The Journal of Pain, Vol 8, No 2 (February), 2007: pp 137-151
Available online at www.sciencedirect.com

ELSEVIER

Effects of Prolonged Wrist Flexion on Transmission of Sensory Information in Carpal Tunnel Syndrome

Richard F. Sesek,* Mehdi Khalighi,* Donald S. Bloswick,* Mark Anderson,† and Robert P. Tuckett††

**Department of Mechanical Engineering, University of Utah, Salt Lake City, Utah.*
†Workcare Clinic, Salt Lake City, Utah.
††Department of Physiology, University of Utah, Salt Lake City, Utah.

Abstract: Carpal tunnel syndrome presents a constellation of symptoms which include discomfort (eg, pain, paraesthesia) and diminished sense of touch. This exploratory study simultaneously measured changes in tactile threshold and discomfort ratings during prolonged wrist flexion in symptomatic patients from a rehabilitation clinic and from a control population. Prolonged (15 min) wrist flexion significantly increased tactile threshold and discomfort ratings above baseline levels in both symptomatic and control populations. Sixty-two percent of the symptomatic sample was found to have abnormal conduction latency. Tactile threshold in symptomatic subjects with normal conduction latency (n = 13) did not differ significantly from control subjects (n = 36) at baseline but showed significant elevation during wrist flexion. In contrast, subjects with abnormal conduction latency (n = 21) exhibited significant elevation relative to control subjects at baseline and throughout wrist flexion as well as a slower recovery after flexion. Conduction latency correlated with baseline (r = .52, *P* < .0001) and 15-min (r = .67, *P* < .0001) tactile threshold for the entire subject population, as well as 15-min threshold (r = .53, *P* = .013) for the subpopulation with abnormal conduction latency. At 2.5 min after flexion, correlation was significant for whole (r = .64, *P* < .0001) and abnormal conduction latency (r = .58, *P* = .0063) samples. Regression slope of tactile threshold versus conduction latency was significantly greater than zero and did not differ significantly from linearity. The study demonstrates that increases in mechanosensory threshold and discomfort ratings during prolonged wrist flexion are more profound (and recovery less rapid) in patients with electrophysiologic evidence of injury.

***Perspective:** This study demonstrates a provocative procedure that enhances the symptoms of carpal tunnel syndrome. This measure may help clinicians discriminate median nerve compression from other types of peripheral nerve injury and help researchers investigate the impact of mechanical stress, tissue compression, and vascular stasis on compression-related neuropathy.*

***Key words:** Nerve entrapment, mechanoreceptor, tactile, conduction latency.*

Carpal tunnel syndrome results from median nerve entrapment at the level of the wrist and is the most frequently encountered compressive neuropathy in clinical practice. When confirmed by electrophysiologic assessment, its prevalence is about 3% among women and 2% among men.[2]

Symptomatic carpal tunnel syndrome can be defined on the basis of "primary" and "secondary" symptoms,[48,64] with primary symptoms being numbness, tingling, and nocturnal complaints and secondary symptoms being pain, weakness, and clumsiness. Primary symptoms are considered more specific to nerve injury, and secondary symptoms are more reflective of soft tissue and other musculoskeletal disorders. Generally, carpal tunnel syndrome worsens with time and can be correlated to histopathologic and pathophysiologic degrees of nerve injury.[21,55,36,8,44,43,47] First-degree injury involves nerve slowing due to conduction block and possi-

Received February 15, 2006; Revised June 26, 2006; Accepted June 30, 2006.
This work was supported in part by NIH grant No. 1 R43 NS40641, in addition to departmental and institutional support.
Address reprint requests to Robert P. Tuckett, PhD, Department of Physiology, University of Utah School of Medicine, 410 Chipeta Way, Rm 156, Salt Lake City, UT 84108-1297. E-mail: bob.tuckett@m.cc.utah.edu
1526-5900/$32.00

doi:10.1016/j.jpain.2006.06.009

bly focal demyelination (without axonal injury) which leads to full recovery. The majority of carpal tunnel patients fall into this category.[43] Second-degree injury involves axonal injury, thus requiring some degree of nerve regeneration with the potential for full recovery. In third-degree injury, nerve function is permanently diminished and degree of recovery is dependent on the amount of scar tissue formation. This would correspond to severe carpal tunnel syndrome. Fourth- and fifth-degree injuries involve severe scar tissue formation or transection, respectively, with expectation of irreversible dysfunction.

Magnetic resonance imaging has increased our understanding of carpal tunnel configuration during wrist movement.[8,36] In flexion, the tunnel's cross-sectional area decreases (ie, flattens) and the distance between the proximal edge of the transverse carpal ligament and the distal radius decreases.[47] In addition, because the median nerve is located between the flexor tendons and carpal ligament, increase in tendon tension is thought to increase pressure on the nerve during flexion.[14] Decreased cross-sectional area increases interstitial pressure. For example, with the wrist in neutral position, normal carpal tunnel pressure is approximately 2.5 mm Hg, and it increases to about 30 mm Hg with maximum flexion.[20] At this pressure epineural blood flow decreases.[53] Above 30 mm Hg, axon transport is impaired and subjects report mild paresthesias.[16] In carpal tunnel patients, average pressure with the wrist in neutral position is about 32 mm Hg.[20] At sustained pressures, the effects on median nerve function become more deleterious, including epineural edema, axon transport block, intraneural ischemia, and endoneural edema.[23,54]

Elevated carpal tunnel pressure increases sensory threshold of fingertips innervated by the median nerve via suppression of action potential transmission.[22,56] Increased threshold is likely due to conduction blockade in the carpal tunnel[27] or to increased action potential dispersion (due to conduction slowing) which reduces postsynaptic potential amplitude and thereby efficacy of synaptic transmission. Because most arteries that perfuse the palm and fingers bypass the carpal tunnel, an acute increase in carpal tunnel pressure is unlikely to alter cutaneous receptor perfusion and therefore mechanoreceptor response is likely to remain normal.

Basing carpal tunnel syndrome diagnosis solely on signs and symptoms can lower reliability, because other disorders such as tendonitis and cervical radiculopathy may present similarly. Quantitative electrophysiologic or sensory testing can confirm the clinical diagnosis; however, psychophysical evaluation with the wrist in a neutral position is not specific for carpal tunnel syndrome, because nerve injury could be due to varied causes (eg, diabetes or cervical radiculopathy). In contrast, differentially comparing threshold before and during a provocation that increases carpal tunnel pressure has been hypothesized to increase sensory evaluation specificity.[6,24]

Our experimental approach was to explore in greater detail than previous studies change in discomfort and tactile threshold during prolonged wrist flexion by comparing a symptomatic carpal tunnel syndrome sample to a nonsymptomatic control. Our hypothesis was that the symptomatic sample would show significantly greater shift in threshold and discomfort from baseline level than the control. During analysis, the symptomatic population was parsed into subsets with normal and abnormal conduction latency to analyze the relationship between baseline latency and shifts in tactile threshold and discomfort during provocation. In addition, tactile threshold on the middle finger (median nerve distribution) was compared to the little finger (ulnar distribution) and to the palmar branch of the median nerve in control and patient populations.

Materials and Methods

This study was approved by the Institutional Review Board at the University of Utah, and an informed consent form was provided for each subject. Subjects had to read and sign the consent form before participating in the experiment. A control sample was recruited from students at the University of Utah. All but 1 control subject had negative nerve conduction latency (see below). All had no history of peripheral neuropathy and no prior injury to the hand or wrist. Patients entering a rehabilitation clinic were selected based on physician assessment of their presenting symptoms as well as medical and work histories. Conduction velocity measurement was not used for inclusion in the patient population. Therefore, the basis for inclusion was presentation with wrist-related symptomatology.

Data were collected in a standardized sequence: questionnaire, clinical signs (Phalen and Tinel), nerve conduction latency, and tactile threshold before, during, and after prolonged wrist flexion. The questionnaire included anthropometric and demographic data such as gender, age, height, weight, and hand dominance, as well as ratings of past and present discomfort while awake and asleep. Subjects estimated their hand discomfort on a 0 to 10 visual analog scale (VAS, 0 = no discomfort, 10 = maximum imaginable discomfort). Phalen[9,39] and Tinel[9,18,39] tests were conducted for all subjects using the 0 to 10 discomfort rating scale. Nerve conduction latency (NCL) was measured (NervePace model 200-VS; NeuMed, Pennington, NJ) from a point just proximal to the wrist to the digital nerve of the middle finger[42] (conduction distance, 14 cm). To minimize temperature-related changes in conduction latency,[15,37] skin temperature was maintained above 29°C. The criterion for a positive NCL test was nerve conduction latency greater than 310 μs, as defined by the manufacturer.

The vibrometer probe (flat, 1.0 mm diameter) was connected to a DC spring-mounted motor (model V2, beryllium copper suspension; Gearing & Watson, East Sussex, UK). A probe-mounted LED radiated light (.1 mm diameter beam) onto a position detector (.1 μm resolution, model S-3931-01; Hamamatsu, Bridgewater, NJ) to produce a voltage proportional to probe position. Probe excursion was controlled with DC negative feedback circuitry, and displacement was independently calibrated

using a micromanipulator (model SM-15M; Narishige, Tokyo, Japan; calibration verified relative to the National Bureau of Standards, Stabro Laboratories, Salt Lake City, UT). Timing and amplitude of vibrometer movement were controlled by PC software (DOS operating system, C++ code) which generated the stimulus waveforms (D-to-A converter, 12-bit resolution). To control skin/probe indentation, the cutaneous surface rested on a flat "firm surround," and the vibrometer probe exited the center of the surround with an initial 100 μm (power off) offset. At the start of stimulation, the computer advanced the probe an additional 200 μm and then vibrated around this set point to maintain constant firm contact with the skin. At the start of the experiment, the software performed a calibration check by exciting the vibrometer with standard voltage waveforms (DC, 50 Hz) and sampling (A-D converter, 12-bit resolution, 5 kHz) the voltage signal from the displacement monitor. If peak-to-peak excursions varied by more than .5% from the preset maximum calibrated excursion, an error message was signaled. This research vibrometer is not commercially available.

The vibrometer stimulus interface was based on previous experimentation.[28,29] In single-unit animal recordings a variety of probe shapes were tested to determine which most reproducibly activated a variety of cutaneous mechanoreceptor afferent receptors. A flat monofilament-sized probe was found to provide consistent activation of a variety of mechanoreceptors when quantifying threshold activation using a series of stimulus waveforms.[58,59] From human psychophysical experiments, we have concluded that depth of cutaneous indentation may be encoded by relative displacement, ie, probe indentation relative to surrounding skin[11,10,45]; therefore the vibrometer interface includes a firm surround such that probe indentation relative to surrounding skin is constantly maintained. Experiments by others[32] suggest that the type I slowly adapting receptor functions as an edge detector; therefore, our small flat probe, centered on the densely innervated finger tip, may be an optimal interface for this slowly adapting neuron. The stimulus frequency of 50 Hz was not chosen for activation of a specific sensory neuron: At this time, it is unknown which sensory channel is most likely to be most compromised in carpal tunnel syndrome. Hence, the strategy for these initial experiments was to target both the slowly adapting receptors and the type I rapidly adapting receptor (Meisner corpuscle) channels by stimulating at a frequency higher than their range of optimal response.

The vibrometer probe was positioned to avoid calluses or scars. The subject was instructed to rest the finger gently on the firm surround and push the event button each time a tactile sensation was felt in the area of stimulation.[31,60] To maintain constant contact between the probe and finger during wrist flexion, subjects were instructed to maintain a constant position and pressure on the probe throughout the test procedure; in addition the experimenter observed that finger position relative to the circular firm surround did not shift during the wrist flexion procedure and ensured that the arm and wrist were comfortable and supported during the test.

Before the test, a demonstration run verified the subject's understanding of the procedure. Sensory threshold was measured using a simple staircase procedure (ie, up-down method[19,41,33]) in which each correct response lead to a decrease in stimulus amplitude and each incorrect response caused an increase. Stimulus amplitude began above normal threshold, and stimuli were randomized in time between 4 and 7 s. The subject pushed an event button each time a vibration was sensed. If the subject pushed the event button within 2 s after the start of the .5-s, 50-Hz stimulus, vibration amplitude on the next trial decreased. If the subject pushed the button outside this 2-s time interval, twice during a stimulus cycle, or did not push the button, the stimulus amplitude increased on the next stimulus cycle. For the first 7 trials, the stimulus changed in 25% increments, thereafter in 10% increments. The test ended after stimulus amplitude had decreased below, and increased above, sensory threshold for 2 complete cycles. The computer stored the amplitude of each stimulus, and the 2-cycle average of reversal points was defined as threshold.

The stimulus trial contained 3 components: baseline, flexion, and recovery. At baseline, tactile threshold was measured in the order of little finger, lateral palm, and middle finger, as well as an initial discomfort rating. Subjects were instructed to flex their wrist in maximum voluntary unforced flexion with the middle finger remaining on the stimulus probe.[42] At the end of 2.5 min, tactile threshold and discomfort estimates were obtained. This sequence was repeated at 2.5-min intervals for 15 min. Following the 15-min flexion, subjects were instructed to remove their hand from the vibrometer and to relieve the stress produced by the flexion posture for 1 min as they saw fit (eg, shake, massage, relax their hand and wrist). After this 1-min recovery period, tactile threshold on the middle finger was remeasured with the wrist in neutral position, a discomfort rating was obtained, and then little finger and lateral palm thresholds were remeasured. Because approximately 90 s was usually required to perform the iterative vibrometry measurement (see above), the final middle finger measurement ("Recovery") ended approximately 2.5 min after the 15-min wrist flexion measurement. Median nerve sensory conduction latency was measured (see above) after the vibrometric measurements.

As shown in Fig 1, a population of control subjects unrelated to the subjects of this study were sampled on their nondominant hand to obtain tactile threshold values for age correction (mean age 40.2 ± 1.2 years, range 20-79 years). These control subjects had no history of wrist trauma, upper-extremity repetitive motion injury, or peripheral sensory neuropathy. In accord with previous studies using a vibrometer of similar probe interface and stimulus algorithm,[28,29,31,60] there was a linear relationship between age and tactile threshold.[29] Mean threshold was 6.6 ± .26 μm (n = 105, regression line slope .085, standard error .020; 95% confidence interval .046-.12). Y-intercept was 3.2 (standard error .82; 95%

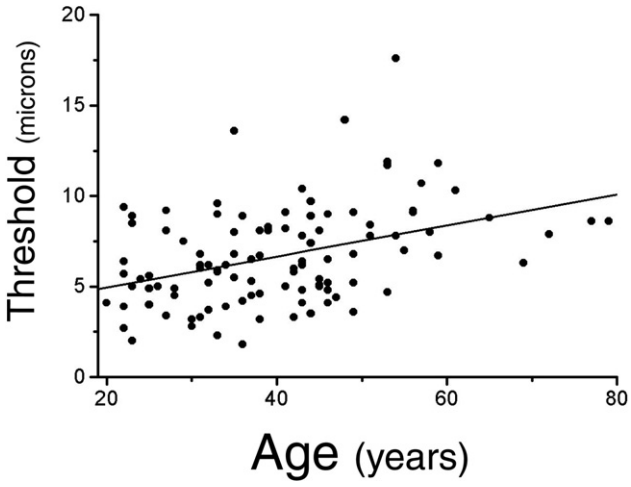

Figure 1. Changes in tactile threshold with age in control subjects without symptoms of carpal tunnel syndrome, wrist injury, or other peripheral neuropathy.

confidence interval 1.6-4.9). Correlation coefficient (r) was .394. The slope differed significantly from zero ($P <$ .0001), and the regression line did not differ significantly from linearity ($P = .798$). Because mean control sample age was approximately 10 years less than the symptomatic sample (26.3 and 37.0 years, respectively), values from the linear regression equation (Fig 1) were used as an age-correction factor and subtracted from measured threshold values in the analysis below.

Data Analysis

Subjects were divided into 3 groups. The symptomatic sample being treated for carpal tunnel syndrome was recruited from a local occupational medicine clinic and divided into 2 groups. One symptomatic sample was patients with symptoms of carpal tunnel syndrome but negative nerve conduction latency NCL (NCL−, latency ≤310 μs). The second symptomatic sample was patients who had symptoms of carpal tunnel syndrome and positive NCL (NCL+, latency >310 μs). Data were tabulated (Excel 97 SR-1; Microsoft, Redmond, WA), and analyses for central tendency were performed using SAS JMPIN v 5.0 (SAS Institute, Cary, NC). Linear regression was calculated including probability that the slope differs from zero and from linearity (Instat v 3.05; GraphPad Software, San Diego, CA) as well as Pearson (r) correlation with runs test to look for departure from gaussian distribution; in which case Spearman correlation was calculated. Unless otherwise stated, significance level was $P <$ .05, 2 tail. Plots were generated (Origin v 5.0; Microcal Software, Northampton, MA; Adobe Illustrator v 8.0, Adobe Systems, San Jose, CA) and results presented as mean ± SEM.

Results

This study included 68 adult subjects (70 individual hands). Control subjects (n = 36, 36 hands, mean age 26.3 years, range 18-52 years) had no history of carpal tunnel syndrome symptoms or severe injury to the hand or wrist. All control subjects except 1 had negative NCL. On the basis of median NCL (see Materials and Methods), symptomatic subjects (n = 34, mean age 37.0 years, range 19-60 years) were divided into positive (NCL+) and negative (NCL−) subpopulations. There were 21 NCL+ hands in 20 subjects, 19 with nocturnal symptoms (ie, pain and paraesthesia). There were 13 NCL− hands in 13 subjects, 10 with nocturnal symptoms. Because this was an exploratory study,[3,4,5,7,12,13,28,29] both hands of 2 patients were included, one being NCL+ bilaterally and the other being NCL+ on one hand and NCL− on the other hand. The stimulus sequence is described in Materials and Methods.

Wrist Flexion–Induced Changes in Tactile Threshold

Control vs Symptomatic Subjects

For the control population, multiple comparison of age-corrected (see Methods and Materials) tactile threshold for baseline (−1.1 ± .3 μm), 2.5 min (1.1 ± .4 μm), 5 min (2.0 ± .5 μm), 7.5 min (2.6 ± .7 μm), 10 min (3.1 ± .7 μm), 12.5 min (3.6 ± .8 μm), and 15 min (4.7 ± 1.1 μm) flexion, and post-flexion recovery (.9 ± .7 μm) differed significantly ($P <$ .0001, repeated measures ANOVA). As shown in Table 1, all paired comparisons with baseline showed significant increase in tactile threshold during flexion and recovery. As illustrated in Fig 2, threshold increased monotonically to a peak change of 5.8 μm at 15 min. Threshold dropped significantly between the 15-min and post-flexion recovery evaluations (−3.8 μm, $P <$ .0001, paired *t* test).

For symptomatic subjects, multiple comparison of age-corrected baseline (1.7 ± .8 μm), 2.5 min (5.4 ± 1.2 μm), 5 min (7.5 ± 1.4 μm), 7.5 min (10.2 ± 1.8 μm), 10 min (14.4 ± 2.9 μm), 12.5 min (17.1 ± 3.2 μm), and 15 min (23.9 ± 5.0 μm) flexion, and post-flexion recovery (7.9 ± 1.6 μm) tactile threshold was significantly different ($P <$ .0001, repeated measures ANOVA). As shown in Table 1, all paired comparisons in the symptomatic sample showed significant increases from baseline. During flexion, the greatest incremental increase in threshold occurred between 12.5- and 15-min evaluations (6.8 μm, 31% of total change, $P = .0023$, paired *t* test). Threshold dropped significantly (−16.0 μm, $P = .0004$, paired *t* test) between the 15-min and post-flexion recovery evaluations.

As illustrated in Table 2, tactile threshold for symptomatic subjects was significantly greater than control subjects for all evaluations. The difference between control and symptomatic tactile thresholds increased continually throughout the flexion procedure, with the greatest divergence occurring at the 15-min interval (19.3 μm; Table 2). The divergence in tactile threshold for symptomatic relative to control subjects dropped −12.2 μm between the 15-min and post-flexion observations.

Conduction Latency

Antidromic sensory NCL measured at the level of the wrist on the control (248 ± 57 μs) and symptomatic (346

Table 1. Change in Tactile Threshold Relative to Baseline During Prolonged Wrist Flexion

	Control		Symptomatic		NCL+		NCL−	
Time (min)	Difference (μM, M ± SEM)	P*	Difference (μM, M ± SEM)	P*	Difference (μM, M ± SEM)	P*	Difference (μM, M ± SEM)	P*
2.5	2.1 ± .4	<.0001	3.7 ± .9	.0003	4.2 ± 1.4	.0064	3.0 ± 1.0	.0138
5.0	3.0 ± .5	<.0001	5.9 ± 1.0	<.0001	6.5 ± 1.4	.0002	4.8 ± 1.2	.0014
7.5	3.7 ± .7	<.0001	8.3 ± 1.4	<.0001	9.5 ± 2.0	.0002	6.4 ± 1.6	.0014
10.0	4.2 ± .8	<.0001	12.3 ± 2.4	<.0001	14.8 ± 3.7	.0008	8.4 ± 1.9	.0010
12.5	4.7 ± .8	<.0001	15.3 ± 2.8	<.0001	19.9 ± 4.3	.0002	8.1 ± 1.8	.0006
15.0	5.8 ± 1.2	<.0001	22.2 ± 4.6	<.0001	30.4 ± 7.0	.0003	9.5 ± 1.9	.0004
17.5 (recovery)	2.0 ± .7	.008	6.2 ± 1.1	<.0001	7.8 ± 1.7	.0002	3.7 ± 1.0	.0032

NOTE. Time is from beginning of wrist flexion to tactile threshold measurement (time zero is baseline, wrist in neutral position). Recovery is measurement of post-flexion threshold obtained approximately 17.5 min after baseline. Difference is the increase in age-corrected threshold (see Fig 1) during prolonged wrist flexion relative to baseline.

Abbreviations: NCL+, symptomatic subjects with median nerve conduction latency that exceeds normal limits; NCL−, symptomatic subjects with normal conduction latency.

*Probability of significant difference from baseline (paired *t* test).

± 181 μs) populations differed significantly ($P < .0001$, *t* test). Based on a cutoff for abnormality of 310 μs (see Materials and Methods), symptomatic subjects were divided into 2 groups: an NCL+ sample with latencies greater than, and an NCL− sample with latencies less than or equal to, normal limits. Control (248 ± 57 μs), NCL+ (406 ± 195 μs), and NCL− (250 ± 85 μs) subjects differed significantly ($P < .0001$, ANOVA). The NCL+ subjects differed significantly from both control ($P < .0001$, *t* test) and NCL− ($P < .0001$, *t* test) subjects, whereas the difference between NCL− and control subjects was not significant.

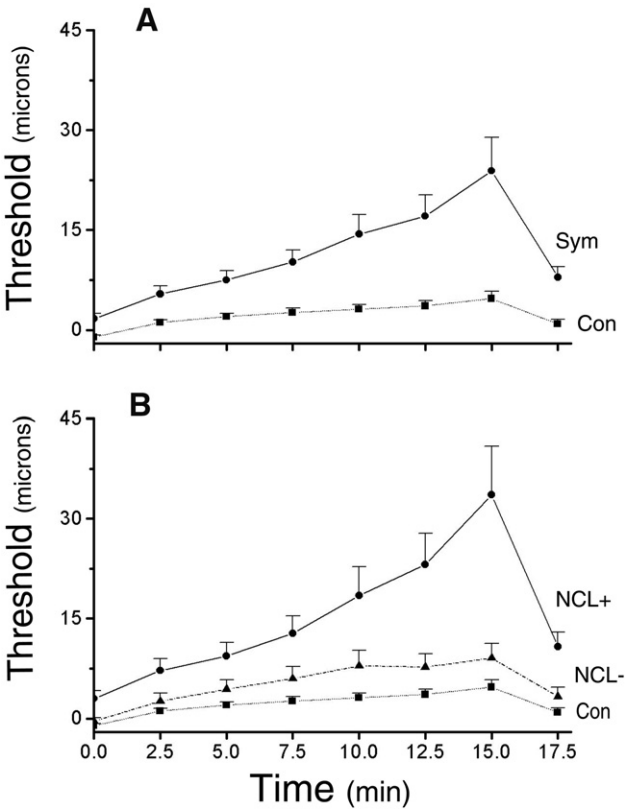

Figure 2. Tactile threshold during prolonged wrist flexion. (**A**) Symptomatic (Sym) and control (Con) samples. (**B**) Positive (NCL+) and negative (NCL−) conduction latency and control. Time: 0.0 min, baseline; 2.5-15 min, flexion; 17.5 min, recovery. Mean ± SEM.

Control vs NCL+ vs NCL− Subjects

For the NCL+ subpopulation, multiple comparison of age-corrected tactile threshold for baseline (3.0 ± 1.2 μm), 2.5 min (7.2 ± 1.8 μm), 5 min (9.4 ± 2.0 μm), 7.5 min (12.8 ± 2.6 μm), 10 min (18.5 ± 4.3 μm), 12.5 min (23.1 ± 4.7 μm), and 15 min (33.6 ± 7.3 μm) flexion, and post-flexion recovery tactile threshold (10.8 ± 2.2 μm) was significantly different ($P < .0001$, repeated measures ANOVA). As shown in Table 1, all paired comparisons were significantly different from baseline in the NCL+ sample. The greatest incremental increase in threshold occurred between 12.5- and 15-min (10.5 μm, 34% of total, $P = .0036$, paired *t* test). Threshold dropped significantly between 15-min and post-flexion (−22.8 μm, $P = .0017$, paired *t* test).

For NCL− subjects, multiple comparison of age-corrected tactile threshold from baseline (−.4 ± .5 μm), 2.5 min (2.6 ± 1.2 μm), 5 min (4.4 ± 1.4 μm), 7.5 min (6.0 ± 1.8 μm), 10 min (7.9 ± 2.3 μm), 12.5 min (7.7 ± 2.0 μm), and 15 min (9.1 ± 2.2 μm) flexion, and post-flexion recovery (3.3 μm ± 1.4) was significantly different ($P < .0001$, repeated measures ANOVA). As shown in Table 1, all paired comparisons were significantly different from baseline for the NCL− sample. Threshold dropped significantly between 15-min and post-flexion samples (−5.8 μm, $P = .0029$, paired *t* test).

Multiple comparison of NCL+, NCL−, and control samples was statistically significant at all time intervals ($P = .0002$, 2.5 min; $P < .0001$, all other times; ANOVA). The NCL+ and control tactile thresholds differed significantly at each evaluation interval (Table 2) and became increasingly divergent as the wrist flexion progressed, with the

Table 2. Differences in Tactile Threshold Between Sample Populations

	Symptomatic Minus Control		*NCL + Minus Control*		*NCL− Minus Control*		*NCL + Minus NCL−*	
Time (min)	*Difference (μM, M ± SEM)*	*P**	*Difference (μM, M ± SEM)*	*P**	*Difference (μM, M ± SEM)*	*P**	*Difference (μM, M ± SEM)*	*P**
0	2.8 ± .8	.0014	4.1 ± 1.0	<.0001	.6 ± .6	ns	3.5 ± 1.6	.0321
2.5	4.4 ± 1.3	.0011	6.2 ± 1.5	<.0001	1.5 ± 1.0	ns	4.7 ± 2.5	ns
5.0	5.6 ± 1.5	.0003	7.5 ± 1.7	<.0001	2.4 ± 1.2	.0462	5.1 ± 2.8	ns
7.5	7.6 ± 1.9	.0002	10.2 ± 2.2	<.0001	3.3 ± 1.6	.0404	6.8 ± 3.7	ns
10.0	11.4 ± 2.9	.0002	15.4 ± 3.4	<.0001	4.9 ± 1.8	.0105	10.5 ± 5.7	ns
12.5	13.4 ± 3.2	<.0001	19.5 ± 3.6	<.0001	4.0 ± 1.8	.0272	15.4 ± 6.1	.0162
15.0	19.3 ± 4.9	.0002	28.9 ± 5.6	<.0001	4.4 ± 2.3	ns	24.6 ± 9.3	.0129
17.5 (recovery)	7.0 ± 1.7	<.0001	9.9 ± 2.0	<.0001	2.4 ± 1.5	ns	7.5 ± 3.1	.0197

Note and abbreviations as in Table 1.

*Probability of significant difference between sample populations (*t* test); ns, not significant.

greatest difference occurring at 15 min (28.9 μm; Table 2). The divergence in threshold dropped 19.0 μm between the 15-min and post-flexion observations.

The NCL− and control thresholds differed significantly between the 5-min and 12.5-min evaluations, with the maximum difference occurring at 10 min (4.9 μm; Table 2), but did not differ significantly at the 15-min and post-flexion intervals. Divergence between NCL− and control dropped 2.0 μm between 15-min and post-flexion observations.

The NCL+ and NCL− thresholds differed significantly at baseline and from 12.5-min through post-flexion recovery, with the maximum divergence occurring at 15 min (24.6 μm; Table 2). The divergence in tactile threshold between NCL+ and NCL− dropped 17.0 μm between the 15-min and post-flexion observations.

Comparison With Little Finger and Palm Thresholds

Tactile threshold data were collected on the little finger (ulnar nerve) and lateral palm (palmar median nerve) distributions before (baseline) and after (recovery) the wrist flexion procedure (Table 3; corresponding middle finger data discussed above are included for comparison). Within the control population, baseline tactile threshold on the middle finger was significantly less than the little finger[29] and the palm ($P = .0078$ and .0001, respectively, paired *t* test). Little finger threshold was also less than palm ($P < .0001$, paired *t* test). This relationship between baseline thresholds was also present in the NCL− sample (middle vs little finger, $P = .0668$; middle vs palm, $P < .0001$; little vs palm; $P = .0016$; paired *t* test). In contrast, for the NCL+ sample middle finger baseline threshold was not significantly greater than for the little finger, but palm was significantly greater than little finger (Table 3; $P = .2912$; middle vs palm, $P < .0013$; little vs palm, $P = .0022$; paired *t* test).

As shown in Table 3, match-paired comparisons of baseline and recovery for the middle finger showed significant increase in threshold during recovery for all sample populations. Similarly, threshold data for little finger and palm showed a consistent increase in recovery threshold for all sample populations but did not reach statistical significance for most comparisons (see Discussion).

Multiple comparison showed little finger thresholds to vary significantly among sample populations for baseline (control, NCL+, NCL− samples: baseline, $P = .0233$; recovery, $P = .0884$; ANOVA), whereas differences in palmar measures were significant for both baseline and recovery (control, NCL+, NCL− samples: baseline, $P =$

Table 3. Comparison of Middle Finger, Little Finger, and Palmar Thresholds Before and After Wrist Flexion

	Middle Finger (μM, M SEM)			*Little Finger (μM, M SEM)*			*Palm (μM, M SEM)*		
	Baseline	*Recovery*	*Dif**	*Baseline*	*Recovery*	*Dif**	*Baseline*	*Recovery*	*Dif**
Control	−1.1 (.3)	.9 (.7)	2.0 $P - .008$	.0 (.5)	.7 (.5)	.7 $P - .0781$	4.9 (1.0)	7.4 (2.2)	2.5 $P - .1504$
Symptomatic	1.7 (.8)	7.9 (1.6)	6.2 $P < .0001$	1.4 (.5)	3.3 (1.1)	1.9 $P = .0463$	12.1 (2.6)	19.1 (4.2)	7.0 $P = .0338$
NCL+	3.0 (1.2)	10.8 (2.2)	7.8 $P = .0002$	1.8 (.6)	3.8 (1.7)	2.0 $P = .1831$	15.3 (4.0)	23.3 (6.0)	8.0 $P = .1362$
NCL−	−.4 (.5)	3.3 (1.4)	3.7 $P = .0032$	.7 (.7)	2.5 (1.1)	1.8 $P = .0324$	7.0 (1.3)	12.6 (2.2)	5.6 $P = .0052$

Note and abbreviations as in Table 1.

**P* is probability of significant difference between baseline and recovery populations (paired *t* test).

.0039; recovery, $P = .0163$; ANOVA). Paired comparison of little finger samples showed baseline control to differ significantly from symptomatic and NCL+ ($P = .0160$ and .0063, respectively, *t* test) and recovery control to differ significantly from symptomatic and NCL+ ($P = .03368$ and .0025, respectively, *t* test). Paired comparison of the palm samples showed baseline control to differ significantly from symptomatic and NCL+ ($P = .0097$ and .0389, respectively, *t* test), and recovery control to differ significantly from symptomatic and NCL+ ($P = .0150$ and $P < .0087$, respectively, *t* test). The remaining combinations did not differ significantly (eg, control vs NCL−, NCL+ vs NCL− samples).

Tactile Threshold vs Conduction Latency

Figure 3 shows scattergrams and regression lines for mechanosensory threshold vs conduction latency at baseline, 15 min flexion, and recovery. As detailed in Table 4, regression line slope differed significantly from zero, and increased approximately 8-fold (from .021 μm/μs at baseline to 0.16 μm/μs at 15-min flexion), then declined to .057 μm/μs at recovery. Data correlations were significant ($P < .0001$), and regression did not differ significantly from linearity. Within the NCL+ sample, tactile threshold did not correlate with conduction latency at baseline but showed significant correlation after 15-min flexion and at recovery, with regression line slope being significantly greater than zero (Table 4). Control and NCL− subpopulation tactile thresholds did not exhibit a significant relationship to conduction latency.

Wrist Flexion-Induced Discomfort

Control vs Symptomatic Subjects

For the control population, multiple comparison of discomfort ratings for baseline (.1 ± 0 units), 2.5 min (.2 ± .8 units), 5 min (.3 ± .1 units), 7.5 min (.6 ± .1 units), 10 min (.8 ± .2 units), 12.5 min (1.1 ± .2 units), and 15 min (1.5 ± .3 units) flexion, and post-flexion recovery (.5 ± .2 units) differed significantly ($P < .0001$, repeated measures ANOVA). With the exception of the 2.5-min evaluation, paired comparisons showed significant increases in discomfort ratings from baseline (Table 5). During flexion, the greatest incremental increase in discomfort occurred between the 12.5- and 15-min evaluations (.3 units, 27% of total increase, $P < .0017$, paired *t* test). As illustrated in Fig 4, discomfort increased monotonically to a maximum at 15 min. The drop in discomfort between the 15-min flexion and post-flexion recovery was significant (−1.0 units, $P < .0001$, paired *t* test).

For symptomatic subjects, multiple comparison of baseline (3.7 ± .3 units), 2.5 min (3.6 ± .3 units), 5 min (4.3 ± .3 units), 7.5 min (4.5 ± .3) units, 10 min (4.9 ± .3 units), 12.5 min (5.6 ± .3 units), and 15 min (5.9 ± .4 units) flexion, and post-flexion recovery (4.5 ± .3 units) discomfort rating was significantly different ($P < .0001$, repeated measures ANOVA). Except for 2.5 min, the symptomatic sample was significantly different from baseline for all evaluations, with the peak difference (2.2 units) occurring at 15 min (Table 5). During flexion, the greatest increase in discomfort between consecutive measurements occurred between the 10- and 12.5-min evaluations (.7 units, 32% of total change, $P < .0001$, paired *t* test). Discomfort dropped significantly (−1.4 units, $P <$

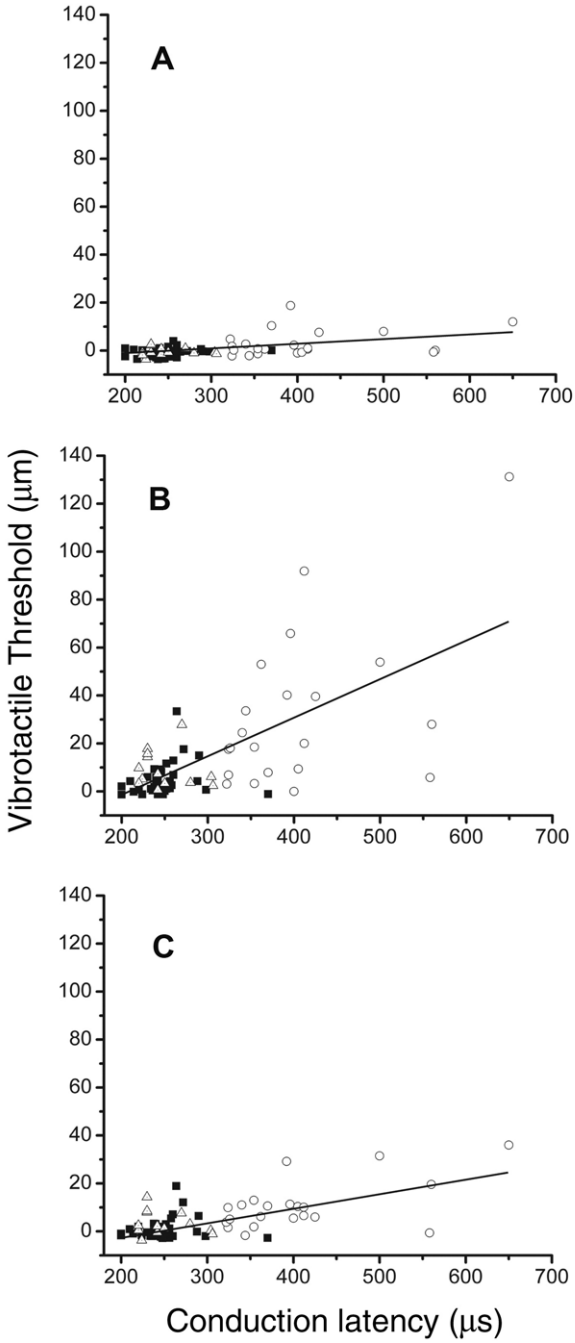

Figure 3. Age-corrected tactile threshold vs conduction latency for baseline (**A**), 15 min flexion (**B**), and recovery (**C**) for whole population samples (N = 70). Table 4 shows statistical (correlation and regression) parameters for whole and subpopulations (control, *solid squares*) and symptomatic patients with normal (*open triangles*) or abnormal (*open circles*) conduction latencies. Some data points are very close to each other and therefore do not print clearly. Number of data points above and below the regression line, respectively: *A*, 29, 41; *B*, 30, 40; *C*, 29, 41. Data did not differ significantly from linearity (runs test: *A*, $P = .64$; *B*, $P = .52$; *C*, $P = .65$).

Table 4. Correlation and regression between tactile threshold and sensory conduction latency

SC	SS	N	S	SCI	SPZ	PSNL	Y	YCI	Pr	PrCI	PPr	Sr	SrCI	PSr
Baseline	Total	70	0.021	0.013 to 0.030	<0.0001	0.65	−6.063	−8.70 to −3.42	0.52	0.32 to 0.67	<0.0001	0.44	0.22 to 0.62	<0.0001
	Control	36	0.013	−0.0072 to 0.033	0.20	0.12	−4.31	−9.37 to 0.76	0.22	−0.12 to 0.51	0.19	0.23	−0.11 to 0.53	0.17
	NCL−	13	0.0022	−0.039 to 0.034	0.90	0.74	0.10	−9.15 to 9.40	−0.040	−0.58 to 0.52	0.90	0.17	−0.43 to 0.67	0.57
	NCL+	21	0.017	−0.011 to 0.045	0.23	0.25	−3.7	−15.36 to 7.92	0.27	−0.18 to 0.63	0.23	0.20	−0.27 to 0.59	0.39
15-min	Total	70	0.16	0.12 to 0.21	<0.0001	0.52	−34.6	−48.27 to −20.93	0.66	0.51 to 0.78	<0.0001	0.52	0.31 to 0.67	<0.0001
	Control	36	0.043	−0.034 to 0.12	0.26	0.93	−6.01	−25.21 to 13.18	0.19	−0.14 to 0.49	0.26	0.35	0.010 to 0.61	0.038
	NCL−	13	−0.036	−0.20 to 0.13	0.65	0.24	18.083	−24.38 to 60.54	−0.14	−0.64 to 0.44	0.65	−0.23	−0.70 to 0.38	0.45
	NCL+	21	0.20	0.046 to 0.34	0.013	0.92	−47.26	−109.27 to 14.75	0.53	0.13 to 0.78	0.013	0.44	−0.0083 to 0.76	0.048
Recovery	Total	70	0.057	0.040 to 0.073	<0.0001	0.65	−12.43	−17.47 to −7.39	0.64	0.48 to 0.76	<0.0001	0.46	0.24 to 0.63	<0.0001
	Control	36	0.020	−0.031 to 0.070	0.43	0.69	−3.99	−16.62 to 8.63	0.14	−0.20 to 0.44	0.43	0.073	−0.27 to 0.40	0.67
	NCL−	13	−0.037	−0.14 to 0.067	0.45	0.15	12.61	−13.73 to 38.96	−0.23	−0.69 to 0.37	0.45	−0.18	−0.68 to 0.43	0.56
	NCL+	21	0.066	0.021 to 0.11	0.0063	0.77	−16.04	−34.79 to 2.70	0.58	0.19 to 0.81	0.0063	0.43	−0.013 to 0.73	0.05

Abbreviations: MSC, major sample category; Baseline, threshold before flexion; 15-min, threshold at 15-min flexion; Recovery, threshold about 2.5 min post flexion; SS, sub-sample; Total, total study sample; Control, normal subjects; NCL−, patients with normal conduction latency; NCL+, patients with abnormal conduction latency; N, sample size; S, slope of regression line; SCI, 95% confidence interval for slope; SPZ, probability that slope different from zero; PSNL, probability that slope significantly departs from linearity; Y, y-axis intercept of regression line; YCI, 95% confidence interval for Y-intercept; correlation; Pr, Pearson correlation coefficient; PrCI, 95% confidence interval for Pr; PPr, Pearson significance level; Sr, Spearman correlation coefficient; SrCI, 95% confidence interval for Sr; PSr, Spearman significance level.

.0001, paired *t* test) between the 15-min and post-flexion recovery evaluations.

As illustrated in Table 6, discomfort ratings for symptomatic subjects were significantly greater than controls at all evaluation periods. With the exception of 2.5 and 7.5 min, the difference between control and symptomatic discomfort ratings increased during the flexion procedure, with the greatest divergence between control and symptomatic discomfort occurring at the 12.5- and 15-min intervals (4.4 units; Table 6). The divergence of symptomatic from control discomfort dropped 0.4 units between the 15-min and post-flexion recovery evaluations.

Control vs NCL+ vs NCL− Subjects

For the NCL+ subpopulation, multiple comparison of discomfort ratings for baseline (3.8 ± .4 units), 2.5 min (3.7 ± .4 units), 5 min (4.5 ± .4 units), 7.5 min (4.8 ± .4 units), 10 min (5.2 ± .4 units), 12.5 min (6.1 ± .4 units), and 15 min (6.6 ± .4 units) flexion, and post-flexion recovery (5.0 ± .4 units) discomfort ratings was significantly different ($P < .0001$, repeated measures ANOVA). Differences between baseline and NCL+ samples were significant for all observations during the wrist flexion procedure except the 2.5-min interval (Table 5). The greatest incremental increase in discomfort occurred between 10 and 12.5 min (.9 units, 32% of total, $P < .0001$, paired *t* test). Drop in discomfort between 15 min and post-flexion recovery was significant (−1.6 units, $P <$ .0001, paired *t* test).

For NCL− subjects, multiple comparison of discomfort ratings from baseline (3.6 ± .4 units), 2.5 min (3.4 ± .4 units), 5 min (3.9 ± .4 units), 7.5 min (4.2 ± .4 units), 10 min (4.2 ± .4 units), 12.5 min (4.6 ± .4 units), and 15 min (4.7 ± .5 units) flexion, and post-flexion recovery (3.7 ± .5 units) did not differ significantly ($P = .3142$, repeated measures ANOVA). With the exception of 2.5 min, paired comparisons in the NCL− sample showed significant differences from baseline (Table 5). The greatest incremental increase in discomfort rating between consecutive measurements occurred between 2.5 and 5 min (.5 units, 50% of total, $P =$ .0028, paired *t* test). The drop in discomfort between 15-min and post-flexion samples was significant (−1.0 units, 93% of total, $P = .0008$, paired *t* test).

Multiple comparison of NCL+, NCL−, and control samples was significantly different at all time intervals ($P <$ .0001, ANOVA). Comparisons of NCL+ and control discomfort ratings were significantly different at each evaluation interval (Table 6). With the exception of the 2.5- and 7.5-min intervals, the difference between NCL+ and control discomfort ratings increased incrementally as the wrist flexion progressed (Fig 4B), with the greatest difference occurring at the 15-min interval (5.1 units, Table 6). The divergence in NCL+ discomfort rating relative to control dropped .6 units between the 15-min and post-flexion observations.

Comparisons of NCL− and control discomfort ratings differed significantly at all evaluation intervals (Table 6). The maximum divergence between control and NCL− discomfort ratings (3.6 units) occurred at baseline. There

Table 5. Change in Discomfort Rating Relative to Baseline During Prolonged Wrist Flexion

	Control		Symptomatic		NCL+		NCL−	
Time (min)	Difference (units, M ± SEM)	P*	Difference (units, M ± SEM)	P*	Difference (units, M ± SEM)	P*	Difference (units, M ± SEM)	P*
2.5	.1 ± .1	ns	.1 ± .1	ns	.1 ± .2	ns	.2 ± .2	ns
5.0	.3 ± .1	.0104	.6 ± .2	.0048	.7 ± .3	.0180	.3 ± .2	ns
7.5	.6 ± .1	.0002	.8 ± .2	<.0001	1.0 ± .2	.0007	.5 ± .2	.0470
10.0	.8 ± .2	<.0001	1.1 ± .2	<.0001	1.5 ± .3	<.0001	.6 ± .3	.0395
12.5	1.1 ± .2	<.0001	1.9 ± .3	<.0001	2.4 ± .3	<.0001	1.0 ± .3	.0088
15.0	1.4 ± .3	<.0001	2.2 ± .3	<.0001	2.9 ± .4	<.0001	1.1 ± .3	.0093
17.5 (recovery)	.4 ± .2	.0093	.8 ± .2	.0028	1.2 ± .3	.0013	.1 ± .3	ns

Note and abbreviations as in Table 1.

*Probability of significant difference from baseline (paired *t* test); ns, not significant.

was no trend toward increased discomfort relative to control and no change in NCL− discomfort rating relative to control between 15 min flexion and post-flexion recovery.

The difference between NCL+ and NCL− discomfort ratings increased gradually but did not reach significance until 12.5 min and reached a peak of 1.9 units at 15 min (Table 6). The divergence in NCL+ discomfort rating relative to NCL− dropped −.6 units between the 15-min and post-flexion observations.

Discomfort vs Conduction Latency

Fig 5 shows scattergrams and regression lines for discomfort rating vs conduction latency at baseline, 15 min flexion, and recovery. As detailed in Table 7, regression line slope differed significantly from zero and increased from .014 units/μs at baseline to .020 units/μs at 15 min flexion, then declined to .016 units/μs at recovery. Data correlations were significant ($P < .0001$). With the exception of baseline, regression did not differ significantly from linearity. The control, NCL−, and NCL+ subpopulations did not exhibit a significant correlation with conduction latency.

Discomfort vs Tactile Threshold

There was a significant correlation (r) between baseline tactile threshold and discomfort rating (r = .4844, $P < .0001$). Linear regression (slope (S) = .2852, standard error (SE) = .06245, confidence interval (CI) = .1604-.4099); Y intercept (Y) = 1.749, SE = .2331, CI = 1.283-2.214) did not differ significantly from linearity ($P = .1745$). After 15 min wrist flexion, correlation between threshold and discomfort increased (r = .5774, $P < .0001$). Linear regression slope decreased (S = .07325, SE = .01265, CI = .04798-.09853; Y = 2.113, SE = .3796, CI = 1.355-2.872) and remained significantly different from zero and not differing significantly from linearity ($P = .3634$). During recovery, correlation decreased toward baseline levels (r = 0.4962, $P < .0001$). Linear regression slope increased (S = .1477, SE = .03133, CI = .08509-.2103; Y = .9252, SE = .4143, CI = .09761-1.753) and did not differ significantly from linearity ($P = .6324$).

Discussion

Changes in Tactile Threshold

The present study quantitatively tracked changes in median nerve tactile threshold and ongoing discomfort rating during a prolonged wrist flexion procedure and investigated the relationship of baseline to post-flexion recovery threshold as well as shifts in threshold for other

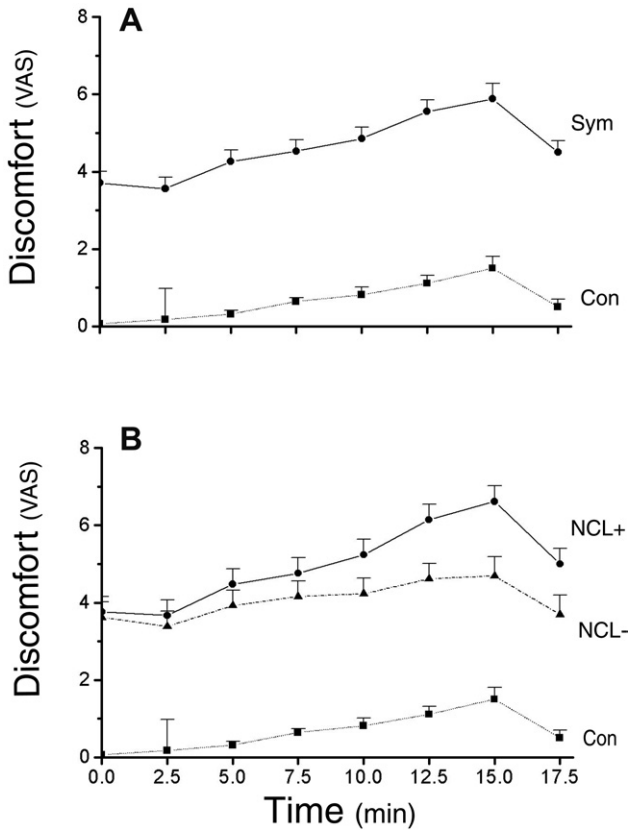

Figure 4. Discomfort ratings during prolonged wrist flexion. (**A**) Symptomatic (Sym) and control (Con) samples. (**B**) Positive (NCL+) and negative (NCL−) conduction latency and control. Time: 0.0 min, baseline; 2.5-15 min, flexion; 17.5 min, recovery. VAS = visual analog scale units. Mean ± SEM.

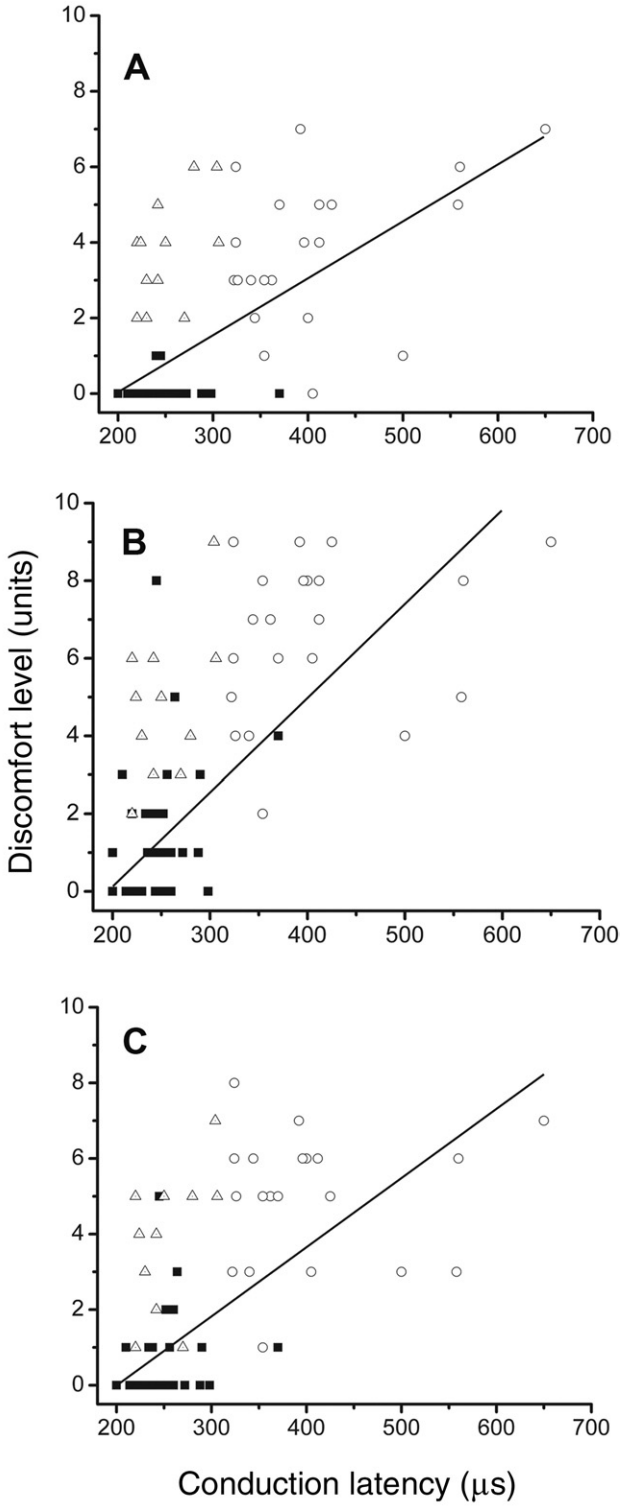

Figure 5. Discomfort rating versus conduction latency for baseline (**A**), 15 min flexion (**B**), and recovery (**C**) for whole population samples (N = 70). Table 7 lists statistical (correlation and regression) parameters for the whole and subpopulations (control, *solid squares*) and symptomatic patients with normal (*open triangles*) or abnormal (*open circles*) conduction latencies. Some data points are very close to each other and therefore do not print clearly. Number of data points above and below the regression line, respectively: *A*, 28, 42; *B*, 29, 41; *C*, 29, 41. Data differed significantly from linearity in graph *A* (runs test: *A*, $P = .021$; *B*, $P = .088$; *C*, $P = .088$).

nerve distributions. At baseline there was a significantly lower tactile threshold in the control population than in the total symptomatic population. Division of symptomatic subjects into subsets with or without electrophysiologic evidence of median nerve compromise (NCL+ or NCL−, respectively) showed baseline sensory deficit to be confined to the NCL+ population (Table 2; Fig 3), suggesting that increases in baseline tactile threshold are associated with conduction latency abnormalities. In control subjects, baseline middle finger threshold was significantly less than for the little finger,[29] perhaps owing to differences in density of median and ulnar nerve innervation. In addition, middle and little finger thresholds were significantly less than palmar thresholds, possibly owing to a lower palmar receptor density.

Injury to the median nerve in carpal tunnel syndrome is likely localized to the carpal tunnel because of its limited compliance; that is, the transverse and dorsal carpal ligaments possess limited stretch. Because water is essentially incompressible, tunnel pressure increases substantially during mechanical maneuvers such as wrist flexion.[34,35,50,51,56] In the control population, over a third of the total increase in tactile threshold occurred within the first 2.5 min of flexion, suggesting an immediate increase in pressure on the median nerve that quickly disrupted action potential transmission. Furthermore, the NCL+ sample threshold at 2.5 min flexion significantly exceeded the control sample (Table 2), suggesting an enhanced suppressive effect on action potential transmission, perhaps due to scar tissue and baseline edema in the carpal tunnel. The lack of a significant increase in discomfort rating above baseline during the first 2.5 min of wrist flexion (Table 5) supports the concept that the immediate rise in tactile threshold is not due to nociception-related modulation of mechanoreceptor channel transmission within the central nervous system.[40,57]

The increase in tactile threshold at 2.5 min flexion in NCL− subjects was not significantly greater than in control subjects; moreover, the difference between NCL− threshold values and the average control threshold did not differ significantly between 5 and 15 min ($P = .3320$, repeated measures ANOVA), suggesting that similar physiologic processes impact mechanosensory action potential transmission across the carpal tunnel in these sample populations. In contrast, the same comparison between NCL+ and average control threshold was highly significant over the same time interval (5- to 15-min evaluations, $P < .0001$, repeated measures ANOVA). Furthermore, relative to the control population, the NCL− population exhibited a peak threshold increase of 4.9 μm over the time course of flexion, whereas the NCL+ population's peak increase was 28.9 μm (Table 2). This increased threshold in the NCL+ population (which generated progressively greater deficits in sensory ability over time) was likely due to increasing vascular stasis, interstitial pressure, inflammatory processes, and hypoxia and supports the contention that prolonged wrist flexion increases diagnostic sensitivity of sensory testing procedures.[5,6,24] Consequently, the rate of rise in tactile

Table 6. Differences in Discomfort Ratings Between Sample Populations

	Symptomatic Minus Control		*NCL+ Minus Control*		*NCL− Minus Control*		*NCL− Minus NCL+*	
Time (min)	*Difference (units, M ± SEM)*	*P*	*Difference (units, M ± SEM)*	*P*	*Difference (units, M ± SEM)*	*P*	*Difference (units, M ± SEM)*	*P*
0	3.7 ± .3	<.0001	3.7 ± .3	<.0001	3.6 ± .2	<.0001	.1 ± .6	ns
2.5	3.4 ± .3	<.0001	3.5 ± .3	<.0001	3.2 ± .3	<.0001	.3 ± .6	ns
5.0	4.0 ± .3	<.0001	4.2 ± .3	<.0001	3.6 ± .3	<.0001	.6 ± .6	ns
7.5	3.9 ± .3	<.0001	4.1 ± .3	<.0001	3.5 ± .3	<.0001	.6 ± .6	ns
10.0	4.0 ± .3	<.0001	4.4 ± .4	<.0001	3.4 ± .4	<.0001	1.0 ± .6	ns
12.5	4.4 ± .4	<.0001	5.0 ± .4	<.0001	3.5 ± .4	<.0001	1.5 ± .6	<.0155
15.0	4.4 ± .5	<.0001	5.1 ± .5	<.0001	3.2 ± .6	<.0001	1.9 ± .7	<.0081
17.5 (recovery)	4.0 ± .4	<.0001	4.5 ± .4	<.0001	3.2 ± .4	<.0001	1.3 ± .6	<.0409

Note and abbreviations as in Table 1.

*Probability of significant difference between sample populations (*t* test).

threshold during flexion may provide a sensitive measure of entrapment-related injury, of the clinical necessity of surgical intervention, and of the prognosis for complete post-surgical recovery.

Recovery

At the cessation of prolonged wrist flexion, there was a rapid drop in sensory threshold. Although remaining significantly above baseline (Table 1), the percentage drop (relative to maximum threshold shift during flexion) was 72%, 74%, and 62% for control, NCL+, and NCL− samples, respectively. In control and NCL− populations, threshold deficit during recovery was approximately equal to the deficit at 2.5 min flexion, suggesting that a rapid drop in interstitial pressure had restored the majority of median nerve axon potential transmission. In contrast, the threshold decrease from a 30.4 μm peak to 7.8 μm at recovery in NCL+ subjects remained significantly higher than at 2.5 min flexion (3.6 μm, $P = .0389$, paired *t* test), suggesting delayed recovery (perhaps due to residual hypoxia or nerve injury). Although the post-flexion time interval required for threshold to return to baseline was not studied, measurement performed on sequential days show that threshold returned to baseline within a 24-h period. Slower recovery in NCL+ subjects suggests that injurious effects accumulate over time. Quantification of recovery may provide an estimate of risk to myelinated neurons exposed to repetitive stressful provocation.

Although there was consistent increase in tactile threshold following prolonged wrist flexion in the little finger and palmar innervations, these increases did not reach statistical significance in the control and NCL+ samples (Table 3), perhaps because threshold measurement was delayed (see Material and Methods). Increased pressure on the ulnar nerve in Guyon's canal[31] during wrist flexion could have contributed to increased little finger tactile threshold, as could increased pressure in the cubital tunnel due to bending the elbow during the procedure.[49,5] Because the palmar branch of the median nerve bypasses the carpal tunnel, the observed increase in threshold following provocation was not anticipated and could be due to pressure on palmar nerve fascicles during flexion. Baseline and recovery palmar thresholds were approximately 300% greater in NCL+ subjects than in control subjects (Table 3). Because the palmar branch lies outside the carpal tunnel, chronic entrapment appears to be an unlikely explanation. Alternatively, palmar mechanoreceptors are in closer proximity to areas of wrist inflammation (which is often associated with carpal tunnel syndrome) than mechanoreceptors innervating the fingertips. Recent experiments have documented modulation of slowly adapting type I mechanoreceptor response via axon reflex mechanisms related to neurogenic inflammation[66] (Zhang and Tuckett, unpublished observations) that might contribute to decreased mechanoreceptor responsiveness.

Changes in Discomfort Ratings

All symptomatic subjects had paresthesia and numbness in at least 1 digit in the median nerve distribution, and most exhibited nocturnal pain and paresthesia. At baseline, discomfort in the control population was negligible (.1 units), whereas both symptomatic samples (NCL+ and NCL−) were essentially identical and significantly elevated (NCL−, 3.6 units; NCL+, 3.8 units) above control. As shown in Table 6, NCL+ discomfort level did not become significantly greater than NCL− until 12.5 min flexion. At 15 min, NCL+ discomfort was 264% greater than the NCL− sample. Interestingly, the difference between control and NCL− discomfort ratings remained essentially constant throughout provocation and recovery (Table 6; variation between 3.2 and 3.6 units), suggesting that prolonged elevation of pressure in the carpal tunnel of NCL− subjects did not increase the activation of nociception-related pathways beyond that found in control subjects and, therefore, that baseline pain levels were not due to peripheral nociceptor sensitization. In contrast to the NCL− sample, whose discomfort ratings fell to baseline within the recovery interval, NCL+ discomfort estimates remained significantly elevated (Table 3; Fig 4).

Because conduction latency measures the status of large (nonnociceptive) afferent neurons (see Introduc-

Table 7. Correlation and Regression Between Discomfort Rating and Sensory Conduction Latency

MSC	SS	N	S	SCI	SPZ	PSNL	Y	YCI	Pr	PrCI	PPr	Sr	SrCI	PSr
Baseline	Total	70	0.014	0.0094 to 0.019	<0.0001	0.021	−2.36	−3.84 to −0.88	0.58	0.40 to 0.72	<0.0001	0.50	0.29 to 0.66	<0.0001
	Control	36	−0.00034	−0.0030 to 0.0023	0.79	>0.99	0.14	−0.52 to 0.80	−0.044	−0.38 to 0.29	0.80	−0.053	−0.38 to 0.29	0.76
	NCL−	13	0.026	−0.00067 to 0.052	0.055	0.73	−2.81	−9.46 to 3.83	0.54	−0.011 to 0.84	0.055	0.46	−0.14 to 0.81	0.11
	NCL+	21	0.0082	−0.0014 to 0.018	0.091	0.092	0.41	−3.61 to 4.44	0.38	−0.064 to 0.70	0.091	0.29	−0.18 to 0.65	0.20
15 min Flexion	Total	70	0.020	0.014 to 0.026	<0.0001	0.088	−2.38	−4.23 to −0.52	0.63	0.47 to 0.76	<0.0001	0.59	0.41 to 0.73	<0.0001
	Control	36	0.013	−0.0050 to 0.032	0.15	0.82	−1.83	−6.43 to 2.78	0.25	−0.090 to 0.53	0.15	0.16	−0.19 to 0.47	0.36
	NCL−	13	0.030	−0.0043 to 0.063	0.081	0.79	−2.68	−11.20 to 5.83	0.50	−0.069 to 0.82	0.081	0.29	−0.33 to 0.73	0.33
	NCL+	21	0.0052	−0.0053 to 0.016	0.32	0.71	4.52	0.14 to 8.88	0.23	−0.22 to 0.60	0.32	0.30	−0.16 to 0.66	0.18
Recovery	Total	70	0.016	0.011 to 0.022	<0.0001	0.087	−2.37	−4.03 to −0.71	0.59	0.42 to 0.73	<0.0001	0.59	0.41 to 0.73	<0.0001
	Control	36	0.0054	−0.0065 to 0.017	0.36	0.93	−0.84	−3.81 to 2.14	0.15	−0.18 to 0.46	0.36	0.25	−0.096 to 0.54	0.14
	NCL−	13	0.029	−0.0039 to 0.062	0.078	0.73	−3.55	−11.82 to 4.72	0.50	−0.064 to 0.83	0.078	0.42	−0.18 to 0.80	0.15
	NCL+	21	0.0015	−0.0078 to 0.011	0.74	0.52	4.40	0.54 to 8.25	0.077	−0.37 to 0.49	0.74	0.089	−0.37 to 0.51	0.70

Abbreviations: MSC, major sample category; Baseline, threshold before flexion; 15-min, threshold at 15-min flexion; Recovery, threshold about 2.5 min post flexion; SS, sub-sample; Total, total study sample; Control, normal subjects; NCL−, patients with normal conduction latency; NCL+, patients with abnormal conduction latency; N, sample size; S, slope of regression line; SCI, 95% confidence interval for slope; SPZ, probability that slope different from zero; PSNL, probability that slope significantly departs from linearity; Y, y-axis intercept of regression line; YCI, 95% confidence interval for Y-intercept; correlation; Pr, Pearson correlation coefficient; PrCI, 95% confidence interval for Pr; PPr, Pearson significance level; Sr, Spearman correlation coefficient; SrCI, 95% confidence interval for Sr; PSr, Spearman significance level.

tion), the finding of difference in discomfort response for NCL− and NCL+ subpopulations was not anticipated, but it supports the possibility of a causal relationship between large fiber injury and neuronal mechanisms of paresthesia (see below) or pain. A possible physiologic link between large fiber damage and peripheral nociceptor sensitization is suggested by observations that injured Schwann cells are capable of cytokine release,[1,26,38] which potentially could induce localized peripheral nociceptor sensitization.[65]

Paresthesia vs Pain

Although much is known about pain-related neuronal pathways, mechanisms of generation and transmission of paresthesia-related signals is poorly understood. They may involve abnormally low levels of activity on tonically active large myelinated neurons (eg, slowly adapting cutaneous or secondary muscle spindle mechanoreceptors) or abnormal patterning of activity on specific sensory channels. Our study design captured patient reports of "discomfort" without attempting to parse discomfort into painful and paresthetic subcomponents. Hence, it is unknown whether pain or paresthesia is the predominant sensory quality that increased during the latter stages of wrist flexion in the NCL+ sample (Table 6; Fig 4B). Previous studies using prolonged wrist flexion have not focused on the relationship between buildup of pain and paresthesia; however, Borg and Lindblom[6] reported an immediate increase in paresthesia that diminished during the later stages of wrist flexion. Such a finding would be consistent with our data if it were found that this delayed decrease in paresthesia were overcome by an increasing level of pain during the later stages of wrist flexion.

Some investigators have classified paresthesia as a primary symptom of carpal tunnel syndrome and pain as a secondary symptom (see Introduction).[48,64] In addition, recent epidemiologic evidence from worker populations suggests that specificity of paresthesias is superior to other symptoms, such as pain ratings, in the diagnosis of carpal tunnel syndrome (K. Hegmann, personal communication). Therefore, quantification of the paresthetic and painful components of discomfort during prolonged wrist flexion may provide insight into the sensory mechanisms of compression-related nerve injury.

Conduction Latency Changes in Carpal Tunnel Syndrome

The present study showed a linear regression relationship between baseline conduction latency and tactile threshold (Table 4) at baseline (Fig 3A), whose slope increased 8-fold during prolonged wrist flexion (Fig 3B) and remained elevated at recovery (Fig 3C), indicating that the greater the conduction latency, the greater the influence of prolonged provocation. In addition, for subjects with abnormal baseline conduction latency (>310 μs), the greater the latency, the more severe the deficit in tactile threshold during prolonged wrist flexion (eg, at 15 min flexion, Pearson correlation = .53, $P = .013$, re-

gression slope = .20 μm/μs), strongly suggesting that in compression-related neuropathy the greater the slowing on large myelinated axons, the greater their susceptibility to provocative stress.

The role of vibrometry in detection of carpal tunnel syndrome remains controversial, with both proponents[6,5,17,24,28,29,30,31,52] and detractors.[15,25,46,61,62,63] The vibrometer interface used in these studies was based on the reproducibility of mechanoreceptor response to threshold stimuli in single-unit recording experiments[58,59] (see Methods) in addition to human carpal tunnel studies using a similar stimulus interface.[28,29,31] Normal threshold on the human finger tip at 50 Hz can be less than 3 μm at 50 Hz (Fig 1), and therefore accurately calibrated instrumentation with reproducible stimulus delivery (eg, double-blind, computer control, standardized psychophysical protocol) is required to reduce variance and thereby aid in detection of slight shifts in sensory threshold produced by early carpal tunnel syndrome. The present study supports the conclusion that prolonged wrist flexion enhances the technique's ability to detect median nerve entrapment.[6,24] However, reproducibility studies (that measure within device and within subject variability) are necessary to demonstrate that the variability of psychophysical threshold measurement is much less than the effect of carpal tunnel syndrome.

Conclusion

This study is descriptive in nature, designed to quantitatively describe sensory channel alterations during increased carpal tunnel pressure; it would be preliminary to assume diagnostic validity, because this was not evaluated within the context of the study. The discovery that baseline sensory threshold for the NCL− symptomatic subpopulation was not significantly different from that for the control population was unanticipated. We are uncertain whether the NCL− sample should be considered electrophysiologic "false negatives." However, its increased tactile threshold over the course of wrist flexion was for the most part significantly greater than for the control sample, suggesting an increased susceptibility to nerve compression. Perhaps NCL− is an intermediate population which is either progressing toward median nerve injury or recovering from previous compression injury (see Introduction). Consequently, we do not view electrophysiological measures to be the "gold standard" for diagnosis of carpal tunnel syndrome. We believe that carpal tunnel syndrome is a progressive pathophysiological process that would be better understood through the use of combined psychophysical and electrophysiological techniques during controlled, provocative maneuvers.

References

1. Al-Shatti T, Barr AE, Safadi FF, Amin M, Barbe MF: Increase in inflammatory cytokines in median nerves in a rat model of repetitive motion injury. J Neuroimmunol 167:13-22, 2005

2. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosen I: Prevalence of carpal tunnel syndrome in a general population. JAMA 282:153-158, 1999

3. Aydin G, Keles I, Ozbudak, Demir S, Baysal AI: Sensitivity of median sensory nerve conduction tests in digital branches for the diagnosis of carpal tunnel syndrome. Am J Phys Med Rehabil 83:17-21, 2004

4. Bodofsky EB, Wu KD, Campellone JV, Greenberg WM, Tomaio AC: A sensitive new median-ulnar technique for diagnosing mild carpal tunnel syndrome. Electromyogr Clin Neurophysiol 45:139-144, 2005

5. Borg K, Lindblom U: Diagnostic value of quantitative sensory testing (QST) in carpal tunnel syndrome. Acta Neurol Scand 78:537-541, 1988

6. Borg K, Lindblom U: Increase of vibration threshold during wrist flexion in patients with carpal tunnel syndrome. Pain 26:211-219, 1986

7. Boyd KU, Gan BS, Ross DC, Richards RS, Roth JH, MacDermid JC: Outcomes in carpal tunnel syndrome: Symptom severity, conservative management and progression to surgery. Clin Invest Med 28:254-260, 2005

8. Britz GW, Haynor DR, Kuntz C, Goodkin R, Gitter A, Kliot M: Carpal tunnel syndrome: Correlation of magnetic resonance imaging, clinical, electrodiagnostic, and intraoperative findings. Neurosurgery 37:1097-1103, 1995

9. Bruske J, Bednarski M, Grzelec H, Zyluk A: The usefulness of the Phalen test and the Hoffmann-Tinel sign in the diagnosis of carpal tunnel syndrome. Acta Orthop Belg 68:141-145, 2002

10. Burgess PR, Horch KW, Tuckett RP: Boring's formulation: A scheme for identifying functional neuron groups in a sensory system. Fed Proc 42:2521-2527, 1983

11. Burgess PR, Mei J, Tuckett RP, Horch KW, Ballinger CM, Poulos DA: The neural signal for skin indentation depth. I. Changing indentations. J Neurosci 3:1572-1585, 1983

12. Caetano MR: Axonal degeneration in association with carpal tunnel syndrome. Arq Neuropsiquiatr 61:48-50, 2003

13. Capone L, Pentore R, Lunazzi C, Schonhuber R: Pitfalls in using the ring finger test alone for the diagnosis of carpal tunnel syndrome. Ital J Neurol Sci 19:387-390, 1998

14. Chaffin DB, Andersson GBJ, Martin BJ: Occupational Biomechanics. New York, NY, Wiley, 2006

15. Checkosky CM, Bolanowski SJ, Cohen JC: Assessment of vibrotactile sensitivity in patients with carpal tunnel syndrome. J Occup Environ Med 38:593-601, 1996

16. Cobb TK, Cooney WP, An KN: Pressure dynamics of the carpal tunnel and flexor compartment of the forearm. J Hand Surg [Am] 20:193-198, 1995

17. Conrad JC, Osborn JB, Conrad KJ, Jetzer TC: Peripheral nerve dysfunction in practicing dental hygienists. J Dent Hyg 64:382-387, 1990

18. Davis EN, Chung KC: The Tinel sign: A historical perspective. Plast Reconstr Surg 114:494-499, 2004

19. Garcia-Perez MA: Forced-choice staircases with fixed step sizes: Asymptotic and small-sample properties. Vision Res 38:1861-1881, 1998

20. Gelberman RH, Hergenroeder PT, Hargens AR, Lundborg GN, Akeson WH: The carpal tunnel syndrome. A study of carpal canal pressures. J Bone Joint Surg Am 63:380-383, 1981

21. Gelberman RH, Rydevik BL, Pess GM, Szabo RM, Lundborg G: Carpal tunnel syndrome. A scientific basis for clinical care. Orthop Clin North Am 19:115-124, 1988

22. Gelberman RH, Szabo RM, Williamson RV, Dimick MP: Sensibility testing in peripheral-nerve compression syndromes. An experimental study in humans. J Bone Joint Surg Am 65:632-638, 1983

23. Gelberman RH, Szabo RM, Williamson RV, Hargens AR, Yaru NC, Minteer-Convery MA: Tissue pressure threshold for peripheral nerve viability. Clin Orthop Relat Res 285-291, 1983

24. Gerr F, Letz R, Harris-Abbott D, Hopkins LC: Sensitivity and specificity of vibrometry for detection of carpal tunnel syndrome. J Occup Environ Med 37:1108-1115, 1995

25. Grant KA, Congleton JJ, Koppa RJ, Lessard CS, Huchingson RD: Use of motor nerve conduction testing and vibration sensitivity testing as screening tools for carpal tunnel syndrome in industry. J Hand Surg [Am] 17:71-76, 1992

26. Hagiwara N, Ikeda K, Higashida H, Tomita K, Yokoyama S: Induction of tumor necrosis factor-alpha in Schwann cells after gradual elongation of rat sciatic nerve. J Orthop Sci 10:614-621, 2005

27. Hansson, S and Nilsson BY: Median sensory nerve conduction block during wrist flexion in the carpal tunnel syndrome. Electromyogr Clin Neurophysiol 35:99-105, 1995

28. Hardy M, Jimenez S, Jabaley M, Horch K: Evaluation of nerve compression with the Automated Tactile Tester. J Hand Surg [Am] 17:838-842, 1992

29. Horch, K, Hardy, M, Jimenez, S, and Jabaley, M: An Automated Tactile Tester for evaluation of cutaneous sensibility. J Hand Surg [Am] 17:829-837, 1992

30. Jetzer TC: Use of vibration testing in the early evaluation of workers with carpal tunnel syndrome. J Occup Med 33:117-120, 1991

31. Jimenez S, Hardy MA, Horch K, Jabaley M: A study of sensory recovery following carpal tunnel release. J Hand Ther 6:124-129, 1993

32. Sensitivity to edges of mechanoreceptive afferent units innervating the glabrous skin of the human head. Brain Res 244:27-35, 7-22-1982

33. Kaernbach C: Simple adaptive testing with the weighted up-down method. Percept Psychophys 49: 227-229, 1991

34. Keir PJ, Bach JM, Rempel DM: Effects of finger posture on carpal tunnel pressure during wrist motion. J Hand Surg [Am] 23:1004-1009, 1998

35. Keir PJ, Bach JM, Rempel DM: Fingertip loading and carpal tunnel pressure: Differences between a pinching and a pressing task. J Orthop Res 16:112-115, 1998

36. Kleindienst A, Hamm B, Hildebrandt G, Klug N: Diagnosis and staging of carpal tunnel syndrome: Comparison of magnetic resonance imaging and intra-operative findings. Acta Neurochir (Wien) 138:228-233, 1996

37. Klinenberg E, So Y, Rempel D: Temperature effects on vibrotactile sensitivity threshold measurements: implications for carpal tunnel screening tests. J Hand Surg [Am] 21:132-137, 1996

38. Kobayashi S, Baba H, Uchida K, Shimada S, Negoro K, Takeno K, Yayama T, Yamada S, Yoshizawa H: Localization and changes of intraneural inflammatory cytokines and inducible-nitric oxide induced by mechanical compression. J Orthop Res 23:771-778, 2005

39. Kuhlman, KA and Hennessey WJ: Sensitivity and specificity of carpal tunnel syndrome signs. Am J Phys Med Rehabil 76:451-457, 1997

40. LaMotte RH, Lundberg LE, Torebjork HE: Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. J Physiol 448:749-764, 1992

41. Linschoten MR, Harvey LO Jr, Eller PM, Jafek BW: Fast and accurate measurement of taste and smell thresholds using a maximum-likelihood adaptive staircase procedure. Percept Psychophys 63:1330-1347, 2001

42. Macdonell R, Schwartz MS, Swash M: Carpal tunnel syndrome: Which finger should be tested? An analysis of sensory conduction in digital branches of the median nerve. Muscle Nerve 13:601-606, 1990

43. Mackinnon SE: Pathophysiology of nerve compression. Hand Clin 18:231-241, 2002

44. Maggi SP, Lowe JB III, Mackinnon SE: Pathophysiology of nerve injury. Clin Plast Surg 30:109-126, 2003

45. Mei J, Tuckett RP, Poulos DA, Horch KW, Wei JY, Burgess PR: The neural signal for skin indentation depth. II. Steady indentations. J Neurosci. 3:2652-2659, 1983

46. Merchut MP, Kelly MA, Toleikis SC: Quantitative sensory thresholds in carpal tunnel syndrome. Electromyogr Clin Neurophysiol 30:119-124, 1990

47. Michelsen H, Posner MA: Medical history of carpal tunnel syndrome. Hand Clin 18:257-268, 2002

48. Nathan, PA and Keniston RC: Carpal tunnel syndrome and its relation to general physical condition. Hand Clin 9:253-261, 1993

49. Novak CB, Mackinnon SE, Brownlee R, Kelly L: Provocative sensory testing in carpal tunnel syndrome. J Hand Surg [Br] 17:204-208, 1992

50. Rempel D, Bach JM, Gordon L, So Y: Effects of forearm pronation/supination on carpal tunnel pressure. J Hand Surg [Am] 23:38-42, 1998

51. Rempel D, Keir PJ, Smutz WP, Hargens A: Effects of static fingertip loading on carpal tunnel pressure. J Orthop Res 15:422-426, 1997

52. Rosecrance JC, Cook TM, Satre DL, Goode JD, Schroder MJ: Vibration sensibility testing in the workplace. Day-to-day reliability. J Occup Med 36:1032-1037, 1994

53. Rydevik B, Lundborg G, Bagge U: Effects of graded compression on intraneural blood blow. An in vivo study on rabbit tibial nerve. J Hand Surg [Am] 6:3-12, 1981

54. Szabo, R. M.: Acute carpal tunnel syndrome. Hand Clin 14:419-429, ix, 1998

55. Szabo, RM and Gelberman RH: The pathophysiology of nerve entrapment syndromes. J Hand Surg [Am] 12:880-884, 1987

56. Szabo RM, Gelberman RH, Williamson RV, Dellon AL, Yaru NC, Dimick MP: Vibratory sensory testing in acute peripheral nerve compression. J Hand Surg [Am] 9A:104-109, 1984

57. Torebjork HE, Lundberg LE, LaMotte RH: Central

changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. J Physiol 448:765-780, 1992

58. Tuckett RP: Response of cutaneous hair and field mechanoreceptors in cat to paired mechanical stimuli. J Neurophysiol 41:150-156, 1978

59. Tuckett RP, Horch KW, Burgess PR: Response of cutaneous hair and field mechanoreceptors in cat to threshold stimuli. J Neurophysiol 41:138-149, 1978

60. Ward, RS and Tuckett RP: Quantitative threshold changes in cutaneous sensation of patients with burns. J Burn Care Rehabil 12:569-575, 1991

61. Werner RA, Franzblau A, Johnston E: Quantitative vibrometry and electrophysiological assessment in screening for carpal tunnel syndrome among industrial workers: A comparison. Arch Phys Med Rehabil 75:1228-1232, 1994

62. Werner RA, Franzblau A, Johnston E: Comparison of multiple frequency vibrometry testing and sensory nerve conduction measures in screening for carpal tunnel syndrome in an industrial setting. Am J Phys Med Rehabil 74:101-106, 1995

63. White KM, Congleton JJ, Huchingson RD, Koppa RJ, Pendleton OJ: Vibrometry testing for carpal tunnel syndrome: A longitudinal study of daily variations. Arch Phys Med Rehabil 75:25-28, 1994

64. You H, Simmons Z, Freivalds A, Kothari MJ, Naidu SH: Relationships between clinical symptom severity scales and nerve conduction measures in carpal tunnel syndrome. Muscle Nerve 22:497-501, 1999

65. Zelenka M, Schafers M, Sommer C: Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain 116:257-263, 2005

66. Zhang J, Huang W, Tuckett RP: C-fiber modulation of the rat type I slowly adapting mechanoreceptor. Neuroscience 115:797-804, 2002