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Longitudinal design for sonographic measurement of median nerve swelling with controlled exposure to physical work using an animal model

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Abstract

This study examined the feasibility of a longitudinal design to sonographically measure swelling of the median nerve due to controlled exposure to a work task and to evaluate the relationship of changes in morphology to diagnostic standards. Fifteen macaca fascicularis pinched a lever in various wrist positions at a self-regulated pace (8 hours/day, 5 days/week, 18–20 weeks). Nerve conduction velocity (NCV) and cross-sectional area (CSA) were obtained every two weeks from baseline through working and a 6-week recovery. Trending across all subjects showed that NCV slowed and CSA at the carpal tunnel increased in the working arm, while no changes were observed in CSA either at the forearm or for any measure in the non-working arm. There was a small negative correlation between NCV and CSA in the working arm. This study provides validation that swelling can be observed using a longitudinal design. Longitudinal human studies are needed to describe the trajectory of nerve swelling for early identification of median nerve pathology.

Keywords

median mononeuropathy; sonography; carpal tunnel syndrome

Introduction

Sonography is becoming widely used in diagnosing carpal tunnel syndrome (CTS). In chronic stages of the disorder, measuring cross-sectional area (CSA) of the median nerve with sonography is up to 93% sensitive and 100% specific (Roll et al. 2011a). In addition to a diagnostic threshold of $10mm^2$, additional parameters have been proposed to distinguish among various severities of the disorder, such as mild, moderate and severe (Wong et al. 2004; Roll et al. 2011b). Research is also evaluating morphologic changes following

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surgical releases of the carpal tunnel, indicating various potential trajectories of continued median nerve swelling and possible eventual remediation (Vogelin et al. 2010; Kim et al. 2012; Pimentel et al. 2013).

Taken together, there is an abundance of research supporting and advancing the use of sonography for diagnosis of CTS in chronic and medical states; however, there is a significant gap in understanding the acute morphologic progression of median nerve pathology. Research related to the acute onset of the disorder is primarily mechanistic, focusing on contributory factors such as repetitive movement, vibration, awkward positions, and anthropometry (Barr et al. 2004; Kamolz et al. 2004; Bongers et al. 2006; Lim et al. 2008). A few imaging studies have attempted to evaluate tissue morphology as a physiologic mechanism in the development of CTS, primarily focusing on the movement of tendons and lumbrical muscles (Cobb et al. 1994; Ham et al. 1996; Yoshii et al. 2009; van Doesburg et al. 2012). However, as with other literature, these imaging studies are primarily mechanistic and only attempt to identify relationships between anthropometry and chronic pathology with little focus on the acute morphologic changes of the median nerve.

We have previously demonstrated that it is feasible to use a longitudinal study design to collect sonographic images in workers to evaluate changes in morphology over time (Evans et al. 2010). There are significant challenges to successfully identify acute changes in median nerve morphology and to establish a link between exposure and morphologic changes in a human model. The primary challenge is that exposure is difficult to control unless the task being completed is routine and highly repetitive, such as assembly line work. Additionally, there are a variety of confounding factors that may include other personal, environmental, and physiological variables (Feuerstein et al. 2004; Roll et al. 2013), which would require significantly large sample sizes. Therefore, even given the availability of a highly standardized exposure pattern in a targeted workforce, no large-scale studies have been completed to investigate acute morphologic changes in the median nerve. Without this research, no evidence exists to provide clear parameters regarding the frequency and duration of the exposure or the sonographic monitoring necessary to demonstrate appreciable change in morphology in the acute progression of median nerve pathology.

To begin evaluating the link between physical task exposure and acute changes in morphology over time, we utilized an animal model. Although rat and rabbit models have been used to study etiologic mechanisms of carpal tunnel syndrome (Clark et al. 2003; Diao et al. 2005), only one case-study report utilizing sonographic imaging to diagnose carpal tunnel in an animal (e.g., cow) was identified in current literature (Lippold et al. 2007). Therefore, we set out to evaluate the novel combination of an animal model and sonographic imaging to evaluate longitudinal changes in median nerve morphology in the acute stages of median nerve pathology. The objectives of this study were to (1) examine the feasibility of sonographically measuring acute changes in the median nerve over time due to controlled exposure to a work task and (2) determine the relationship of changes in morphology to diagnostic standards using electromyography.

Methods

A prospective, longitudinal animal cohort study was approved by the Institutional Animal Care and Use Committee at The Ohio State University. Fifteen macaca fascicularis monkeys were trained to reach through a tube and pinch a lever with varied wrist positions to receive a treat (Sommerich et al. 2007). Once trained, subjects were allowed to work at a self-regulated pace for up to 8-hours a day, 5 days a week. Subjects were only allowed to use their left hand to complete the pinching task and the non-working environment was controlled to ensure that the working hand had no significant additional physical exposure. The working phase lasted for 18–20 weeks and was followed by a recovery phase of 6 weeks, during which the subjects only participated in enrichment activities. One subject sustained a finger injury unrelated to the pinching task and was removed from working earlier than the other subjects. This subject received similar non-work enrichment activities and data collection was continued as scheduled; therefore, because the objectives of this study were to evaluate global trends, the data for this subject were included in the analysis.

Baseline data were collected during initial training and every two weeks thereafter throughout the working and recovery phases. During data collection, the subjects were sedated and wrapped in warm towels to maintain body temperature. Vital signs were monitored throughout data collection and skin temperature was maintained between 35° C and 37° C. At each time point, sensory nerve conduction velocity (NCV) was collected followed by sonographic evaluation of the median nerve. A full description of the data collection protocol for electrodiagnotic testing has been previously reported (Sommerich et al. 2007) and the sonography protocol follows.

Sonographic evaluation was completed with a Logiq i hand-carried unit with a 12-MHz linear transducer (GE Healthcare Ultrasound, Milwaukee, WI). Equipment quality control for maximum penetration, axial resolution, and lateral resolution was completed weekly using a general-purpose urethane tissue-mimicking phantom (CIRS, Inc, Norfolk, VA). The median nerve was evaluated in cross-section, beginning at the mid-forearm and progressing distally to the carpal tunnel. Transverse images were collected at a point approximately half-way between the elbow and wrist, at the entrance to the carpal tunnel identified by the distal end of the radius, and in the proximal carpal tunnel at the level of the pisiform bone (Roll and Evans 2009). Sagittal images of the median nerve were obtained as the nerve passed over the carpal bones into and through the carpal tunnel.

When compared to human studies of the median nerve, the sizes of the structures within the animal subjects were significantly smaller (Figure 1). During baseline data collection of the first three subjects, cine clips were obtained in the transverse plane, moving proximal to distal from the mid-forearm to the carpal tunnel. To ensure accurate identification of structures and validate image acquisition and analysis, still frames from these cine clips were matched to MRI images of these subjects' arms that had been collected on the same date for another portion of the study. The location and boundaries of the median nerve were successfully identified in all sonographic images by the research team. This validated image acquisition protocol and the following image analysis protocol were then completed across all time points in each of the 15 subjects.

Image analysis primarily included measurement of the cross-sectional area (CSA) of the median nerve via a direct trace around the inner hyper-echoic border on each image as has been well described and demonstrated in previous literature (Roll et al. 2011b). To minimize measurement error, measures for each image were completed five times, the highest and lowest measures were dropped and the remaining three measures were averaged. A reference measure of CSA was obtained in the mid-forearm (CSAf) and CSA measures were obtained from images at the distal radius and level of the pisiform. Due to the small size of the subjects' structures, movement of the transducer by less than 1cm sometimes caused difficulty reliably capturing the later two images. Therefore, to reduce potential variance due to positioning error, the largest CSA measure between the images from the distal radius and the pisiform was recorded as the CSA at the carpal tunnel (CSAc). Sagittal images were reviewed, but due to exceptionally small anterior-posterior height of median nerve throughout its course, the researchers determined that neither quantitative nor qualitative measures would be useful due to the high likelihood of measurement error.

To increase sensitivity in analysis due to the longer time period relative to the other phases, the working phase was spilt into two periods (working 1 and working 2) each consisting of data obtained from 9–10 weeks. Descriptive statistics were calculated for NCV, CSAf, and CSAc for the 15 subjects at baseline, across the two periods of the working phase, and during recovery. Aggregate group trend graphs were generated to visually display changes across the four phases for each of the measures. ANOVA was used to determine differences between the two arms in each study phase and differences across the 4 study phases by arm for each of the measures. Pearson's correlation was used to determine the relationship of changes in NCV to each of the sonographic measures considered all together, by arm, and by phase. Data analysis was completed using SPSS Statistics v. 21 (IBM) and statistical significance was set at $p < 0.05$.

Results

Descriptive statistics were calculated for NCV and sonographic measures of the median nerve for both the working (left) arm and non-working (right) arm across the four phases of the study (table 1). NCV, CSAc and CSAf trend graphs were created to explore changes in these measures between the two arms from baseline through working and into recovery across all fifteen subjects (figure 2). In the working arm, (1) dramatic slowing of NCV was noted from baseline into the working phases with slight improvement during recovery; (2) CSAc initially showed a slight decrease followed by a steady increase through the recovery phase; and (3) CSAf did not show any changes across the study phases. No appreciable changes were noted in the trends for any of the measures in the non-working arm.

ANOVA was completed to evaluate statistical differences in these trends. Mean NCV and sonographic measures of the median nerve were not significantly different between the left and right arms at baseline and no significant differences were noted in CSAf between the arms at any of the phases. Additionally, across the four study phases, there were no significant differences in CSAf in the working arm and none of the measures varied significantly in the non-working arm. From baseline in the working arm, NCV slowed significantly ($p = 0.048$) and CSAc significantly increased ($p = 0.047$). These significant

changes across the phases resulted in significant differences in NCV between the left and right arms during the working and recovery phases and significantly larger CSAc in the working arm during late working and recovery.

A small negative correlation was noted between NCV and CSAc across all phases for both arms ($r = -0.140$, $p < 0.01$). When considering data from both arms together and separating out individual phases, a small negative correlation was also noted between NCV and CSAc during the late working phase ($r = -0.210$, $p < 0.01$). No additional significant correlations were observed between NCV and the sonographic measures when considering both arms and all phases together or when looking at individual phases either with both arms together or by individual arm (table 2).

Discussion

The purpose of this study was to establish feasibility and explore the relationship between morphologic changes identified with sonographic imaging to diagnostic testing of clinical pathology in the acute progression of median nerve pathology. The results of this well-controlled, longitudinal animal study provide evidence to support the link between incremental swelling of the median nerve and decreases in nerve conduction velocity. Furthermore, it demonstrates that it is feasible to collect, measure and analyze these data in a longitudinal manner.

Numerous studies provide evidence that asymptomatic controls do not demonstrate any appreciative swelling in the size of the median nerve between the forearm and the carpal tunnel region; however, in a chronic and diagnostic state, the median nerve is significantly swollen within the carpal tunnel. Sonographic diagnosis of carpal tunnel syndrome is indicated by enlargement of the CSA of the median nerve beyond $10mm^2$ within or near the bounds of the carpal tunnel or a change in the size of the nerve in this region relative to other areas by more than $2mm^2$ (Klauser et al. 2010). Despite these diagnostic thresholds, evidence for the use of sonography and electrodiagnostic testing in diagnosing acute or mild stages of the disorder is mixed. Variability in the diagnostic accuracy of sonography is noted when the size of the median nerve is closer to the $10mm^2$ threshold (Hobson-Webb and Padua 2009). Additionally, researchers have noted that some nerve swelling exists in individuals who have not been clinically diagnosed (Moran et al. 2009), including up to 30.5% of individuals with mild symptoms but negative electrodiagnostic test results (Koyuncuoglu et al. 2005).

Although we were unable to document subjective symptom reports in this animal study, the results indicate significant morphologic changes due to repetitive exposure to a task with well-documented physical risk. Swelling of the median nerve was noted across the phases in the working hand, which was significantly different from the relatively static size of the median nerve in the non-working hand. Furthermore, the swelling noted in the working hand only occurred at the wrist and no changes were noted in the proximal nerve. The continued increase in size of the median nerve into the recovery phase once working had ceased was an unexpected finding. It is possible that this continued increase in size was due to the inflammatory sequelae of high exposure to the work task. Other than allowing for rest

during the recovery phase, no specific treatments were provided with the goal of rehabilitating the subjects in this study. Further investigation of inflammation biomarkers and/or histopathology may be necessary in future studies to understand the physiologic etiology leading to the change in median nerve size.

With increased understanding of how and why changes in median nerve size occur over time and how these changes relate to symptoms and other physiologic test results, there is potential to identify thresholds that would trigger preventive interventions. Once these thresholds are defined, sonography may be useful as a tool for periodic workplace-screening tool for early detection of median nerve pathology. Sonography equipment is becoming increasingly portable and, in contrast to electromyography, workers would feel no discomfort during sonographic imaging. Although we have previously demonstrated feasibility for obtaining sonographic data at the work-site, we were unable to document any significant acute morphologic changes in the median nerve due to work exposure either across a work-day, or across a 4–6 week time period (Evans et al. 2010). Although the changes observed in this study were over a very short period of time, the exposure was significantly greater and well controlled. It is not likely that changes in humans would be noted as rapidly, nor would it be as easy to control the exposure. However, because there were changes noted in this well-controlled model, it is provides impetus for the development of studies to explore the progression of morphologic changes in human subjects.

While we were able to demonstrate a link between changes in tissue morphology and physiologic response to nerve conduction at the aggregate level, we did not specifically evaluate the changes across each data collection time point by subject, nor did we investigate the relationship of morphology to NCV within each subject. Instead, the global analysis performed in this study supports the feasibility of documenting aggregate morphologic changes, which informs methods for translating the study to humans. Additionally, this analysis did not evaluate the relationship between the amount or timing of work exposure to changes in NCV or tissue morphology in individual subjects. Data were collected to ensure that all subjects had adequate exposure to the work task and any additional physical exposure was controlled. Furthermore, our investigation of changes in the working versus non-working arms allowed us to minimize bias and more confidently interpret the data. Given the limitations of the analysis in this study, additional analyses of within subject longitudinal trends and relationships among the morphologic sonographic data, physiologic nerve conduction data, and work exposure data is warranted to provide deeper understanding of the global, aggregate trends reported in this manuscript.

Conclusion

This study provides unique evidence related to morphologic changes in the median nerve in the acute, developmental stages of CTS. Using well-controlled task exposure in an animal model, we identified a progressive swelling of the median nerve that correlated to a slowing in nerve conduction across time. Translation of this knowledge to humans is needed to determine the trajectory of morphologic changes due to various exposures and other mechanistic factors. With increased understanding of how the median nerve swells over time

and how these changes relate to symptoms and other physiologic testing, there is potential to enhance early identification and determine thresholds to trigger preventive interventions.

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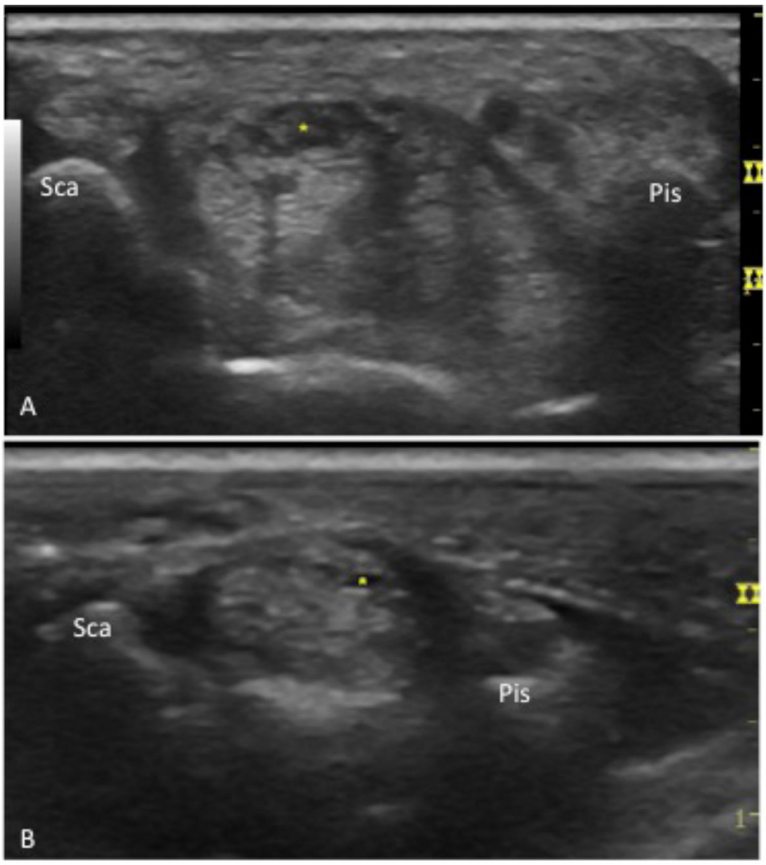

Figure 1.
Comparative images of the median nerve (asterisk) in the carpal tunnel demonstrating the smaller scale and more rounded carpal tunnel in a macaca (B) versus the larger, ovoid carpal tunnel in a human (A). Pis, pisiform; Sca, scaphoid.

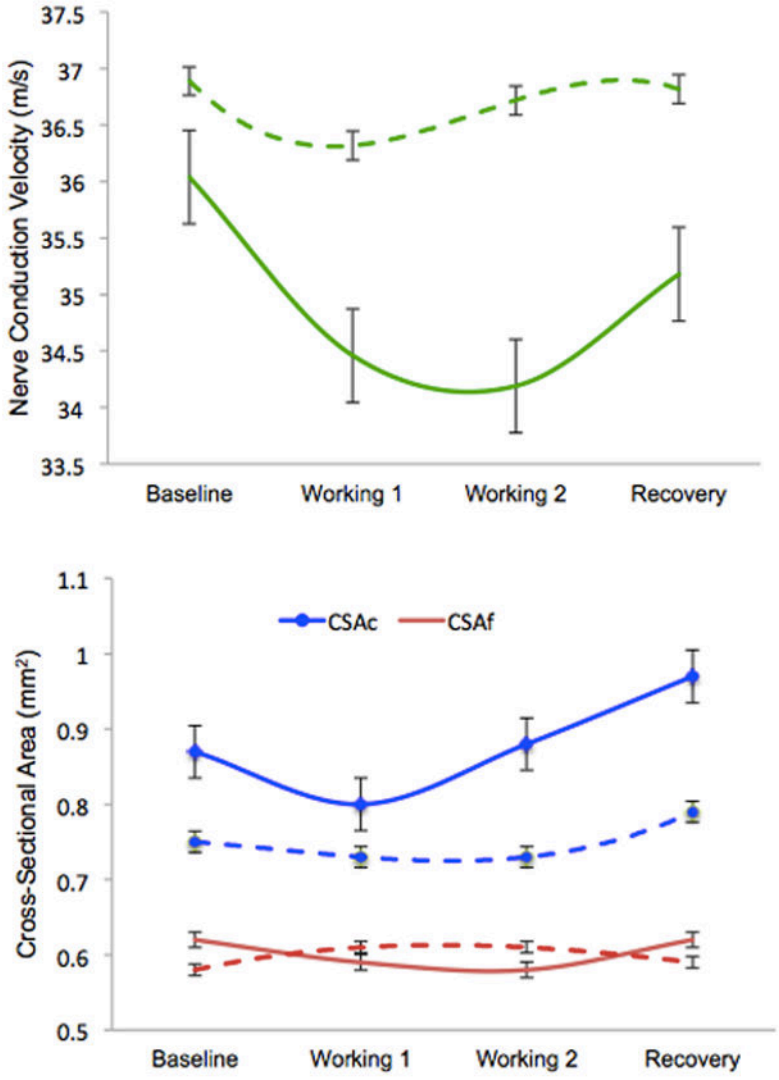

Figure 2.

Trended changes in nerve conduction velocity and cross-sectional area in the working hand (solid lines) and non-working hand (dashed lines) across the study periods (n=15).

Table 1

Average (SD) nerve measurements across study phases in all subjects (n=15)

	Baseline	Working 1	Working 2	Recovery
NCV, m/sec				
* Left	36.04 (3.55)	34.46 (3.72)	34.19 (3.82)	35.18 (3.02)
Right	36.89 (2.44)	36.32 (3.14)	36.72 (2.54)	36.82 (2.71)
CSAf, mm^2				
Left	0.62 (0.13)	0.59 (0.16)	0.58 (0.13)	0.62 (0.15)
Right	0.58 (0.13)	0.61 (0.15)	0.61 (0.15)	0.59 (0.17)
CSAc, mm^2				
* Left	0.87 (0.25)	0.80 (0.26)	0.88 (0.29)	0.97 (0.34)
Right	0.75 (0.22)	0.73 (0.17)	0.73 (0.20)	0.81 (0.19)

* $p < 0.05$ for differences across phases; NCV, nerve conduction velocity; CSAf, cross-sectional area in forearm; CSAc, cross-sectional area in carpal tunnel

Table 2

Correlation of changes in nerve conduction velocity (NCV) to various sonographic nerve measurements across data collection phases (n=15)

	Baseline	Working 1	Working 2	Recovery	All Phases
CSAf	−0.082	−0.060	−0.104	−0.070	−0.077
CSAc	−0.098	−0.110	−0.210*	−0.196	−0.140*

*p < 0.01; NCV, nerve conduction velocity; CSAf, cross-sectional area in forearm; CSAc, cross-sectional area in carpal tunnel