological tissue and the returning echo is then recorded. An image is constructed based on the temporal and acoustic properties of the echo with those returning earlier indicating more superficial structures. The resolution of ultrasound is directly proportional to the frequency of the sound-wave pulses and indirectly proportional to the depth of the image

obtained (Kremkau, 1990). Therefore, high resolution transducers allow for more detailed images of superficial structures.

The development of high-resolution transducers has made ultrasound a standard tool for nerve imaging (Walker et al., 2004). Pathological changes in the nerve can be observed in static and dynamic images obtained from ultrasound, allowing sonography to play a valuable role in the diagnosis of neurological disorders. Significant differences can be observed in the median nerve anatomy with carpal tunnel syndrome. These include increases in the cross-sectional area of the nerve just proximal to the carpal tunnel and the loss of the hyperechoic architecture of normal nerve tissue (Walker et al., 2004).

2.5.5.1 Sonographic Cross-Sectional Area Measurements

Cross-sectional area (CSA) of the median nerve as it approaches the carpal tunnel has been shown to be an accurate diagnostic technique. CSA is a commonly used sonographic parameter as it can be obtained from a static transverse image and is less expensive and more accessible than using MRI. A main limitation with CSA of the median nerve is the wide variability with the mean ranging from 4.8-9.7 mm^2 in controls and 10.7-16.8 mm^2 in CTS patients (Zyluk et al., 2010). As a result, the cut-off value for diagnosing CTS varies depending on the study (9-13 mm^2).

2.5.5.2 Nerve Hypervascularization

Ultrasound has become more established in musculoskeletal research due to recent technological advances as well as its cost effectiveness and availability in

comparison to other diagnostic imaging modalities (Mallouhi et al., 2006; Walker et al., 2004; Kamolz et al., 2001). By imaging the median nerve proximal to the carpal tunnel, intraneural blood flow velocity has been found to be significantly higher in those with CTS with a sensitivity of 83%. The sensitivity increased to 90% when combined with nerve CSA values (Joy et al., 2011). Strong correlations have been found between current diagnostic tests (nerve conduction, nerve CSA) and nerve hypervascularization, suggesting the need to further evaluate intraneural blood flow velocity, especially in those with negative NCS (Joy et al., 2011). In addition, hypervascularization can be detected before the development of nerve swelling and edema, allowing much earlier detection of median nerve damage (Mallouhi et al., 2006). The use of blood flow velocity in the diagnosis of CTS shows the potential for similar improvements in the assessment of CTS risk. Evaluating the changes in blood flow velocity throughout various work tasks may be an effective method to determine their effect on the ischemic changes observed with CTS.

Recent research has found differences between abnormal and normal vasculature in a neutral wrist posture (Evans et al., 2012; Ghasemi-Esfe et al., 2011; Joy et al., 2011; Mallouhi et al., 2006); however, there is a need for a quantitative analysis of intraneural blood vessels in other conditions (Wilder-Smith, 2012). Additional research is needed to define more reliable measures of differentiating normal from abnormal blood flow. The number or density of abnormal blood vessels has not been shown to have a dose-response effect on CTS symptoms (Mawrin et al., 2001). However, the peak systolic velocity may be an accurate measure to quantify the difference between healthy and CTS patients. In

addition, analyzing the rate of blood flow, under different conditions, such as non-neutral postures, has potential to assess for occupational risk factors. A characteristic component in the pathogenesis of entrapment neuropathies is elevated blood flow in the nerve starting several centimetres proximal to the site of compression (Ghasemi-Esfe et al., 2011; Joy et al., 2011). Elevated CTP found in deviated wrist postures and fingertip loads has thought to initiate the ischemic process leading to the development of CTS (Rempel et al., 1997). Thus, quantifying the intraneural blood flow velocity of the median nerve just proximal to the carpal tunnel may provide evidence of nerve compression and risk of CTS.

2.6 Measuring Blood Flow in the Median Nerve

Blood flow is the movement of blood through the vessels of the circulatory system and is expressed in centimetres per second. In the large arteries, it is pulsatile as a result of ventricular ejection but this pulsatility diminishes in amplitude as at the capillary level. For blood flow measurements, all of the ultrasound-based methods use the Doppler Principle. When ultrasound waves are transmitted to a moving object, e.g. red blood cells flowing in an artery, the reflected waves (echoes) will be at a different frequency (Kremkau, 1990). The change in frequency, termed the Doppler shift frequency, is directly related to the velocity of the moving object and the angle at which the ultrasound wave strikes the object (angle of insonation). To measure the blood flow, the Doppler shift equation (1) is rearranged to solve for the velocity of the red blood cells.

$$f = \frac{(2V)(f_o)(\cos\theta)}{C} \qquad (1)$$

The known variables are the approximate velocity of ultrasound in blood (C) and the transmitted ultrasound frequency (f_o). The Doppler shift frequency (f) is the measured variable. A limitation with this technique is the angle dependency. Error in blood flow velocities are reduced with smaller angles of insonation (< 20 degrees), where cosθ is assumed to equal 1. In this assumption, the ultrasound beam is oriented parallel to the direction of blood flow.

Blood flow can be assessed using two different types of displays: the pulsed-wave (PW) Doppler time-velocity graph and the colour Doppler map. PW Doppler displays the spectrum of blood flow velocities found within the sample volume, which is defined as the region interrogated during the collection or the PW gate. PW Doppler is used on peripheral structures and measures flow at specific sites to assess low flow velocities. The specificity of PW Doppler constrains the measurement by imposing a limit on the maximum measurable velocity. The Nyquist limit prevents aliasing of velocities that would appear on the opposite side of the baseline. The combination of colour Doppler and PW Doppler allows real time colour flow patterns mapped within the vessel while displaying blood flow velocities on a time-velocity graph. The colour flow patterns are displayed with the flow toward the transducer coloured as red and the flow away from the transducer coloured blue.

In colour Doppler imaging, the mean blood velocity, amplitude of the echo and variance of the velocities around the mean are calculated. A large variance exists with large, turbulent flow patterns, therefore, temporal and spatial averaging is performed on the data. As a result, hemodynamic details in both temporal and spatial dimensions are

removed. Blood Flow Imaging (BFI) is a directional power Doppler that enhances the colour Doppler imaging by preserving the potentially clinically important hemodynamic details. This allows for better depiction of the small collateral blood vessels. BFI Angio is designed to further improve the visualization of the low flow velocities as a non-directional power Doppler.

2.7 Summary

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy of the upper extremity. There is a need to refine current screening tools to aid in the diagnosis and treatment of the disease. Recent advances in sonography make it a useful non-invasive technique to assess early changes in the pathophysiology associated with diminished nerve function. Impaired function manifests as ischemia of the capillaries that supply the median nerve and can result in hypervascularization of the blood vessels at the proximal level of the carpal tunnel. These changes are detectable with ultrasound using measures of intraneural blood flow. A novel application of this technique is to evaluate the changes in median nerve blood flow in response to workplace exposures associated with increased CTS risk, such as awkward wrist posture and small fingertip forces. These blood flow measures will provide insight into how wrist posture and fingertip force can affect the vascular system of the median nerve and help evaluate CTS risk in the workplace.

CHAPTER 3 – PURPOSES & HYPOTHESES

3.1 Purposes

3.1.1 Measuring Intraneural Blood Flow Velocity in the Median Nerve

The first purpose of this thesis was to quantify intraneural blood flow within the median nerve using sonography. High-resolution ultrasound equipment was optimized to detect low velocities for the evaluation of blood flow in CTS symptomatics.

3.1.2 Effect of Wrist Posture and Fingertip Force on Intraneural Blood Flow

The second purpose of this investigation was to analyze the effect of wrist posture and fingertip force on the rate of blood flow in the median nerve of CTS symptomatics and healthy controls. Both posture and force were evaluated by using a combination of different wrist angles (flexion 30°, flexion 15°, neutral, extension 15°, extension 30°), and fingertip force (0 N, 6 N). Observing changes in blood flow with these established risk factors was hypothesized to help elucidate their effect on nerve function and their role in the pathophysiology of carpal tunnel syndrome. Additionally, the application of sonography to quantify changes in intraneural blood flow associated with occupational risk factors would establish it to be a potential non-invasive measure of carpal tunnel syndrome risk.

3.2 Hypotheses

It was hypothesized that:

1. Compared to neutral, both wrist flexion and wrist extension will result in an increase in blood flow, with wrist flexion having a greater overall change in blood flow velocity.
2. The addition of a fingertip force will increase the intraneural blood flow velocity in all wrist postures.
3. The intraneural blood flow velocity of CTS symptomatics is predicted to be greater than healthy controls in all wrist postures. In CTS symptomatics, severity in the neutral posture is expected to have a positive relationship with blood flow velocity, such that higher severity will have greater baseline blood flow velocity than lower severity CTS patients.

CHAPTER 4 – QUANTIFICATION OF BLOOD FLOW

Measuring Intraneural Blood Flow Velocity in the Median Nerve

This chapter represents the pilot work and development of the technique to measure intraneural blood flow in the median nerve that was used for the study itself. Thus, this chapter includes the commentary on the methods developed (and those attempted) along with an interpretation of those initial findings, which formed the basis for the examination of the blood flow in the median nerve.

4.1 Imaging the Median Nerve

This is the first study to evaluate the median nerve using ultrasonography at the McMaster Occupational Biomechanics Laboratory and the Vascular Dynamics Laboratory. To identify the median nerve, the sonographic scanner was positioned longitudinally at the wrist. The location of the median nerve was found relative to the radial artery (medial and superficial) and flexor tendons (lateral and superficial) at an approximate depth of 0.25-0.5 cm. In colour Doppler mode, the radial artery was easily identified as a hypoechoic band, which represented the lumen of the artery and became filled with shades of bright red to indicate forward blood flow motion. The flexor tendons were more difficult to differentiate from the median nerve due to a similar hyperechoic appearance. Hypoechoic refers to the artery appearing darker than surrounding structures; hyperechoic refers to the tendons and nerve appearing brighter than the surrounding tissues. In addition, the tendons have a more fibrillar pattern, are not compressible and show more motion on active movement of the muscles (Hochman et al.,

2004). Therefore, during finger flexion and extension the tendons were expected to display significantly greater displacement both at the proximal and distal level of the wrist crease compared to the median nerve. The anatomical position of the nerve adjacent and superficial to the index finger flexor digitorum superficialis tendon also helped to identify the nerve. Hochman et al. (2004) and Walker et al. (2004) have described a distinct echotexture with ultrasound imaging of the median nerve. In the longitudinal view, the nerve has a fascicular pattern of uninterrupted hypoechoic bands with intervening linear interrupted hyperechoic bands (Figure 4.1). The hypoechoic bands represent the fascicle and the hyperechoic bands are the supporting epineurium that surrounds each fascicle. In the transverse view, the nerve is composed of multiple hypoechoic circles that vary in size. Each circle represents a fascicle and these are intermingled in a hyperechoic background of the supporting connective tissues (Walker et al., 2004). As the nerve passes through the carpal tunnel, the nerve is seen as a more uniformly hypoechoic structure with more tightly packed fascicles and less intervening hyperechoic connective tissue.

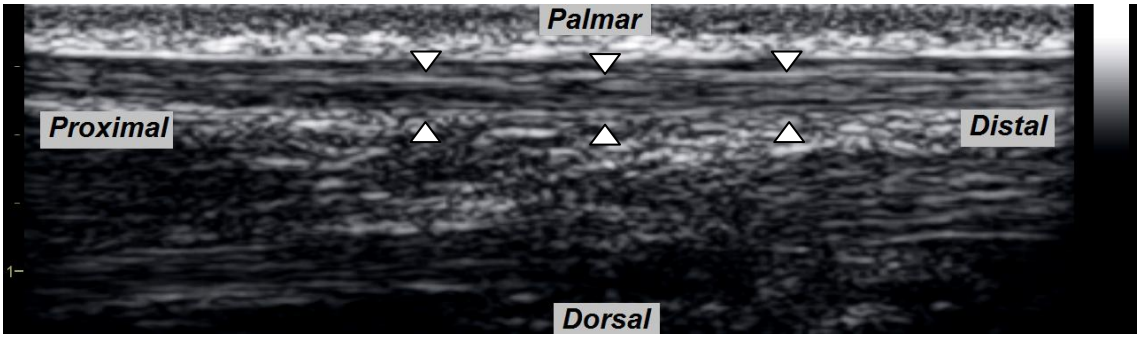

Figure 4.1. Longitudinal view of a healthy median nerve (arrowheads) at the proximal wrist crease. The hypoechoic bands (dark) represent the fascicle and the hyperechoic (light) bands are the supporting epineurium that surrounds each fascicle.

A healthy median nerve lies flat at the level of the pisiform, while the flexor retinaculum is thin and uniform, with mild palmar bowing (Hochman et al., 2004). Compression of the median nerve can result in pathological changes that can be visualized in sonographic images. For example, the median nerve can be enlarged at the level of the pisiform, while the flexor retinaculum might demonstrate greater palmar bowing at the level of the hamate. A common finding is also thickening of the synovium, which surrounds the flexor tendons and median nerve (Ettema et al. 2006). Distal to the carpal tunnel, the nerve can be flattened at the level of the hamate. Many of these findings have important clinical implications as diagnostic criteria.

The median nerve can be imaged both proximal and distal to the wrist crease. With median nerve compression, it has been shown that nerve hypervascularization occurs proximal to the wrist crease and ischemia occurs distal to the wrist crease. Measuring the intraneural blood flow velocity at either, or both, locations would provide information on the pathophysiology of the median nerve. In this study, we have chosen to evaluate the intraneural blood flow velocity of the median nerve at the wrist at the proximal wrist crease level due to difficulties in obtaining an image distally. The length of a linear high frequency transducer is approximately 4.7 cm. The palmar surface of the hand has a slight curvature which, due to the length of the transducer, limits gel coupling and reduces the quality of the image. The problem is further exacerbated if the participant is required to perform a task with their hand or fingers, where alterations of the curvature can affect the image. Another concern beyond the distal wrist crease is the thenar muscles. Often these muscle bellies can interfere with tracking the median nerve

within and distal to the carpal tunnel. Finally, the variation in anatomy between participants can also add to complications with tracking the nerve through the tunnel. For instance, the median nerve separates into two main branches and if the nerve splits very shortly after traversing the carpal tunnel, it can no longer be seen as a uniform structure (Hochman et al., 2004). The median nerve is required to have a certain diameter and level of intraneural blood flow velocity to be imaged in this particular study. As a result, the median nerve is not only difficult to identify distal to the carpal tunnel but it is particularly challenging to maintain a consistent image for the nature of this study. Proximal to the carpal tunnel, the median nerve remains in a stable position with only minor adjustments needed with changes in wrist posture. Therefore, intraneural blood flow velocity can be recorded in a more consistent manner with less likelihood for error.

4.2 Optimizing the Ultrasound Settings

The appropriate ultrasound application was difficult to establish. Previous studies utilized a musculoskeletal setting to quantify intraneural blood flow of the median nerve (Evans et al., 2012; Wilder-Smith, 2012). The musculoskeletal setting, on the Vivid Q system (GE Healthcare) with a 12L transducer, reported no colour maps (no blood flow) over the median nerve and poor colour mapping over the radial artery. Therefore, it was decided to explore alternate ultrasound settings. The upper extremity artery (UEA) application was selected because it offered the best combination of both B-mode and colour Doppler imaging of the nerve. The pulse repetition frequency was adjusted to 0.8 kHz to optimally detect low velocities. This setting was also used by

Mallouhi et al. (2006). No improvements with colour mapping were found with 0.4, 0.6 or 1.4 kHz. The low velocity reject was set to the lowest setting (0.3 cm/s) to avoid filtering any low velocities from the signal. The power was tested over the entire range and was set to 0 db (100%) to reduce noise. The lateral average was also set to the lowest setting to include low velocities; however, this could potentially increase the probability of noise. BFI is an enhanced colour flow mode with added speckle information to visualize the blood flow direction but this did not seem to improve the image. BFI Angio was used to test participants that did not present with colour maps in colour Doppler mode. BFI Angio is advantaged in detecting non-directional flow with improved sensitivity to low velocities.

To further explore the use of colour Doppler/BFI Angio and PW Doppler in the measurement of intraneural blood flow, we tested the sensitivity of each application to detect increases in intraneural blood flow. This was done to determine if higher velocities could be detected with the current settings and if it could be limited by low velocities. In healthy individuals, we varied conditions that included holding overhead postures, holding a flexed wrist posture for 10 minutes, arm resistance exercises (push-ups), arm cardiovascular activities (arm ergometer) and holding a pinch grip for 5 minutes. The idea was to systematically increase heart rate and blood flow to the hand. However, no colour was observed over the median nerve in colour Doppler or BFI Angio mode. At baseline, a non-directional signal was found over the median nerve in PW Doppler. Changes in the signal were detected following the activities to suggest that it may be used to detect low velocity blood flow. Firstly, the PW Doppler gate was placed over different

areas of the image including the bone, skin, gel standoff pad and tendons. No signal was found over areas where we did not expect to measure blood flow such as on the gel standoff pad and bone. A second test was done involving a blood pressure cuff to occlude blood flow to the distal arm. The PW Doppler gate was placed over the nerve with the non-directional signal present. A cuff was placed over the upper arm and inflated to 200 mmHg for five minutes. Visible signs of blood occlusion were observed on the subject's hand and coincided with the immediate disappearance of the signal. The cuff was released and the signal returned to baseline. Therefore, in healthy subjects, a non-directional signal was observed as intraneural blood flow even though no colour mapping was obtained. As a result, both PW Doppler and colour Doppler settings were optimized for measuring low flow velocity in healthy controls and then, tested on an individual with carpal tunnel syndrome. The specific colour Doppler settings were then adjusted based on the colour mapping seen with the CTS patient until the best image was established.

4.3 Adaptations to the Protocol

To use PW Doppler on the median nerve, a custom gel pad was necessary to achieve the appropriate depth. In duplex mode, the PW Doppler gate was unable to reach the superficial location of the median nerve. Using a gel pad (approximately 0.25 cm), the median nerve was observed at a greater depth in the image. This allowed the PW Doppler gate to be positioned over the nerve with a simultaneous live B-mode image.

Wrist postures of 45° extension and flexion were eliminated from this study. Pilot testing determined that 45° was too extreme for the participants to maintain for the length of the study. Healthy controls experienced pain and discomfort at 45° and had difficulty keeping the 6 N force constant. In addition, a 10 N finger force level was tested with healthy controls, but was also found to be too difficult to sustain over the 5 wrist postures. Thus, 6 N was determined as the most difficult force level while still being able to maintain for up to 3 minutes in each wrist posture.

CHAPTER 5 – METHODS

Effect of Wrist Posture and Fingertip Force on Intraneural Blood Flow

5.1 Participants

Ten CTS symptomatic and nine healthy volunteers aged 18 to 55 were recruited for this study. Only participants with carpal tunnel syndrome or who were experiencing pain, tingling or numbness of the hand were included in the CTS symptomatic group. All participants completed a brief questionnaire (Appendix A) to screen for musculoskeletal disorders of the hand and wrist as well as other health conditions that may influence the vascular or nervous system. Exclusion criteria for the control group included symptoms of peripheral neuropathy (pain, tingling, numbness, weakness of the upper extremity) and/or diagnosis of carpal tunnel syndrome. In addition, the control group was required to have a negative Phalen's Test, a score of 0 on Levine's CTS Questionnaire and a score of 0 on Katz hand diagram. Exclusion criteria for both groups included previous wrist surgery, radial malunion, colles fracture, bifid median nerve, persistent median artery, degenerative joint disease, arthritis of the wrist/hand, gout, hemodialysis, sarcoidosis, amyloidosis, hypothyroidism and diabetes mellitus. In addition, resting seated blood pressure was measured using automated oscillometry for all participants and any participants with abnormal blood pressure (≥140 mmHg systolic; ≥90 mmHg diastolic) were excluded from the study. After explaining the study protocol in detail, written informed consent was obtained from all participants (Appendix D). The study was approved by the Hamilton Health Sciences/McMaster Health Sciences Research Ethics Board.

5.2 Qualitative Assessments

The Phalen's Test was performed on each participant. The test consisted of participants actively holding their right wrist in full flexion for 60 s and reporting symptoms associated with median nerve compression. Symptom severity and functional status were evaluated using Levine's CTS Questionnaire (Appendix B). This questionnaire is based on a typical twenty-four hour period during the past two weeks and each question is scored from 0 (none) to 4 (very severe). A Katz hand diagram (Appendix C) was used to document both the location and type of symptom (pain, tingling, numbness, decreased sensation). The hand diagram was completed as a baseline and revisited throughout the study if there were changes in the participant's symptoms.

5.3 Experimental Set-Up

Participants were seated facing an adjustable table that allowed the right shoulder to be fully adducted. The right elbow was supported below on a padded surface and positioned in a flexed posture (~120^{o}). The right forearm was immobilized in a supinated position using a custom thermoplastic splint. The dorsal surface of the right hand was placed on a padded surface and was strapped down to fix the palm. This helped to maintain a constant wrist angle without impeding wrist and finger movement and limited pronation of the hand. To adjust the wrist posture, the forearm support was kept in a fixed position, while the hand support was attached to a hinge that could move the wrist into five different flexion/extension wrist angles (Figure 5.1). For each wrist

position, the participant's distal wrist crease was aligned with the hinge joint. All wrist postures were tested with and without the addition of a force component consisting of a 6 N fingertip press based on previous studies of occupational tasks (Keir et al., 1998; Rempel et al., 1997). A slot was placed in the hand support of the apparatus in line with the participant's middle finger. A force transducer (MLP50, Transducer Techniques, Temecula, CA, USA) was attached on one end to a padded metal ring (with adjustable diameter) and on the other end to a screw that fit through the slot (Figure 5.1). The metal ring/force transducer moved the length of the slot to adjust for the participant finger length. For the force trials, the participant's middle finger was placed so that the distal phalange was centered through the metal ring. Participants were instructed to press up with their fingertip. Visual feedback of their force was provided using a custom program (LabView 8.5, National Instruments, Texas, USA) with a target line set to 6 N. Force was collected at a sample rate of 2000 Hz and reviewed after the trial to ensure the participants maintained the correct level of force throughout the trial.

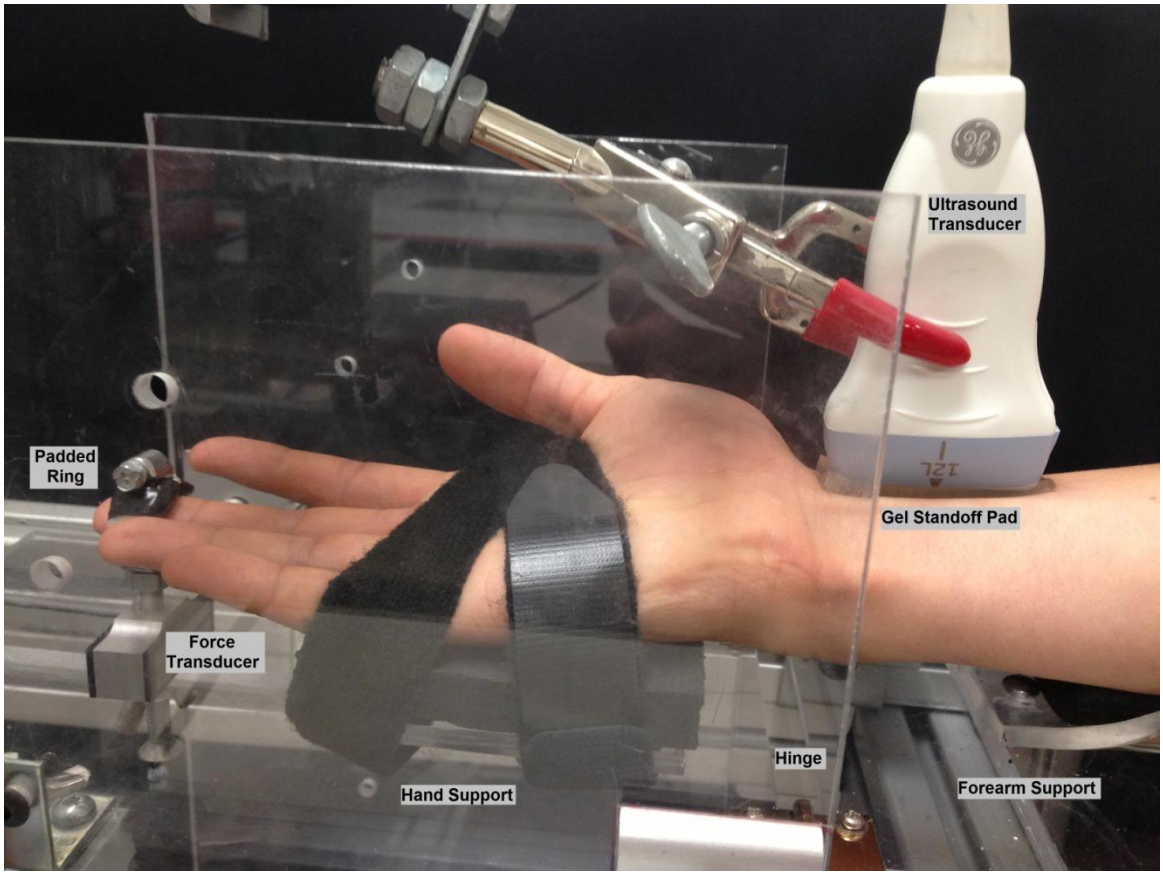

Figure 5.1. Experimental set-up indicating hand and wrist posture, padded ring attached to force transducer, location of the hinge linking the forearm support and hand support and the location of the ultrasound transducer (probe).

5.4 Sonographic Measurements

A sonographic system (Vivid Q, General Electric Healthcare, Milwaukee, WI) equipped with a high frequency (12 MHz) linear array transducer (12L, General Electric Healthcare) was used to examine the median nerve. Grayscale images of the median nerve were obtained in both the transverse and longitudinal planes using ultrasound gel. The probe was placed on the palmar wrist surface of the skin at the proximal wrist crease (proximal to the carpal tunnel) and in line with the median nerve. A neutral wrist posture

was maintained by padding under the dorsum of the hand and the fingers were kept in a semi-flexed, relaxed position. The transverse images were taken proximal to the carpal tunnel at the level of the pisiform and used to determine the CSA of the nerve.

Electrocardiography (ECG) was used to monitor heart rate throughout the study. Electrodes were placed on both clavicles and the left lower rib. Electrode sites were cleaned and/or shaved if necessary. The ECG was displayed on the Vivid *Q* sonographic machine and used later in the analysis of the signal.

Intraneural blood flow velocity was evaluated in the longitudinal plane with a custom gel standoff pad (Aquaflex Gel Pad; Cone Instruments, Solon, OH) to increase the depth of the nerve in the image for PW Doppler. To avoid compression and occlusion of the blood vessels, minimal pressure was applied to the skin through the transducer. PW Doppler was used to obtain quantitative measurements of the blood flow waveform. An optimized upper extremity artery (UEA) setting was used for all participants (Table 5.1). PW Doppler was collected in duplex mode with a simultaneously live grayscale image and spectral waveform.

Colour Doppler was used prior to the PW Doppler as a qualitative measure of blood flow. The colour window dimensions were modified to include the median nerve. When a colour map was present on the median nerve, the location of the greatest colour scale intensity was used as the position of the PW Doppler gate (1 mm). This marked the location of the highest area of blood flow on the median nerve. If the direction of flow could be determined, a 20° beam steer angle and angle correction factor was applied. Five seconds of systolic pulsations was required to ensure stability of the signal.

However, when a colour map was absent on the median nerve, the PW Doppler gate (1 mm) was positioned over the median nerve until a signal was obtained. This signal was required to have consistent positive deflections and reach five seconds of steady state. No steer angle or angle correction was used since the direction of flow was indeterminate.

Table 5.1. Sonographic equipment and optimized parameters.

System	Vivid Q, GE Healthcare (Milwaukee, WI)
Probe	12 MHz linear (12L)
Application	Upper Extremity Artery (UEA)
Depth	3.0 cm
Frequency	12 MHz
Continuous Tissue Optimization (CTO)	ON
CTO Gain	55-65
Low Velocity Reject / Wall Filter	0.3 cm/s
Pulse Repetition Frequency (PRF) / Scale	Low (0.8 kHz)
B-Mode Gain	12
Compound	ON
Colour Window	Small, over median nerve
Power	0 dB (100%)
Sample Volume / PW Doppler Gate	Wide, highest area of colour (0.98 mm)
Colour/PW Frequency	5 MHz

Blood flow velocity measurements of the median nerve were evaluated in five wrist postures including 30^{o} flexion, 15^{o} flexion, neutral, 15^{o} extension and 30^{o} extension. PW Doppler was used to record the initial peak systolic velocities in the neutral position. Blood flow velocity was recorded after steady state was achieved in each of the wrist postures. Steady state was determined as a consistent signal over a five second interval. Participants rested between trials for approximately 3 minutes until their blood flow reached their initial velocities. Trial order was block randomized by wrist posture. For

all postures, participants performed the condition with no force followed by 6 N of force. This was done because the force trial had a greater chance of fatigue than the no force trial. The force was sustained for 2-3 minutes and the nerve blood flow was recorded throughout until blood flow had reached a steady state. All data was exported for further analyses in EchoPac (post-processing software, General Electric Healthcare).

For a subset of 5 healthy participants, a reliability analysis of the PW Doppler measurements was performed. The full protocol was repeated a minimum of two weeks later to test the reliability of the intraneural blood flow velocity measurement.

5.5 Data Analysis

5.5.1 Experimental Groups

Each participant was classified into an experimental group based on symptoms and sonography assessment. A control (N=9) group and a CTS symptomatic (N=9) group were determined, in addition to a CTS individual (N=1) that required a separate analysis (Figure 5.2). The control group was characterized by no clinical signs or symptoms of CTS and showed no colour maps using BFI Angio. The CTS symptomatic group reported CTS symptoms, did not score positively on all clinical tests and were absent of colour maps. The CTS individual reported the classic symptoms of CTS and demonstrated colour maps with BFI Angio.

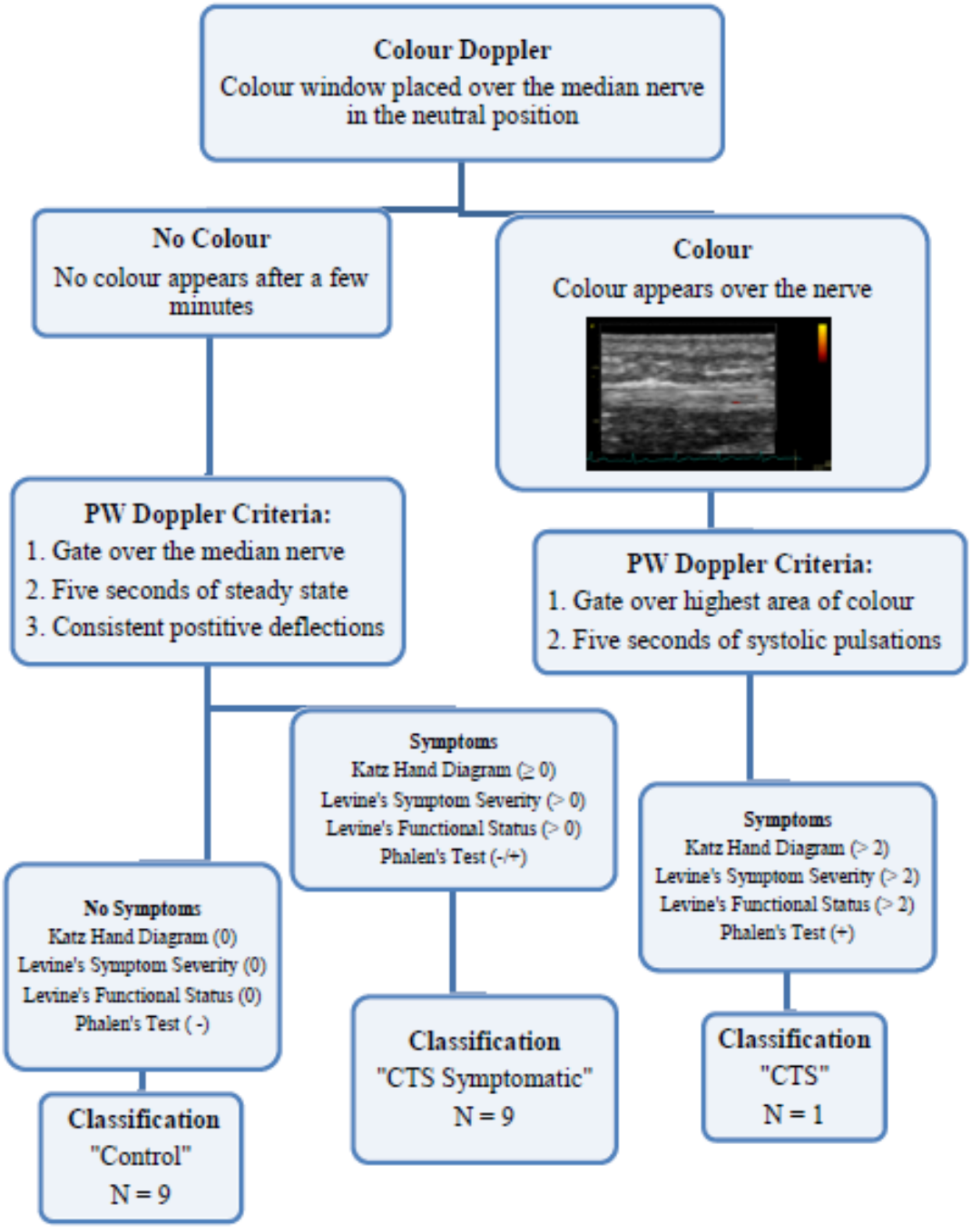

Figure 5.2. Decision flowchart for classifying participants into experimental groups.

5.5.2 Qualitative Assessments

The Phalen's Test was considered positive if participants reported pain, tingling or numbness in the median nerve distribution over the course of the one minute procedure (Georgiew, 2007). The overall Levine's Symptom Severity and Functional Status score was calculated as the mean of all the scores for each section (Levine et al., 1993). The Katz hand diagrams were scored independently by two researchers, who were masked to the participant's performance in the study. Scoring was performed twice, two weeks apart, according to the scoring criteria described by Franzblau et al. (1994). Each baseline hand diagram was scored "unlikely" (0), "possible" (1), "probable" (2) or "classic" (3) for CTS. The baseline hand diagrams were used to compare to other variables in the study while the changes throughout the task were used for observational purposes. Table 5.2 shows the scores for Levine's symptom severity scale, Levine's functional status scale and symptoms reported on the Katz hand diagram.

Table 5.2. Characteristics of study participants including qualitative (clinical) CTS tests.

Variable	**Control (N=9)**	**CTS Symptomatic (N=9)**	**CTS (N=1)**
Age*	29 (10)	36 (15)	51
Gender	1 M, 8 F	2 M, 7 F	1 F
CSA at inlet (cm^2)*	0.10 (0.04)	0.09 (0.02)	0.11
Right Hand Dominance	9	9	1
Levine's Symptom Severity Score*	0	1.75 (0.54)	3.64
Levine's Functional Status Score*	0	1.32 (0.93)	2.88
Phalen's Test (+)	0	4	1
Katz Hand Diagram (>0)	0	6	1

** Mean with standard deviation*

5.5.3 Sonographic Measurements

5.5.3.1 Cross-Sectional Area

Transverse images of the median nerve were obtained at distal wrist crease as the nerve approached the carpal tunnel inlet. The CSA of the median nerve was measured using electronic calipers (EchoPac, General Electric Healthcare). The nerve was outlined using the internal rim using area measurement software and rounded to the nearest 0.01 cm^2. Values greater than 0.10 cm^2 were considered abnormal and a possible sign of CTS (Visser, 2008).

5.5.3.2 Intraneural Blood Flow Velocity

Of the ten participants reporting CTS symptoms, one participant (CTS individual) fit the criteria for colour maps present on the median nerve. As a result, directional intraneural blood flow was observed in the CTS individual (N=1) while the remaining control (N=9) and CTS symptomatic (N=9) groups had non-directional intraneural blood flow in the neutral posture with no force. Directional blood flow was defined by the colour maps. If no colour was present, the blood flow was considered non-directional. If colour was present, the colour map was required to show a longitudinal pattern. If a longitudinal pattern was seen, the alignment of the blood vessel was considered to be in that direction and an angle correction factor was applied. Without a direction of the blood vessel, no assumption can be made about the direction of the blood flow and no angle correction can be used. Therefore, the CTS individual was not included in the statistical

analysis as the angle-corrected directional values could not be compared to non-directional values.

The signal of the CTS individual (directional blood flow) was collected with a 20° steer angle and an angle correction factor of 68°. The directional, pulsatile signal was analyzed by averaging the peak systolic velocity (cm/s) of three cardiac cycles within 5 s of steady state (Figure 5.3). The signal of the control and CTS symptomatic (non-directional blood flow) varied between pulsatile and non-pulsatile. The pulsatile signals were analyzed by taking the peak systolic velocity (cm/s) of a three cardiac cycles within 5 s of steady state (Figure 5.4). The non-pulsatile signals were analyzed by taking the mean peak velocity (cm/s) of a consistent 5 s of steady state (Figure 5.5). The mean peak velocity of all participants for each posture and force level was determined and separated by classification.

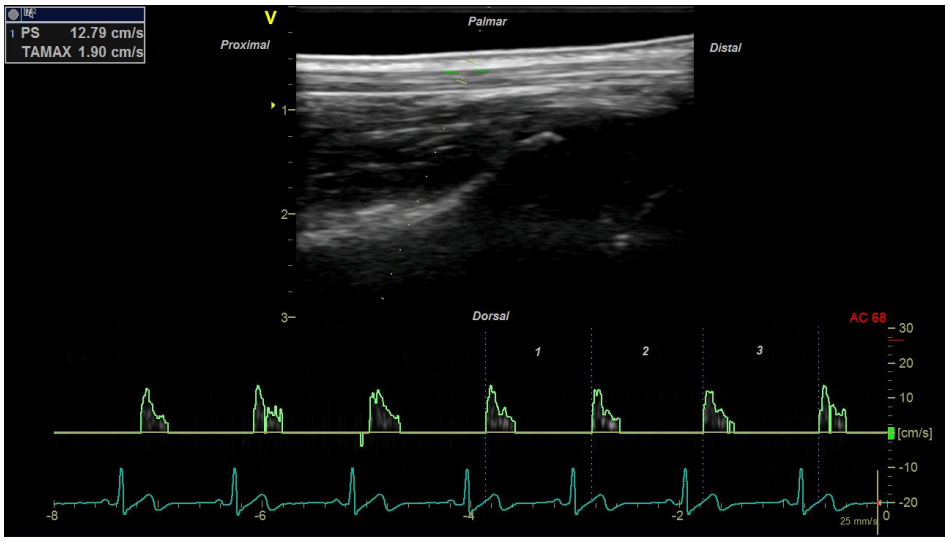

Figure 5.3. Directional, pulsatile intraneural blood flow in the CTS individual. The PW Doppler gate is positioned over the median nerve at the level of the proximal wrist crease. Angle correction factor of 68° was used. Mean peak systolic velocity (cm/s) was taken as an average of three cycles.

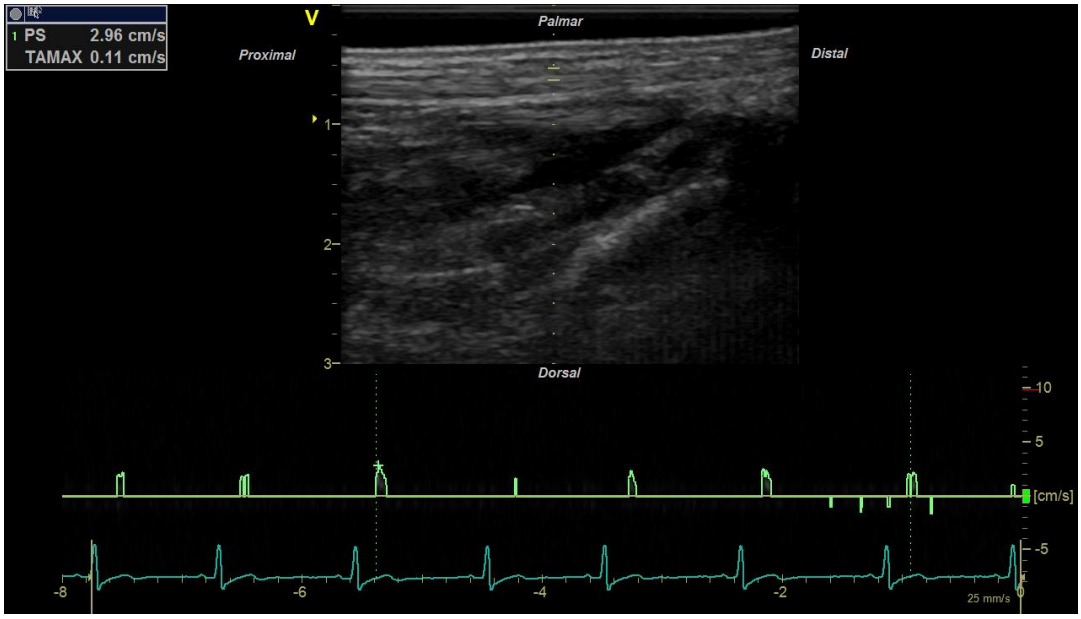

Figure 5.4. Non-directional, pulsatile intraneural blood flow with the PW Doppler gate positioned over the median nerve at the level of the proximal wrist crease. Mean peak systolic velocity (cm/s) was taken as an average of three cycles.

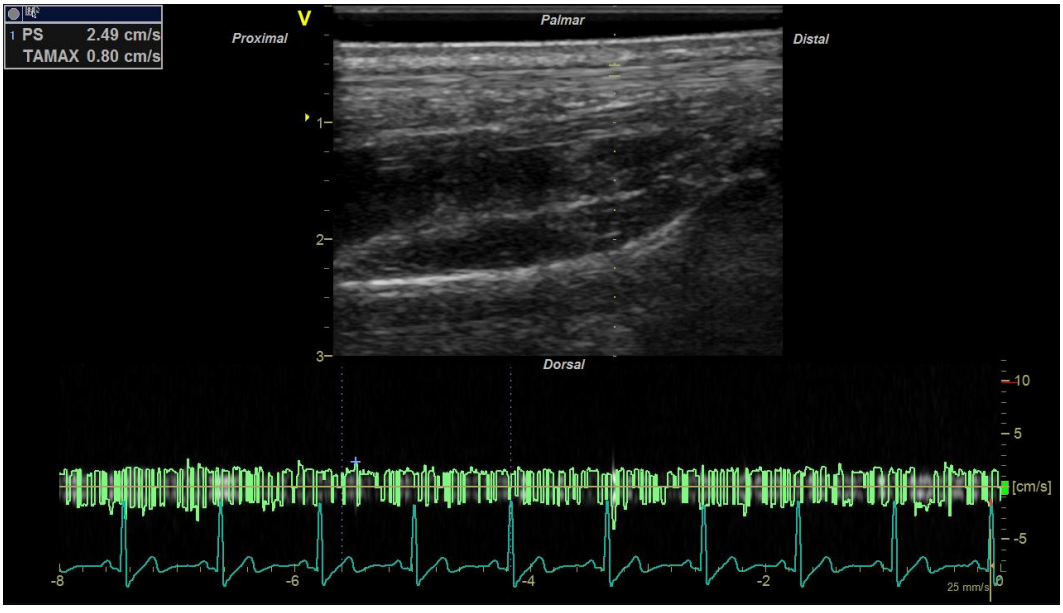

Figure 5.5. Non-directional, non-pulsatile intraneural blood flow with the PW Doppler gate positioned over the median nerve at the level of the proximal wrist crease. Mean peak velocity (cm/s) was taken from a consistent 5 s of steady state.

5.6 Statistical Analysis

All statistical analyses were performed using SPSS Statistics 17.0 with the significance level set at $p < 0.05$. The control and CTS symptomatic groups (non-directional blood flow) were used for statistical analysis; the mean and standard deviation were reported for the CTS individual (directional blood flow). A repeated measures mixed design ANOVA tested the effects of posture and force on intraneural blood flow velocity and compared the results between experimental groups. The independent within-subjects variables were five wrist postures (15^o, 30^o flexion; neutral; 15^o, 30^o extension) and two force levels (0N, 6N). The independent between-subjects variables were two experimental groups (control, CTS symptomatic). The dependent variable was the peak velocity of intraneural blood flow (cm/s). Post hoc comparisons were conducted with Tukey's HSD tests. Pearson product-moment correlations (r) were performed on all qualitative assessments (Katz hand diagram, Levine's CTS questionnaire, Phalen's Test), nerve CSA and the mean peak blood flow velocities.

The reliability of the mean peak velocity of intraneural blood flow (cm/s) was tested in five healthy participants using a paired samples t-test. The mean peak velocity of each independent variable (wrist posture, force) were compared between day 1 and day 2 to determine if the results were significantly different.

CHAPTER 6 – RESULTS

6.1 Qualitative Assessments

The CTS symptomatic group was not clinically diagnosed but showed a significant correlation with four commonly used diagnostic tools: a positive Phalen's test ($r = 0.535$, $p < 0.022$), a higher Katz hand diagram score ($r = 0.620$, $p < 0.006$), a higher Levine's Symptom Severity score ($r = 0.925$, $p < 0.0005$) and a higher Levine's Functional Status score ($r = 0.730$, $p < 0.001$) (Table 6.1). Levine's Symptom Severity Scale also correlated with Katz hand diagram ($r = 0.525$, $p < 0.025$) and Levine's Functional Status Scale ($r = 0.772$, $p < 0.0005$). In addition, Levine's Functional Status Scale correlated with Katz hand diagram ($r = 0.713$, $p < 0.001$).

Table 6.1. Pearson product-moment correlations (r) of the qualitative assessments and nerve CSA (* denotes a significant association between the tests, $p < 0.05$).

	Age	Phalen's Test	Katz Hand Diagram	Levine's Symptom	Levine's Function	CSA in Neutral
Experimental Group	0.305 (p < 0.218)	**0.535* (p < 0.022)**	**0.620* (p < 0.006)**	**0.925* (p < 0.0005)**	**0.730* (p < 0.001)**	0.130 (p < 0.606)
Age		-0.050 (p < 0.843)	0.187 (p < 0.457)	**0.506* (p < 0.032)**	0.285 (p < 0.252)	0.302 (p < 0.224)
Phalen's Test			0.265 (p < 0.288)	0.341 (p < 0.166)	0.404 (p < 0.096)	-0.159 (p < 0.528)
Katz Hand Diagram				0.525 (p < 0.025)	**0.713* (p < 0.001)**	-0.060 (p < 0.813)
Levine's Symptom					**0.772* (p < 0.000)**	0.211 (p < 0.400)
Levine's Function						-0.052 (p < 0.838)

Six of the nine participants in the CTS symptomatic group received a score on the Katz hand diagram with three scoring 1, two scoring 2 and one scoring 3. All the control subjects were required to score 0 on the Katz hand diagram. Thus, there was a strong correlation ($r = 0.620$, $p < 0.006$) between the experimental group and the Katz hand diagram score. When compared to the peak blood flow velocity, the Katz hand diagram score only correlated with flexion 15° with no force ($r = 0.656$, $p < 0.003$) and flexion 30° with force ($r = 0.535$, $p < 0.022$). In addition, Katz hand diagram was used to document any symptoms after each trial. Table 6.2 shows that the CTS symptomatic group was more prone to symptoms than the control group. Pain and tingling were the most common symptoms.

Table 6.2. Katz hand diagram results, demonstrating the symptoms that occur after each trial. CTS symptomatics were more prone to symptoms than the control group but the control group was not without symptoms. All symptoms were documented after the force trials; no symptoms were reported after the no force trials.

		Pain		Tingling		Numbness		Decreased Sensation	
Flexion 30°	Control	2/19	11%	4/19	21%	0/19	0%	0/19	0%
	CTS	4/19	21%	4/19	21%	1/19	5%	1/19	5%
	All	**6/19**	**32%**	**8/19**	**42%**	**1/19**	**5%**	**1/19**	**5%**
Flexion 15°	Control	1/19	5%	2/19	11%	0/19	0%	0/19	0%
	CTS	5/19	26%	3/19	16%	3/19	16%	0/19	0%
	All	**6/19**	**32%**	**5/19**	**26%**	**3/19**	**16%**	**0/19**	**0%**
Neutral°	Control	1/19	5%	0/19	0%	0/19	0%	0/19	0%
	CTS	3/19	16%	4/19	21%	1/19	5%	0/19	0%
	All	**4/19**	**21%**	**4/19**	**21%**	**1/19**	**5%**	**0/19**	**0%**
Extension 15°	Control	3/19	16%	1/19	5%	0/19	0%	0/19	0%
	CTS	2/19	11%	5/19	26%	1/19	5%	0/19	0%
	All	**5/19**	**26%**	**6/19**	**32%**	**1/19**	**5%**	**0/19**	**0%**
Extension 30°	Control	3/19	16%	0/19	0%	1/19	5%	0/19	0%
	CTS	5/19	26%	2/19	11%	2/19	11%	1/19	5%
	All	**8/19**	**42%**	**2/19**	**11%**	**3/19**	**16%**	**1/19**	**5%**

6.2 Sonographic Measurements

6.2.1 Cross-Sectional Area

The CSA of the median nerve at the distal wrist crease in the neutral position significantly correlated with the peak blood flow velocity at neutral with no force ($r = 0.495$, $p < 0.037$).

6.2.2 Intraneural Blood Flow Velocity

Two main effects (wrist posture, force) and a trend (experimental group) are shown on Figure 6.1; no interaction effects were found. There was a significant main effect of force on blood flow velocity ($F_{1,16} = 28.039$, $p < 0.0005$). The mean peak blood flow velocity was greater with force (3.56 cm/s) compared to without force (2.81 cm/s) (Figure 6.2A). This was consistent over all wrist postures in both experimental groups.

A significant main effect of wrist posture was found ($F_{4,64} = 3.163$, $p < 0.020$) (Figure 6.2B). Deviated wrist postures produced greater blood flow velocities than the neutral wrist posture. Post hoc analysis revealed that flexion 30° ($p < 0.002$), flexion 15° ($p < 0.004$), and extension 30° ($p < 0.002$) were significantly different than neutral. The three wrist postures of flexion 30° (3.37 cm/s), flexion 15° (3.27 cm/s), and extension 30° (3.29 cm/s) had significantly higher blood flow velocities than the neutral (2.87 cm/s) wrist posture. The blood flow velocity in extension 15° (3.13 cm/s) was also higher than neutral but did not reach statistical significance ($p < 0.099$). Additionally, there was a significant quadratic relationship between wrist posture and intraneural blood flow velocity ($p < 0.0005$).

A trend was shown in peak blood flow velocity between the two experimental groups as the mean peak blood flow velocity of CTS symptomatics (3.34 cm/s) was slightly higher than the healthy controls (3.03 cm/s) and this difference approached statistical significance ($F_{1,16} = 4.121$, $p < 0.059$) (Figure 6.2C).

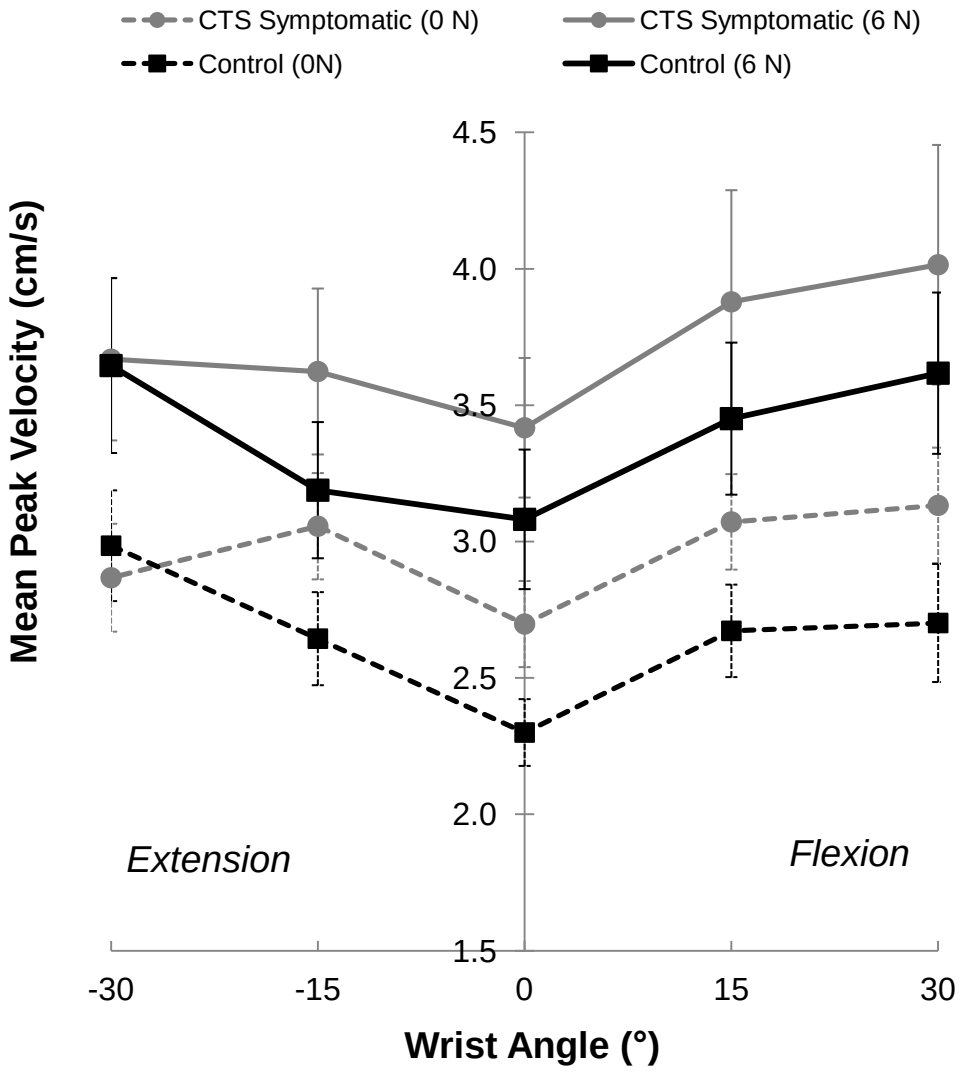

Figure 6.1. Mean peak velocity (cm/s) with standard error of the intraneural blood flow of the median nerve at the proximal level of the carpal tunnel in controls and CTS symptomatics with and without a 6 N fingertip force in five wrist postures.

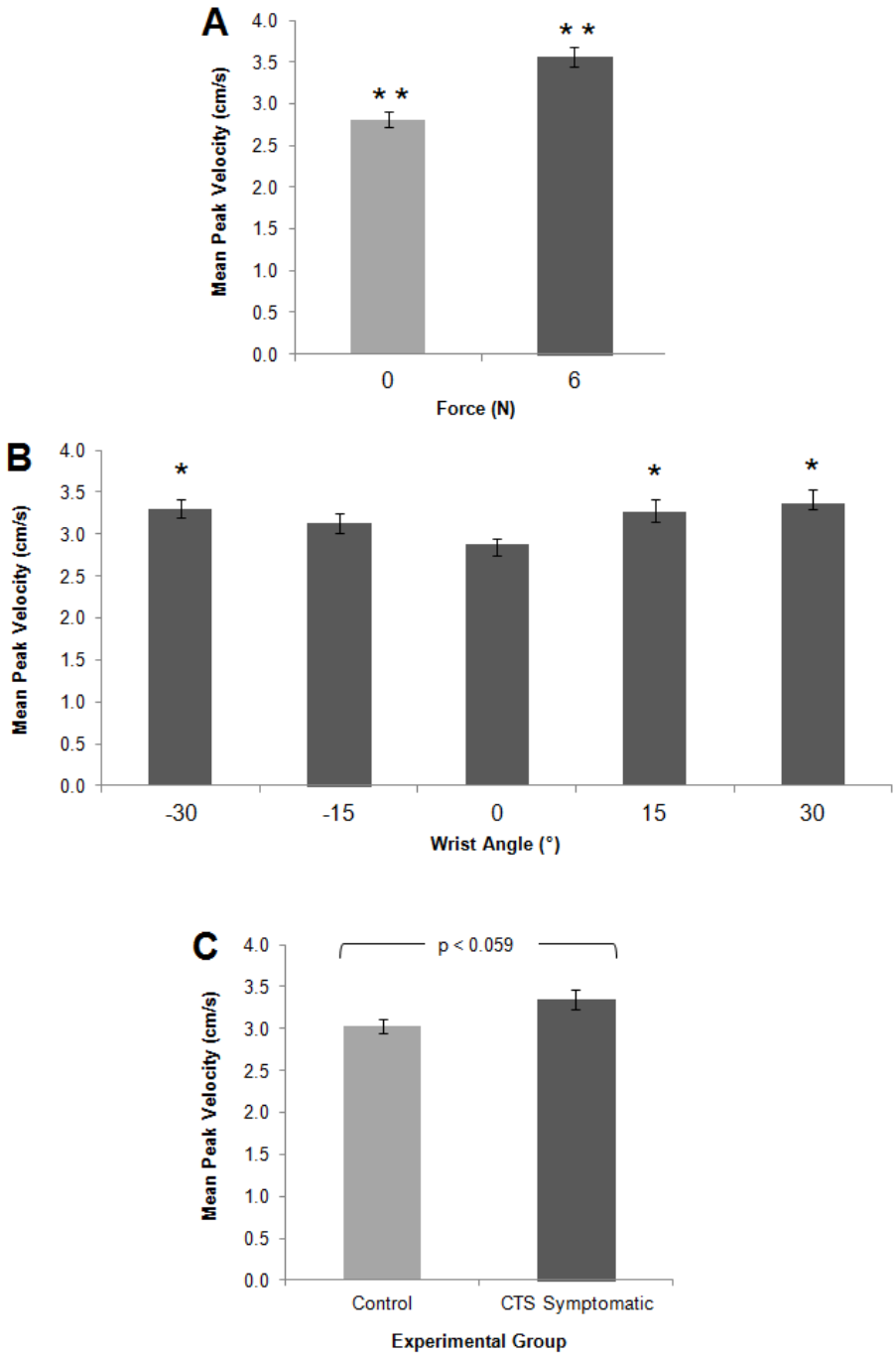

Figure 6.2. Mean peak intraneural blood flow velocity (cm/s) with standard error to illustrate (A) a force main effect (** significantly different, $p < 0.0005$), (B) a wrist posture main effect (* significantly greater than 0°, $p < 0.02$), and (C) a general trend in the experimental group ($p < 0.059$).

The mean peak velocity in the neutral wrist posture with no force represented a baseline measure. The baseline (neutral, no force) velocity in the CTS symptomatic group was generally higher than the control group; however, this was not consistent for all subjects (Figure 6.3). The baseline results for the CTS individual were included in Figure 6.3 to demonstrate the difference. The CTS individual showed a greater peak velocity than the other groups but the magnitude cannot be directly compared due to the angle correction factor. As a result, the blood flow velocity for the CTS individual was not compared to the other groups but the descriptive statistics are shown in Table 6.3.

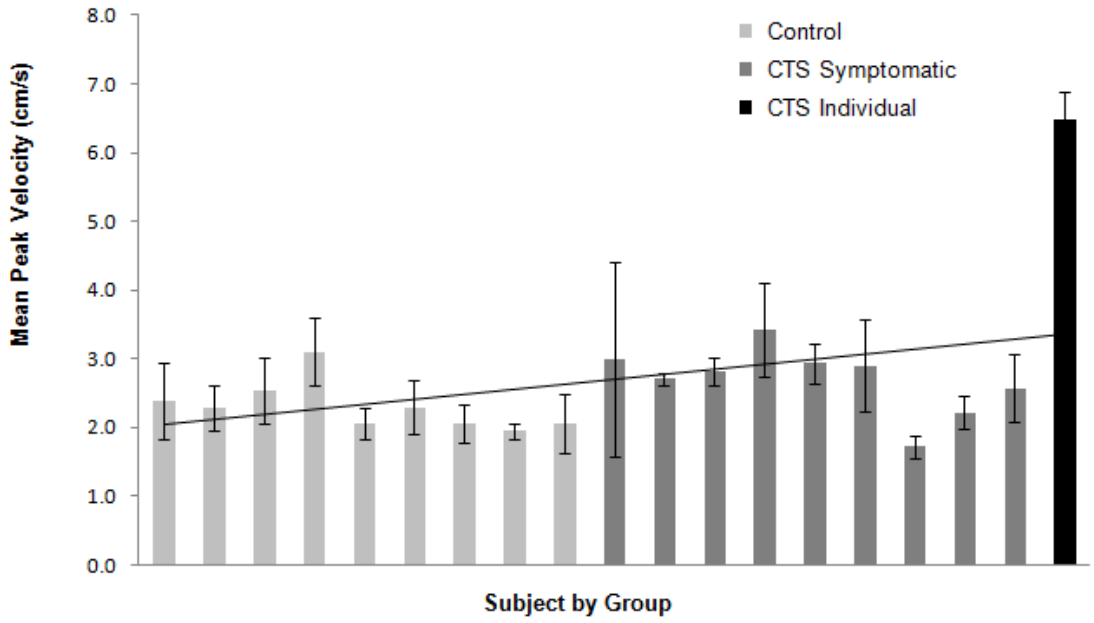

Figure 6.3. Mean peak velocity (cm/s) with standard deviation of each subject, separated by group, in a neutral wrist posture with no force. A linear trend line demonstrates the mean velocity of the CTS symptomatic group is higher than the mean velocity of the control group. The mean velocity of the CTS individual is shown for comparison.

Table 6.3. Mean peak intraneural blood flow velocity (cm/s) with standard deviation of the CTS individual (N=1). The velocity was corrected for the angle of insonation (68°) using the BFI Angio images.

		Wrist Posture				
		Flexion 30°	**Flexion 15°**	**Neutral**	**Extension 15°**	**Extension 30°**
Force	**0 N**	5.90 (±0.59)	8.01 (±0.43)	6.47 (±0.42)	11.72 (±1.60)	8.49 (±1.60)
	6 N	10.36 (±1.02)	13.54 (±0.85)	11.80 (±0.74)	9.56 (±0.60)	10.46 (±2.19)

6.3 Reliability Analysis

In a subset of five participants from the control group, the mean peak velocity (cm/s) of all trials (Figure 6.4A) showed no significant difference from day 1 to day 2 ($p < 0.991$). When grouped by force (Figure 6.4B) and wrist posture (Figure 6.4C), there was still no significant difference.

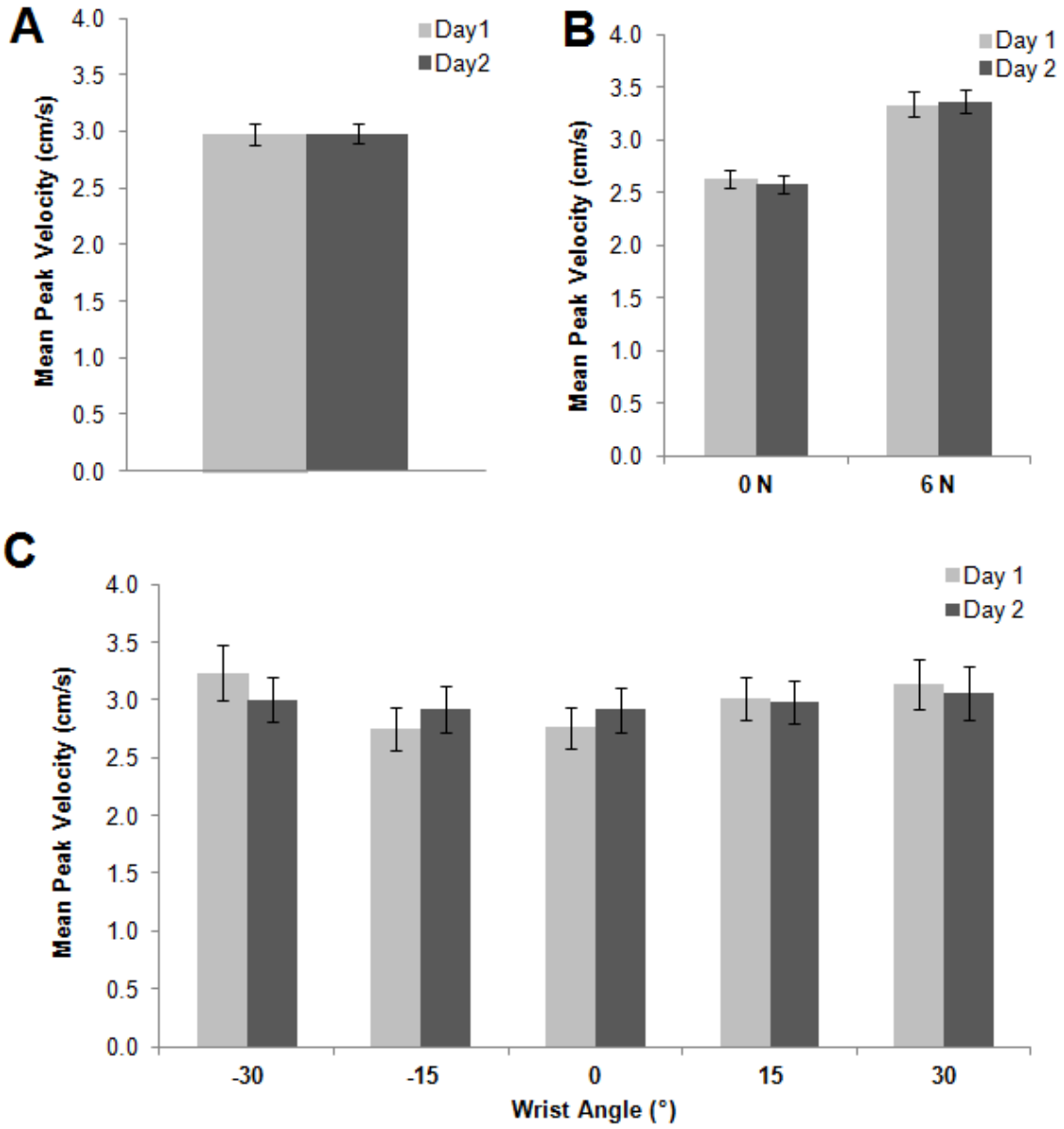

Figure 6.4. A paired samples t-test (N=5) for the mean peak blood flow velocity (cm/s) with standard error of all trials showed (A) no significant difference between the mean values from day 1 to day 2. Similarly, no significant difference was found (B) when grouped by force level or (C) when grouped by wrist posture.

CHAPTER 7 – DISCUSSION

7.1 Discussion

An enlarged, more vascular median nerve is a common pathophysiological change in patients with CTS (Joy et al., 2011). Many sonographic studies have examined pathological increases in CSA but few studies have examined nerve hypervascularity. This study represents the first attempt to use pulse wave (PW) Doppler to measure changes in intraneural blood flow to quantify the effects of occupational risk factors for CTS, including deviated wrist posture and force. The rate of blood flow was successfully quantified in ten conditions, five wrist postures and two force levels. Prior to this study, intraneural blood flow velocity has only been achieved in the neutral posture with no other conditions evaluated.

There are three main findings in this study. First, the results of the study suggest that intraneural blood flow velocity has a positive quadratic relationship ($p < 0.0005$) with deviated wrist postures. It was hypothesized that compared to neutral, both flexion and extension postures would increase blood flow, with wrist flexion having the greatest change in blood flow. This was found to be true in all postures. Compared to neutral, both wrist extension at 30° (+0.42 cm/s) and wrist flexion at 15° (+0.39 cm/s) increased blood flow with the greatest increase in wrist flexion at 30° (+0.49 cm/s). Though it did not reach statistical significance ($p < 0.099$), extension 15° also followed the trend and had a higher blood flow velocity (+0.25cm/s) than neutral. Second, the results of this study suggest that intraneural blood flow velocity (proximal to the carpal tunnel) had a positive relationship with force. It was hypothesized that the addition of a fingertip force

would increase the blood flow in all wrist postures. The 6 N force increased the blood flow velocity by 0.75 cm/s, significantly higher than without force ($p < 0.0005$). Third, the results of this study suggest a general trend in intraneural blood flow velocity between the CTS symptomatic group and the control group. It was hypothesized that the group with a greater severity would have higher velocities than the lower severity/control group. The trend showed higher velocities with those experiencing CTS symptoms (+0.31 cm/s) than those with no symptoms. It is possible that the level of severity of the CTS symptomatic group may have played a role in the magnitude of difference as severity has been linked to hypervascularity (Mohammadi et al., 2012). In this study, the CTS symptomatic group reported a low severity level. The trend shows potential for significant differences with the addition of higher severity CTS patients that may have greater hypervascularization.

Based on previous findings of hypervascularization in CTS patients (i.e. proximal to the wrist), blood flow was expected to be altered in the CTS symptomatic group. The exact pathophysiology of this increase in blood flow is not well understood but the proximal hypervascularization is theorized to be a compensatory response to the distal ischemia caused by the nerve compression (Joy et al., 2011). A difference of 10% can be seen in the magnitude of the blood flow velocity between the control and CTS symptomatic groups, indicating that there is potentially a pathophysiological increase in blood flow found with the deviated wrist posture and fingertip force. Therefore, the instantaneous increase in the blood flow velocity may be a pathophysiological response when the median nerve is compressed. The acute stages of nerve compression are

thought to be primarily vascular (Lundborg, 1988) with damage to the blood-nerve barrier endoneurial capillaries leading to edema and increase in fluid pressure. Rydevik and Lundborg (1977) found evidence of epineurial edema within 2 hours of pressurization at 50 mmHg, demonstrating that high CTP over a short period of time will cause changes within the carpal tunnel. It is well documented that deviated wrist postures and fingertip force can dramatically change the fluid pressure in the carpal tunnel (Keir et al., 2007; Keir et al., 1998; Keir et al., 1997; Rempel et al., 1997). For the fluid pressure in the carpal tunnel to increase, there must be an increase in fluid, without the release of the fluid. Potentially, the hypervascularization (or increase in flow) combined with the venous congestion (or lack of release) is what causes the increase in CTP. The speculation that the dynamics of the carpal tunnel mimic a closed compartment may support the theory that an immediate increase in blood flow in necessary to cause the acute edema. Therefore, the increase in blood flow found in this study may be the initiation of these changes in fluid pressure that occur within a few hours of compression. Consequently, proximal hypervascularization may prove to be an indicator of injury risk.

The risk of developing CTS can be further evaluated with some of the results of this study. The current data indicate that, even in healthy individuals, the stress on the median nerve during deviated wrist postures and fingertip force may affect the intraneural vascular system. This is a new finding that has not previously been examined. With greater duration, the deviated wrist postures may prove to be detrimental to the nerve of both experimental groups. Furthermore, this is the first study to measure intraneural blood flow velocity with and without a fingertip force. The 6 N force is a relatively small

magnitude, yet still elicited a detectable change in blood flow velocity in both groups, indicating that a small level of force held for several minutes may be a risk factor for median nerve compression. It is predicted that higher forces may prove to be more detrimental to the median nerve but more research is required to make that conclusion. Interestingly, no interaction effects were found with wrist posture and fingertip force despite a previous report of higher CTP with deviated wrist postures in combination with a force task than independently (Luchetti et al., 1998).

Another factor to consider with the fingertip force is the normal physiological response that occurs with exercise. In response to strenuous exercise, the arterioles vasodilate, the flow resistance decreases and an increase in blood flow is seen in the vessel. The fingertip press may be causing an increase in blood flow to the hand in response to the exertion at the fingertip. It is difficult to differentiate between normal vasodilation and pathological vasodilation, also known as hyperemia. The general trend of higher blood flow velocity with the CTS symptomatic group (Figure 6.1) suggests the likelihood that this is indeed a pathological response and pathological vasodilation is occuring. An additional finding that supports this theory is that the fingertip press triggered symptoms in CTS patients, supporting similar findings by Rempel et al. (1997). Interestingly, transient symptoms, such as numbness and tingling in the innervated digits, were also triggered in some control subjects (Table 6.2). This further validates the theory that a pathological response is occurring.

Clinical severity has been shown to have a positive correlation with increased vascularity within the carpal tunnel with evidence of a linear correlation between nerve

CSA, a clinical diagnostic technique, and intraneural blood flow velocity (Joy et al., 2011; Tuncali et al., 2005). Previous studies have only scanned the median nerve in a neutral, relaxed position. This study showed similar findings with a positive correlation between nerve CSA and peak blood flow velocity at baseline (neutral with no force). No correlations were found in the other wrist postures. CSA showed no correlation with the Katz hand diagram. This was an unusual finding as they are both commonly used in the clinical diagnosis of CTS. Variations in distance from the carpal tunnel can greatly affect the measurement. The CSA images were taken at the distal wrist crease, just proximal from the carpal tunnel and kept consistent with the level of the pisiform. Since the nerve was not imaged directly in the carpal tunnel, there may be slight variations in magnitude from other studies. Additional differences might include the caliper thickness within the EchoPac software and the experimenter measurement error. All CSA measurements were performed by one researcher to ensure consistency and they were blinded to each file to eliminate experimenter bias.

The Katz hand diagram, Phalen's test and Levine's CTS questionnaire were used in this study as qualitative assessments of CTS; however, no correlations were found with baseline (neutral, no force) velocity data. To be used as a diagnostic tool, the baseline velocity should correlate well with other diagnostic techniques. However, this does not discount the use of intraneural blood flow velocity as a potential diagnostic tool. The low severity level of our CTS symptomatic group is likely a limitation that should be investigated in future studies. Furthermore, each diagnostic technique has their own limitations and the "gold standard" of NCS was not used in this study. For this study,

these qualitative measures were used to classify each participant into experimental groups and not to evaluate their reliability as a diagnostic technique. Future research comparing the intraneural blood flow velocity with patients with positive NCS may provide a more reliable evaluation of this relationship. Joy et al. (2011) found significant pathological differences in blood flow with severe CTS patients and Mallouhi et al. (2006) reported a more reliable evaluation of velocity in patients diagnosed with NCS. Nonetheless, it is noteworthy that we found a trend for differences in intraneural blood flow velocity between the CTS symptomatic and control group. The experimental groups defined in the study correlated well with four commonly used clinical tests ($p < 0.05$). In addition, higher blood flow velocities were found in the median nerve of the CTS symptomatic group ($p < 0.059$). These findings suggest that hypervascularization has potential for a diagnostic tool; however, it may not have the accuracy for mild cases of CTS. Further research with clinically diagnosed CTS patients may help clarify this relationship.

The reliability of the intraneural blood flow measurements was evaluated in five control subjects with a repeat of the protocol after two weeks. The data shows no significant differences between the mean peak velocities from day 1 to day 2 ($p < 0.991$). Since no significant changes were found using the small sample size (N=5), this suggests intraneural blood flow may prove to be a reliable measurement and shows potential for more applications in the ergonomic field. A more sophisticated reliability test should be conducted as the next step to establishing intraneural blood flow velocity as a widespread technique.

Finally, the most severe participant recruited for this study had a distinct vascularity that was unlike any of the other participants. Based on the qualitative (clinical) CTS tests (Table 5.2), the CTS individual was the only participant recruited that was positive for all clinical tests. Consequently, the CTS individual was separated from the other data based on the following unique qualities. First, the median nerve showed colour maps. This indicated higher blood flow velocities than the other groups as the settings were not sensitive to obtain results from participants with lower blood flow velocities. Second, with these colour maps, the blood vessels of the nerve were depicted as flowing in a longitudinal direction. This was subtle but allowed the estimation of the direction of flow and an angle correction to increase the accuracy of the measurement. Third, the strong pulsations of the vessel were unique to this individual and were not comparable to the small pulsatile flow observed in other groups. The large pulsations allow for more consistent data collection and more reliable data analysis. The distinct differences that were found in this CTS individual indicate that perhaps the CTS symptomatic group were not severe enough to capture the full extent of hypervascularization that occurs with CTS. In addition, it supports that a significant main effect of experimental groups may occur with clinically diagnosed CTS patients. This finding also shows promise that the qualitative assessments would correlated well with intraneural blood flow velocity if more participants with positive tests were studied. Mohammadi et al. (2012) reported that hypervascularization is less common in patients with less severe CTS (mild NCS), indicating that severity plays a role. The hypervascularization seen in the CTS individual demonstrates the difference in magnitude

and pulsatility between mild and severe CTS patients. With colour maps and pulsatile flow, the intraneural blood flow can be more easily detected and tracked throughout different conditions. Therefore, the recruitment of more severe CTS patients may increase the feasibility of the study and will aid in the further investigation of the effect of wrist posture and force.

7.2 Limitations and Potential Methodological Improvements

The main limitation encountered with this project was the small sample size, specifically with the CTS symptomatic group, due to being an exploratory study. It was difficult to recruit participants that had the classic symptoms of CTS without using clinically diagnosed CTS patients. Furthermore, the age was not consistent for each experimental group and an even distribution may improve the correlation results of the qualitative assessments. Although differences were detected with deviated wrist postures and force, a larger sample size would provide greater statistical power.

A limitation with the force task was maintaining a constant 6 N exertion for three minutes. In particular, a number of the CTS symptomatic participants were unable to complete the task and opted to stop at 2 minutes. A positive relationship was established between force and intraneural blood flow using two levels, 0N and 6N; however, more increments are needed to test the linearity of the relationship. The results of this study provide insight into the changes that occur and the potential for intraneural blood flow to change with different levels of forces.

Using PW Doppler to find intraneural blood flow velocity was a meticulous process. Interestingly, it was much easier to measure the intraneural blood flow in the CTS symptomatic group than the control group, likely due to the higher velocities. In controls that presented difficulty obtaining a signal, we found very low velocities that did not follow the expected posture effect seen in other subjects. This could be an indication that the technique is limited in detecting very low blood flow velocities. Without successful colour Doppler to find a high area of blood flow, the median nerve had to be scanned thoroughly to determine the ideal placement of the PW Doppler gate. Maintaining an image of the same segment of median nerve throughout each posture was very difficult. When the wrist angle is changed, the proximal forearm shifts slightly in the longitudinal direction, requiring the need to reposition the transducer. The angle dependency of PW Doppler makes it challenging to obtain a clear waveform in all regions of the nerve. As a result, there was a lack of consistency with the area of the nerve being tested for all trials. Blunt and Stratton (1956) found regional difference in the vascular supply of the nerves due to anatomical variations, noting differences in proximal and distal parts of the sciatic nerve. Therefore, peak blood flow velocity may vary depending on the PW Doppler gate placement and variations in both depth and longitudinal position. In addition, the accuracy of the blood flow velocity measurement is dependent on the Doppler alignment. The transducer position should align the ultrasound beam with the flow direction in order to minimize the error in velocity measurements. Without knowledge of the blood vessel direction, no angle correction was could be applied as the blood flow had no determinate direction. This potentially limits the accuracy of the

magnitude of the results; however, no correction was used so that within-subject comparisons between postures and force were possible. Furthermore, the technique was limited by the resolution of the ultrasound machine. A higher frequency transducer of 18 MHz may provide more consistent velocity measurements than the 12 MHz transducer used in this study (Wilder-Smith, 2012).

The data collected by PW Doppler was not consistently observed and several measurements were taken in each posture to ensure the steady state was captured. Not all measurements resulted in the required minimum of five seconds of consistent velocity and were subsequently omitted. Furthermore, the technical difficulty experienced in the analysis of the signal varied for each participant as some measurements had to be manually adjusted when the low velocity could not be evaluated properly by the auto-calculation software. Only a few participants showed visual changes in blood flow within the nerve sheath using the colour Doppler (BFI Angio) and this was not consistent for all postures. None of the visual changes showed a linear or directional pattern. No colour Doppler was expected in the healthy control group; however, more severe CTS patients and improvements on the colour Doppler settings may elicit a higher detection rate amongst the CTS symptomatic group. The presence of colour patterns will facilitate effortless detection of intraneural blood flow and yield a more accurate depiction of the vascular structures within the nerve.

CHAPTER 8 – THESIS SUMMARY AND FUTURE DIRECTIONS

8.1 Thesis Summary and Conclusions

This study presents information on a new methodology to measure intraneural blood flow that is applied in a unique way to evaluate CTS risk factors. Relationships were found between intraneural blood flow velocity and both deviated wrist postures and fingertip force. This study represents the first step to using intraneural blood flow as a measure of nerve hypervascularization and understanding the vascular phenomenon that occurs with peripheral nerve compression. The pathophysiological nature of the nerve hypervascularization remains unclear but this study sheds insight on the role of posture and force on the vascular system of the peripheral median nerve. Sonographic measurements of intraneural blood flow has potential to be a measure of median nerve dysfunction and deserves further investigation as a diagnostic tool for CTS as it is a readily available, painless and highly-detailed technique.

8.2 Contributions of Thesis

This study demonstrates that measuring intraneural blood flow velocity using sonography is a feasible technique but requires comprehensive examination of the nerve and strict data analysis criteria. This thesis represents an application of sonographic intraneural blood flow measurement with ergonomic implications that had not previously been investigated. The data suggests that the effect of non-neutral wrist postures and fingertip force on the intraneural vasculature of the median nerve is consistent with occupational risk factors. The evaluation of blood flow is important in detecting the acute

stages of median nerve compression, such as inflammation and nerve edema. With continued exploration, this method may be used for the early diagnosis of CTS before the distal nerve becomes ischemic and severely damaged, in addition to further exploring the role of occupational risk factors that contribute to chronic median nerve compression. The details provided by this thesis may lead to the replication of these results to further validate the technique.

8.3 Future Directions

The results warrant future research exploring the role of intraneural vascular pressure in CTS and assessing PW Doppler as a potential tool to quantify intraneural blood flow velocity in not only CTS patients but in healthy individuals as well. The reliability of the technique shows potential and a large scale reliability test, to further solidify these findings, should be explored. Median nerve vascularity will need to be investigated further in the assessment of individuals with mild cases of CTS. The evaluation of clinically diagnosed CTS patients will be a valuable addition to this research to evaluate those with pulsatile flow in the intraneural vessels as the single individual evaluated in this study appeared to present with very different blood flow patterns in comparison to those classified as “symptomatic”. Clinics in the area have therefore been contacted to recruit more severe CTS patients.

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APPENDIX A:
PARTICIPANT QUESTIONNAIRE

Participant Questionnaire

Changes in Intraneural Blood Flow in the Median Nerve Following Postures Associated with Risk of Carpal Tunnel Syndrome

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PARTICIPANT IDENTIFICATION

Name: _____ ***Date:*** _____
Age: _____

HANDEDNESS

1) Are you are you right-handed or left-handed or ambidextrous (use both hands equally)?

right-handed □ ***left-handed*** □ ***ambidextrous*** □

HEALTH HISTORY

1) Have you ever had any of the following health conditions and/or treatment protocols performed on you currently and/or in the past? [*please check all that apply*]

□ Diabetes mellitus
□ Thyroid condition (e.g. hypothyroidism)
□ Gout
□ Amyloidosis
□ Sarcoidosis
□ Renal failure (or hemodialysis)
□ Degenerative joint disease
□ Arthritis of the wrist/hand
□ Corticosteroid injection
□ Cervical radiculopathy
□ Peripheral neuropathy
□ Radial malunion
□ Colles fracture
□ Wrist/hand musculoskeletal disorder
□ Flexor tendonopathy
□ Carpal tunnel syndrome
□ Ultrasound/laser/soft tissue treatment
□ Wrist/hand surgery
□ Pain/tingling/numbness of the hand

2) Are you currently on any medications that affect blood flow? ***Yes*** □ ***No*** □

* If ***yes***, please list:

_____
_____
_____

WORK HISTORY

1) Occupation: _____

2) Hours at work per week: _____

3) Years at current job: _____

4) Typical tasks performed at work: _____
_____
_____
_____
_____
_____

5) Have you ever-experienced a wrist or hand injury? ***Yes*** □ ***No*** □

* If ***yes***, please elaborate (type of injury, onset of injury, what do you attribute it to, how long have you have had the injury, symptoms, treatment of injury, time off work): _____
_____
_____
_____
_____

I verify that I have answered the above questions to the best of my knowledge. I understand that no confidential health information will be released without my written consent.

_____	_____	_____
Name of Participant (Print)	Signature	Date

_____	_____	_____
Name of Research Investigator Obtaining Consent (Print)	Signature	Date

APPENDIX B:
LEVINE'S CARPAL TUNNEL SYNDROME QUESTIONNAIRE

CTS QUESTIONNAIRE

The following questions refer to your symptoms for a typical twenty-four hour period during the past two weeks (circle one answer to each question).

SEVERITY SCALE: 0 = None or Never; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe

SYMPTOM SEVERITY SCALE

QUESTION SEVERITY SCORE 0= NONE; 4=SEVERE	0	1	2	3	4
1. How severe is the hand or wrist pain that you have at night?	0	1	2	3	4
2. How often did hand or wrist pain wake you up during a typical night in the past two weeks (times/night)?	0	1	2-3	4-5	5+
3. Do you typically have pain in your hand or wrist during the daytime?	0	1	2	3	4
4. How often do you have hand or wrist pain during the daytime (times/day)?	0	1-2	3-5	5+	constant
5. How long, on average, does an episode of pain last during the daytime (minutes)?	0	<10	10-60	>60	constant
6. Do you have numbness (loss of sensation) in your hand?	0	1	2	3	4
7. Do you have weakness in your hand or wrist?	0	1	2	3	4
8. Do you have tingling sensations in your hand?	0	1	2	3	4
9. How severe is numbness (loss of sensation) or tingling at night?	0	1	2	3	4
10. How often did hand numbness or tingling wake you up during a typical night during the past two weeks?	0	1	2-3	4-5	5+
11. Do you have difficulty with the grasping and use of small objects such as keys or pens?	0	1	2	3	4

FUNCTIONAL STATUS SCALE

QUESTION SEVERITY SCORE 0= NONE; 4=SEVERE	0	1	2	3	4
1. Writing	0	1	2	3	4
2. Buttoning of clothes	0	1	2	3	4
3. Holding a book while reading	0	1	2	3	4
4. Gripping of a telephone handle	0	1	2	3	4
5. Opening of jars	0	1	2	3	4
6. Household chores	0	1	2	3	4
7. Caring of grocery bags	0	1	2	3	4
8. Bathing and Dressing	0	1	2	3	4

COMMENTS:

_____
_____
_____
_____

ID _____
DATE _____

M /F _____ **AGE**_____ **DOI** _____

Levine DW, Simmons HP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, Katz JN. A self-Administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone and Joint Surgery, 1993; 75-A:1585-1592.

APPENDIX C:
KATZ HAND DIAGRAM

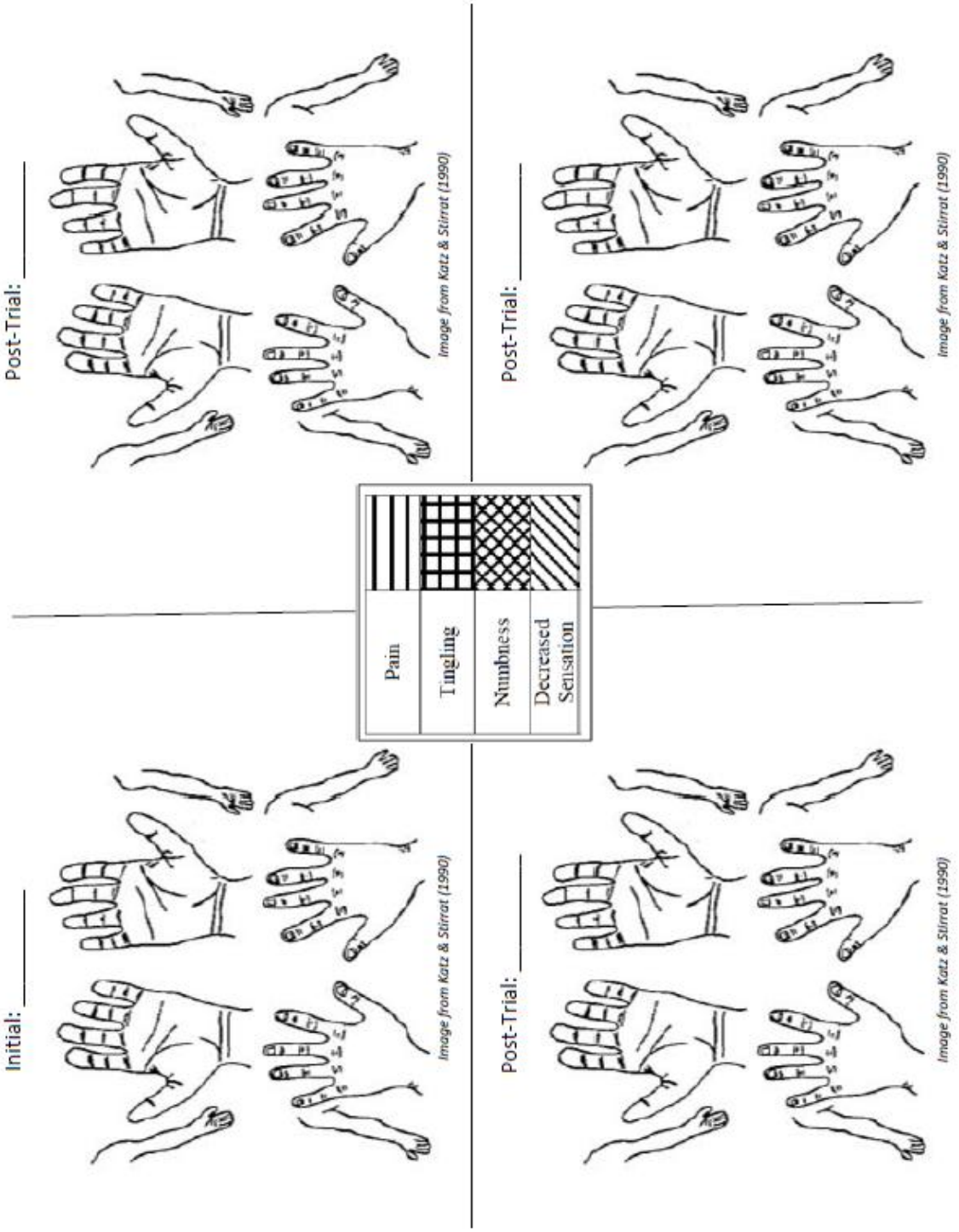

Table 1 Scoring criteria for hand diagrams

Rating	Description of area shaded on the hand[a]
Classic (3)	Tingling, numbness, burning or pain in at least 2 of the digits (thumb, index and long). Symptoms in palm and dorsum of hand excluded; small finger symptoms, wrist pain or radiation proximal to the wrist allowed. • *For index and long digits, must include shading between the distal tip and the proximal finger crease volarly, and include >1/2 of the middle phalanx &/or some of the distal phalanx. For thumb, must include shading in the distal phalanx volarly.* • *Digit may include shading dorsally from fingernail to the distal MP mark on the hand diagram.* • *If joint of digit (including MP) is the only area shaded and less than half of two adjacent phalanges, this may be considered arthritic complaints.*
Probable (2)	Same shading as for classic but allowed the shading to extend into the palm volarly unless it was confined to the ulnar aspect of the palm.
Possible (1)	Tingling, numbness, burning, or pain in at least one of the digits (thumb, index and long). • *May include the dorsum of the hand*
Unlikely (0)	No shading of the primary digits or shading restricted to the dorsum of the digits only.

[a] Modifications to rules in italics

APPENDIX D:
ETHICS AND CONSENT FORM

McMaster University

Letter of Information and Consent

Changes in Intraneural Blood Flow in the Median Nerve Following Postures Associated with Risk of Carpal Tunnel Syndrome

Local Principal Investigator: Peter Keir, PhD
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Sponsor: This study is funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada

Introduction

You are being invited to participate in a study about musculoskeletal disorders of the wrist and hand. Carpal tunnel syndrome is a common musculoskeletal disorder of the wrist and hand that is caused by compression of the median nerve at the wrist. Understanding how the nerve becomes damaged inside the carpal tunnel (or wrist) is important in determining the development of wrist and hand musculoskeletal disorders. The median nerve can be seen non-invasively using ultrasound.

Purpose of the Study

The purpose of this study is to measure changes in blood flow in the median nerve following different wrist postures using ultrasound imaging.

Faculty of Health Sciences/McMaster
JAN 04 2013
Research Ethics Board

Procedures Involved in the Research

You will be asked to complete a questionnaire about your handedness (i.e. left-handed or right-handed), general health, as well as musculoskeletal disorders of the wrist and hand. Following the questionnaire, you will complete a testing protocol no longer than 3 hours. You will be seated comfortably while the ultrasound technician applies ultrasound gel on the wrist of your dominant hand. Next, you will be asked to complete a series of wrist postures and fingertip forces while an ultrasound probe records images of the nerve in the carpal tunnel. Each type of posture will last no longer than 20 minutes (with rest in between each posture). Ultrasound images will be collected before and after each posture and/or fingertip exertion.

Potential Harm, Risk or Discomfort

Ultrasound is a safe imaging tool used to visualize tissues within your body. The wrist postures and fingertip exertions in this study might cause you minimal discomfort due to fatigue in some rare cases. However, we do not foresee any risks from your participation in this research. If you do feel any muscular discomfort or pain, please tell the ultrasound technician. In the event that you do feel pain while performing any of the tasks, the study will be stopped immediately to ensure your safety.

Potential Benefits

This research will not benefit you directly, except for knowing that you are helping further our understanding about the influence of wrist postures and fingertip exertions on the vasculature structures in the median nerve. Ultimately, we hope to prevent musculoskeletal disorders in the workplace.

Payment and Reimbursement

You will receive $30.00 for your time for participating in this study. If you withdraw from this study at any time, you will still receive prorated compensation.

Confidentiality

Your identity will be kept confidential. We will not use your name or any information that would allow you to be identified. The data obtained in this study will be used for research and teaching purposes only. Information directly pertaining to you will be stored in a locked cabinet or on a password protected computer. Your individual data will be kept confidential to the fullest extent of the law. We will treat all information provided to us as subject to researcher-participant privilege.

Participation

Your participation in this study is voluntary. If you decide to participate, you can choose to stop at any time, even after signing the consent form, or partway through the study. If you decide to

stop participating in this study, there will be no consequences to you. Also, all of your data will be permanently deleted.

This study has been reviewed by the Hamilton Health Sciences/McMaster Faculty of Health Sciences Research Ethics Board (HHS/FHS REB). If you have any concerns or questions about your rights as a participant or about the way this study is conducted, contact the Office of the Chair of the HHS/FHS REB at (905) 521-2100 (× 42013).

Information about the Study Results

You may obtain information about the study results by contacting Katherine Wilson at (905) 525-9140 (× 20175) or Dr. Peter Keir at (905) 525-9140 (× 23543).

Information about Participating in this Study

If you have questions or require more information about the study itself, please contact Katherine Wilson or Dr. Peter Keir.

INFORMED CONSENT

I have read the information in this information and consent form about a study being conducted by Katherine Wilson and Dr. Peter Keir at McMaster University. I have had the opportunity to ask questions about my involvement in this study, and to receive any additional details I wanted to know about the study. I understand that I may withdraw from the study at any time, if I choose to do so. I have been given a signed copy of this form. I agree to participate in this study.

Name of Participant (Print)	Signature	Date

In my opinion, the person who has signed above is agreeing to participate in this study voluntarily, and understands the nature of the study and the consequences of participation in it.

Name of Research Investigator Obtaining Consent (Print)	Signature	Date