Study Title: 4DCT Wrist Biomarkers During Resisted and Unresisted Tasks in Healthy Controls

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General Study Information

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Protocol version number and date: 4.3 10/10/2023

Research Question and Aims

Specific Aim #1: Quantify 4DCT wrist biomarkers during resisted and unresisted tasks in healthy controls. Healthy controls without any history of wrist injury or diseases will be scanned using 4DCT during wrist movement to characterize gapping at the scapholunate, radiolunate, and radioscaphoid joints ("radiocarpal joint and scapholunate interval") as well as at the scaphotrapezium, scaphotrapezoid, and trapeziotrapezoid joints ("scaphotrapeziotrapezoid [STT] joint"), as well as any other wrist joints captured within the imaging fields-of-view (i.e., trapeziometacarpal [TMC] joint). The existing device used to hold and guide subject's wrists will be modified to provide resistance to movements. The scientific premise for this aim is our pilot cadaveric[21,22] and patient imaging[23] using 4DCT.
Hypothesis: *Scapholunate distances and bilateral asymmetry will be greater in the resisted tasks as compared to the unresisted tasks in both male and female subjects. Secondarily, gapping in females will be greater than males.*

Study Design and Methods

Methods:

4DCT Imaging
A research CT scanner (Siemens NAEOTOM Alpha) or another dual source CT scanner will be used for imaging. Two independent but identical x-ray tubes are mounted on a rotating gantry at a 94 degree offset, with respective detector arrays opposing them. 4D (3D + time) CT imaging acquires high-temporal resolution, continuous or intermittent images over the width of the detector array in the superior-inferior direction. A bilateral static CT scan of the left and right wrist will first be performed. After that, four dynamic CT scans (4DCT) will be performed, two on each wrist, while patients are performing one of three types of movements: 1) passive and active grip; 2) unresisted and resisted flexion-extension; 3) unresisted and resisted radial-ulnar deviation. The passive/unresisted movements account for one dynamic CT scan and the active/resisted movements account for the second dynamic CT scan, for each wrist, for a total of 4 dynamic CT scans. In all conditions, the forearm will be restrained in a padded support channel to prevent upper arm movement and limit shoulder motion without affecting wrist and hand movement. Tasks will be performed using an ambidextrous, multipurpose mechanical device that will guide the left or right hand through the prescribed motion. Light resistance loading, which can be enabled or disabled, will be generated during hand motion This custom device will consist of a single hand restraint or grip, a low-friction linear stage, a spring-loaded resistance mechanism, and a base, all made of plastic. For the dynamic scans, sequential, dual-source scanning mode is used which is similar to CT perfusion imaging. In this mode, imaging data of a moving joint are continuously acquired without table translation. Two seconds of

data will be acquired for each movement (full cycles of open/closed active grip, flexion-extension, or radial-ulnar deviation).

Image processing

Seventeen image volumes will be reconstructed over the 2 second cycle using the commercially implemented dual-source cardiac reconstruction algorithm, resulting in a voxel dimension of 0.234 x 0.234 x 0.600 mm. 3D images of each of the 17 volumes, which are evenly distributed (temporally) across the motion cycle, will be generated using volume rendering techniques (VRT) and 4D movies will be made using the scanner's image processing workstation. All images will be stored in DICOM format for determination of metrics and biomarkers. All of the DICOM volumes will be processed using Analyze Pro (Mayo Foundation of Medical Education and Research), Cloud Compare, Mesh Lab, and existing software previously developed by our study team in Matlab (Mathworks, Inc.) platforms. Three-dimensional bone shape analysis will be conducted using open-source ShapeWorks software developed at University of Utah (https://www.sci.utah.edu/software/shapeworks.html).

Aim 1:

Bilateral 4DCT scans will be performed on 30 healthy controls (15 males, 15 females) without any history of wrist injury or disease. Subjects will be randomly assigned to one of three groups of 10 subjects using stratified randomization to ensure equal distribution of sex in each group (5 males, 5 females); order of testing (unresisted and resisted) will be randomized within each group. 4DCT wrist data will be obtained while subjects in each group perform one of the following tasks through a full range of motion, bilaterally: 1) passive and active grip; 2) unresisted and resisted flexion-extension; and 3) unresisted and resisted radial-ulnar deviation. Subjects in group 1 will perform the task with the wrist in neutral position. Auditory cues will be given to subjects in all groups via metronome to ensure the full motion cycle is performed in 2 seconds (length of each individual scan). Resistance will be standardized across participants. The dynamic image sequence will be processed using existing software tools to obtain metrics quantifying the size and location of gapping (palmar or dorsal) at the scapholunate, radiolunate, and radioscaphoid joints as well as at the scaphotrapezium, scaphotrapezoid, and trapeziotrapezoid joints—as well as any other wrist joints that may be captured in the imaging field-of-view—during the movement cycles.

Expert Consensus

addendum for protocol v4.3 (10/10/2023): To select the most appropriate bone surfaces to include in the aforementioned analyses, a standardized three-dimensional rendering of a scaphotrapeziotrapezoid (STT) joint will be circulated to a panel of Mayo Clinic hand surgeons for an expert consensus using Microsoft Forms. The Form will be anonymous, and accessible only to those with a @mayo.edu e-mail address. The data being circulated do not contain original patient data and will be used for a technical decision in a software parameter.

addendum for protocol v4.2 (02/15/2023): Due to a software malfunction during the scans for the first subject, only half of this subject's dataset was retained. A replacement subject will be recruited for this subject's group (female, radial-ulnar deviation, unloaded first).

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual: 31 healthy control subjects; up to 15 Mayo Clinic Hand Division surgeons

Subject population (children, adults, groups):

Control subjects without any history of wrist injury or disease will be recruited.

Exclusion Criteria:
Exclusion criteria which will be applied to both wrists for control subjects are as follows:
1) previously-diagnosed rheumatological conditions or connective tissue diseases;
2) inability to be appropriately positioned in the scanner for the imaging;
3) congenital malformations of the wrist or forearm;
4) diagnosed wrist osteoarthritis
5) age under 18 or over 60.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	x	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	x	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	x	x
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	x	
Social Security number	x	
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	x	
Street address, city, county, precinct, zip code, and their equivalent geocodes	x	
Phone or fax numbers	x	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Data Analysis Plan:

Aim 1:

Normalized volar/dorsal location of the gapping at the scapholunate, radioscaphoid, and radiolunate joints as well as the scaphotrapezium, scaphotrapezoid, and trapeziotrapezoid joints—as well as other wrist joints in the acquired field-of-view—for the 15 male and 15 female subjects will be analyzed. Three-dimensional bone shape variations will be quantified. Magnitude and direction of contact center migration, bilaterally, will be analyzed during the 17 time steps during each movement. The primary assessment will be of the scapholunate distances as well as STT interosseous distances and bilateral asymmetry between the unresisted and resisted tasks in both male and female subjects. The secondary assessment will be of the scapholunate gapping as well as STT interosseous distance differences between males and females. The differences in bilateral migration of the contact center in the one limb as a percent normalization relative to the contralateral limb values will be determined and described using the t-distribution. These analyses will be repeated by sex, and other subgroups that become apparent during the study. With a sample size of 30, using a two-sided size 0.05 t-test, we will have 80% power to detect an effect size of 0.53 for the analysis of quantitative outcomes.