Towards Development of a Nonhuman Primate Model of Carpal Tunnel Syndrome: Performance of a Voluntary, Repetitive Pinching Task Induces Median Mononeuropathy in *Macaca fascicularis*

Carolyn M. Sommerich,[1] Steven A. Lavender,[1,2] John A. Buford,[3] Jacob J. Banks,[1,3] Sahika Vatan Korkmaz,[1] William S. Pease[4]

[1]Department of Industrial, Welding and Systems Engineering, The Ohio State University, 1971 Neil Avenue, Room 210, Columbus, Ohio 43210

[2]Department of Orthopaedic Surgery, The Ohio State University, Columbus, Ohio

[3]Department of Physical Therapy, The Ohio State University, Columbus, Ohio

[4]Department of Physical Medicine and Rehabilitation, The Ohio State University, Columbus, Ohio

Received 7 July 2006; accepted 30 November 2006

Published online 22 February 2007 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jor.20363

ABSTRACT: This study investigated changes in median sensory nerve conduction velocity (SNCV) over several weeks of exposure to a voluntary, moderately forceful, repetitive pinching task performed for food rewards by a small sample of young adult female monkeys *(Macaca fascicularis)*. SNCV, derived from peak latency, decreased significantly in the working hands of three of the four subjects. The overall decline in NCV was 25%–31% from baseline. There was no decrease in SNCV in the contralateral, nonworking hands. Several weeks after being removed from the task, SNCV returned to within 87%–100% of baseline. MRI showed enlargement of the affected nerves near the proximal end of the carpal tunnel, at the time of maximal SNCV slowing. This new animal model demonstrates a temporally unambiguous relationship between exposure to a moderately forceful, repetitive manual task and development of median mononeuropathy at the wrist, and recovery of SNCV following termination of task exposure. This study contributes to the pattern of evidence of a causal relationship between manual work, median mononeuropathy, and carpal tunnel syndrome in humans. In the future, this new animal model could be used to characterize dose–response relationships between risk factors and carpal tunnel syndrome. © 2007 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 25:713–724, 2007

Keywords: animal model; carpal tunnel syndrome; work-related musculoskeletal disorder; electrodiagnosis; median mononeuropathy

INTRODUCTION

Carpal tunnel syndrome (CTS) results from compressive forces acting on the median nerve within the carpal tunnel and is the most commonly encountered peripheral neuropathy.[1,2] In the US, the median lost workdays for CTS is 28, four times the value for all occupational injuries and illnesses combined.[3] There is still debate, however, about whether CTS is a work-related disorder. Some consider the evidence equivocal, because of the many nonoccupational risk factors for CTS: gender (female),[4,5] age, obesity, reduced fitness, smoking, alcohol and caffeine use, diabetes, renal disease, thyroid disease, pregnancy, lactation, sports participation,[2] and genetics.[6] Falkiner and Myers[2] concluded that work is the probable cause of CTS only for forceful hand work under cold conditions; in most other cases, they concluded work was only the "straw that broke the camel's back." Alternatively, Bernard[7] reviewed over 30 epidemiological studies of workplace factors and CTS and determined that, on balance, the evidence supported an association between CTS and highly repetitive work, forceful work, and combinations of risk factors. Viikari-Juntura and Silverstein[8] reviewed epidemiological, experimental, cadaver, and animal studies and found a compelling connection between external, physical factors (posture, force, repetition, and external pressure) and changes in carpal tunnel pressure (CTP). They

Correspondence to: Carolyn M. Sommerich (Telephone: 614-292-9965; Fax: 614-292-7852; E-mail: sommerich.1@osu.edu)

concluded that there is sufficient evidence to suggest that duration, frequency, or intensity of exposure to forceful repetitive work and extreme wrist postures is likely to be related to occurrence of CTS in working populations.

Regardless of whether a case of CTS is caused by work, certain underlying pathologies have been described. One mechanism of nerve damage in CTS may be mechanical trauma during work. Forces acting on the contents of the carpal tunnel include: normal contact forces between adjacent tissues, as described by a pulley model;[9] shear (traction) forces;[10] and hydrostatic pressure.[11] These forces are affected by increasing flexor tendon tension and by increasingly nonneutral wrist postures, among other factors. Extra material in the carpal tunnel (muscle fibers, excessive synovium, excessive interstitial fluid, etc.) will also increase these forces. Externally applied forces, as from a tool handle, are also transmitted to tissue within the carpal tunnel.[12] Pressure can be exerted on the median nerve from direct contact with other structures in the wrist or increased hydrostatic pressure. Hydrostatic pressure as low as 20–40 mmHg can adversely affect nerve function (circulation, axonal transport, and impulse conduction[13,14]). These pressure levels can be induced when hands are used in ordinary ways. CTP in healthy people exceeds these levels when assuming nonneutral wrist postures.[15] Exerting a 5 N pinch (about 5%–10% of adult maximum pinch strength) can raise CTP to 30 mmHg.[16]

When these working conditions are chronic, secondary changes may add to the problem. Proliferation of connective tissue in response to repeated stress can increase nerve compression during work,[12,13] and increased pressure may persist after work in patients with CTS.[17] Inflammation in response to the injury produces swelling of the nerve itself that is visible with magnetic resonance imaging,[18,19] compounding the increased pressure within the carpal tunnel. If these mechanisms are correct, then a task requiring moderately forceful pinching with a nonneutral wrist posture may be sufficient to expose the median nerve to damaging forces. And, if such a task produces CTS as a chronic disorder, median nerve dysfunction should develop over a period of several weeks and edema of the nerve should be evident.

For a prospective research study to address questions of CTS etiology, an animal model with appropriate wrist and hand anatomy is required. In humans, the carpal tunnel contains the median nerve and tendons of flexor digitorum superficialis and profundus (FDS and FDP, respectively), flexor pollicis longus (FPL), and flexor carpi radialis (FCR; in its own sub-tunnel); 10 tendons in all. Adjacent to the median nerve are the tendons of the FPL and FDS1 (FDS to index finger) muscles, so to model pinching, these tendons should be similar in the animal model. Napier considered the macaque's hand function to be identical to humans when performing a grasp and key pinch.[20,21] Although the macaque does not have a separate FPL muscle, the radial part of FDP produces a tendon that travels though the carpal tunnel adjacent to the median nerve and attaches to the distal phalanx to flex the thumb, as in humans. This tendon and that of FDS1 remain adjacent to the median nerve, so the tendons in the carpal tunnel are homologous. Thus, the macaque is an appropriate animal model to address CTS etiology.

The main objective finding in clinical studies of CTS is decreased median nerve conduction velocity, which is taken as evidence of median nerve mononeuropathy at the wrist. This same measure has been used in recently developed animal models that mimic human occupational overuse exposure. One model uses anesthetized rabbits, in which the FDP m. is repeatedly stimulated to elicit a specified force against a load cell.[22] An alternative to this is a dose–response model in which a semi-permanent catheter is inserted into the rabbit and is inflated to known pressures.[23] The rabbit is free to ambulate, and over a period of days or weeks, median nerve impairment develops. In a rat model, subjects perform a voluntary, repetitive, low force grasping or high force pulling task.[24,25] In the pulling task, work is not limited to the paw. The shoulder is engaged in reaching and the opposite limb has increased weight-bearing demands. Through electrodiagnostic testing, these models have shown median nerve conduction impairment in their subjects, similar to that seen in humans with CTS. A prior monkey model placed a silastic tube around the median nerve to produce direct nerve damage, so this was not a model of a work-related disorder.[26]

Diagnosis of CTS in humans rests on more than decreased median nerve conduction velocity. Exact case definitions vary, but there must be pain or paresthesia in the median nerve distribution of the hand. In animal models, symptoms cannot be reported to investigators. Hence, other objective measures may be used to confirm and explore mechanisms of median nerve damage. As the analog of pain or paresthesia, impaired task performance is taken as consistent with discomfort.[24,25] Overall, findings from existing animal

 DOI 10.1002/jor

models have helped reveal and define pathophysiological mechanisms of median mononeuropathy as the physiological equivalent of CTS, and have demonstrated cause and effect relationships between exposure to certain conditions and development of median nerve damage.

A monkey model involving volitional activity could extend these findings to show that median nerve mononeuropathy at the wrist can occur as a direct result of manual work. Once developed, the model could also be used to study dose–response relationships between CTS and workplace risk factors, including excessive force, nonneutral wrist postures, and grip type. With these long-range goals in mind, the objectives of the current study were to: 1) demonstrate a nonhuman primate model for the study of CTS caused by chronic overuse of the hand; and 2) quantify the natural history of the recovery process.

MATERIALS AND METHODS

Subjects

Four adult female *Macaca fascicularis* monkeys were used in the study. See Table 1 for subject characteristics. Experimental procedures were approved by Ohio State University's ILACUC and subject care was according to the NIH Guide for the Care and Use of Laboratory Animals.

Task and Training

The task required subjects to sustain a pinch grip of 20% of their estimated maximum voluntary exertion (MVE) for 3 s, with the wrist flexed about 60° at a rate of up to 6/min. Task parameters were based on risk factors commonly identified in the epidemiological literature,[7,8] with some specific parameters adopted from a CTS case-referent study of manufacturing jobs. That study found pinch forces >1 kg occurring more than 10 times/h, elementary operations requiring <10 s, breaks or changes in activity for less than 15% of the workday, no job rotation, and manual supply of workstations (i.e., workers brought parts to the workstation rather than having parts fed by a machine) were associated with CTS.[27] For women, who were 85% of the workforce in the study, a 1 kg pinch corresponds to approximately 20% MVE.[28]

A task apparatus (Fig. 1) was attached to each subject's cage. To perform a pinch, subjects reached through a tube and flexed the wrist to about 60° to grasp a pair of tongs in a pad-pad pinch. Resistance was provided by a compression spring between the tongs. Closure of the tongs required a combined effort from the thumb and fingers. The design of the apparatus required the subject to use the left hand for the task. A string threaded through a pulley circuit that included a potentiometer provided an analog record of the degree of tong closure. This signal was monitored by a LabView (National Instruments, Austin TX) program that controlled the task and recorded performance data. A successful pinch resulted in delivery of a food pellet (#F0059, 45 mg banana-flavored pellets; BioServe, Inc., Frenchtown, NJ). A full day's food ration was about 2,100 pellets. The balance of the diet was provided by monkey chow and fresh fruits and vegetables at day's end, to keep the animals healthy while maintaining the incentive to perform. Weighings every 2 weeks assured adequate nutrition.

To reduce the chance of an acute inflammatory response to an abrupt increase in hand use, pinch force and daily exposure duration to the task were gradually increased during the training period. The absolute value

Table 1. Subject Characteristics[a]

Characteristics	M1	M2	M3	M4
Age (years)[b]	9	10	8.5	5
Mass (kg)	4.0	4.0	4.5	5.3
Height (cm)	69.2	67.3	71.0	66.0
Hand length (cm)	8.3	8.2	7.9	7.6
Hand breadth (cm)	3.2	3.1	3.1	3.3
Forearm circumference (cm)	10	10.3	10	12.2
Forearm length (cm)	13.1	13.7	11.9	13.4
Wrist circumference (cm)	6.7	6.9	7.3	7.4
Wrist depth/width ratio[c]	0.77	0.76	0.77	0.77
Pinch force variables used in study protocol				
Estimated maximum pinch strength (N)**	3.69	4.03	4.71	4.88
Force required to complete a pinch (N)	0.75	0.86	0.86	1.25
Percentage of estimated maximum pinch strength	20%	21%	18%	25%

[a]Upper extremity dimensions are from the left limb and obtained as defined in Banks et al.[29] at the beginning of the study.
[b]These ages are approximately comparable to 30–40 years of age in humans.
[c]Determined based on the predictive regression equation using wrist circumference.[29.]

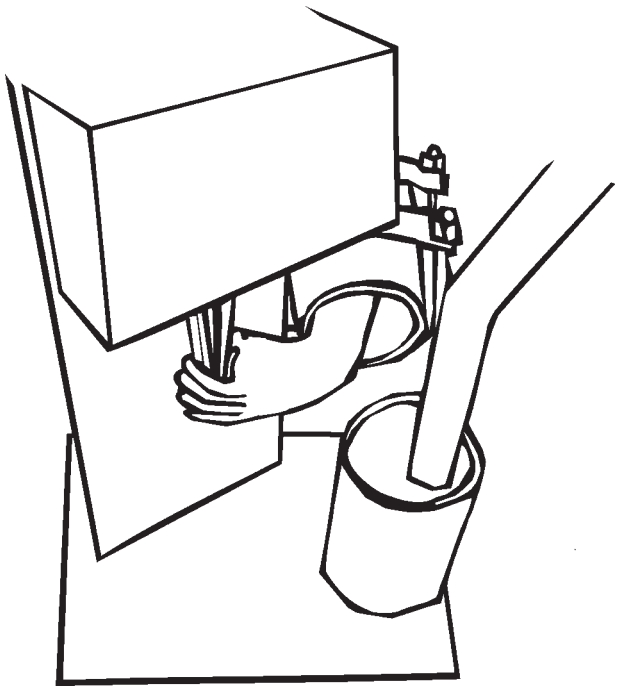

Figure 1. The pinching apparatus that was mounted on each subject's cage. The subject's left hand is illustrated reaching through the tube to pinch the tongs. The housing above the tongs protected the potentiometer and provided a constraint to the excursion of the tongs. To the right, the angled tube shows the path for pellet delivery into a food well.

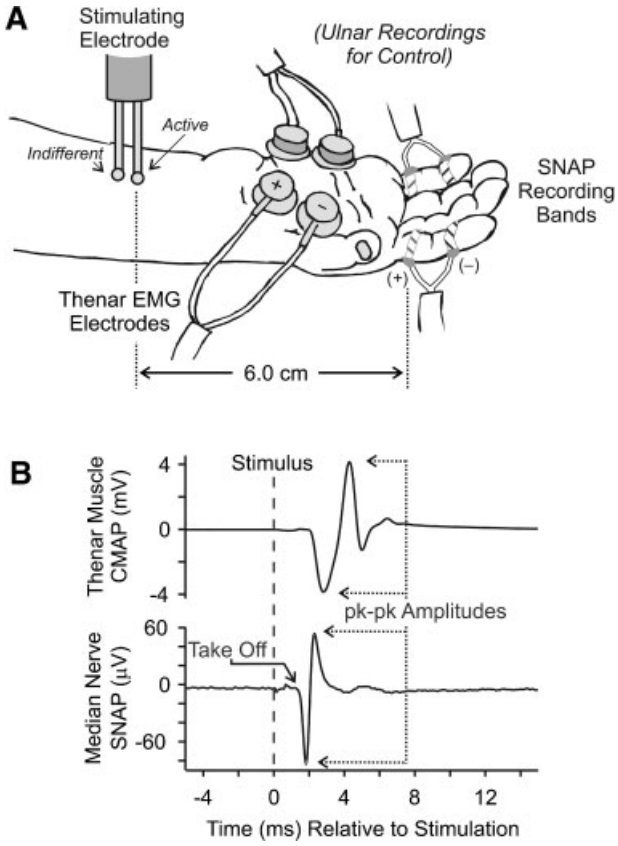

Figure 2. Nerve conduction velocity testing of the median and ulnar nerves: (A) experimental setup for testing the right hand (nonworking) is illustrated with the stimulating electrode in position over the median nerve; (B) a normal nerve conduction velocity test. The latencies were measured as described in the methods.

of the target force of 20% MVE was determined from a regression equation for pinch strength of *Macaca*[29] that provided an estimated 20% MVE threshold target for each subject (Table 1). Elapsed time from initial exposure to the apparatus to performance of the complete task at the required resistance ranged from 5 to 15 weeks. Once trained, subjects were given the opportunity to work 8 h/day (up to 2,880 trials), 5 day/week, except for NCV testing days, when they worked only half of the day.

Electrodiagnostic Testing

The primary dependent variable in the study was median SNCV. The experimental setup for NCV testing of the median and ulnar nerves is shown in Figure 2. During testing, all subjects were initially sedated with Ketamine hydrocholide (13 mg/kg i.m.) and were anesthetized with Isoflorane (1%–2%) inhaled through a mask. Core temperature was monitored rectally.

Electrode sites were shaved and cleaned with a 70% solution of isopropyl alcohol in water. Compound motor action potentials (CMAPs) were measured via two pairs of standard 5-mm Ag/AgCl EMG disc electrodes, filled with electrode gel, and attached via adhesive collars. Electrodes were positioned over the thenar and hypothenar eminences. The reference and active electrodes were placed over the distal tendon and muscle belly motor point, respectively, 1.5 cm apart. Sensory nerve action potentials (SNAPs) of digits 2 and 5 were recorded via pre-gelled, self-adhesive Ag/AgCl TECA NCS2000 disposable ring electrodes (L: 5.5 cm, W: 3.75 mm; Viasys Healthcare Madison, Wisconsin). The active electrode (E1, proximal) was placed as close to the proximal digital crease as possible and the reference electrode (E2, distal) was placed 1 cm distal to that; the interelectrode distance was restricted by the *Macaca's* relatively small hands. A common ground electrode (10-mm Ag-AgCl disc) was attached to the dorsum of the hand. Shielded recording leads were connected to a differential preamplifier near the subject. Another differential amplifier further amplified and filtered the signals. CMAPs and SNAPs were amplified with a gain of 0.5 K and 10 K, respectively. An analog filter with bandpass of 20 Hz–2 KHz was used for all signals. The amplifier system provided a 94db CMRR.

Stimulation was applied through a bipolar stimulating electrode (Grass-Telefactor Model F-BSE1, Astro-Med, Warwick, RI), driven by a battery-powered, optically isolated, current controlled stimulus isolation unit (2200 Analog Stimulus Isolator, A-M Systems, Inc.,

 DOI 10.1002/jor

Sequim, WA). Electrode tips were 2-mm diameter gold-plated silver spheres separated by 5 mm. To stimulate at a reproducible distance proximal to the carpal tunnel, a line was drawn across the forearm 6 cm from the proximal ring electrode (E1) on digit 2. For median nerve stimulation, the stimulating electrode was placed lateral to the palmaris longus tendon. For the ulnar nerve, the electrode was placed medial to the flexor carpi ulnaris tendon on the same line drawn for the median nerve stimulation. Warm packs around the trunk and limbs were used to maintain hand temperature at approximately 35°C.[30] Hand temperature was continuously recorded with a thermal transducer (YSI 427 pediatric temperature probe, YSI Temperature, Inc., Yellow Springs, OH, and Grass-Telefactor model P122 amplifier with TPA) taped to the palm at the distal wrist crease. Infrequently, recorded hand temperature at the time of testing fell below 34°C, and a conservative, small temperature correction was applied to the measured SNCV. The correction was based on pilot work and is on a scale consistent with the literature.[31]

Median nerve testing was conducted every 2 weeks by authors J. J. B. and S. V. K. working together with our animal care technician; none were blinded to subject exposure. Stimulus delivery and data acquisition were performed with Spike 2 software and a Power 1401 acquisition unit (CED, Cambridge, UK). Sampling frequency for recording was 40 kHz per channel at 16-bit ADC resolution. To limit time of anesthesia for routine testing, ulnar nerve stimulation was only performed at baseline prior to training and for confirmation when a positive diagnosis of median mononeuropathy was suspected. For median and ulnar nerve stimulation, CMAPs, SNAPs, and temperatures were recorded for all four sets of electrodes to ensure that median nerve stimulation did not produce hypothenar CMAPs or 5th digit SNAPs, and likewise for the specificity of ulnar nerve stimulation. The testing protocol for each nerve began with determining the minimum current required to evoke a SNAP. Current was incrementally increased until there was saturation (maximum response) of the SNAP and CMAP. The computer was then programmed to control delivery of stimulus pulses at a variety of amplitudes at equal intervals between subthreshold and supramaximal intensities for that session. Five stimuli were delivered for each amplitude, with order of stimulus amplitude randomized to avoid order effects.

Calculation of SNCV from latency required identification of an appropriate test current for each testing session based on recruitment curves for the SNAPs and CMAPs. The Spike2 software was set to routinely produce recruitment curves, plotting stimulus current on the abscissa versus peak-to-peak amplitude of SNAP and CMAP on the ordinate. From the recruitment curve, currents that produced maximal amplitudes of the SNAP and CMAP were identified. The test current was identified as the stimulus intensity that evoked a maximal SNAP, which was typically about 1.1 times the current required for a maximal CMAP.[32]

The latency of the SNAP's onset and peak depolarization were measured from the averaged responses to the five stimuli at the selected test current. The onset point was defined as the onset of a negative slope with a 12.5% gradient during the initiation of the SNAP (Fig. 2B). SNCV were calculated from onset and peak latencies; the distance measured between the distal stimulating electrode and proximal recording electrode (6 cm) was divided by the latency to calculate velocity. Peak measurements were more stable, because they were relatively insensitive to variations in the noise of the recording across sessions. Onset latencies may be more sensitive to the early onset of nerve conduction impairment, but are also less stable between sessions, because variations in baseline noise can affect the ability to detect onset. As such, and due to the longitudinal variability in peak-to-peak amplitude, SNCV derived from peak latency was chosen as the primary dependent measure for this model. CMAPs were used only to verify that the muscle was maximally recruited at the stimulus current chosen for calculation of SNCV; no velocity measurements were based on the motor responses. The CMAPs were also used to confirm that the stimulus current from median nerve stimulation produced responses only in the thenar muscles.

For testing this new model, we adopted a conservative case definition to guard against false positives[33] and declaring normal work-induced SNCV decline as CTS.[34] In the current study, a case of CTS was operationally defined as a mononeuropathy resulting in a 25% decrease in median SNCV derived from peak latency. This exceeds the 2 standard deviation decline typically used in human diagnostic testing (2 SD corresponds to a 9%–14% decline in SNCV from peak latency and an 11%–27% decline in SNCV from onset latency).[35] In the rabbit model, as another benchmark, CTS was operationally defined as a 15% delay from baseline in distal motor latency.[23] To confirm a suspected case, a recognized expert in electrodiagnostic medicine (author W. S. P.) conducted extensive testing comparing ulnar and median nerve responses from the wrist to those evoked from around the elbow for the left (working) and right (nonworking) limbs. Testing with stimulation distal to the carpal tunnel was infeasible due to the extremely short distances involved (< 3 cm). To demonstrate a persistent, unambiguous decline in SNCV, consecutive readings 2 weeks apart each demonstrating at least a 25% decline from baseline were required by predetermined protocol before the subject was removed from the task and allowed to recover.

Magnetic Resonance Imaging and Analysis

Bilateral MR images of the wrists were collected for all four subjects. Images for subjects M1–3 were collected when CTS was diagnosed in M1 and M3. Images for M4 were collected at baseline and at diagnosis. Imaging was performed in a 4.7 Tesla MRI unit (Biospec 47/40, Bruker Instruments, Inc., Billerica, MA). Two types of sequences were collected: gradient echo fast imaging (GEFI, TR = 500 ms, TE = 5 ms, flip angle = 30°) and

high resolution spin echo with relaxation enhancement (RARE, TR = 2540.4 ms, TE = 28.8 ms). Slice thickness was 1 mm with a gap of 0.2 mm. Axial and coronal images were collected and examined for anatomical anomalies (none were identified). Only RARE axial images were quantitatively analyzed. A custom pick-up coil was affixed via a splint to the ventral aspect of the wrist for improved signal-to-noise ratio in the vicinity of the wrist. A custom-built Plexiglas holder kept the wrist centered in the coil with a consistent location for both wrists across subjects. Subjects were under anesthesia for the procedure.

Images were analyzed using frame grabber software (Scion Image for Windows, Beta 4.02, Fredrick, MD). Nerve intensity and cross-sectional area were quantified. Intensity was assessed by calculating the signal difference to noise ratio (SDNR), comparing the median nerve to the extensor tendons. A publicly available MATLAB routine was adapted for calculating areas from the images.[36] For tracing areas, the outermost pixels of the structure were followed, similar to the method described by Monagle et al.[37] Assessments were performed collaboratively (authors S. V. K. and J. J. B.). They were not blinded to subject status, however since features were not being subjectively graded, but assessed quantitatively, this was not considered a significant weakness of the methodology.

Cytokine Analysis

Blood samples were collected every 2 weeks from M4, from baseline to diagnosis. Samples were also collected from M1 and M3 at diagnosis and from M2 at the same time, to analyze the serum for pro-inflammatory cytokines. Serum, rather than tissue, was sampled to avoid risk of tissue damage. Few commercially available kits have been shown to be effective for sampling cytokines in monkeys. As such, testing was limited to examining samples for elevated levels of IL-6 and TNF-α; IL-1 could not be tested. IL-6 and TNF-α are important pro-inflammatory proteins (cytokines) that are active at the acute stage of response to trauma and other perturbations. Serum levels of IL-6 and TNF-α were measured using an enzyme linked immunosorbent assay (ELISA; BD Biosciences, San Jose, CA).

RESULTS

Three of the four subjects developed CTS in the working hand as a result of exposure to the repetitive pinching task, as defined by reduction in SNCV. Consistent with those results, MRI showed an enlarged portion of the median nerve in the proximal region of the carpal tunnel in the three affected subjects' working hands.

Task Performance

Graphs in Figure 3A illustrate the number of attempted and successful pinches for each subject, along with cumulative workload associated with attempts and successes, from task introduction to diagnosis. Attempts include successful pinches and those of sufficient force, but insufficient duration. The period of work is divided into initial training, when parameters such as force and pinch hold time were being adjusted towards the criterion values, and the period of the full task, when training was complete (Fig. 3A). In training, there was often a relatively high number of attempts relative to successes, but as the task was learned, the proportion of successful attempts increased. As the force level and pinch hold time increased during training, attempts and successes per day for M2 and M3 tended to decline. The trend in subject M1 was a general increase in work over time; M4 had a high work rate from the outset. The average pellets consumed daily ranged from 580 to 900 during training and 470 to 1,230 on the full task. In subjects M3 and M4, the number of successful trials per day appeared to decline around the time of diagnosis with CTS, which is when the plotting of work stops. Subject M4 demonstrated a particularly abrupt decline from her previously high work rate, and almost completely stopped working for a couple of days. The plots of cumulative work show that M1 and M2 achieved comparables levels of output over the period of performance; in comparison, M3's output was less and M4's more.

Electrodiagnostic Testing Results

Results of the nerve conduction velocity tests for the median nerve are illustrated in Figure 3B, which identifies training and work periods for M2 and training, work, and recovery periods for M1, M3, and M4. M1 and M3 met the stopping criteria of at least a 25% decline in SNCV for two successive readings (roughly equal to a change in peak latency from 2.0 ms to 2.5 ms). M4 was removed from the task with only one reading at 25% below baseline and the next at 21% because, as described above, the number of pinches declined abruptly to virtually nil the week following the first 25% below reading. The abrupt decline in performance likely indicated the subject was experiencing discomfort. When confirming CTS via NCV testing, the ulnar nerve was also tested bilaterally. No changes were seen in ulnar nerve conduction velocity. Of the eight median nerves tested, only those of the working hands showed an increased latency in subjects diagnosed with CTS. Regression analyses showed highly significant relationships between cumulative workload and

 DOI 10.1002/jor

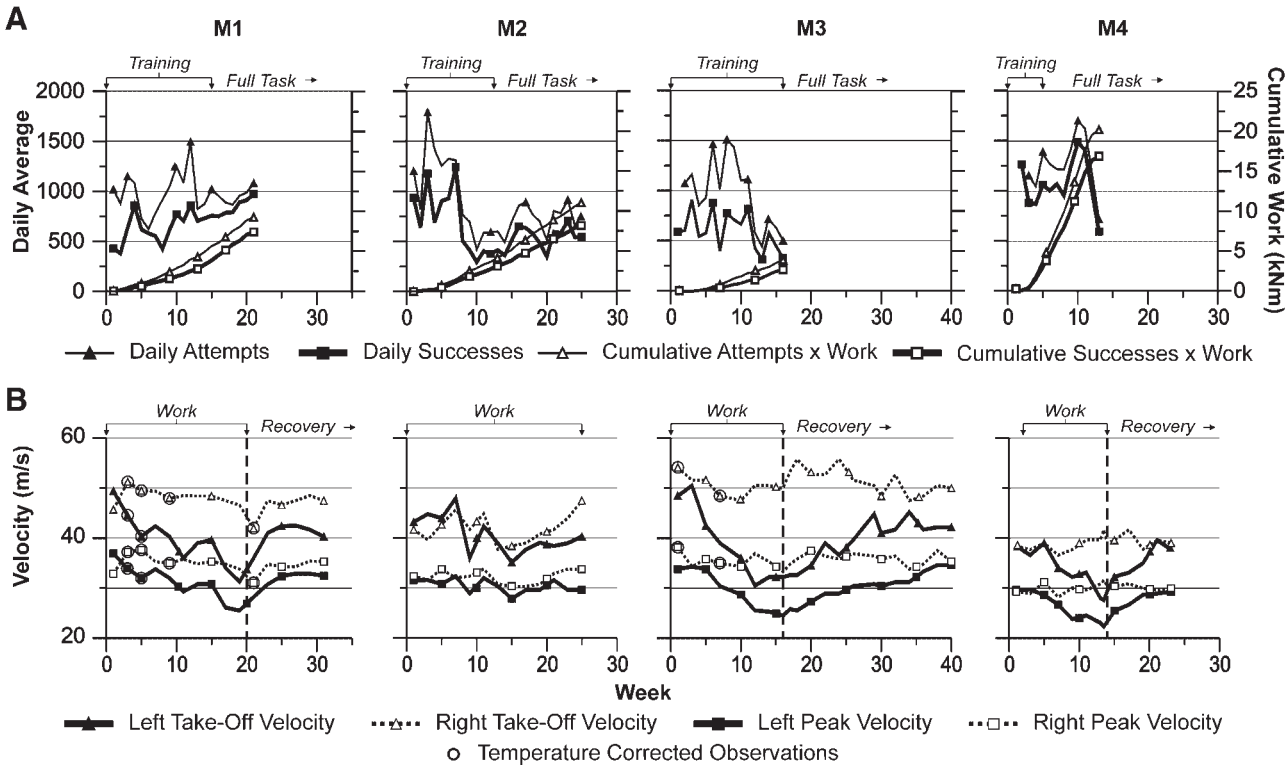

Figure 3. (A) The number of attempted and successful pinches for each subject is plotted along with corresponding measures of cumulative work. Cumulative work was the product of pinch force, pinch distance, and number of pinches. Values are daily averages over the course of each week on the task. (B) The results of the median nerve conduction velocity tests for the left (working hand, solid lines) and right (nonworking hand, dotted lines) hands. The time of diagnosis with median mononeuropathy is indicated by the dashed vertical line. Temperature correction is explained in the methods.

decline in SNCV for the working (left) hands of M1, M3, and M4 (R^2: 0.86, 0.91, 0.89, respectively; all p-values <0.001), and no significant relationships for the nonworking hands or for either of M2's hands. Further evidence of the association between performing the task and development of CTS comes from observing the recovery of SNCV in the subjects after they were taken off the task. Figure 3B shows steady recovery in SNCV of the left median nerve in the affected subjects, leveling off at 87%–100% of baseline.

MRI

Consistent with SNCV results, MRI showed an increase in the cross-sectional area of the median nerve within the carpal tunnel in the affected subjects' working hands (Fig. 4). Nerve image intensity also showed differences between working and nonworking hands in the affected subjects. Increased image intensity, quantified as SDNR, was seen when comparing M4's data at baseline and at diagnosis (Fig. 5). For M4, median nerve intensity at the level of the pisiform bone for left and right hands at baseline was 24.4 and 19.2, respectively, and at diagnosis was 33.6 and 23.9, respectively.

Cytokine Analysis

The analysis did not find elevated IL-6 or TNF-α levels in any serum samples. These results are consistent with Freeland et al.,[38] who found elevated levels of IL-6 only in tissue samples from CTS patients. Barbe et al.[39] found elevated levels of IL-1α in serum from rats performing a high repetition, negligible force grasping task, while Freeland et al.[38] did not find elevated IL-1 in serum from CTS patients or controls.

DISCUSSION

The primary goal of this study was achieved: a unilateral, volitional task containing several risk

factors associated with CTS in human epidemiological research induced median mononeuropathy in the monkey. The validity of the model was further strengthened by the improvement in median nerve function that occurred while subjects were removed from the task. Both impairment and recovery required several weeks to accomplish, and so support this as a model of chronic exposure. Developing a reliable and reproducible experimental model for median mononeuropathy (which corresponds physiologically with CTS in humans) may provide a means to study dose–response relationships between median nerve impairment and work exposure limited to the hand and wrist. This model may also support studies on intervention effectiveness.

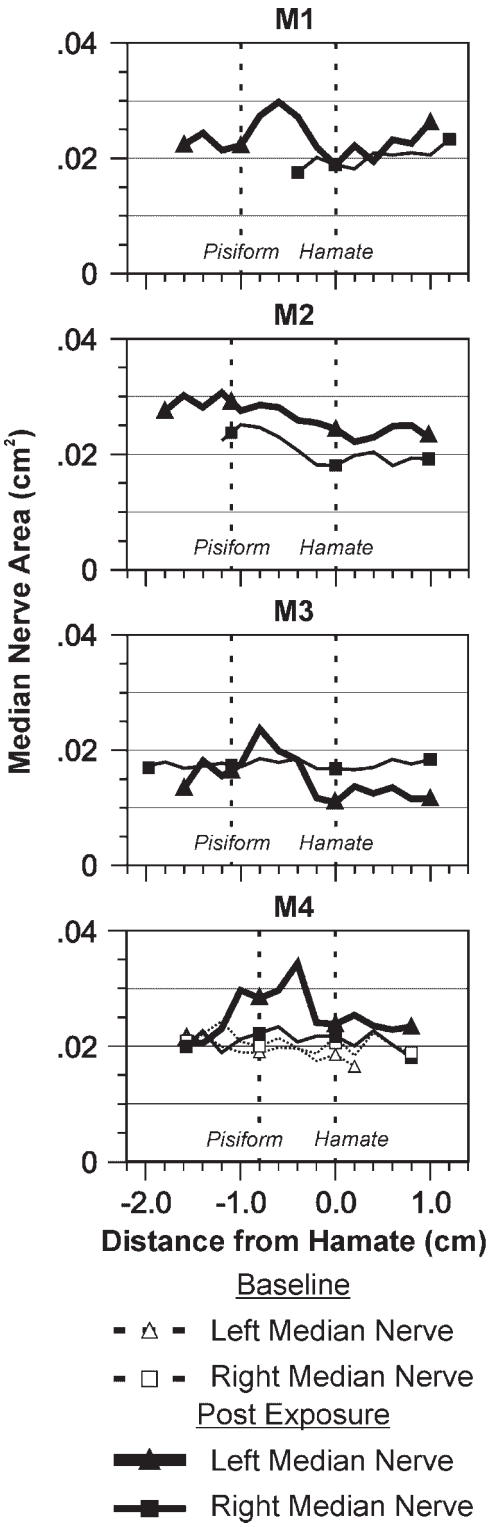

Figure 4. Median nerve cross-sectional area estimated from MRI. Data were collected at diagnosis for M1, M3, and M4. Baseline data were also collected for M4. The distance from the hamate was calculated based on the slice thickness of the serial images. The increased area of the nerve was evident in the proximal part of the carpal tunnel, around the level of the pisiform, for subjects M1, M3, and M4, the individuals diagnosed with median mononeuropathy. This pattern was not evident for M2, or for any of the right hand nerves, or in the baseline for M4.

A *Macaca fascicularis* model for the study of CTS has a high degree of face validity for a number of reasons, including the anatomical similarities between *Macaca* and humans. A "true" opposable thumb, seen in Old World Monkeys like the *Macaca fascicularis*,[40] is needed for controlled grasping and pinching.[20,21] Both species use the same muscles for these movements. The macaque's thumb is relatively short compared to a human's, but since the pinch forces in this study were based on values expected for the macaque, this difference was accounted for. Innervations, attachments, and functions of the forearm flexor muscles are nearly identical, as well.[41] Other anatomical correlations, such as the ratio of flexor physiological cross-sectional area to extensor (0.58 for *Macaca* vs. 0.62 for humans),[42] are very close, also, and show a well-balanced forearm. The carpal bones of both *Macaca* and human have a distinguishable proximal and distal row arrangement,[43] giving rise to the posterior border of the carpal tunnel. The anterior border of the carpal tunnel, the flexor retinaculum, is the same for both, as well.[43]

There are differences between *Macaca* and human; those pertinent to the model of CTS are discussed here. First, the FDP in the *Macaca* represents a combination of the FDP in human anatomy and the FPL.[43] In the *Macaca*, the FDP has two parts: radial and ulnar. The radial side provides muscle fibers that correspond to FPL in humans, but also lateral fibers that are incorporated into the FDP. As with the human FPL, the pollical tendon travels through the carpal tunnel to

 DOI 10.1002/jor

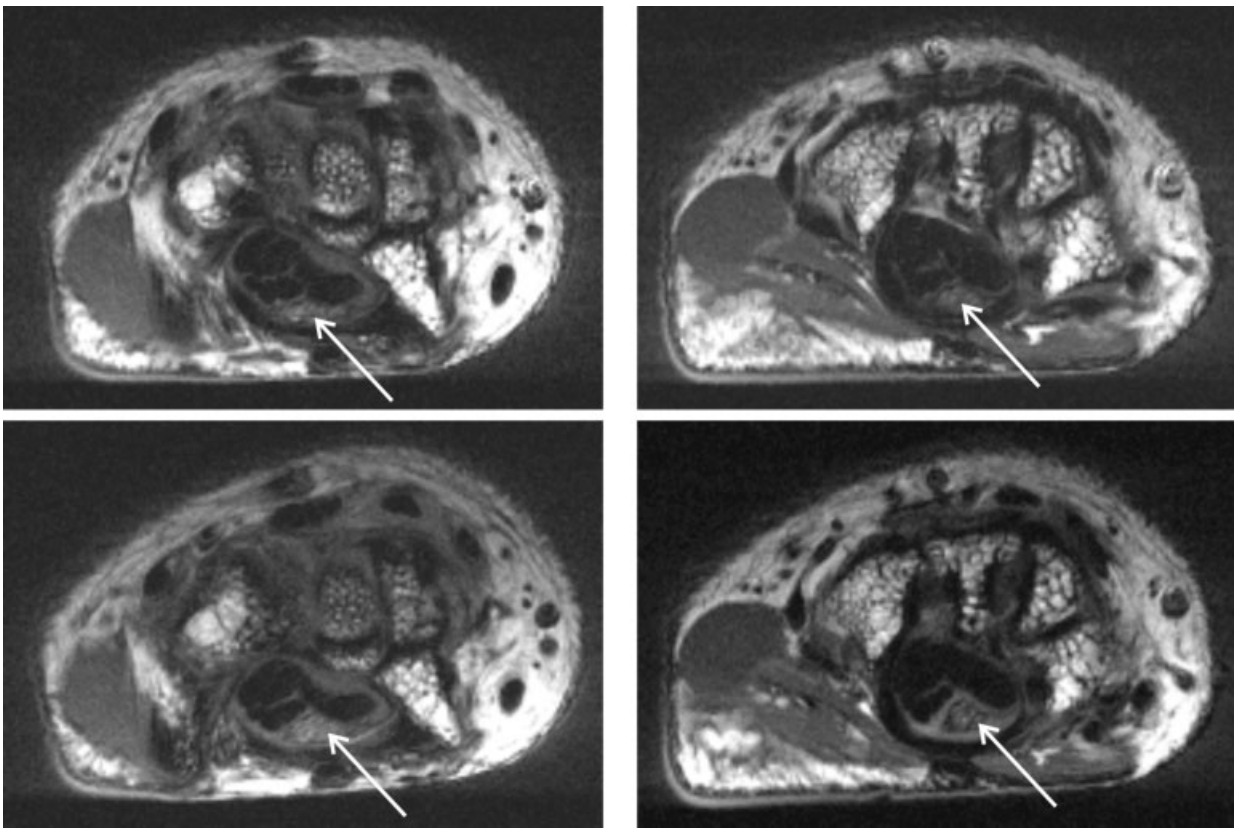

Figure 5. MRIs for M4. Baseline images on the top row; images taken at point of CTS diagnosis on bottom row. Images on left are at pisiform level; hamate on the right. White arrows point to median nerve; note plumper shape of the nerve in the images in the lower row. Also note the thickness of connective tissue around the median nerve in the lower right image.

the thumb's distal phalanx. This factor is most relevant to the model of CTS. Second, the *Macaca* FDP is only innervated by the median nerve. In humans, the FDP is co-innervated by the ulnar and median nerves. The ulnar nerve innervates the ulnar side, while the median innervates the radial side of the muscle.[41] Since the point of innervation should be proximal to the area of damage caused by CTS, this difference should not affect the model. Third, humans have eight carpal bones vs. *Macaca's* nine. The additional bone is the os centrale positioned between the scaphoid and capitate. The human fetus has this bone until the third month of gestation, when it is fused permanently to the scaphoid.[44] This fusion allows for increased stability of the wrist.[45] The presence of the os centrale permits an extra rotation, termed midcarpal rotation.[46] We have attempted passive rotation of the wrist and hand of an adult male macaque, and were only able to rotate it slightly relative to the forearm, no more so than could be accomplished by passive rotation of a human hand. To further compare the species, as part of our preliminary research, three monkey forearms and one human forearm were cross-sectioned at the same relative location. The tunnel-to-wrist cross-sectional area ratios were similar between human and monkey (10% and 8%, respectively), as were nerve-to-wrist ratios (0.6% and 0.7%, respectively). Despite these differences, the critical similarity is the juxtaposition of the median nerve with the FDP tendons.

The only other animal model that has demonstrated a relationship between voluntary upper limb work and the development of median mononeuropathy is the rat model.[24,25] In separate studies, they have explored the effect of low and high force manual tasks on median nerve impairment and task performance. They have also described mechanisms of neurotrauma and neuroinflammation. Taken in light of the debate in the human epidemiological literature, however, there is one important limitation to the rat model. Although the effector in the rat model is the forepaw,[24,25] the task, particularly in the study of

high force,[25] is essentially a whole body task. It is not uncommon in some occupations for a worker to support his/her weight on one hand while working with the other, so the rat task is occupationally realistic. However, when the researchers see changes in the other limbs, it is not possible for them to conclusively determine whether there is a systemic effect that is caused solely by the exposure of the working limb or whether these systemic effects results from exposure of the entire body.[25] This is important to the question of work-relatedness of CTS, because some suggest that occurrence of bilateral CTS is evidence against CTS being work-related. Our model complements the rat model by demonstrating in an animal model that when only one hand performs a task, median mononeuropathy develops only in that hand.

We now have evidence that, in rabbits, rats, macaques, and humans, repetitive tasks that likely impose stress on the median nerve within the carpal tunnel can all result in median nerve impairment. This makes it hard to argue that work exposure in humans is not a causative factor for CTS, or that cold exposure is a co-requisite. Second, in the present model, the mechanism of exposure is a voluntary exertion of one hand in a task with work rates, force levels, hold durations, and postures that are well within the range of occupational tasks. As designed, the task would rate a Strain Index value of 6–13.5 for humans, signaling it should pose some risk for distal upper extremity disorder.[47] These values are well within the range of jobs the authors studied in developing the Index (0.8–54).

Limitations

The addition of a completely unexposed control group would strengthen the design of the present study. However, the unexposed hand served as a within-subject control for changes over time not associated with work. The finding that one of the four subjects did not develop CTS, despite a comparable level of work, could also be seen as a limitation, or as an example of variation in risk among the population. Regardless, even though this subject did not meet our criteria for CTS, SNCV trended lower over time ($p = 0.05$) for that subject (M2), though the R^2 value was small at 0.3. The MRI for this subject showed a larger median nerve on the left side than on the right throughout the carpal tunnel (Fig. 4). This is may represent an early stage of inflammation, reflecting a subclinical case of median mononeuropathy. If so, this subject may have self-limited her work rate such that the problem did not progress further. Her average weekly number of pinches after achieving full task status was less then the other subjects (although her average weekly pinches during training were not lower). Perhaps humans who do not develop CTS despite performance of risky tasks have learned alternative strategies or self-limit their exposure in ways that allow them to stay below the threshold for development of CTS.

One of the primary limitations of a voluntary model is limited control over exposure. More generally speaking, temporal aspects of exposure pose a scaling challenge for animal models. Several small animal models expose subjects for 2 h/day, 3 days/week.[22,24,25,39,48] though other patterns are used as well.[49,50] In a rat model of rotator cuff tendinitis, the exposure (1 h/day, 5 day/week) was based on equating the number of strides per day for the subjects to "the number of strokes an elite swimmer may take during a typical training protocol."[49] In the present model, exposure was modeled on the typical 40-h work week. The subjects were free to execute as many trials as possible in that time (up to 6 rep/min within the 8 h day). A "perfect day" would have involved 2,880 trials; a full day's ration of food from pellets alone is about 2,100 pellets by weight. Hence, with performance rates peaking at around 1,500 successes per day, there should have still been some room for further work had the subjects been sufficiently motivated. But in practical terms, we suspect that 1,500 successes a day represents the limit for monkeys performing this task. Despite the variation in exposure among subjects, the time frame in which the impairment developed in our subjects was similar to reports of CTS development in humans (10–12 weeks),[51] which signals the validity of the temporal exposure characteristic of this model. Another limitation of the study is the small number of subjects. However, this is offset by the extensive longitudinal data collected for each subject.

Conclusions

Animal models provide an opportunity to control many of the risk factors that are associated with CTS in humans, thus affording opportunity to study the effect of physical (occupational) risk factors in the development of median nerve impairment. The present study demonstrates that in three of four macaques performing a voluntary pinching task with multiple risk factors, median mononeuropathy at the wrist (the equivalent to CTS in humans) could be diagnosed after

 DOI 10.1002/jor

3–4 months of work. This sets the stage for further studies with this model to define risk factors, assess ergonomic interventions, and test treatments for CTS.

ACKNOWLEDGMENTS

This study was supported by a grant from the National Institute for Occupational Safety and Health, R21 OH008273, and from a subcontract to R24 HD39627 (Northwestern University, PIs: W. Z. Rymer and E. Roth). Early support was provided by the Department of Industrial, Welding and Systems Engineering, Department of Orthopaedic Surgery, and the College of Engineering at The Ohio State University. We thank S. Moran and P. Wassenaar, and Drs. M. McCain, C. Whitacre, P. Schmalbrock, and S. Sammet for their assistance with the project. We also thank the anonymous reviewers of the first draft of this manuscript for their constructive criticisms and thoughtful suggestions.

REFERENCES

1. Werner RA, Andary M. 2002. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol 113:1373–1381.
2. Falkiner S, Myers S. 2002. When exactly can carpal tunnel syndrome be considered work-related? Aust N Z J Surg 72:204–209.
3. Bureau of Labor Statistics (BLS). 1994–2004. Annual survey of occupational injuries and illnesses. Available at: http://www.bls.gov/iif/oshcdnew.htm.
4. Franklin GM, Haug J, Heyer N, et al. 1991. Occupational carpal tunnel syndrome in Washington State, 1984–1988. Am J Public Health 81:741–746.
5. Islam SS, Velilla AM, Doyle EJ, et al. 2001. Gender differences in work-related injury/illness: analysis of workers compensation claims. Am J Ind Med 39:84–91.
6. Hakim AJ, Cherkas L, El Zayat S, et al. 2002. The genetic contribution to carpal tunnel syndrome in women: a twin study. Arthritis Rheum 47:275–279.
7. Bernard BP. 1997. Musculoskeletal disorders and workplace factors. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.
8. Viikari-Juntura E, Silverstein B. 1999. Role of physical load factors in carpal tunnel syndrome. Scand J Work Environ Health 25:163–185.
9. Armstrong TJ, Chaffin DB. 1979. Some biomechanical aspects of the carpal tunnel. J Biomech 12:567–570.
10. Goldstein SA, Armstrong TJ, Chaffin DB, et al. 1987. Analysis of cumulative strain in tendons and tendon sheaths. J Biomech 20:1–6.
11. Keir P, Wells RP, Lavery W. 1997. The effects of tendon load and posture on carpal tunnel pressure. J Hand Surg [Am] 22:628–634.
12. Cobb TK, An KN, Cooney WP. 1995. Externally applied forces to the palm increase carpal tunnel pressure. J Hand Surg [Am] 20:181–185.
13. Rydevik B, Lundborg G, Bagge U. 1981. Effects of graded compression on intraneural blood flow. J Hand Surg 6:3–12.
14. Szabo RM, Gelberman RH. 1987. The pathophysiology of nerve entrapment syndromes. J Hand Surg 12A:880–884.
15. Keir PJ, Bach JM, Rempel DM. 1998. Effects of finger posture on carpal tunnel pressure during wrist motion. J Hand Surg [Am] 23:1004–1009.
16. Keir P, Bach JM, Rempel D. 1998. Fingertip loading and carpal tunnel pressure: differences between a pinching and a pressing task. J Orthop Res 16:112–115.
17. Szabo RM, Chidgey LK. 1989. Stress carpal tunnel pressures in patients with carpal tunnel syndrome and normal patients. J Hand Surg 14A:624–627.
18. Jarvik JG, Yuen E, Haynor DR, et al. 2002. MR nerve imaging in a prospective cohort of patients with suspected carpal tunnel syndrome. Neurology 58:1597–1602.
19. Cudlip SA, Howe FA, Clifton A, et al. 2002. Magnetic resonance neurography studies of the median nerve before and after carpal tunnel decompression. J Neurosurg 96: 1046–1051.
20. Napier JR. 1960. Studies of the hands of living primates. Proc Zoo Soc Lond 133:647–657.
21. Napier JR. 1961. Prehensibility and opposability in the hands of primates. Symp Zoo Soc Lond 5:115–132.
22. Rempel DM, Diao E. 2004. Entrapment neuropathies: pathophysiology and pathogenesis. J Electromyogr Kinesiol 14:71–75.
23. Diao E, Shao F, Liebenberg E, et al. 2005. Carpal tunnel pressure alters median nerve function in a dose-dependent manner: a rabbit model for carpal tunnel syndrome. J Orthop Res 23:218–223.
24. Clark BD, Barr AE, Safadi FF, et al. 2003. Median nerve trauma in a rat model of work-related musculoskeletal disorder. J Neurotrauma 20:681–695.
25. Clark BD, Al-Shatti TA, Barr AE, et al. 2004. Performance of a high-repetition, high-force task induces carpal tunnel syndrome in rats. J Orthop Sports Phys Ther 34:244–253.
26. Mackinnon SE, Dellon AL, Hudson AR, et al. 1985. A primate model for chronic nerve compression. J Reconstr Microsurg 1:185–195.
27. Roquelaure Y, Mechali S, Dano C, et al. 1997. Occupational and personal risk factors for carpal tunnel syndrome in industrial workers. Scand J Work Environ Health 23:364–369.
28. Mathiowetz V, Kashman N, Volland G, et al. 1985. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 66:69–74.
29. Banks J, Lavender SA, Buford J, et al. Measuring pad-pad pinch strength in a non-human primate: *Macaca fascicularis*. J Electromyogr Kinesiol (in press).
30. Rempel D, King K, Robertson J, et al. 2001. An in vivo model for entrapment neuropathy due to repeated finger loading. In: Proceedings of the 47th Annual Meeting, Orthopaedic Research Society, San Francisco; p 0734.
31. Johnson EW, Ortiz PR. 1966. Electrodiagnosis of tarsal tunnel syndrome. Arch Phys Med Rehabil 47:776–780.
32. Adour KK, Sheldon MI, Kahn ZM. 1977. Comparative prognostic value of maximal nerve excitability testing (NET) versus neuromyography (NMG) in patients with facial paralysis. Trans Pac Coast Otoophthalmol Soc Annu Meet 58:29–42.

33. Werner RA. 2006. Evaluation of work-related carpal tunnel syndrome. J Occup Rehab 16:207–222.
34. Kearns J, Gresch EE, Weichel CY, et al. 2000. Pre- and post-employment median nerve latency in pork processing employees. J Occup Environ Med 42:96–100.
35. Jablecki CK, Andary MT, Floeter MK, et al. 2002. Second AAEM literature review of the usefulness of nerve conduction studies and needle electromyography for the evaluation of patients with carpal tunnel syndrome. Muscle Nerve http://www.aanem.org/documents/CTS.pdf.
36. Zhao K. 2003. Compute the area and judge the direction of a closed curve. Available at: http://www.mathworks.com/matlabcentral/fileexchange/loadFile.do?objectId=3284objectType=file
37. Monagle K, Dai G, Chu A, et al. 1999. Quantitative MR imaging of carpal tunnel syndrome. AJR Am J Roentgenol 172:1581–1586.
38. Freeland AE, Tucci MA, Barbieri RA, et al. 2002. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. Microsurgery 22:378–385.
39. Barbe MF, Barr AE, Gorzelany I, et al. 2003. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. J Orthop Res 21:167–176.
40. Napier JR. 1993. Hands. Princeton, NJ: Princeton University Press. 58.
41. Liu J, Lau HK, Pereira BP, et al. 1996. Terminal nerve branch entries (motor points) of forearm muscles: a comparative study between monkey and human. Acta Anat (Basel) 155:41–49.
42. Cheng EJ, Scott SH. 2000. Morphometry of Macaca mulatto forelimb. I. Shoulder and elbow muscles and segment inertial parameters. J Morph 245:206–224.
43. Howell AB, Straus WL. 1933. The muscular system. In: Hartman CC, Straus WL, editors. The anatomy of the rhesus monkey (Macaca mulatto). New York: Hafner; p 67–175.
44. Schultz AH. 1962. The physical distinctions of man. In: Howel W, editor. Ideas on human evolution. Cambridge, MA: Havard University Press.
45. Kelly RE. 2001. Tripedal knuckle-walking: a proposal for evolution of human locomotion and handedness. J Theor Biol 213:333–358.
46. Jenkins FA. 1981. Wrist rotation in primates: a critical adaptation for brachiators. Symp Zool Soc Lond 48:429–451.
47. Moore JS, Garg A. 1995. The strain index: a proposed method to analyze jobs for risk of distal upper extremity disorders. Am Ind Hyg Assoc J 56:443–458.
48. Barr AE, Barbe MF. 2004. Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders. J Electromyogr Kinesiol 14:77–85.
49. Carpenter JE, Flanagan CL, Thomopoulos S, et al. 1998. The effects of overuse combined with intrinsic or extrinsic alterations in an animal model of rotator cuff tendinosis. Am J Sports Med 26:801–807.
50. Soslowsky LJ, Thomopoulos S, Esmail A, et al. 2002. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. Ann Biomed Eng 30:1057–1063.
51. Tichauer ER. 1978. The biomechanical basis of ergonomics. New York: Wiley Interscience.