

Comparison of Magnetic Resonance Imaging & Sonography in an Animal Model in the  
Acute Stages of Carpal Tunnel Syndrome

**THESIS**

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## **Abstract**

Carpal Tunnel Syndrome (CTS) is a musculoskeletal disorder characterized by the compression of an enlarged or inflamed median nerve as it passes through the carpal tunnel and deep to the flexor retinaculum. CTS is one of the most common entrapment syndromes of the upper limbs, with hundreds of thousands of new cases of CTS reported by the Centers for Disease Control and Prevention in the United States every year (CDC,2012). Presently, according to the ACR Appropriateness Criteria, Magnetic Resonance Imaging (MRI) has a rating of nine out of ten as the best choice for diagnosing CTS in patients with persistent wrist pain after the initial radiograph. The Appropriateness Criteria also lists musculoskeletal (MSK) sonography with a rating of one out of ten; however, qualities such as accessibility, cost effectiveness, being less invasive, relatively painless, time effectiveness, as well as providing real time imaging, may provide additional information in conjunction with Magnetic Resonance. The purpose of this study was to evaluate the significance, if any, through quantitative analysis of the median nerve, between Magnetic Resonance and Sonography in the acute stages of CTS. Imaging was performed on Maccaca fascicularis monkeys at baseline, working, and recovery intervals. The data was collected from two independent, blinded researchers, one certified in Magnetic Resonance, the other certified in Sonography. Although each study demonstrated no conclusive comparison between MRI and

Sonography in the evaluation of the median nerve, the information gained regarding study protocol is invaluable to provide feedback to design a higher level clinical study. MSK sonography may be a useful tool in combination with MRI, to diagnose CTS, with minimal discomfort to the patient. More research needs to be conducted in the acute stages of CTS before the patient reaches the advanced, symptomatic stages, in the form of a clinical human study.

This document is dedicated to my wife Patty and my daughter Avery.

## **Acknowledgments**

I would like to sincerely thank Dr. Kevin Evans for his assistance and knowledge in the completion of this thesis. His persistence and attention to detail have kept me on track and help me utilize professional skills that I did not believe I could possess. I would also like to thank Dr. Steffen Sammet for his expertise in the field of Magnetic Resonance and assistance using the MIPAV software. He has provided on-going support and was a pivotal resource for the completion of the second study. Thank you to Dr. John Buford for sharing his images from his lab and allowing me to analyze them at length. Without his contribution this thesis would not be possible.

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## **Chapter 1-Introduction**

### *Background and Setting*

Carpal tunnel syndrome (CTS) is a common musculoskeletal condition resulting from the compression of the median nerve at the level of the carpal tunnel (Goddard et al., 2012). Thought to be caused by recurrent, repetitive motion, the symptoms of CTS, such as tingling, burning, or sensory disturbances, are caused by inflammation and compression of the median nerve (Acu et al., 2012). As the most frequently reported peripheral nerve entrapment syndrome, 5.8% in women and 0.6% in men, CTS incapacitates patients in the late stages of the disorder (Nucir et al., 2012). More common in middle aged women, CTS also affects patients with diabetes, and women during pregnancy (Goddard et al., 2012). Usually recognized in the later stages, CTS could account for substantial lost revenue, due to patients being out of work for treatment and recovery.

Currently, the treatment for CTS falls under two categories: conservative and surgical. Conservative intervention is undertaken on patients with mild to moderate symptoms, and surgical intervention is routinely performed on patients in the late stages of the disorder and complaining of severe pain (Goddard et al., 2012). Treatment usually ensues after the onset of symptoms, in the mild to severe range of symptoms where

imaging can have a significant role in the diagnoses and planning of patients with symptomatic CTS.

Imaging of the wrist for visualization of the carpal tunnel and the median nerve can have an impact on the treatment planning and the type of surgical intervention (Allen, 2012). The American College of Radiology (ACR) ranks imaging modalities as to their effectiveness based on a scale from one to ten in the appropriateness criteria for chronic wrist pain. Currently, following diagnostic radiography, magnetic resonance imaging (MRI) ranks 9 out of 10 in order of appropriateness for further evaluation of the wrist (ACR, 2012). On the same scale, the ACR ranks sonography as a one, in evaluation of chronic wrist pain (ACR, 2012).

To date, the literature is lacking in the area on prevention and asymptomatic onset of CTS. The ACR imaging criteria mainly focuses on the advanced, symptomatic stages of CTS, when a medical treatment or surgical intervention is almost certainly required for recovery and alleviation of the patients' symptoms. Behazdi et al performed a prospective evaluation of acute wrist injury and the application of MRI in the initial stages of wrist injury. Not specifically focused on CTS, but other common musculoskeletal wrist injuries, they discovered that four out of five patients with acute wrist injury and a negative radiographic study were to demonstrate positive pathological findings on MRI (Behazdi, 2012). Further research needs to be implemented in the area of acute injury of CTS, and given the frequency of asymptomatic signs for patients in the acute stages; the need for a concise diagnostic screening tool is becoming increasingly necessary. Due to the frequent occurrence of CTS within the current population,

preventative measures need to be explored in order to prevent the advanced, symptomatic stages of CTS.

The current literature focuses on tissue injury, motor dysfunction, and behavior decrement, which mainly represents the advanced, symptomatic stages of CTS. More imaging research is necessary to further investigate the areas of task demands and microtrauma which could intercept the devastating consequences of CTS (See Figure 1.0). A proactive imaging screening tool is necessary to prevent future occurrences of CTS within the working population.

The focus on most of the research is at the late, progressive stages of CTS, far beyond the point where a therapeutic intervention would be beneficial. Although some progressive studies have demonstrated that MRI can play a more beneficial role in the detection of pathological findings immediately post trauma, the onset of the pathology without immediate symptoms is a subject that requires further exploration. Barr and Barbe have developed a conceptual schematic, based on a literature review of the evidence. The current clinical research, which the ACR appropriateness criteria is based on, focuses on the areas of tissue injury, motor dysfunction, and behavior decrement.

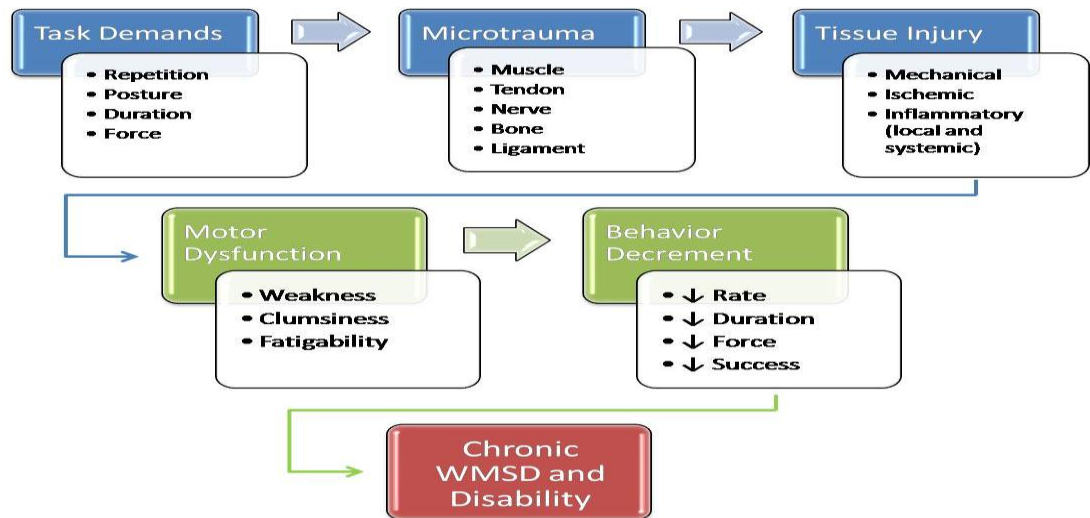


Figure 1.0 Barr and Barbe, Carpal Tunnel Syndrome Conceptual Schematic, 2002.

### *Research Question*

Can median nerve enlargement be detected with MRI and compared to sonography after repetitive work exposure with cross sectional area measurements (CSA) and the evaluation of signal to noise (SNR)?

### *Objectives of the Study*

The objective of this study was to ascertain if a comparison could be made between MRI and sonography in the acute stages of carpal tunnel syndrome. An additional objective was to explore the ACR appropriateness criteria in the early, asymptomatic stages of CTS.

### *Definition of Terms*

For the purpose of this research study, the following terms are conceptually and operationally defined as follows:

Signal to noise ratio (SNR)-ratio of signal relative to noise; used to describe the relative contributions to a detected signal of the true signal and random superimposed noise; signal /noise =SNR (Kaut Roth, 2011) (Bushong, 2003).

Carpal tunnel syndrome- a compressive mononeuropathy, caused by mechanical distortion due to a compressive force on the median nerve at the level of the wrist (Goddard, 2012).

T1 Weighted imaging- an image that demonstrates the differences in the T1 times of tissues; demonstrates the amount of longitudinal relaxation time of a tissue (Kaut Roth, 2011) (Bushong, 2003).

T2 Weighted imaging- an image that demonstrates the differences in the T2 times of tissues; demonstrates the loss of transverse magnetization of a tissue (Kaut Roth, 2011) (Bushong, 2003).

#### *Limitations of the Study*

The study was a preclinical, longitudinal, animal study limiting the generalization to the greater population. Although preclinical studies are among the lowest levels of evidence, the information obtained helps aid in developing the research process and data acquisition of future studies (Jenicek, 2003). This allows for higher level studies to be executed in a specific area prior and information to be gained to execute a more structured research design. By trialing hypothesis and protocols in a preclinical model, the researcher may gain further information about what study design and protocol may best work for a specific cohort and or clinical trial. The results of a preclinical trial are not to be generalized to the overall population, but can be used to gather further

information on a subject and provide more structured feedback and results to develop a strict research design.

## **Chapter 2:**

### **The Use of MRI to Longitudinally Monitor the Progression of MMN in an Animal Model: A Preclinical Study.**

#### **ABSTRACT**

**OBJECTIVE.** The objective of this study was to ascertain if any relationship could be observed with quantitative measurement of the median nerve by means of image analyses following repetitive work in *Maccaca fascicularis*.

**MATERIALS AND METHODS.** Three cohorts of *Maccaca fascicularis* monkeys were imaged at three separate time points. Axial T1 weighted images were obtained and analyzed using MIPAV by an ARRT registered MRI technologist. Subjective measurements were traced around the median nerve at the levels of the pisiform and the radius, in which the cross-sectional area was calculated for each time point.

**RESULTS.** Analyses of the T1 magnetic resonance images showed no direct measurable difference from the baseline, recovery, or final imaging time points.

**CONCLUSION.** Although no direct relationship could be made between the measurements of work exposure and median nerve enlargement on MRI T1 imaging, a more structured imaging protocol and procedure could yield more conclusive results when strictly followed.

**Keywords.** MMN, Carpal tunnel syndrome, Median nerve, MRI

Median Mononeuropathy (MMN), also known as carpal tunnel syndrome (CTS), is a common musculoskeletal disorder characterized by the compression of an enlarged and inflamed median nerve as it passes through the carpal tunnel and flexor retinaculum. The acute systemic response of inflammation is activated after the initial trauma to limit the extent of the damage and initiate repair of the damaged tissue. This inflammation caused by increased vasculature permeability allows for high signal intensity within and around the median nerve on Magnetic Resonance Imaging (MRI). Presently, according to the ACR Appropriateness Criteria, MRI has a rating of nine out of ten as the gold standard for diagnosing CTS in patients with persistent pain, numbness, and tingling, and ultrasound at rating of one. The objective of this study was to ascertain if any relationship could be observed with quantitative measurement of the median nerve by means of MRI image analyses following repetitive work in *Macaca fascicularis*. An additional objective is to evaluate if any a relationship can be made between MRI T1 weighted images and sonographic measurements of inflammation caused by repetitive work motion in the *macaca fascicularis* monkeys and the enlargement of the median nerve due to inflammation.

MRI T1 weighted images, obtained at baseline, recovery, and final, were evaluated using the established diagnostic criteria. Increased signal intensity of the median nerve on T2 weighted images and bowing of the flexor retinaculum, along with increased cross-sectional area, flattening of the median nerve, and peritendon pathology, are common indications of CTS on MRI.<sup>1</sup> Quantitative measurement of the median nerve within the carpal tunnel is a common application of MRI in evaluating the wrist for CTS,

but distinctive standards have not been established. Burnham et al found that the median nerve cross-sectional area was larger in 50% of the subjects that had carpal tunnel syndrome, when compared to those who were asymptomatic.<sup>2</sup> This study was conducted with a small sample size of volunteers (n=16), with imaging on 25 wrists total.<sup>2</sup> A study with a larger sample size and randomized subjects would have made a stronger comparison. Although MRI is the gold standard due to its ability to evaluate soft tissue structures and osseous components simultaneously, cross-sectional data is up for debate due to the user variability and the structural variations of the carpal tunnel within the subjects.<sup>3,2</sup> Literary consensus seems to maintain that of MRI and US are most beneficial when utilized in conjunction with one another for thorough evaluation of the median nerve, surrounding structures, and to rule out pathology.<sup>3,4,5,6</sup> Inconsistency in the literature abounds on the role and level that cross sectional area (CSA) ultrasound measurements should be taken.<sup>5</sup> Inflammation and the resulting swelling of the median nerve is indicative of pathology, but trying to isolate specific criteria for CSA utilizing MRI is subject of debate. Chang et al, evaluated CSA measurements of MRI and US at rest, and in the grasp position and found that the diagnostic accuracy were similar between the two modalities.<sup>6</sup> Currently, the gold standard in the diagnosis of CTS is establishment of median nerve hypertrophy using nerve conduction studies (NCS), but limitations such as false positives and false negatives, leave alternate methods of diagnosis an area left to be explored.<sup>7</sup> MRI and US are possibilities for CTS diagnosis that could provide greater utility when evidence can be establish to determine and outline the specific role.

To determine the effectiveness of using MRI T1 imaging as a longitudinal imaging outcome measure of MMN, our study retrospectively analyzed the blind measurements of the median nerve at two separate locations, the radius and pisiform, at three separate time points, pre and post work exposure. The MRI T1 weighted images were analyzed after consequential repetitive movements to evaluate if any measurable changes were present. Establishing a direct relationship would lead to further research in prevention and treatment of MMN/CTS. Given the lack of research in the literature in the specific area of detection of acute inflammation, the objective is to evaluate the median nerve for the presence of mononeuropathy following work exposure with MRI.

### **Material and Methods**

The study was approved by The Ohio State University's Internal Review Board for both the prospective execution of the study and the retrospective analysis of the imaging data. A study approved by the Institutional Animal Care and Use Committee (IACUC) board of review was completed using 15 *Macaca fascicularis* monkeys as subjects in MMN research. During a 20-week working phase, the 15 *Macaca fascicularis* monkeys were exposed to a repetitive pinching task affecting the left wrist, with the intention of inducing MMN.<sup>8</sup> The retrospective preclinical longitudinal study was conducted over the period of one year by an ARRT registered technologist in MRI. Calculations were performed on MRI T1 weighted images of CSA (mm<sup>2</sup>) at three separate time points. Three cohorts of *Macaca fascicularis* monkeys were imaged at baseline, prior to any work exposure; at working, and recovery, following work exposure. Baseline and recovery scans occurred within an average time frame of 8.53 months with

a range of 7 to 11 months. A TA BioSpec 94/30 MRI System equipped with a 9.4T horizontal bore magnet was used to image the subjects in an isolated research laboratory. The magnet operates at 400 MHz and functions on a ParaVision™ 4.0 software platform adapted from the TopSpin 1.5 (Bruker BioSpin; Billerica, MA). Each subject was packed into a warm plastic cylinder. Then, a 3.5 mm quadrature coil was placed anterior to the wrist while utilizing a 20 cm spatial gradient for signal acquisition. The subjects' wrist was splinted with a rectangular piece of flexi-glass and held in place by adhesive tape. The subjects were continuously monitored throughout the scan with a small animal monitoring system -Model 1025 (Small Animals Instruments, Inc. Stony Brook, NY). All imaging protocols were approved by the institutions' Institutional Animal Care and Use Committee (IACUC) board of review. Each subject was scanned in the lateral decubitus position, with their shoulder flexed, and their palm supinated. Low resolution localization images were acquired in the axial, coronal, and sagittal planes. Thirty-two axial T1 and T2 weighted images were obtained with a 1mm slice thickness and a skipping of 0. A high resolution, 512x512 imaging matrix was utilized.

A registered MRI technologist blindly analyzed the T1 weighted images acquired using MIPAV (Medical Image Processing, Analysis, and Visualization) software. MIPAV is endorsed by the National Institute of Health to quantitatively evaluate computed tomography, positron emission tomography, and magnetic resonance images. MIPAV can be downloaded from the National Institute of Health (NIH) website: <http://nih.gov/>. Following the download, the MIPAV software can be accessed using the hyperlink. Under the File tab, on the drop down menu, there is an Open Image option, after

choosing this selection, Image sequence is the next tab. This selection will allow the option to load multi imaging modalities for image analyses utilizing MIPAV. Once the image series had been selected, the T1 MR image with the pisiform, and the T1 MR image with the last inferior view of the radius were selected. The median nerve was then subjectively traced using the Draw Polygon Voxel of Interest (VOI). Once the VOI was drawn, a right mouse click on the VOI would reveal a drop down menu. From the drop down menu, View VOI Properties was selected. Under the Statistics to Calculate, Area was selected, and the Calculate icon, in the bottom right hand of the box was selected, producing the area for the traced median nerve.

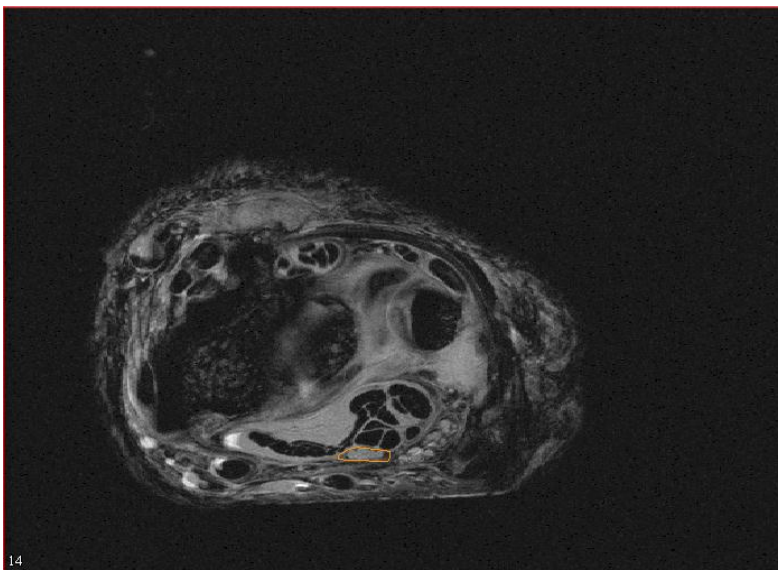


Figure 2. Axial T1 Weighted Image, Median Nerve Trace Measurement at the Pisiform-Subject X at the Recovery Time Interval

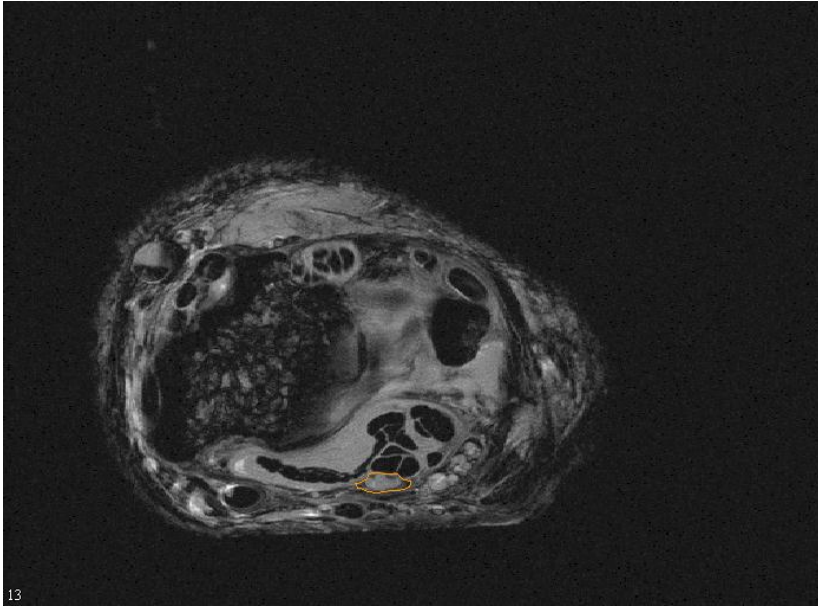


Figure 3. Axial T1 Weighted Image, Median Nerve Trace Measurement at the Radius-Subject X at the Recovery Time Interval

For this study, Digital Imaging and Communications in Medicine (DICOM) images, a common standard format to store and view medical images, were uploaded into MIPAV and then the median nerve was traced and analyzed at the levels of the pisiform and the distal radius. Five separate cross sectional areas (CSA) were marked and calculated in millimeters squared ( $\text{mm}^2$ ) around the median nerve at the level of the radius and the pisiform. The highest and lowest outliers for each CSA were discarded and then an average was calculated from the remaining three data points.

## Results

The research questions posed were:

1. *Is a measureable increase present on T1 weighted MRI imaging noted from baseline to post work exposure?*

Based on working with the data set to evaluate the CSA for the subjects for any observable enlargement from baseline, working, and recovery, in a preclinical study with Volz et al., unexpected results were discovered. Some subjects demonstrated expected results; for example, (Subject A), CSA measurements that would enlarge as the subjects were exposed to work, and then enlarge or shrink, due to inflammation or median nerve atrophy. However, other subjects CSA measurements demonstrated the opposite; such as, (Subject E), where CSA measurements demonstrated that the median nerve decreased in size from baseline, working, and recovery. The study continued with the use of sonography as an appropriate imaging technique after it was determined that without manipulation of the median nerve, that MRI and US suggested no statistical difference.<sup>9</sup>

Upon initial analyses of the MRI T1 weighted images, the median nerve demonstrated no expected measureable difference between baseline, recovery, and final MR imaging. Following work exposure, the median nerve would be expected to enlarge due to inflammation and increased vascular permeability. The median nerve revealed no discernible difference leading to the second research question:

*2. Was a positional variation present amongst the subjects that contributed to erroneous results upon data analyses of the T1 weighted images?*

Additional MR T2 imaging was acquired in the coronal plane, which allowed for further image analyses for the possible presence of ulnar and radial deviation. A trace line was placed at the level of the pisiform and at the distal portion of the radius using the MIPAVE VOI tool, then the New VOI tab, and then selecting the Draw Line VOI option. The line was then highlighted, and the Edit VOI tab was selected, then Copy

VOI. Then median nerve was then located and then the trace lines that were placed at the levels of the pisiform and the radius were then placed on the image with the median nerve. This was done by selecting the VOI tab, then the Edit VOI, and then Copy VOI. The lines were parallel to one another. After the trace lines were placed on a COR T2 image slice of the median nerve, using the appropriate land marks, an angle was placed at the level of the radius using the Protractor Tool from the table options. The angle was then adjusted, so it was following the trajectory of the median nerve. Given appropriate positioning, the angle of the median nerve should be close to perpendicular between the trace line placed at the radius and the pisiform. An extreme angle of greater than 90 degrees is suggestive of radial deviation, or less than 90 degrees is suggestive of ulnar deviation in the coronal plane. All coronal T2 image analyses on Subjects R, S, T, U, W, and X, yielded some degree of ulnar or radial deviation. These subjects were chosen due to the axial T1 trace measurements being recently completed. Further image analyses on sagittal images would also be helpful to determine if there was any amount of flexion or extension involved; however, no imaging in the sagittal plane was performed in this study.

The subjects were weighed ten times over the course of the study. An average weight was then calculated. All participants involved in the study were female.

Table. 1 Maccaca Fascicularis Weights/Gender

<i>SUBJECT</i>	<i>WEIGHT</i>	<i>GENDER</i>
Subject R	4.00kg	Female
Subject S	5.42kg	Female
Subject T	3.80kg	Female
Subject U	4.11kg	Female
Subject W	4.87kg	Female
Subject X	4.57kg	Female

The hypothesis is that the acute inflammation of the median nerve will be detected through blind measurements of the median nerve at two separate locations, the radius and pisiform, following work exposure. The MR T1 weighted images were analyzed after sequential repetitive movements to evaluate if any measurable changes were present. Establishing a direct relationship could lead to further research in prevention and treatment of carpal tunnel syndrome. The MRI T1 measurements yielded no direct correlation following work exposure to median nerve enlargement, leading to ancillary coronal analyses to investigate a possible cause for the erroneous results.

Table. 2 MRI Axial T1 Weighted Image, Left (working) Pisiform Trace Measurements of the Median Nerve.

<i>SUBJECT</i>	<i>BASELINE CSA MEAN</i>	<i>WORKING CSA MEAN</i>	<i>RECOVERY CSA MEAN</i>
Subject A	1.72	1.91	1.88
Subject B	1.84	2.22	1.47

<b>Subject C</b>	2.14	2.27	2.09
<b>Subject D</b>	1.87	2.46	2.18
<b>Subject E</b>	2.00	1.75	1.61
<b>Subject F</b>	1.96	1.59	2.66
<b>Subject H</b>	1.71	1.95	2.15
<b>Subject I</b>	3.93	2.33	2.46
<b>Subject J</b>	1.74	1.49	
<b>Subject K</b>	3.65	1.53	
<b>Subject L</b>	1.46	1.42	1.57
<b>Subject M</b>	2.83	1.99	2.54
<b>Subject N</b>	2.98	1.96	2.64
<b>Subject O</b>	2.78	3.11	2.03
<b>Subject Q</b>	2.20	2.22	
<b>Subject R</b>	1.99	1.81	
<b>Subject S</b>	1.27	2.09	
<b>Subject T</b>	1.77	2.08	2.24
<b>Subject U</b>	2.31	2.53	2.86
<b>Subject W</b>	2.10	2.26	2.77
<b>Subject X</b>	2.04	2.03	1.83
<b>Subject Y</b>	2.17	2.38	1.89

Trace measurements of the median nerve performed at the level of the pisiform following work exposure on the axial T1 weighted images demonstrated unexpected results. Subject A, for example, behaved as expected, with median nerve measurements increasing from baseline to working, then getting smaller, possibly due to atrophy. Subject E, however, did not demonstrate expected results. The largest measurement of the median nerve was at baseline, and then measurements decreased substantially from working to recovery.

Table 3. MRI Axial T1 Weighted Image, Left (working) Radius Trace Measurements of the Median Nerve.

<i>SUBJECT</i>	<i>BASELINE CSA MEAN</i>	<i>WORKING CSA MEAN</i>	<i>RECOVERY CSA MEAN</i>
Subject A	1.42	3.71	1.67
Subject B	1.60	4.02	1.69
Subject C	1.92	2.06	2.30
Subject D	1.67	4.42	2.01
Subject E	3.62	3.17	1.74
Subject F	1.75	2.98	2.63
Subject H	1.71	4.34	3.79
Subject I	2.24	2.51	2.61
Subject J	2.31	2.75	
Subject K	1.50	1.47	
Subject L	1.59	1.45	1.60
Subject M	5.25	2.22	2.24

Subject N	2.95	2.20	2.64
Subject O	5.67	2.84	2.29
Subject Q	4.31	1.99	
Subject R	1.92	2.10	
Subject S	1.92	2.04	
Subject T	1.84	2.04	2.28
Subject U	2.39	2.54	2.28
Subject W	1.99	2.44	2.70
Subject X	2.08	2.22	1.99
Subject Y	1.87	2.42	1.98

Trace measurements of the median nerve performed at the level of the radius on axial T1 weighted images behaved in a similar manner as the trace measurements of the median nerve completed at the level of the pisiform. Trace measurements were not demonstrating expected results from baseline, working, to recovery imaging intervals.

Table. 4 Coronal T2 Weighted Image, Median Nerve Angle with Ulnar/Radial Deviation.

<i><b>Subject</b></i>	<i><b>Degree from median nerve</b></i>	<i><b>Deviation</b></i>
Subject R	83 degrees	Ulnar deviation
Subject S	96.9 degrees	Slight Radial deviation
Subject T	78 degrees	Ulnar deviation
Subject U	78 degrees	Ulnar deviation
Subject W	102 degrees	Radial deviation
Subject X	76 degrees	Ulnar deviation

The supplemental image analyses were performed on coronal T2 weighted images that were also acquired. A positional variation could possibly account for the unexpected results yielded upon axial T1 weighted image CSA analyses. Given the small area between the radius and the pisiform, the median nerve should be relatively perpendicular amongst the two points. A median nerve trajectory within these two points of less than 90 degrees would be indicative of ulnar deviation, and greater than 90 degrees would indicate radial deviation.



Figure 4. Coronal T2 Weighted Image of Subject W during the Recovery Time Interval. Subject W is displaying a median nerve trajectory of 102 degrees, with the MIPAV software protractor tool, between the radius and the pisiform trace measurements.



Figure 5. Coronal T2 Weighted Image of Subject R during the Working Time Interval. Subject R is displaying a median nerve trajectory of 83 degrees, with the MIPAV software protractor tool, between the radius and the pisiform trace measurements.

## Discussion

Currently, this study represents a retrospective analysis of research data acquired on *Maccaca fascicularis*, but more research is necessary with the help of a larger sample size to gather further information to substantiate if a relationship can be determined. The current research has not documented acute inflammation within imaging across two separate modalities. A thorough research methodology would need to be performed by a registered technologist with a specialization in magnetic resonance. Given the inconclusive results from the data analyses, a strict structured positioning aid would be appropriate with optimal coil placement over the anterior aspect of the wrist would be essential to be certain that all imaging on all subjects are standardized at each imaging time interval to increase the reproducibility. Ideally, each subject should have a

reproducible mark or imaging landmark placed on the dorsal aspect of the hand, at the levels of the radius and ulna. This mark would be a reproducible landmark that can be utilized for a landmark for each subject at each imaging interval. A dedicated wrist coil would be ideal for optimal SNR and image quality. A positioning apparatus is necessary in order to completely immobilize the subjects and eliminate the possibility for a variation in the degree of ulnar and radial deviation, and flexion and extension. A material with no magnetic susceptibility, such as Plexiglas, would be optimal. Plexiglas should be placed, anterior/posterior, and lateral/ medial to limit any possible positioning error. Each subject should be imaged, at each imaging interval, while in the positioning aid. Although a dedicated wrist coil would be ideal, it is not necessary to obtain quality MR images, a small extremity coil could also be utilized. The coil should be placed anterior to the wrist, and in the center of the imaging landmark on the subject to obtain optimal SNR and imaging outcomes.

The results of the Magnetic Resonance T1-weighted image analyses of the cross sectional areas of the Maccaca fascicularis monkeys yielded inconclusive results. A possible reason for the erroneous data could be due to the varying degree of positioning error. A rigorously followed imaging protocol is essential to rule out any experimenter bias. Some degree of error is expected during all aspects of research although the researcher strives to eliminate and compensate for all threats to validity; some threats are only evident after the experiment and data acquisition. A more structured research methodology with a larger sample size is warranted to ascertain if a relationship can be established between magnetic resonance and sonography in the acute stages of CTS.

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### **Chapter 3:**

#### **Retrospective Analysis of Signal Intensity of MRI T2 Weighted Imaging Compared to Contrast Enhanced Ultrasound Imaging of CTS in an Animal Model**

##### **ABSTRACT**

**OBJECTIVE.** The objective of this study was determine if any comparisons could be made between the SNR on MRI T2 weighted images and the CEUS on Maccaca fascicularis following repetitive work exposure.

**MATERIALS AND METHODS. :** A single cohort of Maccaca fascicularis monkeys were imaged at three separate time points with magnetic resonance and CEUS. Axial T2 weighted images were obtained and analyzed using MIPAV by an ARRT registered MRI technologist. Axial ultrasound images were acquired in real time by two ARDMS certified sonographers. Subjective measurements were made around the median nerve at the levels of the pisiform and the radius on both MRI and CEUS images. Sequential measurements were also performed to calculate the SNR of the slice.

**RESULTS.** Analyses of the MRI T2 images and CEUS images, at specific imaging intervals, showed no direct comparison between the two modalities.

**CONCLUSION.** No comparison could be made between the SNR on MRI T2 weighted images and the CEUS measurements of the median nerve following work exposure, a more structured imaging protocol and procedure could yield more conclusive results.

**Keywords.** MMN, CTS, Median nerve, MRI, SNR, CEUS

The American College of Radiology (ACR) Appropriateness Criteria for chronic wrist pain is firm that diagnostic radiography is the first line of imaging for chronic wrist pain, due to the low cost, simplicity, and direct evaluation of the osseous structures.<sup>1</sup> The ACR reached the guideline after a thorough systematic review of available literature. Systematic reviews are of the highest level of evidence due to the intense, methodical review the current literature to date, in order to answer a specific question, which is a prime example of evidence based practice. According to the ACR guideline, if the patients' pain cannot be determined from diagnostic radiography, further imaging is warranted to diagnose and return the patient to baseline. Magnetic Resonance Imaging (MRI) has long been the modality of choice for further evaluation of the wrist joint and the surrounding structures. MRI is the gold standard for its ability to evaluate osseous structures, tendons, and soft tissue structures for inflammation, and instability, with a rating of 9 out of 10 by the ACR, as the most appropriate imaging procedure.<sup>1</sup> Specifically the T2 weighted imaging sequence will demonstrate low, intermediate, or high signal depending on the level of edema and healing, and the age of the pathology.<sup>2</sup> Inflammation due to acute or chronic injury is a result of increased expression of prostaglandin E2 and vascular endothelial growth factor increases the vasculature permeability of the median nerve and the surrounding structures.<sup>3</sup> Swelling of the median nerve and increased signal to noise ratio (SNR) on T2 images is indicative of axonal transportation, myelin sheath deterioration, or edema, which are trademark diagnostic signs when evaluating the wrist with MRI.<sup>2,3</sup> The capability of MRI to accurately portray wrist structures and pathology is highly dependent on field strength

and the availability of a dedicated wrist coil.<sup>2</sup> A higher field strength magnet provides a higher signal to noise ratio, and contrast to noise ratio, which will allow for a higher resolution image with a thinner slice thickness, and ultimately result in a more detailed, higher diagnostic quality exam for patients. The T2 imaging sequence at high magnetic field strength is a useful sequence to evaluate inflammation and to determine if a surgical intervention is necessary.<sup>3,4</sup> The use of MRI T2 weighted imaging in the detection of inflammation of the median nerve within the carpal tunnel in the wrist has long been a staple in the standard wrist protocol, due its relative diagnostic sensitivity.<sup>3,4</sup>

In the same guideline, after thorough review of the literature, the ACR also ranked gray-scale Ultrasound (US) in the use of chronic wrist pain. The ACR ranked gray-scale US at a 1, usually not appropriate as an imaging resource.<sup>1</sup> US is used routinely to evaluate for wrist ganglia, tenosynovitis, tendon rupture, and undiagnosed pain and swelling, although, supplementary applications of measurements of triangular fibrocartilage complex (TFCC) thickness, detection of the TFCC, evaluation of the scapholunate and lunotriquetral tears, and supplemental diagnosis of carpal tunnel syndrome are also performed.<sup>1</sup> Gray-scale US is beneficial in conjunction with other modalities to gain further information. The use of gray-scale US is valuable for its ability to detect the thickening of the median nerve, flattening of the nerve within the tunnel, and bowing of the flexor retinaculum, which are indicative of wrist pathology.<sup>3</sup> Gray-scale US is routinely used to gauge the cross-sectional area of the median nerve as normal, mild, moderate, and severe, to classify the severity of carpal tunnel syndrome, according to several studies, but the debate remains as to the level at which the measurement should

be acquired.<sup>3</sup> However, Deniz et al found that US could be used as a first-step test for simple cases and MRI could be utilized for more complex diagnostic cases.<sup>6</sup> Further investigation by Evans et al found that Doppler evaluation of intravascular flow within the median nerve could add an additional use for gray-scale US in the assessment of chronic wrist pathology.<sup>7</sup> Although the specific use of gray-scale US in the evaluation of CTS is widely used, the exact role of its application is subject of some debate.

Contrast enhanced ultrasound (CEUS) is another aspect of sonography that is being explored and experimented within the United States for further evaluation of pathology. The basis of CEUS is administering a micro bubble contrast into the venous circulation of the patient and then using the probe to evaluate the microvascular circulation of the tissue, the median nerve in this instance. The use of CEUS is not approved for use on patients by the Food and Drug Association (FDA) and was therefore excluded in the systematic literature review performed by the ACR to construct the guideline. The use of CEUS is routinely practiced in Europe for evaluation of patients with chronic wrist pain.

The European standard for US of the wrist includes evaluation of the dorsal wrist followed by the palmar aspect with flexion, extension, ulnar and radial deviation, pronation and supination.<sup>8</sup> The median nerve is evaluated during the ventral wrist examination. The tunnel is assessed in its entirety, from proximal to distal along the short axis.<sup>8</sup> There is no evidence from the European Society of Musculoskeletal Radiology to suggest that further examination involving measurements and Doppler imaging of the median nerve should be a part of the standard protocol. The advantages of

US are debated throughout Europe as they are in the United States, but the evidence suggests that US provides valuable information in the depiction of soft tissue and tendinous lesions, in addition to joint effusions, ruptures of ligaments, and median nerve measurements.<sup>8,9</sup> The overall consensus is that gray-scale US can provide useful information given certain examination findings, but could potentially provide more clinically relevant information as new technology and imaging protocols are developed and evaluated.

The standard European protocol for chronic wrist pain and wrist injuries also holds MRI as the standard imaging modality. Following the initial clinical evaluation for carpal tunnel syndrome, this involves a comprehensive physical examination using the thumb abduction test, testing for a tincl sign, and the phalen test. This is also the standard protocol of physical examination in the United States. The thumb abduction test evaluates the strength of the abductor pollicis brevis muscle, which is solely innervated by the median nerve; weakness of the muscle is associated with CTS.<sup>10</sup> The tincl sign is tested by striking the anterior aspect of the patients wrist with the evaluators' index finger over the flexor retinaculum and volar carpal ligament. If a tingling sensation, radiating from wrist to hand following the median nerve distribution is experienced by the patient, a positive tincl sign is observed, and indicative of median nerve inflammation.<sup>10</sup> The phalen test is evaluated by having the patient to hold both wrists in a fully palmar-flexed position with the dorsal aspect of the hands pressed together for one minute, numbness and paresthesia along the median nerve distribution is suggestive of CTS.<sup>10</sup> After the preliminary physical examination, MRI is the preferred imaging modality for assessment

of edema, ligamentous damage, and inflammation.<sup>2,11</sup> Often physical examination findings do not effectively rule out pathology or other injury.<sup>12</sup> MRI is also the modality of choice following standard radiographs in most clinical scenarios due to the common knowledge that MRI provides the most comprehensive evaluation of the wrist, including bone marrow and soft tissues, such as ligaments, tendons, and muscles, but specific indications for MRI continue to involve soft tissue and osseous pathology.<sup>12, 13</sup>

### **RESEARCH QUESTION:**

The objective of this study was determine if any comparisons could be made between the SNR on MRI T2 weighted images and the CEUS on Maccaca fascicularis following repetitive work exposure. Therefore, the research questions were:

Can MRI T2 weighted imaging be compared to CEUS US to evaluate inflammation of the median nerve within the carpal tunnel?

What additional information does CEUS US add MRI T2 weighted imaging in the diagnosis of median nerve pathology within the carpal tunnel?

### **METHODS**

A retrospective preclinical longitudinal study was conducted over the period of a year by an ARRT registered technologist in MRI. Two ARDMS registered sonographers scanned and evaluated the wrist area within 1-7 days post MRI.

Three cohorts of Maccaca fascicularis monkeys were imaged at baseline, prior to any work exposure; at recovery, and following work exposure. The study was initially performed with 15 *Macaca fascicularis* monkeys. For the purpose of this study, the subjects were narrowed down to R, S, T, U, W, and X, due to the imaging time points.

These subjects US scan dates closely matched the MRI scan dates, as the other subjects did not, therefore could not be appropriately analyzed for comparison. Baseline and recovery scans occurred within an average time frame of 8.53 months with a range of 7 to 11 months. A TA BioSpec 94/30 MRI System equipped with a 9.4T horizontal bore magnet was used to image the subjects in an isolated research laboratory. The magnet operates at 400 MHz and functions on a ParaVision™ 4.0 software platform adapted from the TopSpin 1.5 (Bruker BioSpin; Billerica, MA). Each subject was packed into a warm plastic cylinder. Then, a 3.5 mm quadrature coil was placed anterior to the wrist while utilizing a 20 cm spatial gradient for signal acquisition. The subjects' wrist was splinted with a rectangular piece of flexi-glass and held in place by adhesive tape. The subjects were continuously monitored throughout the scan with a small animal monitoring system -Model 1025 (Small Animals Instruments, Inc. Stony Brook, NY). All imaging protocols were approved by the institutions' Institutional Animal Care and Use Committee (IACUC) board of review. Each subject was scanned in the lateral decubitus position, with their shoulder flexed, and their palm supinated. Thirty-two axial T1 and T2 weighted images were obtained with a 1mm slice thickness and a skipping of 0. A high resolution, 512x512 imaging matrix was utilized. The registered MRI technologist blindly analyzed the T2 weighted images acquired using MIPAV (Medical Image Processing, Analysis, and Visualization) software. MIPAV is endorsed by the National Institute of Health to quantitatively evaluate CT, PET, and MRI images. Digital Imaging and Communications in Medicine (DICOM) images, a common standard format to store and view medical images, were uploaded into MIPAV and then the median nerve was

traced and analyzed at the levels of the pisiform and the distal radius. The average voxel intensity and signal to noise ratio was calculated, and were then statistically analyzed.

A musculoskeletal sonography protocol was refined and replicated to evaluate the size and shape of the median nerve quantitatively and qualitatively.<sup>9,14</sup> Three sonographers used a GE Logiq *i* hand-carried unit (HCU) (GE Healthcare, Milwaukee, WI, USA) to scan the subjects, using a 12.0 MHz linear probe, with a bandwidth of 7-12 MHz. A 12.0 MHz frequency was selected; the time gain compensation controls were aligned vertically and centered, with Harmonics and CrossBeam® also being utilized. Each wrist was scanned in both the axial and longitudinal planes in order to obtain multiple views of the median nerve. In the axial plane, dynamic clips were stored as the scan progressed distally. Weekly quality control measurements were performed with the transducer and a tissue mimicking phantom throughout the study to monitor and document reliable equipment performance.

The equipment and dosing trials of the radial artery facilitated an imaging protocol for contrast enhanced ultrasound (CEUS) study of the median nerve. Additionally, a multi-incremental sampling method for imaging was chosen, based on an unbiased decision unit of time. The imaging samples were captured at baseline and then every 30 seconds, until 7 minutes elapsed from the initial injection. Choices were limited as to the method for image analysis given the restrictions imposed by the United States Food and Drug Administration, on the use of CEUS. Given our situation, a manual system was chosen for counting power Doppler pixels on the multi-incremental images that were captured throughout the series of imaging trials. The Klauser method for

counting power Doppler pixels with the region of interest (ROI) was utilized.<sup>15,16</sup> We also became aware of a semi-automatic method for assessing the enhanced vascularity around the median nerve. PixelFlux software, a semi-automatic flow quantification analysis tool for tissue and organ perfusion was used to evaluate the median nerve. The initial region of interest (ROI) was selected over the median nerve, then a trace ROI was then drawn around the median nerve for flow evaluation. The PixelFlux Scientific software allowed for up loaded images to have a manual ROI selected around the median nerve and then automatic calculation of the intensity of the pixels in the region.

## **RESULTS**

As the sample size was small (n=6), statistical analyses were not able to be performed on the T2 data points at the level of the pisiform and the radius, and the statistics are limited to a descriptive study. The analysis revealed that there was no correlation between the data points of the median nerve at the level of the pisiform and the radius. The subjects were limited to the recovery period due to the time constraints between the MR images and the US. The mean signal to noise (SNR) across all subjects at the level of the pisiform was 8.48; and the mean at the level of the radius was 8.86. The median signal to noise (SNR) across all subjects at the level of the pisiform was 7.99; and the median at the level of the radius was 8.38.

After reviewing data from the recovery period, we are left with US intensity measurements for subjects at year 3: subjects (S, T, U, W, X, and Y). Due to the small sample size (n=6), the best decision was to define the data descriptively as opposed to

performing any statistical tests or analyses. Descriptive statistics for the ultrasound and MRI measurements are given below, followed by box plots of each of each variable.

Years 3 consisted of the following subjects:

Year 3 – R, S, T, U, V, W, X, Y

### *Image Analysis-MRI*

MIPAV, a NIH endorsed imaging evaluation tool was used to perform the trace measurements and obtain the variables used to calculate the signal to noise ratio (SNR). The mean voxel intensity of the median nerve was divided by the standard deviation of noise, calculated in air. The mean SNR across all subjects at the level of the pisiform was 8.48; and the mean at the level of the radius was 8.86. The median signal to noise (SNR) across all subjects at the level of the pisiform was 7.99; and the median at the level of the radius was 8.38.

Table 5. Contrast Enhance Ultrasound Voxel Intensity and MRI Signal to Noise Ratio of the Median Nerve of Subjects S, T, U, W, X, Y at the Recovery Time Interval.

#### **Subjects at Recovery Period**

<b><i>Subject</i></b>	<b><i>Time Point</i></b>	<b><i>US Avg ROI</i></b>	<b><i>US Avg Max ROI</i></b>	<b><i>MRI Voxel Intensity</i></b>	<b><i>MRI SNR Median Nerve</i></b>
<u>S</u>	3	0.27733	0.52387	5008.25	8.53
<u>T</u>	3	0.30640	0.50973	5012.60	7.88
<u>U</u>	3	0.21200	0.30587	5057.40	8.54
<u>W</u>	3	0.71253	2.22060	5891.24	8.23
<u>X</u>	3	0.25987	0.45213	5325.64	7.88
<u>Y</u>	3	0.25860	0.43767	5859.66	12.09

Table 6. Data Table for Contrast Enhanced Ultrasound Average Region of Interest and MRI Signal to Noise Ratio Cross Sectional Area trace measurements of the Median Nerve at the Recovery Time Interval.

<i><b>Variable</b></i>	<i><b>N</b></i>	<i><b>Minimum</b></i>	<i><b>25<sup>th</sup>Pctl</b></i>	<i><b>Median</b></i>	<i><b>Mean</b></i>	<i><b>75<sup>th</sup>Pctl</b></i>	<i><b>Maximum</b></i>
<b>CEUS Avg ROI</b>	6	0.21	0.26	0.27	0.34	0.31	0.71
<b>MRI SNR</b>	6	7.88	7.88	8.38	8.86	8.54	12.09

Boxplots were plotted for the MRI Signal to Noise Ratio of the Cross Sectional Area trace measurements of the median nerve data and the Contrast Enhanced Ultrasound Cross Sectional Average Region of Interest data. MIPAV software was utilized for acquiring the MRI data and PixelFlux software was utilized for acquiring the CEUS data.

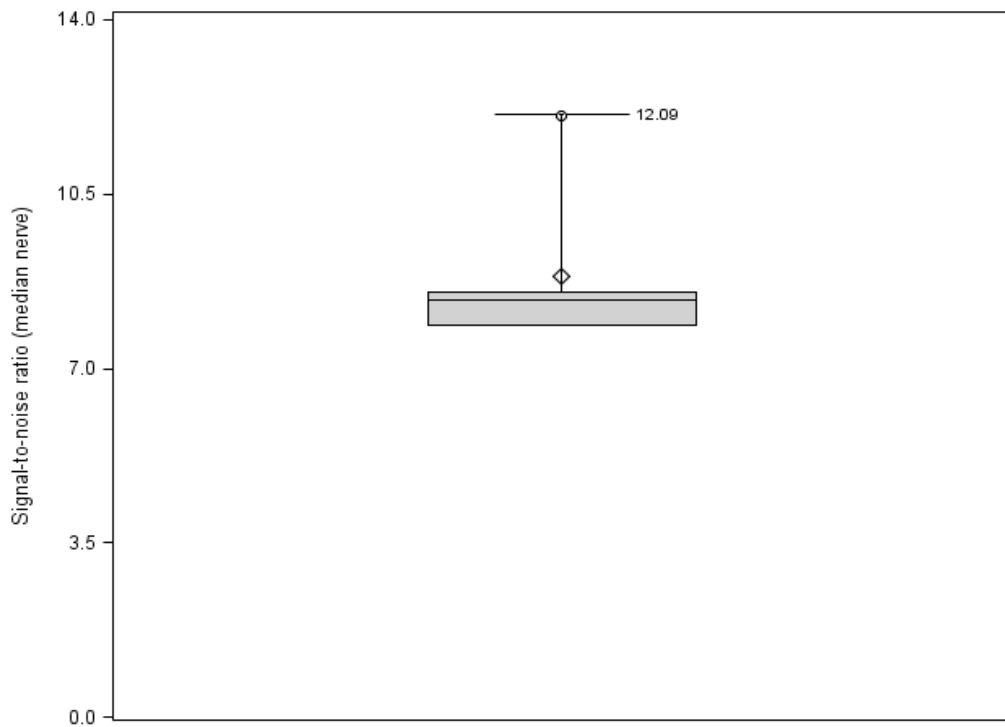


Figure 6. Box plot – MRI Signal to Noise Ratio of the Median Nerve. Box plots display a box with whiskers at opposite ends. The box represents the middle 50% of the distribution, a line within the box designates the median, and whiskers portray the distance to the prescribed endpoints. The median was 8.38, with a maximum outlier of 12.09, and a minimum outlier of 7.88. Outliers for box plots (shown in plots with a circle symbol) were defined as distances greater than  $1.5 \times \text{IQR}$  above the 75<sup>th</sup> percentile or  $1.5 \times \text{IQR}$  below the 25<sup>th</sup> percentile IQR ( $\text{IQR} = 75^{\text{th}} \text{ percentile} - 25^{\text{th}} \text{ percentile}$ ). Those data points labeled as outliers are defined using a small sample; therefore, this type of labeling is subjective. The boxplot depicting SNR displays a relatively small distribution.

Trend graphs were also composed in an attempt to possibly observe a relationship between SNR and the subjects' exposure to work. The expected results would be for SNR to increase due to increased vascular permeability and inflammation.

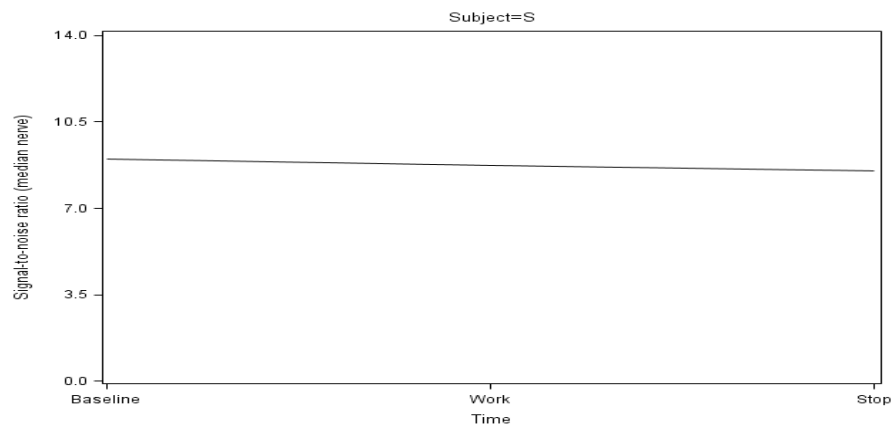


Figure 7. Trendgraph -Subject S- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts the signal to noise ratio of Subject S declining slightly from roughly 9.2, to 9, then to 8.8.

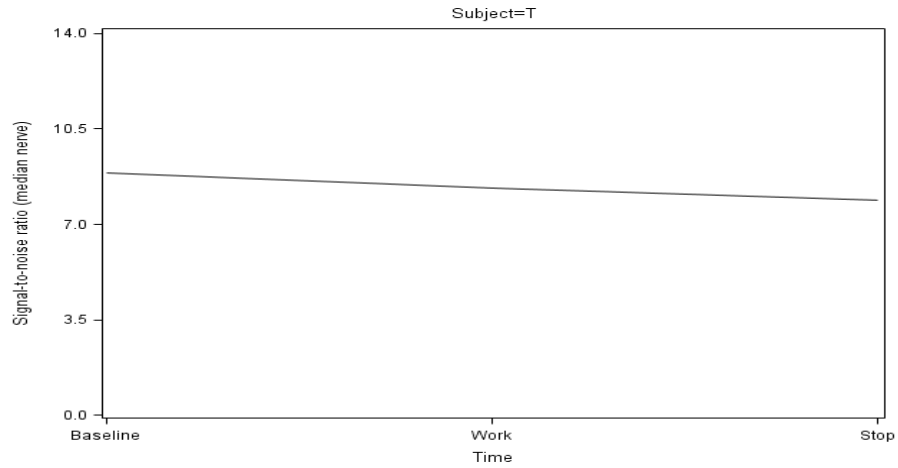


Figure 8. Trendgraph -Subject T- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts the signal to noise ratio of Subject T declining from roughly 8.9, to 8.5, then down to 8.0.

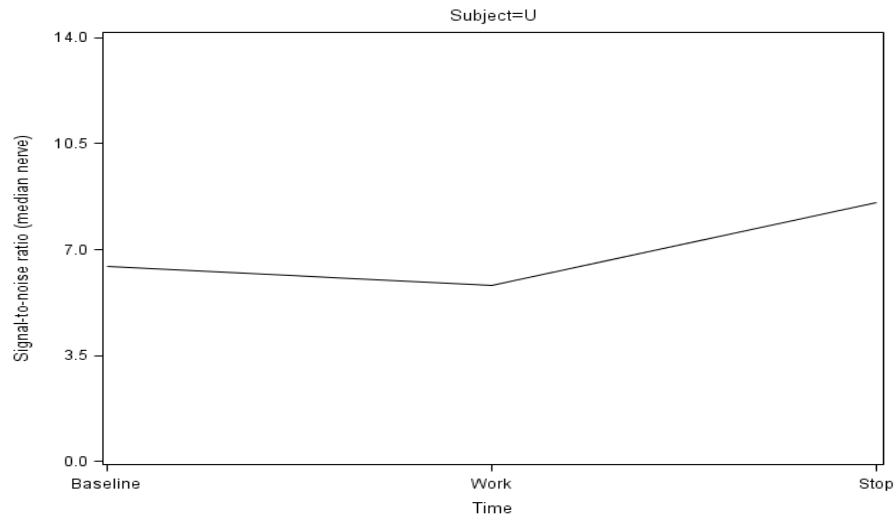


Figure 9. Trendgraph -Subject U- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts the signal to noise ratio of Subject U declining slightly from 6.5, to 6.0, then rising to 8.0.

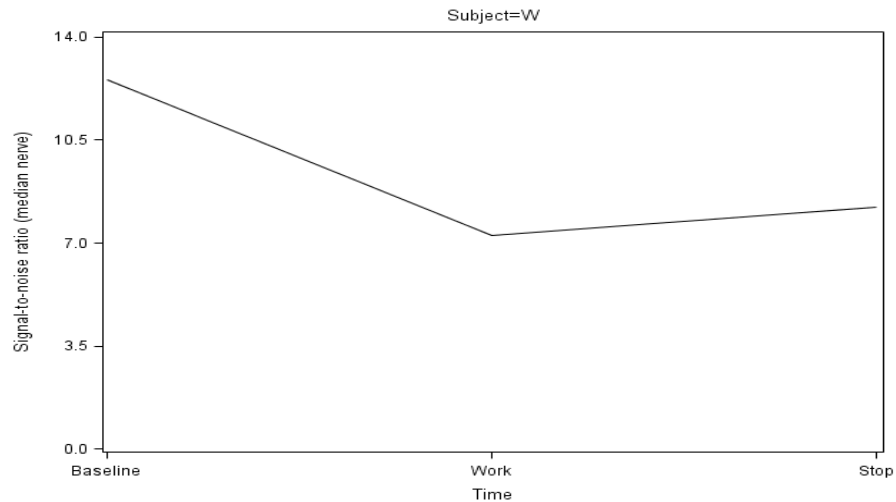


Figure 10. Trendgraph -Subject W- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts the signal to noise ratio of Subject W declining from 12, to 7.2, then rising again to 8.0.

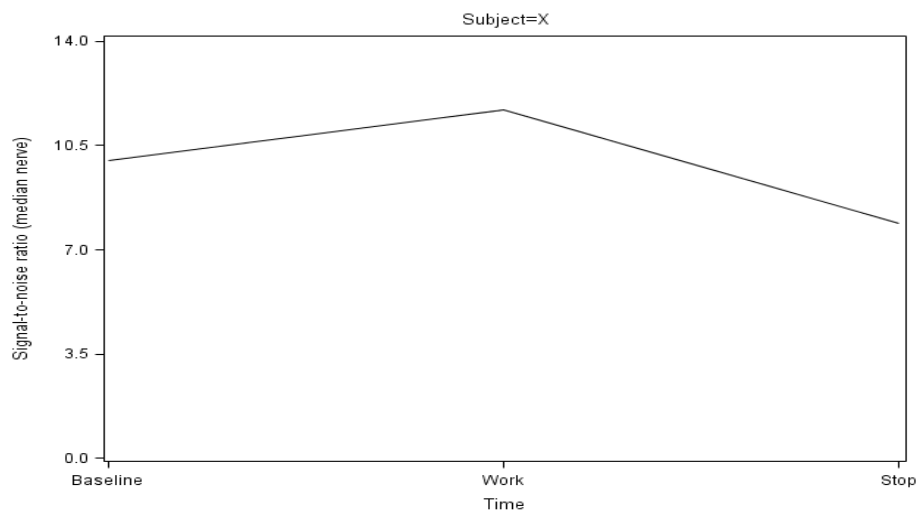


Figure 11. Trendgraph -Subject X- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts

the signal to noise ratio of Subject X rising from 10, to 11.5, then dropping again to 8.0.

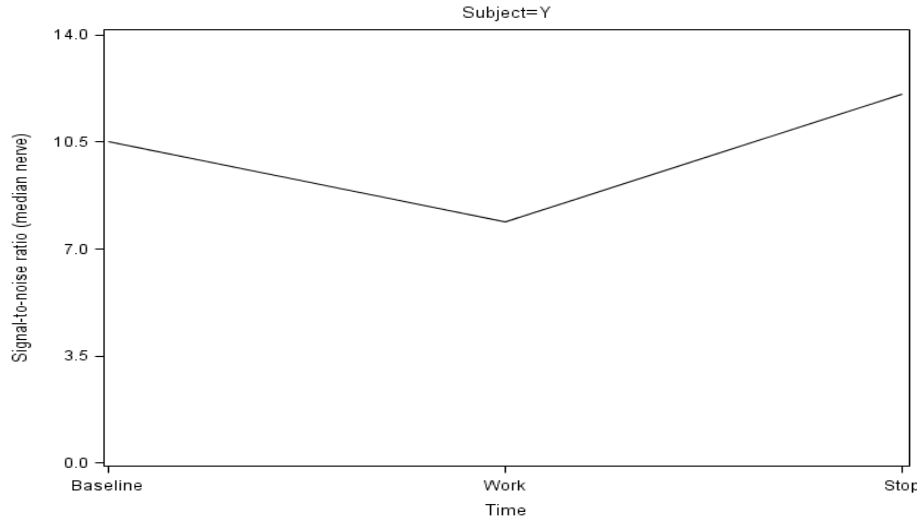


Figure 12. Trendgraph -Subject Y- MRI Signal to Noise Ratio of Cross Sectional Area of the trace measurements of the median nerve vs. Work Exposure. The trendgraph depicts the signal to noise ratio of Subject Y declining from 10.5, to 8.5, then rising again to 12.5.

The trendgraphs also depicted erroneous, unexpected results between the various subjects. No two subjects were exactly alike; SNR dramatically decreased or remained relatively the same following work exposure.

#### *Image Analysis-US*

The semi-automatic use of PixelFlux Scientific software to determine the amount and intensity perineural vascularity was completed for a semi-automatic measure compared to the system of counting pixels in a defined area. The mean for the subjective counting of pixels across all subjects was 3.85, SD 2.17. The objective maximum intensity of the CEUS of perineural vascularity was 1.89, SD 1.53. The objective average intensity of the CEUS of perineural vascularity was 0.39, SD 0.16.

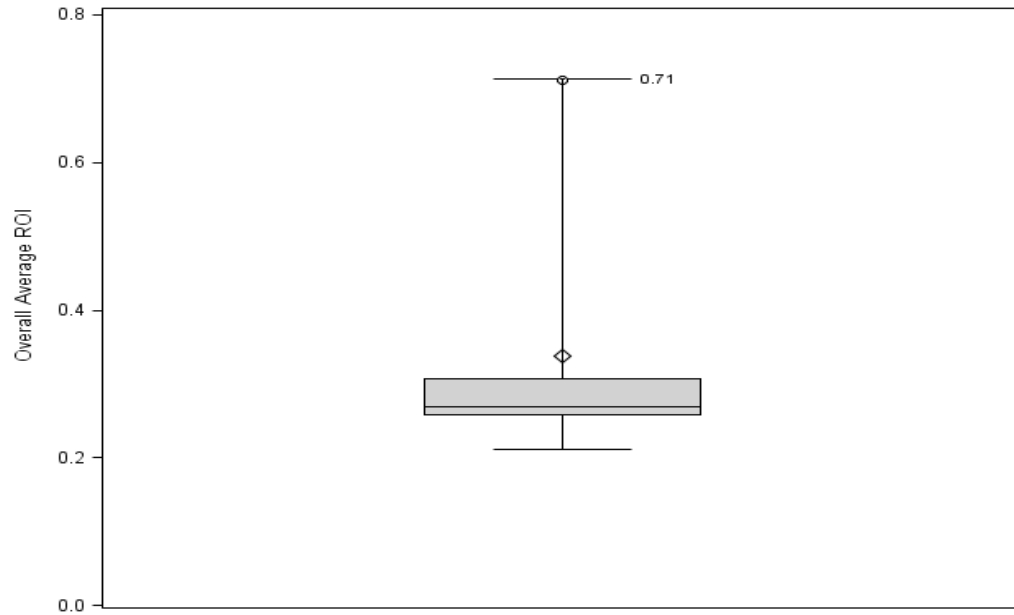


Figure 13. Box plot – Contrast Enhanced Ultrasound Average Region of Interest of the Median Nerve. Box plots display a box with whiskers at opposite ends. The box represents the middle 50% of the distribution, a line within the box designates the median, and whiskers portray the distance to the prescribed endpoints. The median is roughly .27 and the maximum outlier being 0.71, and the minimum outlier being 0.21. Outliers for box plots (shown in plots with a circle symbol) were defined as distances greater than  $1.5 \times \text{IQR}$  above the 75<sup>th</sup> percentile or  $1.5 \times \text{IQR}$  below the 25<sup>th</sup> percentile IQR ( $\text{IQR} = 75^{\text{th}} \text{ percentile} - 25^{\text{th}} \text{ percentile}$ ). Those data points labeled as outliers are defined using a small sample; therefore, this type of labeling is subjective.

The boxplot of the CEUS overall average ROI of the median nerve displayed a wider range of data points, therefore a much wider distribution than the SNR boxplot.

The CEUS data analyzed with PixelFlux were Average intensity across the ROI (Avg ROI) and Average maximum intensity across the ROI (Avg Max ROI). Due to the

use of a mean for average signal intensity with the ROI across the various time points acquired with CEUS, an average of an average would need to be calculated to compare to the Mean SNR from the MRI data. Producing an average of an average is not a credible statistic; consequently, no comparison could be made between the two modalities. However, average Max ROI can be compared to Mean SNR, but the problem that remains is that pixel intensity strength is being compared to voxel intensity strength.

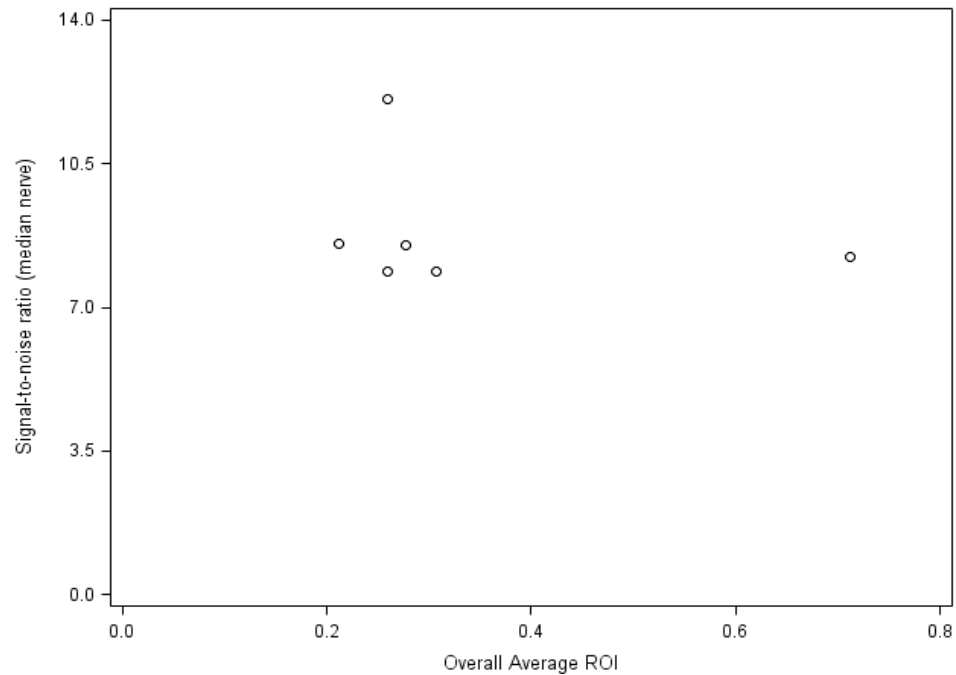


Figure 14. Scatterplot – MRI Signal to Noise Ratio Cross Sectional Area trace measurements of the median nerve plotted against vs Contrast Enhanced Ultrasound Average Region of Interest. The data in Table 6. is depicted in the form of a scatterplot using MRI SNR on the y-axis and CEUS Overall Average ROI on the x-axis. The scatterplot also depicted no observable correlation between MRI and CEUS.

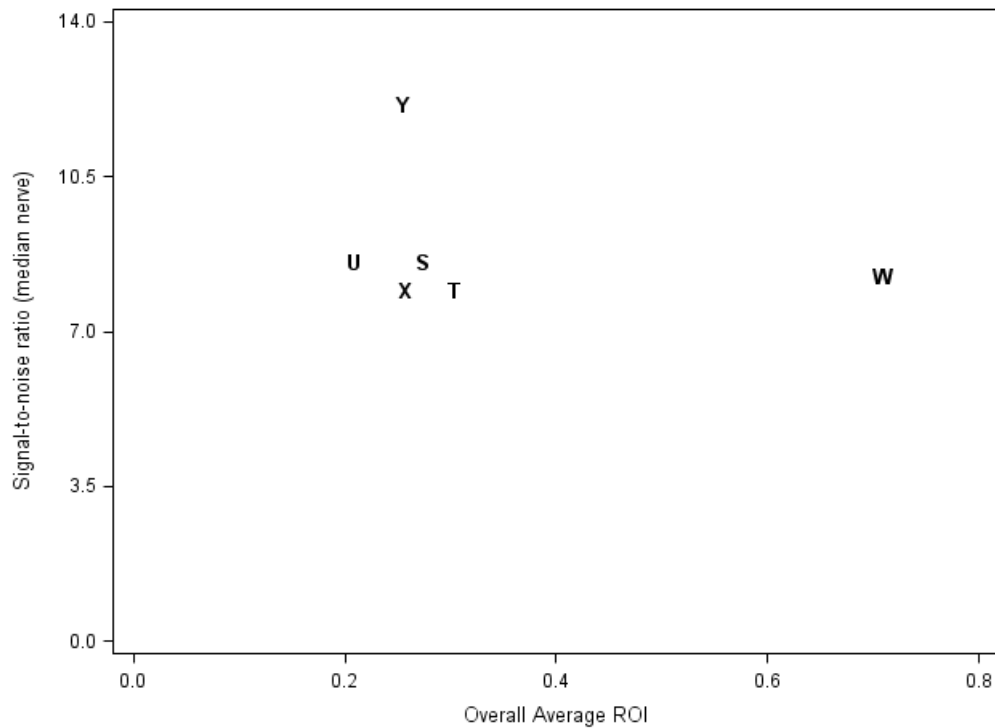


Figure 15. Scatterplot – MRI Signal to Noise Ratio vs. Contrast Enhanced Ultrasound Average Region of Interest (with subjects defined at data points). The same scatterplot is depicted using the data points the subjects labeled at data points. This scatterplot further depicts no observable correlation between MRI and CEUS by using the subjects. Scatterplots were again produced using MRI SNR on the y-axis and CEUS Overall Average ROI on the x-axis.

## DISCUSSION/CONCLUSION

Statistical analyses on the MRI T2 weighted images and contrast enhanced US images have yielded inconclusive results. There is no definitive comparison between the signal to noise ratio on MRI T2 weighted images and the overall average region of interest on Contrast Enhanced Ultrasound. Given the limitations of the small sample size; to answer the question of how does MRI T2 weighted imaging compare to CEUS

US Doppler to evaluate inflammation of the median nerve within the carpal tunnel, is MRI T2 weighted imaging more sensitive than CEUS US Doppler to assess changes of the median nerve in the carpal tunnel, and Could CEUS US Doppler aid MRI T2 weighted imaging in the diagnosis of median nerve pathology within the carpal tunnel? The data analyses is inconclusive as to if a comparison can be derived. A more comprehensive study needs to be completed with strict imaging guidelines. A larger sample size needs to be gathered and assessed with magnetic resonance and ultrasound on a stringent time basis and minimal time between imaging to appropriately and accurately obtain data measurements for comparison. Imaging acquisition times should be extremely close in proximity to ascertain if a comparison can be determined between imaging modalities. An extensive interval between imaging with MRI and US could yield erroneous results and exclude data, as encountered during this study. A larger sample size would provide a thorough representation of subjects to detect any median nerve pathology that could potentially be evaluated. A rigorous protocol for MRI acquisition would be essential to the research design and performed by an ARRT certified technologist. The subjects should be placed in a dedicated imaging apparatus without room for flexion, extension, or ulnar/radial deviation, to limit any possibility for a positional variation that could influence data measurements. Anatomical landmarks, such as the middle of the carpals, or a marker, could be utilized for reproducibility on all subjects during each imaging interval. The imaging protocol should consist of a standard matrix, TR, TE, number of slices, NEX, bandwidth, and flip angle, which should remain constant for all subjects throughout the study during each image acquisition. Keeping

parameters and external variables constant would increase measurement reliability and possibly account for some of the erroneous data. Reducing the amount of variability during imaging acquisition will provide the basis for a stronger research design and provide reproducible imaging protocols to ascertain if a comparison can be established between magnetic resonance imaging and sonography in the acute stages of carpal tunnel syndrome.

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## **Chapter 4: Discussion**

The National Institutes of Health (NIH), through the Clinical Trials registry and results database defines a clinical trial as a clinical study involving research using human volunteers that is intended to add medical knowledge. The National Center for Biotechnology Information (NCBI) further defines a clinical study as a research study which tests out a drug or other intervention to assess its effectiveness and safety with the goal to answer scientific questions and find better ways to treat individuals with a specific disease. In order to progress to a clinical study, preclinical data needs to be acquired to test the safety and effectiveness of the treatment or intervention (Guyatt, 2002) (Jenicek, 2003) (Marchevsky, 2002). The goal of the study was to evaluate if a comparison could be made between MRI and sonography in the acute stages of carpal tunnel syndrome (CTS) and develop an imaging protocol that could be applied to a higher order study. Most of the literature to date encompasses the symptomatic stages, when the damages of CTS have often already occurred, long past the acute stages, when microtrauma has started developing. The hope was to begin to address the long recovery from this compressive disorder and lost revenue due to employees taking time away from work. This study was a preclinical, longitudinal, study which does not allow for generalizations to be made to the greater population. Although preclinical studies are among the lowest levels of evidence, the information obtained helps aid in the research process and data

acquisition in a specific area prior to developing a more structured research design (Jenicek, 2003). By trialing hypothesis and protocols in a preclinical model, the researcher may gain further information about what study design and protocol may best work for a specific cohort, prior to a clinical trial. Although this study was not generalizable to the overall population, typically this kind of research can be used to gather further information on a clinical subject and provide translational information that would promote going from “bench to bedside.”

Although both studies demonstrated no measureable outcome, the information should be applied and altered to construct a rigorous clinical study design.

Study #1 demonstrated that no direct relationship could be found between the measurements of work exposure and median nerve enlargement on MRI T1 imaging. Additional analyses of the T2 coronal images demonstrated that varying degrees of ulnar and radial deviation were present amongst the subjects. Degrees of anterior and posterior deviation were not able to be evaluated due to the lack of sagittal images in this cohort. The positional variations between the subjects could have led to the erroneous measurements. The data was obtained from animal subjects that were exposed to working conditions, but the participation of the subjects would need to be discretely measured.

Study #2 revealed no comparison could be made between the SNR on MRI T2 weighted images and the CEUS measurements of the median nerve following work exposure. Positioning variations could also account for the SNR variations between the subjects during the imaging intervals. Placement of the subjects' wrist within the immobilization

device, coil placement, and location of the subject within the bore of the scanner could allow for variability of SNR measurements between the subjects. Imaging parameters, such as time to repeat (TR) and time to echo (TE) could also allow for variations in SNR.

Clinically, discussion continues about the compatible role that MRI and sonography can have in the diagnosis of upper extremity conditions (Khachi, 2007).

Unfortunately, these recommendations are based on lower level evidence, such as, professional practice experience with imaging specific conditions and this ranks at the anecdotal level of evidence based practice. A specific example would be the use of MRI and sonography to provide diagnostic information on epicondylitis (Miller, 2002). In this small cohort study, a convenient sample of clinical patients was evaluated with both MRI and sonography. This study found that sonography was as specific, but not as sensitive and recommended the use of MRI on patients who were symptomatic, but demonstrated normal findings with sonography. Harnessing the positive diagnostic attributes of these two modalities could help to raise the positive predictive value for many upper extremity conditions but continued research is needed. The use of sonography in patients suffering from musculoskeletal pathology has long been utilized for many years to effectively evaluate the anatomy without delaying care due to additional tests and costly procedures. Algra et al found MRI and sonography to be relatively similar in the positive and negative predictive values upon evaluation on the shoulder for full-thickness rotator cuff tears. They concluded that given the similar sensitivity and specificity of these two modalities, that the use of sonography would be more cost efficient to precede the more expensive MRI procedure.

The American College of Radiology (ACR) frequently updates the information for all radiology exams based on evidence based medicine and current up-to-date literature. Based on these practice guidelines and imaging algorithms, physicians can manage a patients' care without subjecting them to multiple exams that allow for no further gain in diagnostic information. The ACR Appropriateness Criteria for Chronic Wrist Pain and ACR Practice Guideline for MRI of the Wrist have both been revised in 2012 in response to ongoing research and publications within the area of chronic wrist pain and pathology. Both ACR documents maintain that MRI is the modality of choice after the primary imaging modality of diagnostic radiography is deemed unremarkable. However, the ACR ranks each modality and recommends the role and function given certain circumstances, but does not mention or detail the use any modality in conjunction with one another. The use of multiple imaging modalities concurrently may provide additional information regarding chronic wrist pain. In addition, a proactive imaging screening tool is essential to prevent future occurrences of CTS within the working population. The establishment of a relationship between the two modalities could provide a more cost effective way to evaluate the wrist with sonography before moving on the more expensive gold standard of MRI.

The ACR continues to evaluate the literature and ongoing research and is in constant need of higher levels of evidence to further substantiate the current findings or steer the guideline in a new direction. This study was an attempt to establish a detectable relationship between MRI and sonography. The results of the study were inconclusive, but have added further information regarding imaging protocols. This process is the

mechanism for staging a more rigorous study for the use of MRI and sonography in tandem to better image the early developmental stages of CTS.

## **Chapter 5: Conclusion**

Though not generalizable to the greater population, detailed imaging protocol information can be obtained from the study design and implementation. The information gained will help to adapt the imaging protocols from the preclinical studies to provide a more structured research design and allow for decreases in the internal threats to validity in a clinical study. If an animal model were to be carried out, a larger sample size with subjects that were not part of any prior research studies would be necessary to substantiate the results. Each subject for the study should have not participated in any previous research studies. The researcher should maintain strict control over extraneous variables that the subject may be exposed to; such as, medications, non-work exposure activities, etc. should be considered to avoid confounding influences or otherwise manipulating the data. Imaging should be obtained at specific, structured imaging intervals to attempt to reduce the confounding variables that could affect the results. The imaging and subsequent image analyses should be performed by a specialized technologist certified in the specific area of acquisition. Each subject should have a mark or marker placed on the dorsal aspect of the hand, at the levels of the radius and ulna. This mark should be a reproducible landmark that can be utilized as an external structural landmark for each subject at each imaging interval. A dedicated wrist coil would be an ideal piece of equipment to obtain images with the best SNR and CNR. This coil would allow for optimum positioning and decrease the amount of user error and variability in

positioning. Although a dedicated wrist coil would be ideal, it is not imperative to obtain quality MR images, a small extremity coil could be also be utilized. The coil should be placed anterior to the wrist, and in the center of the mark on the subject to obtain optimal SNR and imaging outcomes. A positioning apparatus is necessary in order to completely immobilize the subjects and eliminate any degree of ulnar and radial deviation, and flexion and extension. A nonferromagnetic material, with no magnetic susceptibility, such as Plexiglas, would be ideal. See Appendix A, page 59. The material should be placed, anterior/posterior, and lateral/ medial to limit any possible positioning error between subjects. Each subject should be imaged, at each imaging interval, while in the positioning aid.

Although the study was susceptible to bias and contains limited translation to the general population, extensive knowledge is gained in the area of clinical design and implementation (Guyatt, 2003). The information from the preclinical study can be applied to a cohort study that is designed to eliminate internal and external validity threats that can often be problematic. This prospective cohort could be consented from various sites and institutions; however, given the focus of the study in the area of microtrauma, employees engaged in occupational repetitive tasks would be the ideal group. Employees engaged in factory or assembly line work would be a good fit for a prospective cohort of subjects. The researcher, ideally a registered sonographer, could provide lunch to participants that are experiencing some discomfort related to CTS, but not yet symptomatic enough to elicit an appointment with a physician. Exclusion criteria could include: no prior diagnosis of CTS in the effected wrist, no prior surgery on the

effected wrist, and no physical therapy intervention. The subjects could be evaluated with sonography on the suspicion of acute CTS. The subjects that are symptomatic and demonstrate some anatomic findings of CTS upon sonographic evaluation could be screened and then enrolled in the second phase of the study, involving MRI of the wrist. The participants that follow through with the MRI examination could be offered a gift card or other compensation for their participation. The MRI examination should be performed by a registered MRI technologist and all supplemental image analyses. The positional errors that were discovered in the preclinical study can be applied to the clinical study during the imaging acquisition process to reduce any possibility that a positional variance could account for effects on the acquired data. Although results of the earlier studies were limited, the results could prevent positioning errors that could be applied on a larger scale to a human study. These results would insure that the MRI images could be used as the gold standard for diagnostic correlation in comparison with other imaging modalities. Of the research completed on the late, symptomatic stages of musculoskeletal pathology, the use of sonography prior to the use of MRI is promising and the need for further information to evaluate this practice is merited (Khachi, 2007) (Miller, 2002) (Algra, 1999).

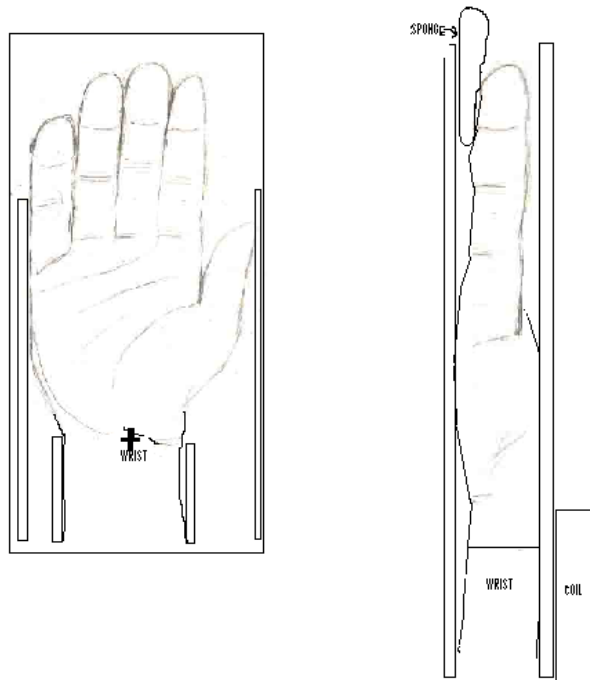
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## Appendix A: Proposed Prototype for MRI Plexiglas Wrist Positioning Aid



Proposed Prototype for MRI Plexiglas Wrist Positioning Aid. To insure proper scan planes are achieved and optimum SNR is gained.