BIOMARKERS OF UPPER-EXTREMITY SOFT TISSUE PATHOLOGY IN WHEELCHAIR USERS WITH SPINAL CORD INJURY

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Wheelchair users with spinal cord injury (SCI) use upper-extremities to perform most activities, which may lead to upper-extremity pain. Wheelchair transfers and propulsion expose shoulder and wrist soft tissues to repetitive and forceful loads that can contribute to pathology. The proceeding investigations aim to further understand how wheelchair activities contribute to the development of soft tissue pathology using ultrasound and chemical biomarkers. The first three studies describe how wheelchair transfers effect ultrasound markers for pathology. A sample of wheelchair users with SCI was recruited and performed eighteen transfers within 10 minutes. Ultrasound images of the biceps and supraspinatus tendons were collected before and after transfers to assess tendon width, brightness, and composition. Clinical ultrasound markers were collected at the start of the protocol. Better transfer technique correlated with fewer ultrasound markers of shoulder pathology, and less transfer-related shoulder pain. Repeated-transfers acutely increased biceps tendon width and median nerve cross-sectional area; changes were influenced by greater bodyweight and specific transfer skills. A novel method of measuring glenohumeral joint (GHJ) inflammatory cytokines, using microdialysis, was developed for the final study. Six able-bodied veterans and one individual with SCI were recruited. A microdialysis catheter was inserted into the posterior GHJ space under ultrasound guidance. Participants performed a wheelchair propulsion and transfer protocol. Microdialysis samples and ultrasound were collected before and after the activity, and 30 and 60 minutes post-activity. IL-1RA and RANTES changed after the activity. Smaller RANTES increases were correlated with

greater propulsive forces. Greater changes in IL-8 and IL-1RA were associated with darker tendons after activity, which indicates intratendinous edema. The findings suggest that inflammatory cytokine expression (local to the GHJ) contributes to rotator cuff tendinopathy. Furthermore, forceful upper-extremity activity may contribute to tendinopathy by amplifying cytokine expression. Biochemical markers are a valuable measure of inflammation that is reflective of soft tissue pathology and may provide investigators with a sensitive method to determine different wheelchair techniques that dampen the inflammatory response. Results from these studies indicate that wheelchair activities may cause an acute inflammatory response that affects tendon health, and that using better technique may help prevent the development of pathology.

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1.0 INTRODUCTION

1.1 SHOULDER AND WRIST PATHOLOGY IN WHEELCHAIR USERS WITH SPINAL CORD INJURY

The shoulder is the primary site of pain among wheelchair users. In manual wheelchair users with SCI, the prevalence of shoulder pain is reported to be between 31% and 73%.[1-4] Shoulder pain has the potential to negatively affect functional independence, quality of life, employment, and participation in activities, and has been functionally and economically equated to a higher level of injury.[1, 5-9] Pain can reduce arm range of motion in people with tetraplegia, further affecting functional independence.[8] The most common causes of chronic shoulder pain in people with SCI are musculoskeletal injuries to the rotator cuff tendons.[1, 10]

Many authors have attributed the high prevalence of shoulder pain in manual wheelchair users to their reliance on their upper limbs to perform activities of daily living [10-12]. Repetitive weight bearing activities such as transfers, propulsion, and pressure relief place large loads on soft tissues of the shoulder[13, 14]; pain is highly associated with wheelchair propulsion and transfers, among other activities of daily living.[6, 15] Other pressure relief options exist to greatly reduce or eliminate loads on the shoulder[16, 17], yet wheelchair users still must regularly transfer and propel to remain independent. Unfortunately, shoulder pain can further reduce independence by preventing individuals from propelling or transferring and participating in activities.[6, 18]

Natural healing and repair of tendons is a slow process that only occurs if overload is reduced or eliminated. Wheelchair users must use their arms throughout the day, which greatly complicates the healing process. Perhaps as a result, individuals typically seek treatment after the pain is severe and limits independence.[6] Conservative and surgical treatments that are sought after are often costly and ineffective in this population.[15, 18, 19] Given the decrements in quality of life, functional independence, employment, and other factors brought about by shoulder pain, prevention of rotator cuff tendinopathy is of the utmost importance in this population.

Carpal tunnel syndrome (CTS) is another musculoskeletal disorder that is highly prevalent amongst wheelchair users with SCI. Seventy-eight percent of participants in a study by Yang, et al. met electrodiagnostic criteria for median mononeuropathy, with 57% reporting symptoms.[20] One cause of CTS is compression of the median nerve within the carpal tunnel that causes pain, paresthesia, and numbness in the hand and wrist. Anatomically, nine flexor tendons and the median nerve travel through the rigid carpal tunnel (the space between the ventral transverse carpal ligament and dorsal carpal bones). When exposed to certain stimuli, hydrostatic pressures within the carpal tunnel can increase and damage the nerve.[21] Chronic exposure to elevated pressures can inhibit intraneural blood flow and nerve function, mechanically damage myelin, and promote inflammation.[21]

Carpal tunnel pressures increase in a dose-dependent fashion when exposed to force and repetition in healthy, able-bodied individuals.[21] This is perhaps why wheelchair propulsion and transfers have been hypothesized as potential causative factors in the development of CTS in people with SCI. However, few studies have investigated the pathophysiology of CTS with respect to different wheelchair activities and how technique influences the development of the syndrome. Studies by Boninger, et al. have reported electrodiagnostic abnormalities that were

associated with higher propulsive forces and stroke frequencies, and more constrained wrist motions.[22, 23] Impink, et al. observed differences in the median nerve response to wheelchair propulsion between symptomatic and asymptomatic individuals with SCI; specifically, a larger CSA at the pisiform in the symptomatic individuals, which was measured with quantitative ultrasound.[24] Using the wick catheter technique, Gellman, et al. observed carpal tunnel pressures of between 180 and 220 mmHg during a weight-relief raise maneuver.[25] Weight-relief and transfer maneuvers are similar in that both require an individual lifting their bodyweight and placing large loads on their upper-extremity. Therefore, it is reasonable that the loads imparted on the hand and wrist during transfers[26] contribute to median neuropathy. Using ultrasound to measure the median nerve's response to transfers would provide evidence that this activity does contribute to the development of CTS.

1.2 ROTATOR CUFF PATHOPHYSIOLOGY

Soft tissue injuries of the shoulder rank among the highest in clinical frequency in the general population.[27] Up to one-third of individuals experience shoulder pain at least once in their lifetimes, with approximately 14.7 new cases occurring in every 1000 patients annually.[28] A variety of treatment options exist for rotator cuff pain and pathology in the able-bodied population. Nonsurgical strategies have been developed to strengthen rotator cuff muscles, restore range of motion, improve endurance, and reduce pain.[29] Strengthening of the rotator cuff muscles helps to control superior migration of the humeral head and reduce impingement. Patients generally report positive outcomes after physical therapy, including improvements in physical function and reductions in pain.[30] Rotator cuff surgery improves general health and

health-related quality of life, yet direct costs can be greater than $10,000.[19, 31] Several promising biological therapies (e.g. growth factors, gene therapy, tissue engineering) are being explored to regenerate damaged tendon tissue; however, these treatments are still being developed.[32] While many treatment modalities do exist, preventing the longitudinal development of rotator cuff injuries can help to ward off the associated detriments in quality of life or independence.

There are several theories to explain the causes of rotator cuff pathology and the associated pain. In general they are multifactorial and involve dysfunction of either the subacromial bursa or muscles and tendons of the rotator cuff, or both.[33] The current model of rotator cuff tendinopathy is a process that describes mechanical and physiological changes in response to overload – loads over the physiological limit.[34, 35] The acute response (i.e. normal tendon overload) is one of adaptation and occurs after training or exercise. In this state, collagen turnover increases and collagen cross-links are formed: non-helical amino- and carboxy-terminal propeptides located at each end of procollagen molecules are cleaved and deposited into the bloodstream[36]; non-helical amino- and carboxy-terminal cross-linked telopeptides of type I collagen aid in cross-linking of collagen molecules and linking to other structures in the matrix.[37, 38] What results is a tendon with greater fiber cross-sectional area (CSA), collagen composition, and overall stiffness that can withstand greater loads before failing.[39-46]

When applied loads exceed the physiological capacity of the rotator cuff tendons, a typical reaction is one of tendon upregulation. The first stage is referred to as reactive tendinopathy and is observed in an acutely overloaded tendon. Pain and swelling are present along with upregulation of vascular endothelial growth factor (VEGF), indicating the formation of new blood vessels[33]; infiltration and proliferation of blood vessels in tendon tissue alter mechanical strength of the tendon and may also have a role in the pain experienced in rotator

cuff pathology.[47] Chronic exposure to overload will progress to tendon disrepair and eventually degenerative tendinopathy, which is characterized by areas of acellularity, disorganized matrix, vascularity, and little collagen content. Pain and swelling are present, commonly during and after movement and activity. Pathological changes experienced at this stage are largely irreversible and may lead to rotator cuff tears.[33]

Research has deduced that the development of rotator cuff tendinopathy is caused by both intrinsic and extrinsic factors. In rats, exposure to overuse led to significant degenerative changes of the supraspinatus tendon that mimic those in humans, including increased CSA and decreased maximum stress and elastic modulus. These responses were accompanied by greater concentrations of angiogenic biomarkers, increased cellularity, rounded cell shapes, and a disorganized collagen matrix.[48-51] In a separate model, overuse also led to systemic dose-dependent increases in inflammatory biomarkers – interleukin-1α (IL-1α), IL-1β, RANTES (Regulated on Activiation, Normal T-cell Expressed and Secreted), and tumor necrosis factor-α (TNF-α). Increases in pain biomarker concentrations were also observed.[52-57] In humans, Carp, *et al.* showed sera concentrations of IL-1β, IL-6, and TNF-α were correlated with severity of upper extremity overuse disorders.[58] This group found moderate to high positive correlations between scores on the upper-body musculoskeletal assessment, an ordinal scale designed to quantify severity of upper-extremity overuse disorders. A separate study found patients with rotator cuff pathology possessed higher concentrations of serum inflammatory (IL-1β, IL-6, IL-8, and IL-10) and angiogenic biomarkers (VEGF, basic fibroblast growth factor, angiogenin) when compared to healthy controls.[59] At their insertion, rotator cuff tendons and the joint capsule form a contiguous structure.[60, 61] It is possible that subclinical joint and tendon inflammation are also interrelated, yet this has not been explored.

Overuse is often accompanied by damage from physical contact with bony structures of the shoulder. Rotator cuff tendons become compressed between the greater tuberosity of the humerus, anterior portion of the acromion process, and coracoacromial ligament.[62] Vertical forces on the humerus are normally suppressed by actions of the rotator cuff.[63] It is likely chronic weakening of these tendons from intrinsic degradation that reduces the ability of the rotator cuff to suppress vertical forces.[64] The humerus migrates superiorly and acromiohumeral distance (AHD) is further reduced; a smaller AHD is commonly observed in patients with signs and symptoms of rotator cuff pathology and implicated in its etiology.[62] Rat models of tendinopathy revealed the combination of compression and overuse induced the greatest degenerative changes, compared to only compression or overuse.[49, 65]

In wheelchair users with SCI, the contribution of degeneration from intrinsic and extrinsic factors has not thoroughly been explored. The present study seeks to investigate intrinsic factors to degeneration; that is, the chemical state of the tendon. However, the interplay between intrinsic and extrinsic factors is complex and both processes are interwoven. As a result of its complexity, authors have only been able to postulate about the order by which the degenerative process occurs.[34] As it relates to wheelchair users, many of whom are chronically in a state of overuse, the process becomes even more complex. During many activities of daily living – including propulsion and transfers – the rotator cuff is highly active.[66-68] These activities are load-bearing and repetitive; thus, rotator cuff tendons are prone to both fatigue and acute effects of overuse. Further, the awkward upper-extremity positions required to perform these activities facilitate a reduced subacromial space. This can initiate external degenerative processes of rotator cuff tendons via friction between adjacent tissues. To add to its complexity, individuals in this population do not have the opportunity to rest and reverse the effects of degeneration.

What follows with respect to rotator cuff tendons is a reduced capacity to withstand the repetitive loading imparted by wheelchair activities. Tendons weaken due to chronic inflammation and tendon weakening, initiating contact with surrounding bony structures, and commencing a degenerative positive-feedback loop.

The design of the present study does not allow the direct investigation of the exact contribution of extrinsic factors to chemical changes that will be observed. However, it does allow investigation into the acute effects of both. This provides a starting point for future investigations into how the combination of extrinsic and intrinsic factors affects tendon health in human populations.

1.3 MICRODIALYSIS TO MEASURE JOINT AND SOFT TISSUE PATHOLOGY

The microdialysis technique offers the unique ability to collect information about the *in vivo* biochemical state of a localized area. The technique involves inserting a catheter with a semi-permeable membrane into the interstitial space of the anatomical location of interest. Through passive diffusion, molecules of low molecular-weight (e.g. cytokines including Interleukins) filter through the membrane and collect in the fluid travelling through the catheter. This fluid is isotonically-matched to extracellular fluid, commonly a Ringer's acetate solution. Thus, samples should reflect the *in vivo* chemical state of the extracellular fluid and provide information about inflammatory activity in that area.[69, 70]

Investigations using microdialysis have yielded information about local inflammatory changes in load-bearing tendons during exercise. Changes in metalloproteinases-2 and -9 (MMP-2 and -9) reflect changes in ECM turnover and have been observed in the Achilles tendon of

healthy volunteers after an exercise bout.[71] Differences in collagen synthesis and degradation in response to eccentric exercise were found between participants with and without Achilles tendinopathy; those with injuries showed an increase in synthesis, whereas those without showed no changes.[43] Also enhanced are vasodilatory mediators in interstitial space around tendons.[72] Another group utilized microdialysis to measure the inflammatory response to exercise in the knee joints of women with osteoarthritis. Catheters were placed intra-articularly and adjacent to the synovial tissue. Increases in IL-10 were observed in the pathological joints that were not observed in joints without pathology.[73]

As previously stated, the localized nature of this technique allows collection of information that otherwise may not be apparent. For example, investigators observed increases in metabolic factors in painful Achilles, patellar, and extensor carpi radialis brevis tendons – namely glutamate and lactate[74]; these increases were often accompanied by an absence of inflammatory factors[75-77], implying tendon pain is not always mediated by inflammation. These observations may not be present in sera, nor would the differences in vasodilatory[78] and inflammatory[79] mediators between muscle and peritendinous tissue be apparent. Previous groups have used this technique to investigate chemical changes in painful tendons in response to therapy. Results of these studies indicate improvements in pain are less related to reductions in inflammation[77] or collagen turnover[43] and more so to reductions in metabolic factors.

1.4 WHEELCHAIR TRANSFER ERGONOMICS

Wheelchair transfer tasks place high compressive loads on tendons of the shoulder and are emphasized in the etiology of shoulder pain and tendinopathy [11, 26, 80-83]. People with SCI have

identified transfers as an activity that generates the highest levels of pain with respect to other activities of daily living.[6, 84] Approximately 15 to 20 transfers are performed daily.[12, 85] Any decrement in upper limb strength can greatly diminish the ability to independently transfer and lead an active lifestyle.

Transfer technique is largely dependent upon personal characteristics as well as environmental factors.[26] Individuals with SCI who have limited function of their lower extremities often perform sitting pivot transfers. The transfer movement can grossly be divided into three phases: preparation, lift, and descent. First, users will typically approach the target surface from the side, moving the chair as close as possible to the surface. The individual would then scoot their buttocks forward and place their feet in a stable position on the floor or footplate.[26] The leading arm (on the target surface) is generally flexed and abducted at the shoulder prior to lifting while the trailing arm (on the initial surface) is neutral or adducted; both elbows are slightly flexed at the elbow and both hands in extreme extension.[80]

They then lift their body off of the chair using the muscles in their arms and use their feet as a fulcrum to pivot their body and descend onto the surface.[66, 83, 86] During the lift phase the majority of body weight is supported by the upper extremities. Large vertical forces are felt at the shoulder of the trailing arm, which moves into flexion and abduction as the individual transfers their trunk to the other surface. At this point vertical forces diminish in the trailing arm and are shifted to the leading arm which is adducted and in a neutral flexed/extended position. At the end of the lift phase a large reaction force is observed under the buttocks as the individual lands on the target surface.[81] Transfer biomechanics can differ depending on physical characteristics of the individual and environment, especially the height of the target surface.[81]

Evidence suggests certain techniques can be protective of soft tissues in the shoulder, while improper technique can increase the risk of damage. Individuals who performed the "head-hips" technique experienced lesser forces on the trailing arm and greater trunk torsional velocity.[86] The "head-hips" maneuver involves the individual flexing their trunk then moving their pelvis onto the target in a direction opposite of their head. Trunk flexion reduces the distance between shoulders and buttocks, which may reduce activity of the rotator cuff and prevent impingement.[87] Extreme shoulder flexion, extension, internal rotation, and abduction can decrease subacromial space and cause impingement[62]; large vertical forces placed on the upper extremities in this position can compress and damage rotator cuff tendons. Placing the hands closer to the body allows upper extremity muscles to carry more of the load and limits shoulder movement. Utilizing a handgrip can help to stabilize the upper extremity, allowing for a more controlled transfer that reduces stress on the shoulder, elbow, and wrist[88] Placing the feet on the floor absorbs upwards of 30% of bodyweight, ultimately reducing shoulder moments.[88] Research suggests a slower, smoother, and more controlled transfer limits vertical forces on the upper extremities.[89] The aforementioned techniques have been incorporated into the Transfer Assessment Instrument (TAI), an objective measure of transfer quality that can be used as a reference when training individuals to transfer.[90, 91] Work by Tsai, et al. has shown that use of TAI techniques can reduce joint loading[88], and that transfer training using the TAI as a framework can improve transfer biomechanics.[92]

1.5 WHEELCHAIR PROPULSION ERGONOMICS

Wheelchair propulsion has long been indicated as a causative factor in the development of shoulder pain and pathology [11, 15]. Propulsion is a variable and complex motion that is divided into two phases, push and recovery. During the push phase, the shoulder goes from an extended to flexed position and experiences decreased abduction and internal rotation.[93, 94] The elbow is moved from extension into flexion and the handrim is "pulled" in the sagittal plane; the individual then extends their elbow and "pushes" the handrim until release. Active muscles that counterbalance the large external moments imparted on the shoulder from the handrim are those that transfer force from the humerus to the trunk: anterior deltoid, pectoralis major, long head of the biceps, serratus anterior, supraspinatus, and infraspinatus.[68, 95, 96] During the recovery phase, the shoulder is extended and the arm is brought back to its starting position. Fewer muscles are involved in the recovery phase: primarily the supraspinatus, subscapularis, medial and posterior deltoids, and middle trapezius.[68, 96] Rotator cuff tendinopathy in this population could be related to weakening of the supraspinatus tendon from constant loading during both phases of propulsion.

Repetitive, load-bearing forces and moments are applied to the handrim during propulsion.[94] Tangential forces are aligned with the movement and are responsible for moving the chair forward. Radial and axial forces act perpendicularly to tangential forces and act to keep friction between the hand and handrim.[97, 98] Forces felt at the shoulder are typically higher than those felt at the elbow or wrist.[97] The force necessary to push the wheelchair can be affected by a number of things, including speed, injury level, incline, surface resistance, tire pressure, axle position, and weight.[98-105] The latter four characteristics affect tire rolling resistance, optimization of which can help attenuate the development of shoulder pain or pathology.[106]

The repetitive movements associated with propulsion are believed to be partly responsible for the accumulation of shoulder pain and pathology in wheelchair users. Mercer, *et al.* found wheelchair users who experienced greater shoulder joint forces exhibited more physical examination and radiological signs of shoulder pathology.[107] Propulsion patterns can affect development of upper extremity repetitive strain injuries; specifically, those who propelled in a semi-circular motion tended to spend more time on the handrim in push phase and make fewer strokes.[108, 109] Demographic factors can have an influence over development of shoulder pain and pathology. Collinger, et al. [110] used quantitative ultrasound (QUS) to show subjects who were older, heavier, and had used their wheelchairs for longer also possessed signs of tendon degeneration. The same group found that duration of wheelchair use, degree of baseline shoulder pathology influenced changes in tendon appearance after wheelchair propulsion that indicated acute inflammation.[111] Resultant forces and stroke frequencies also influenced the QUS responses[111], and have previously been associated with median neuropathy.[22] From these studies it was hypothesized higher propulsive forces and stroke frequency will contribute to the cytokine response to propulsion.

1.6 CONCLUSION

Repetitive joint loading during wheelchair propulsion and transfers are the probable culprit behind the high rates of soft-tissue pathology observed in wheelchair users with SCI. Previous investigators have found that propulsion technique affects the ultrasonographic response to intense wheelchair propulsion. It is also possible that technique influences the response to wheelchair transfers, and that the use of more ergonomic techniques can delay the progression of

pathology. It is likely that these activities cause an acute inflammatory response that occurs on a molecular level and manifests as tendinopathy after continued exposure; however, this remains to be tested. The purpose of the following studies is to better understand how wheelchair activities contribute to upper-extremity pathology by investigating ultrasonographic responses of the median nerve and shoulder tendons to transfers; furthermore, by establishing a connection between activity-dependent responses in inflammatory cytokines and ultrasonographic markers of shoulder tendinopathy.

2.0 RELATIONSHIP BETWEEN TRANSFER QUALITY AND ULTRASOUND MARKERS FOR SHOULDER SOFT TISSUE PATHOLOGY

2.1 ABSTRACT

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Objectives: To evaluate how transfer technique and subject characteristics relate to ultrasound measures of shoulder soft tissue pathology, and self-reported shoulder pain during transfers in a sample of wheelchair users with spinal cord injury (SCI).

Design: Cross-sectional observational study.

Setting: Research laboratory, national and local veterans' wheelchair sporting events.

Participants: A convenience sample of 76 wheelchair users with non-progressive SCI. Participants were over 18 years old, greater than one year post-injury, and could complete repeated independent wheelchair transfers without the use of their leg muscles.

Interventions: N/A

Main Outcomes: Transfer pain items from the Wheelchair User's Shoulder Pain Index; Transfer technique assessed using the Transfer Assessment Instrument (TAI); shoulder pathology markers examined using the Ultrasound Shoulder Pathology Rating Scale (USPRS).

Results: Better transfer technique (higher TAI) correlated with less global shoulder pathology (partial-η^2=.061, p<.10), less supraspinatus pathology (partial-η^2=.065, p<.05), and less pain during transfers (partial-η^2=.068, p<.05). Greater age was the strongest predictor of greater pathology (USPRS total: partial-η^2=.222, supraspinatus grade: partial-η^2=.177, p<.01). An interaction between technique and weight was found (p<.10): participants with lower bodyweights showed a decrease in pathology markers with better transfer technique (low-weight: R^2=0.422, p<.05; middle-weight: R^2=0.200, p<.01), while those with higher weight showed little change with technique (R^2=0.018, p>.05).

Conclusions: Participants with better transfer technique exhibited less shoulder pathology and reported less pain during transfers. The relationship between technique and pathology was strongest in lower-weight participants. While causation cannot be proven due to study design, it is possible that using a better transfer technique and optimizing bodyweight could reduce the incidence of shoulder pathology and pain.

2.2 INTRODUCTION

Wheelchair users with spinal cord injuries (SCI) rely on their upper limbs to perform most activities of daily living. Thus, they are susceptible to shoulder pain and injury[16] that can negatively affect quality of life and participation in activities.[9] Individual characteristics such as age, injury level, injury duration, bodyweight, and gender are also associated with shoulder

pain.[16, 84, 107, 110, 112-117] Performance of wheelchair activities, such as transfers and propulsion, is critical for maintaining independence and mobility but has been implicated as an additional contributing factor.[16] Successful transfer performance makes it possible for users to freely move in and out of their wheelchair and onto other surfaces. Unfortunately, transfers also expose users' shoulders to high loads, often in positions of impingement.[26] Transfers are reported by people with SCI as one of the most painful activities to perform.[84] If a wheelchair user is unable to transfer because of pain or injury, his or her quality of life can be compromised.[7]

The demand placed on the shoulders during transfers may also culminate in rotator cuff injury or pathology. Ultrasound studies have revealed high frequencies of shoulder pathology in people with SCI.[110, 112, 118] Among the soft tissues of the shoulder, the literature suggests the supraspinatus tendon is the most prevalent site of pathology.[112, 119, 120] The supraspinatus is responsible for aiding in suppression of humeral superior migration during load-bearing activities and is active throughout all phases of a transfer.[26] As a result, the tendon is susceptible to chronic degeneration which can manifest structural weakness, potentially culminating in a tear.[33]

Transfer technique is likely dependent on training, level of injury, upper limb strength, anthropometrics, wheelchair setup, and the immediate environment. Evidence suggests that different transfer skills and environments influence upper limb biomechanics[26] and that the use of more ergonomic techniques may help to prevent pain and pathology. The Transfer Assessment Instrument (TAI) is an objective tool that was designed to quantify transfer ability by assessing a user's technique.[90, 91] Utilizing skills highlighted by the TAI can reduce loading on the shoulder in different populations of wheelchair users, including people with SCI.[88] However, the relationship between transfer technique and shoulder pain/pathology has not been evaluated. As

well, transfer technique may offset the deleterious effects of subject characteristics such as bodyweight; this remains to be tested.

The purpose of this study was to investigate if transfer technique, measured using the TAI,[90, 91] correlates with ultrasound measures of shoulder pathology and subjective measures of shoulder pain. A secondary objective was to examine whether subject characteristics relate to shoulder pathology and pain. It was hypothesized that wheelchair users with SCI who transferred using better technique (higher TAI scores) would exhibit less shoulder pathology and report less pain.

2.3 METHODS

2.3.1 Subjects

Wheelchair users with SCI were recruited for this cross-sectional study using flyers and research registries, at the 2012 and 2013 National Veterans Wheelchair Games (Richmond, VA; Tampa, FL), and at the 2014 Paralyzed Veterans of America Buckeye Games (Geneva, OH). Participants were included if they had a non-progressive SCI requiring use of a manual wheelchair for the majority of mobility (>40 hours/week), could independently transfer to-and-from a surface within 30 seconds (with or without the use of assistive equipment), had used a wheelchair for over one year, and were older than 18 years of age. Participants were excluded if they reported using their leg muscles to aid in transfers, upper extremity pain or injury that limited their ability to transfer, or current or recent history of pressure sores or cardiopulmonary problems that could

be exacerbated by transfers. Institutional Review Board approval was obtained prior to study commencement, and all individuals provided written informed consent before participation.

An a priori power analysis on pilot data of the correlation between TAI and Ultrasound Shoulder Pathology Rating Scale (USPRS) scores (N=6; R^2=0.185) found 70 subjects would allow us to achieve over 80% power to detect statistical significance, assuming a two-tailed hypothesis with five predictors and α=0.05.

2.3.2 Demographics, Pain, and Pathology

Participants first completed a general questionnaire to collect demographic information (age, date of injury, injury level, gender); these factors have been identified as potential risk factors for shoulder pain and pathology.[16, 84, 107, 110, 112, 114-117] Injury duration was calculated by subtracting the injury date from the date of their participation. Their bodyweight was measured by subtracting their wheelchair weight from the combined weight of the user and the chair, acquired using a wheelchair scale (Befour, Inc., Saukville, WI, USA).

Participants then completed the Wheelchair User's Shoulder Pain Index (WUSPI), a 15-item questionnaire that employs the use of visual analog scales to quantify shoulder pain experienced during a variety of daily activities.[121, 122] WUSPI scores can range from 0 (no pain) to 150 (maximum pain). The three questions regarding pain during transfers (e.g. from a bed to a wheelchair, wheelchair to a car, and wheelchair to the tub/shower) were analyzed for the present study. The total WUSPI has high test-retest reliability (ICC: 0.99, p<.0001), as well as the three transfer items (ICCs between 0.97 and 0.99, p<.0001) when used by people who use wheelchairs for the majority of mobility.[121] It has been validated by correlating index scores with shoulder range of motion measurements.[121]

A physician performed an upper extremity motor exam using the International Standards for Neurological Classification of Spinal Cord Injury,[123] to calculate upper extremity AIS motor score. Strength in muscles innervated by C5-T1 spinal nerves are assigned a score between 0 and 5 (total of 25 per limb), with higher scores indicating greater strength. Sensory information was not collected as part of this exam.

Participants underwent clinical ultrasound examinations by one of two physiatrists with extensive experience in musculoskeletal ultrasound who were blinded to demographic and pain questionnaire results. While inter-rater reliability of the USPRS has not been determined, the two physicians completing the exam designed the measure and have tested hundreds of participants.[112] The USPRS,[110, 112] a 23-point scale designed to assess shoulder pathology by assigning numerical scores to ultrasound findings, was used to grade shoulder pathology. The USPRS has been validated against demographic risk factors and physical examination tests for pathology.[112] Higher scores indicate more pathology. Static tests included evaluation of biceps and supraspinatus appearance; smoothness of the humeral greater tuberosity cortical surface; presence or absence of joint effusion; and bursal thickness. Dynamic tests evaluated the degree of soft tissue impingement during external (supraspinatus tendon) and internal rotation (subscapularis/biceps tendons). Scoring criteria are given more detail in Table 1. The USPRS was only performed on the non-dominant shoulder to control for the effects of handedness. Biomechanical differences have been noted between trailing and non-trailing arms[124]; however, study design ensured the non-dominant arm acted as both trailing and leading, accounting for these differences.

Table 1. Frequencies of subject ultrasound shoulder pathology grades from the Ultrasound Shoulder Pathology Rating Scale.

	Item Grade						
USPRS Item	0	1	2	3	4	5	6
Biceps Tendinopathy*	26 (37.7)	33 (47.8)	5 (7.2)	1 (1.5)	1 (1.5)	0 (0.0)	3 (4.3)
Supraspinatus Tendinopathy*	7 (10.1)	21 (30.4)	5 (7.2)	16 (23.2)	15 (21.7)	4 (5.8)	1 (1.5)
Subscapularis Impingement†	43 (62.3)	21 (30.4)	5 (7.2)	0 (0.0)	-	-	-
Supraspinatus Impingement†	25 (36.2)	29 (42.0)	11 (15.9)	4 (5.8)	-	-	-
Cortical Irregularity‡	9 (13.0)	36 (52.2)	14 (20.3)	10 (14.5)	-	-	-
Joint Effusion§	63 (91.3)	6 (8.7)	-	-	-	-	-
Bursal Thickness‖	55 (79.7)	14 (20.3)	-	-	-	-	-

USPRS = Ultrasound shoulder pathology rating scale
* 0 = normal, 1 = mild tendinosis, 2 = severe tendinosis, 3 = intrasubstance abnormality, 4 = partial-thickness tear, 5 = focal full-thickness tear, 6 = massive full-thickness tear.
† 0 = no impingement, 1 = mild impingement, 2 = moderate impingement, and 3 = marked impingement.
‡ 0 = smooth hyperechoic cortical surface, 1 = mild cortical irregularity or hypoechoic surface, 2 = moderate cortical irregularity, 3 = marked cortical irregularity or pitting.
§ 0 = absent, 1 = present.
‖ 0 = normal, 1 = >2mm thick

2.3.3 Transfer Assessment Instrument

After completion of the physical examinations, one of four physical therapists, who were trained to evaluate transfers, assessed participants' transfer technique using the TAI.[90, 91] The TAI is highly reliable, with interrater and intrarater ICCs ranging from .81-.85 and .74-.88, respectively.[90] The therapists were blinded to demographic and pain questionnaires, and ultrasound examination results. The TAI quantitatively measures the safety and quality of transfers in wheelchair users, and has been biomechanically validated.[88, 91] The scale consists of

two parts. However, because scores from the two parts are highly correlated (Pearson's r=.749, p<.001), and part 2 uses items from part 1,[90] only part 1 items were used in this study. Part 1 is comprised of 15 items that identify specific skills that can reduce upper-extremity loading. A rater observes one or more transfers while identifying which skills are performed. Items assess wheelchair position, feet placement, flight movement, proper utilization of handgrips, landing ability, and shoulder position.[90, 91] Depending on whether or not individuals complete the skill a "yes" (1 point) or "no" (0 points) is assigned; a "N/A" is given if the skill does not apply to the individual's situation. Individual skill scores are summed, multiplied by 10, and then divided by the number of applicable items to determine a total score.

2.3.4 Statistical Analysis

Significance was set a priori to p<.05, with trends reported as p<.10. All analyses were run using SPSS 22 (SPSS, Inc., Chicago, IL). Descriptive statistics were calculated for demographic, pain, and pathology outcomes, including means and standard deviations, medians, and ranges. Data and residuals were examined for normality using the Shapiro-Wilk test. Graphical techniques were used to detect presence of outliers, heteroscedasticity, multicollinearity, and independence and distribution of residuals. Pearson's r and Kendall's tau-b were calculated to test for multicollinearity of continuous and discontinuous predictor and outcome variables, respectively.

Multiple linear-regression models were built to test how TAI part 1 total score (TAI-1) was related to USPRS and WUSPI scores, when controlling for potential risk factors for pain and pathology (injury level referenced to paraplegia, gender referenced to males, injury duration, bodyweight, age). A multivariate multiple linear-regression model was built using general linear model procedures. Dependent variables were USPRS total score, and supraspinatus tendinopathy

subscale grade; the USPRS examines other markers that are indicative of supraspinatus pathology (e.g. cortical surface irregularity and glenohumeral joint effusion[125]), so this sub-analysis may yield additional information. Independent variables included the aforementioned subject characteristics, TAI-1 score, and the weight/TAI-1 interaction. A univariate multiple linear-regression model was then built to test whether subject characteristics and TAI-1 score were related to transfer-related WUSPI score (dependent variable).

In order to graphically interpret the interaction, participants were placed in low-, middle-, and high-weight groups. Those with bodyweights less than 1 standard deviation (SD) from the mean were placed in the low-weight group. Those within 1 SD of the mean were in the middle-weight group, and those with bodyweights greater than 1 SD above the mean were placed in the high-weight group. One-way analysis of variance tested mean differences in TAI-1 score, injury duration, and age between weight groups.

2.4 RESULTS

2.4.1 Participants

Seventy-six wheelchair users with SCI were recruited for this study. Demographic information is presented in Table 2. Sixty-nine were included in the final analysis: six were found not to meet inclusion criteria during informed consent or testing (two had a progressive spinal cord disease, four used their leg muscles for transferring) and one did not complete the physical examination protocols.

Table 2. Subject demographic information, including shoulder pathology and transfer technique.

	Mean (SD)	Median	Range
Age	44.3 (12.6)	47	19 – 73
Years Since Injury	15.9 (11.1)	14.8	1.5 – 44.2
Bodyweight	84.2 (19.2)	80.7	50.9 – 135.4
TAI Score	6.96 (1.63)	7.31	3.08 – 10.0
WUSPI Transfer Score	2.3 (4.5)	0.0	0.0 – 21.2
USPRS Score	6.4 (4.0)	6	0 – 18
Injury Level	19 Tetraplegia*, 50 Paraplegia†		
Race/Ethnicity	30 Black, 35 White, 2 Hispanic, 2 Multiracial		
Gender	60 Male, 9 Female		

TAI = Transfer Assessment Instrument
USPRS = Ultrasound Shoulder Pathology Rating Scale
WUSPI = Wheelchair User's Shoulder Pathology Rating Scale
N = 69
*Median upper extremity motor score: 35
†Median upper extremity motor score: 50

2.4.2 Transfer Technique, Pain, and Pathology

Descriptive statistics for WUSPI and USPRS scores are presented in Table 2, and USPRS item frequencies are in Table 1. The multivariate analysis (Table 3) revealed inverse relationships between TAI score and USPRS score ($p<.05$), and supraspinatus tendinopathy score ($p<.05$). Univariate analysis found an inverse relationship between TAI score and WUSPI pain-during-transfers score (Table 4; $p<.05$). Age accounted for the most variability in USPRS total score and supraspinatus tendinopathy (Table 3, $p<.01$). No other relationships were found between TAI scores, subject characteristics, and USPRS or pain scores.

Table 3. Univariate multiple linear-regression model evaluating correlations of transfer technique (Transfer Assessment Instrument score) and subject characteristics with shoulder pain during transfers (Wheelchair User's Shoulder Pain Index item score).

Predictor Variables	*B*	*B SE*	*95% CI*	*Partial* η^2	*p*
Intercept	11.045	5.764	-0.476, 22.567	.056	.060
Gender	-0.093	1.670	-3.431, 3.246	.000	.956
UL Motor Score*	-0.161	0.070	-0.301, -0.020	.078	.026
Age	0.036	0.051	-0.065, 0.138	.008	.478
Injury Duration	0.032	0.055	-0.077, 0.141	.005	.562
Weight	0.019	0.030	-0.041, 0.078	.006	.534
TAI*	-0.724	0.340	-1.403, -0.044	.068	.037

TAI = Transfer Assessment Instrument

Model trended toward significance, $p < .10$, $R^2 = .178$, Adj $R^2 = .098$, $F(6,62) = 2.238$

* Significant predictor ($p < .05$)

Table 4. Multivariate multiple linear-regression model evaluating correlations of subject characteristics, Transfer Assessment Instrument (TAI) scores, and the weight/TAI interaction with Ultrasound Shoulder Pathology Rating Scale scores and supraspinatus tendinopathy grade.

Predictor Variables	*B*	*B SE*	*95% CI*	*Partial* η^2	*p*
	USPRS Total Score*				
Intercept	0.796	4.364	-7.931, 9.522	.001	.856
Gender	-0.708	1.234	-3.176, 1.760	.005	.568
UL Motor Score	0.015	0.056	-0.097, 0.126	.001	.795
Age‡	0.161	0.039	0.084, 0.239	.222	<.001
Injury Duration	0.015	0.041	-0.067, 0.098	.002	.708
Weight	0.009	0.022	-0.035, 0.053	.003	.679
TAI§	-0.500	0.251	-1.002, 0.003	.061	.051
Weight/TAI Interaction§	0.023	0.013	-0.004, 0.050	.045	.094
	Supraspinatus Tendinopathy Grade†				
Intercept	1.656	1.823	-1.989, 5.302	.013	.367
Gender	-0.240	0.516	-1.271, 0.791	.004	.644
UL Motor Score	-0.003	0.023	-0.049, 0.044	.000	.905
Age‡	0.059	0.016	0.026, 0.091	.177	.001
Injury Duration	-0.008	0.018	-0.042, 0.026	.004	.638
Weight	-0.002	0.009	-0.021, 0.016	.001	.800
TAI‡	-0.216	0.104	-0.426, -0.006	.065	.044
Weight/TAI Interaction	0.008	0.005	-0.003, 0.019	.033	.156

TAI = Transfer Assessment Instrument
USPRS = Ultrasound Shoulder Pathology Rating Scale
* Model significant at $p < .001$, $R^2 = .454$ Adj $R^2 = .392$, $F(7,61) = 7.257$
† Model significant at $p < .001$, $R^2 = .372$, Adj $R^2 = .300$, $F(7,61) = 5.154$
‡ Significant predictor ($p < .05$)
§ Predictor trended toward significance ($.05 \leq p < .10$)

There was no relationship between weight and USPRS score. Because this was counter to what was expected based on the literature,[22, 107, 110] a secondary analysis was performed to examine whether the effects of weight on USPRS scores were mediated by TAI-1 scores. The interaction between weight and TAI scores was found to influence USPRS scores (p<.10), yet not supraspinatus tendinopathy score. Investigation of the interaction graph (Figure 1) revealed inverse, linear relationships between TAI and USPRS in the low-weight ($R^2 = 0.422$, Adj. $R^2 =$

0.364, p<.05) and middle-weight (R^2 = 0.200, Adj. R^2 = 0.182, p<.01) groups; the strongest was observed in the low-weight group. Little change in USPRS was observed with TAI score in the high-weight group (R^2 = 0.018, p>.05). No differences in TAI score existed between weight groups (p>.05).

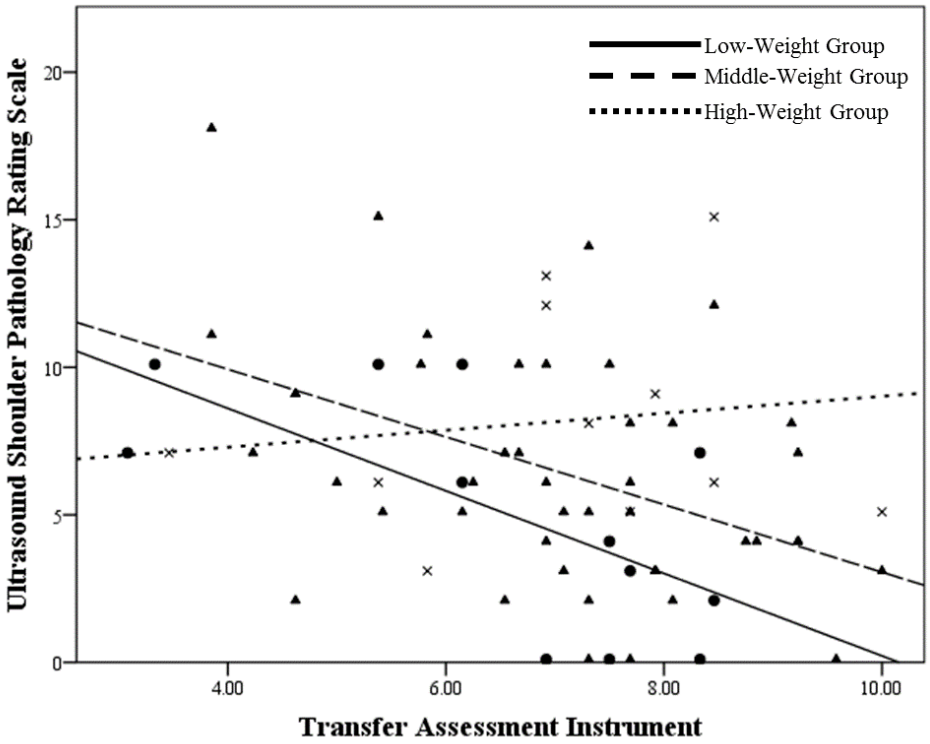

Figure 1. Interaction effect of bodyweight and Transfer Assessment Instrument (TAI) scores on Ultrasound Shoulder Pathology Rating Scale (USPRS) scores. The figure shows that USPRS score declined with increasing TAI score in the low-weight group, R^2 = 0.422, p<.05 (circles, N = 12) and middle-weight group, R^2 = 0.200, p<.01 (triangles, N = 46). In the heaviest group, there was no interaction between the USPRS and TAI scores R^2 = 0.018, p>.05 ("x" symbols, N = 11).

2.5 DISCUSSION

Shoulder pain and pathology are significant problems in people with SCI, negatively affecting independence and ultimately quality of life.[85, 116] Surgical and conservative treatments for rotator cuff pathology are not always successful[84, 126]; thus, alteration of modifiable factors such as transfer technique through intervention may be vital in preventing such injuries. The present study found participants with better transfer technique, measured using the TAI, exhibited less shoulder pathology and self-reported shoulder pain. In addition, relationships between transfer technique and shoulder pain and pathology were found to be mediated by bodyweight.

Consistent with previous literature,[110, 112] some degree of supraspinatus tendinopathy was observed in most individuals (Table 1). In the current study, higher grades of tendinopathy were observed in participants with worse transfer quality. The TAI gives points for placing the shoulder in positions of external rotation and decreased elevation.[26] These skills may protect the tendon by limiting its involvement during the transfer and its exposure to harmful contact with shoulder bony structures. It is also possible that the body positions and wheelchair setup prescribed by the TAI can prevent rotator cuff fatigue, potentially maintaining a larger subacromial space.[127] Further kinetic and electromyographical testing may reveal more information about why these relationships were observed.

Previous studies have reported findings that increased bodyweight is associated with shoulder pathology.[107, 110, 112] However, no such relationship was present in the current sample. This prompted the investigation of a potential interaction effect between transfer technique and bodyweight. When examining the interaction effect (Figure 1, participants with higher bodyweight exhibited similar USPRS scores regardless of their TAI score. There was an inverse linear relationship between transfer technique and pathology in the low- and middle-weight

groups; the strongest relationship was observed in those with the lowest weight. The results also suggest that there may be a weight above which using better technique does not impact tendon health. It is important to note that it is more difficult to obtain a clear image when imaging people who are overweight, which may introduce variability in ultrasound measurements.

Observations made in the present study indicate transfer technique may play a role in pain generation during transfers. Specifically, participants who had higher TAI scores (better technique) reported less pain during transfers. The ergonomic improvements afforded by the TAI may attenuate pain by reducing upper limb loading and shoulder impingement.[88, 90] It is possible that the acute pain caused by performing poor transfers progresses to chronic pathology, as evidenced by ultrasonographic observations. It is not known whether the reductions in pain are clinically-significant; however, considering the importance of transfers in maintaining independence, any decrease in transfer-related pain may improve quality of life.[9]

Decades of SCI research have identified various demographic risk factors for the development of shoulder pain and pathology, including age, injury duration, and injury level.[1, 8, 110, 112, 114-117] When transfer technique was included as a covariate in the present analysis, the only subject characteristic that correlated with pain or pathology was age. Pathology may develop more as a result of age-related factors[33] in combination with how activities such as transfers are performed. Further, better technique may help overcome upper limb strength and mobility limitations experienced by those with higher-level injuries, potentially diminishing shoulder damage.[88] These observations are potentially clinically important because they highlight transfer technique as a modifiable risk factor; that is, an individual can be trained to transfer better at any point after their injury. This training may help to offset injury development associated with subject characteristics that cannot be modified through intervention. However,

longitudinal testing is needed to determine whether TAI-based interventions affect the development of pain or pathology.

2.5.1 Limitations

Based on the cross-sectional design of this study, it is not known whether individuals maintained their transfer technique over time, or if they modified it in response to pain- or pathology-related weakness. A longitudinal design would provide more decisive conclusions about the relationship between transfer technique, pain, and pathology. Many participants were tested at wheelchair sporting events, and may have been more active than the general population of wheelchair users with SCI; this would potentially affect generalizability of the results and statistics of the regression models. However, similar activity levels[128] and upper limb pain and pathology[129, 130] have been reported between wheelchair athletes and non-athletes. Further, participation in the games could indicate more independence which could also impact results. Considering the ordinal nature of the pain and pathology outcome measures, a larger and more heterogenous sample may have yielded more information.

2.6 CONCLUSION

The current study found a relationship between transfer technique, bodyweight, and shoulder pathology. Participants with better transfer technique, measured using the TAI, and less bodyweight were found to exhibit fewer ultrasonographic markers of shoulder pathology. Better transfer technique was correlated with less supraspinatus tendinopathy and shoulder pain during

transfers. Adapting a better transfer technique may help reduce the development of shoulder pain and pathology; however, longitudinal and interventional testing is necessary to confirm this hypothesis.

3.0 ACUTE EFFECTS OF WHEELCHAIR TRANSFERS ON QUANTITATIVE ULTRASOUND MARKERS FOR BICEPS AND SUPRASPINATUS TENDINOPATHY

3.1 ABSTRACT

This chapter has been published in the American Journal of Physical Medicine and Rehabilitation. Full citation: Hogaboom NS, Huang BL, Worobey LA, Koontz AM, Boninger ML. Ultrasonographic markers for biceps and supraspinatus tendon degeneration after repeated wheelchair transfers in people with spinal cord injury. American Journal of Physical Medicine and Rehabilitation, 2016, 95(11), 818-830.

Objective: To investigate how wheelchair transfers influence acute changes in ultrasound markers for biceps and supraspinatus tendon degeneration and to determine how such changes correlate with transfer technique and demographic characteristics.

Design: Participants underwent quantitative ultrasound examinations for markers of biceps and supraspinatus tendon degeneration (tendon width, echogenicity, variance, contrast) before and after a stressful repeated-transfers protocol. The Transfer Assessment Instrument was completed for each participant to identify transfer skills. Linear-regression tested whether demographics and transfer skills correlated with ultrasound measures.

Results: Sixty-two wheelchair users with spinal cord injury were included (39 with paraplegia, 23 with tetraplegia). Biceps tendon width increased after repeated-transfers ($p<.001$). Participants with higher bodyweight experienced greater increases in biceps width post-transfers ($\beta=.109$, $p<.05$). Skills evaluating body position relative to the target surface and safe and stable hand and arm positions affected changes in biceps and supraspinatus width and echogenicity ($p<.05$).

Conclusions: Repeated transfers caused measurable changes in biceps tendon width in a subset of participants. Changes in biceps and supraspinatus ultrasound measures were related to bodyweight and performance of specific transfer skills. Further testing is needed to confirm whether the clinical meaning of the observed relationships and whether using certain transfer skills and reducing bodyweight can attenuate the development of tendinopathy.

Keywords: Spinal Cord Injuries; Wheelchairs; Ultrasonography; Cumulative Trauma Disorders; Tendinopathy

3.2 BACKGROUND

There are over one-quarter of a million individuals in the United States living with a spinal cord injury (SCI).[131] Following a SCI, many individuals must transition to use of a wheelchair. This often entails heavy reliance on their upper-extremities to facilitate mobility and independence. Unfortunately, the anatomy of the shoulder does not fully protect underlying soft tissues from the joint loading that occurs during wheelchair use. Thus, wheelchair users have a risk of developing shoulder pain and injury, which can negatively impact their independence and quality of life.[7]

Wheelchair transfers are a highly-repetitive, load-bearing movement undertaken by people with SCI to maintain independence.[7] They require lifting one's body weight out of the wheelchair and shifting it onto another surface, such as a bathtub or car seat. Unfortunately, this necessary activity can also lead to shoulder pain and pathology.[7, 26] Large vertical forces are placed on both upper extremities while in awkward positions, which can place high stress and strain on shoulder tendons.[26] The resulting overuse initiates a host of degenerative factors that can weaken these tissues and induce pain.[34] Acute degenerative effects of overuse can normally be reversed given proper rest and reductions in loading.[34] However, wheelchair users cannot sufficiently rest without limiting their mobility and independence, and thus their quality of life.[16] As life expectancies continue to rise in this population,[7] it is important to identify methods of curtailing such degeneration and preserving functional mobility.

Tendons of the supraspinatus and long head of the biceps muscles are common sites of pathology in people with SCI;[10, 119, 120, 130] biceps tendinopathy is often present along with pathology of the supraspinatus.[11] Using ultrasound, Brose, et al. observed some degree of supraspinatus and biceps tendinopathy in 100% and 80% of their sample of individuals with SCI, respectively.[112] Common ultrasonographic signs of bicipital and supraspinatus tendinopathy include greater thickness, less echogenicity, and loss of normal fiber structure of the tendon.[132] Quantification of tendon structure and texture provides investigators with a method to objectively describe these characteristics.[133] Previous investigators have used quantitative ultrasound (QUS) techniques to evaluate changes in biceps and supraspinatus tendon appearance after wheelchair propulsion.[111, 134] Van Drongelen observed decreases and increases in biceps tendon echogenicity and thickness, respectively, after a wheelchair sporting event that were

related to playing time.[134] In a study by Collinger, et al., changes in biceps tendon greyscale appearance were affected by injury duration and propulsion biomechanics.[111]

While it is generally understood that transfers contribute to upper limb dysfunction, using certain techniques may be more protective of soft tissues and preventative of pain and pathology.[7, 16, 26] However, the relationship between transfer technique and shoulder health has not been elucidated. Finding such a relationship may help identify certain techniques that can delay or prevent upper limb soft tissue injuries. The present study sought to observe the acute effects of wheelchair transfers on ultrasonographic appearance of shoulder tendons of wheelchair users with SCI. QUS measures of biceps and supraspinatus tendon thickness, echogenicity, greyscale variance, and greyscale contrast were chosen for analysis; these variables describe tendon characteristics that are related to tendinopathy and have been correlated with risk factors for injury in people with SCI.[110, 111] A secondary objective was to examine how demographic factors and transfer technique affected tendon responses to the activity. Repeated transfers were hypothesized to cause acute changes in biceps and supraspinatus tendon appearance, measured using QUS. It was further hypothesized that baseline and changes in QUS would be related to demographic risk factors for injury and transfer technique, as measured by the Transfer Assessment Instrument (TAI).

3.3 METHODS

3.3.1 Participants

Individuals with SCI were included in the study if their injury was non-progressive and occurred over one year prior to testing; they used a wheelchair for the majority of mobility (over 40 hours/week); they could independently transfer to-and-from a surface within 30 seconds with or without equipment; and they were over the age of 18 at the time of testing. They were not included if they self-reported upper extremity pain or injury that inhibited their ability to transfer; active use of their leg muscles while transferring; a history of pressure sores within the prior 3 months; or a history of cardiopulmonary problems that could have been exacerbated by physical activity. Participants were recruited at a research laboratory using fliers and research registries; at the 2012 and 2013 National Veterans Wheelchair Games (Richmond, VA and Tampa, FL, USA); and the 2014 Paralyzed Veterans of America Buckeye Games (Geneva, OH, USA). All participants underwent informed consent prior to commencement of the study, which was approved by the appropriate Institutional Review Boards.

An a priori power analysis found 77 subjects would achieve an 80% power to detect statistical significance. This was based on pilot data of the correlation between TAI scores and tendon width (N=6; R^2=.15), assuming a two-tailed hypothesis with five predictors and an α of 0.05.

3.3.2 Demographics

A demographic questionnaire collected information about age, time since injury, ethnicity/race, injury level, and gender. Participants' weights were measured using a wheelchair scale, by subtracting wheelchair weight from the combined subject and wheelchair weights.

3.3.3 Quantitative Ultrasound

A previously-described QUS protocol[133] was followed to image participants' biceps and supraspinatus tendons. One set of images was collected after demographic information, and before any transfers were completed (baseline images). A second set was collected immediately following the repeated-transfers protocol (post-transfers images). All images were collected on the non-dominant shoulder to control for potential confounding effects of handedness. A single investigator collected all images. These measurements have high reliability when taking serial images of the supraspinatus and biceps tendons, and have been validated against measures of shoulder tendinopathy and pain.[110, 133]

When imaging the biceps tendon, participants were positioned with their non-dominant elbow flexed to 90 degrees, forearm supinated, and wrist resting on the ipsilateral thigh. This position provides an unobstructed image of the tendon with its fibers oriented perpendicularly to the transducer, creating a clear image of collagen fiber structure.[133] The widest part of the tendon was located in the longitudinal view, with the apex of the humeral lesser tuberosity at the edge of the image (Figure 2). A hyperechoic A-shaped steel reference marker was taped to the participants' skin at the distal end of the transducer footprint. This skin-based marker remained in place throughout the activity, limiting variations in probe placement after the baseline image

and thus improving reliability. Crossbars on the marker create a distinct interference pattern at the top of the captured image (Figure 2). A 2-centimeter-wide region of interest (ROI) is determined 1.5 centimeters relative to the center of the interference pattern, and is considered a representative sample of the tendon for analysis. Top and bottom borders of the ROI are defined using the top and bottom edges of the tendon on the image (Figure 2).[133]

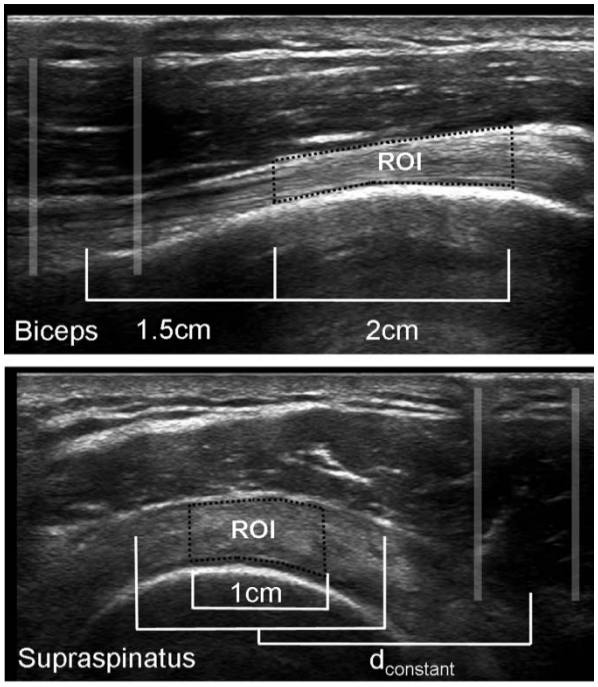

Figure 2. Biceps and supraspinatus quantitative ultrasound images. The region of interest (ROI) is a constant distance ($d_{constant}$) from the center of the hyperechoic interference patterns created by the skin-based marker (vertical grey bars) and is bounded above and below by the top and bottom edges of the tendon. The apex of the lesser tuberosity is located on the right side of the image when imaging the biceps tendon. Adapted from Collinger et al., 2009.[133]

To image the supraspinatus tendon, participants placed their non-dominant arm in a modified Crass position[135]; specifically, with the shoulder extended and externally rotated, and the elbow flexed so their hand was on their lower back (or a corresponding location on the back

of the wheelchair). This position exposes the supraspinatus tendon from under the acromion to accommodate better viewing, and can optimize repeatability of measurements.[133, 135] The widest part of the tendon was located in transverse view (Figure 2), at which point a second steel reference marker was attached to the skin at the proximal end of the transducer footprint.[133]

Follow-up QUS was completed after the repeated-transfers protocol. As the reference marker remained on the subject during transfers, marker placement did not need to be repeated. Imaging was completed following the same methods described above for baseline testing. Imaging parameters (e.g. gain, depth, focus) were held constant between subjects and time points for comparison.[133]

3.3.4 Image Analysis

Tendon characteristics can be quantified by computing the greyscale value of pixels within the tendon.[133, 136, 137] Healthier tendons possess well-organized bundles of fibers in parallel alignment, a higher percentage of collagen, and reduced infiltration of blood vessels and fluid.[33] Imaged with ultrasound, these tendons are expected to have a highly aligned fibrillar pattern, appearing more heterogenous and bright with less swelling.[110, 132] The four QUS variables that describe these characteristics and were used in this study include mean width, mean echogenicity, greyscale variance, and greyscale contrast.[133] Tendon width was defined as the average distance between top and bottom borders of the ROI. Echogenicity and variance were defined as average pixel intensity and distribution within the entire ROI, respectively. Contrast measured variations in pixel intensity in a perpendicular direction, providing information about fiber alignment. A healthier tendon would exhibit greater echogenicity, variance and contrast, and lesser width.[110]

Each image was uploaded into a custom MATLAB (MathWorks, Inc., Natick, MA, USA) program that blinds the evaluator to subject ID and image collection time point. The evaluator defined the ROI as the center point between interference patterns (Figure 2). The upper and lower boundaries of the ROI were traced; the average distance between points on the *y*-axis is determines tendon width. A histogram is created representing the spread of greyscale values of each pixel within ROI, ranging from 0 (darkest) to 255 (brightest); echogenicity describes the mean greyscale value, and variance the heterogeneity of the histogram. Contrast describes differences in intensity between neighboring pixels and is calculated from a co-occurrence matrix derived from the ROI.[133]

3.3.5 Transfer Assessment Instrument

After completing baseline examinations, a physical therapist graded four transfers using the TAI.[90, 91] Two transfers were to-and-from an adjustable mat table positioned at a height level to the user's wheelchair seat. The next were to-and-from a mat positioned 2 inches higher. All transfers were performed using the participants' own wheelchairs.

The TAI is a two-part assessment that provides objective and quantifiable information regarding the safety and technique of wheelchair users' transfers. Examples include appropriate positioning of the individual and the wheelchair during each step of the transfer, and control and smoothness of motion during the transfer. The TAI was designed using clinical practice guidelines,[16] reviews of the literature, and current best practices for transfer training.[90, 91] It has been proven reliable and was recently biomechanically validated.[88, 90, 91] Part 1 breaks the transfer down into 15 skills or "items" (Table 5). Upon examination of the transfer, each item is assigned either a "Yes" (1 point) or "No" (0 points) depending on whether or not they perform

the skill correctly, or a “not applicable” (N/A) if that skill does not apply to their situation. Points are summed, multiplied by 10, and then divided by the number of applicable items to calculate total part 1 score. The twelve items in part 2 are scored on a 5-point Likert scale and completed after all transfers have been performed. This portion summarizes how well the participant performed different skills, and use part 1 scores in their grading. Item scores are summed, multiplied by 2.5 and divided by the number of applicable items. Total part 2 scores lie on a scale from 0 to 10, with 10 indicating the individual correctly performed all applicable skills. As part 1 identifies specific skills that can be targeted with intervention, and both parts were highly correlated (r=.713, p<.001), part 2 was not analyzed.

3.3.6 Repeated-Transfers Protocol

Once TAI scoring was completed on the four initial transfers described above, the repeated-transfers protocol began. Participants performed 18 transfers to-and-from a height-adjustable mat, based on the estimated of number of transfers performed per day by people with SCI.[85] Movement from one surface to the other (e.g. wheelchair to mat) was considered one transfer. The protocol was split into three sets of six transfers; a 60-second break provided between each set allowed for a short resting period. The first and last sets were level transfers to a mat table. The middle set was performed onto the mat table raised 2 inches higher. One transfer was performed every 15 seconds, timed by a metronome.

3.3.7 Statistical Analysis

Significance was set *a priori* to $\alpha=.05$, and trends were reported as $p<.10$. All analyses were run using SPSS 22 (SPSS, Inc., Chicago, IL, USA). Injury level was dichotomized into paraplegia (T1 or lower) and tetraplegia (C7 and higher). Data and residuals were examined for normality using the Shapiro-Wilk test. Graphical techniques were used to detect presence of outliers, heteroscedasticity, multicollinearity, and independence and distribution of residuals. Pearson's *r* was calculated to test for multicollinearity. Acute changes in QUS variables between baseline and post-transfers were analyzed using paired *t*-tests; Bonferroni corrections were applied for each variable per tendon ($\alpha=.0125$).

Multiple-linear regression models were built to test how subject characteristics and transfer technique correlated with chronic (baseline) and acute changes in tendinopathy markers. Independent variables included subject characteristics (duration of injury, bodyweight, gender referenced to male, and injury level referenced to paraplegia) and TAI part 1 total score.[16, 138] Tendon depth from the skin was also included as a covariate, as the thickness of tissue between the tendon and transducer can affect the grayscale measures. Dependent variables included baseline and post-transfers QUS. Models with post-transfers QUS as the dependent variable also included baseline QUS as a covariate. The strategy of including baseline QUS as a covariate allowed us to investigate whether a greater departure from baseline was influenced by the different predictor variables. Similar to analysis of covariance, this evaluates the contribution of the independent variables on acute QUS changes.

Table 5. Descriptions and distributions of Transfer Assessment Instrument part 1 items.

Item Number and Description	Baseline			
	0	1	2	N/A
1. The subject's wheelchair is within 3 inches of the target on which he/she is transferring	16	1	45	0
2. The angle between the subject's wheelchair and the surface to which he/she is transferring is approximately 20-45 degrees.	19	1	42	0
3. The subject attempts to position his/her chair to perform the transfer forward of the year wheel (i.e., does not attempt to transfer over the rear wheel)	15	4	41	2
4. If possible, subject removes his armrest or attempts to take it out of the way.	22	1	23	16
5. The subject performs a level or downhill transfer, whenever possible.	0	0	0	62
6. The subject places his/her feet in a stable position (on the floor if possible) before the transfer.	26	7	29	0
7. The subject scoots to the front edge of the surface before he/she transfers (moves his buttocks to the front 2/3 of the seat)	13	3	46	0
8. Hands are in a stable position prior to the start of the transfer.	0	1	61	0
9. A handgrip is utilized correctly by the leading arm (when the handgrip is within the individual's base of support).	22	31	9	0
10. A handgrip is utilized correctly by the trailing arm (when the handgrip is within the individual's base of support).	26	29	7	0
11. Flight is well controlled.	0	0	62	0
12. Head-hips relationship is used (the head moves in the opposite direction of the hips to make the transfer easier to perform).	31	6	25	0
13. The leading arm is correctly positioned (i.e. not extremely internally rotated, and abducted 30-45 degrees)	3	2	57	0
14. The landing phase of the transfer is smooth and well controlled (i.e. hands are not flying off the support surface, subject is sitting safely on the surface).	1	3	58	0
15. If an assistant is helping, the assistant supports the subject's arms during the transfer.	0	0	0	62

No relationships were observed between TAI total score and QUS markers. As participants may perform different skills yet yield the same TAI score, it was hypothesized that specific skills would be more strongly related than overall technique. To test relationships between QUS markers and transfer skills, TAI item scores from the two level transfers were summed. This resulted in scores of 0, 1, 2, or N/A for each item; a 0 indicated the individual did not perform the skill, while a 1 or 2 indicated they performed the skill on one or both of the transfers,

respectively. Items 5 and 15 (Table 5) were eliminated *a priori* because surface height was controlled and no assistance was allowed. Testing relationships between TAI items (transfer skills), baseline QUS markers, and QUS changes required two steps:

1. Items were entered into stepwise linear-regression models (backwards elimination) with baseline or post-transfers QUS as dependent variables. These models were meant to determine which items had the greatest relationship with QUS variables; correlations with $p \leq .10$ were then entered into regression models described in step 2.
2. Linear-regression models (forced entry) were then created containing TAI items from step 2 and the demographic risk factors described above. In all models with post-transfers QUS as the dependent variable, baseline QUS was entered as a covariate to test the influence of independent variables on QUS changes.

3.4 RESULTS

3.4.1 Participants

Seventy-six participants were recruited for this study. Nine participants were found not to meet inclusion/exclusion criteria during informed consent or the testing procedure: 4 were able to stand without assistance, 3 participants were unable complete the transfer or physical examination protocols, and 2 participants reported progressive spinal cord diseases. Images from an additional 5 participants were not clear enough to analyze reliably. These individuals were heavier (>100 kilograms); high levels of subcutaneous adipose tissue can reduce image quality and make it more difficult to reliably define tendon borders during analysis. The final data set

included 62 participants (39 with paraplegia, 23 with tetraplegia; 53 male, 9 female; 26 Black, 35 White, 1 Multiracial). On average subjects were 45.9±12.9 years of age with 16.4±11.5 years since injury, and weighed 79.8±18.9 kilograms. Average part 1 TAI scores were 7.00±1.54.

Table 6. Quantitative ultrasound means (standard deviations) for biceps and supraspinatus tendons. Paired t-test statistics are presented with mean difference absolute values and 95% confidence intervals of the differences between baseline and post-transfers.

Quantitative Ultrasound Measures		Baseline	Post-Transfers	MD	*95% CI of Difference*		*t(61)*	*p*
					Lower	*Upper*		
Biceps	Width (mm)	5.10 (1.53)	5.35 (1.58)	0.25	0.12	0.38	-3.775	<.001
	Echogenicity	119.0 (29.38)	116.7 (27.82)	-2.3	-5.41	0.86	1.453	.151
	Variance	2052.1 (786.13)	1948.3 (836.12)	-103.8	-243.48	35.98	1.485	.143
	Contrast	5.43 (2.20)	5.17 (1.93)	-0.26	-0.56	0.03	1.801	.077
Supraspinatus	Width (mm)	6.34 (1.17)	6.42 (1.15)	0.08	-0.02	0.20	-1.567	.122
	Echogenicity	96.42 (25.84)	95.96 (24.94)	-0.46	-3.68	2.74	0.291	.772
	Variance	1699.8 (771.2)	1660.7 (851.0)	-39.1	-149.12	71.03	0.709	.481
	Contrast	3.97 (1.47)	3.77 (1.45)	-0.20	-0.49	0.09	1.361	.179

Note. Tendon width is measured in millimeters (mm). Greyscale variables are unitless. MD = mean difference between baseline and post-transfers.

3.4.2 Acute Ultrasound Changes

Biceps tendon width significantly increased after transfers (Table 6; p<.001). No significant changes were observed in other QUS variables (Table 6). Numbers of subjects who surpassed minimal detectable changes are described in Table 7.[133]

Table 7. Minimal detectable changes (MDC) reported for quantitative ultrasound measures. Frequencies and percentages are reported of subjects who did not exceed MDC in either direction, or exhibited decreases or increases past MDC.

Quantitative Ultrasound Measures		MDC	< -MDC (%)	±MDC (%)	> +MDC (%)
Biceps	Width (mm)	0.63	3 (4.8)	46 (74.2)	13 (21.0)*
	Echogenicity	24.76	2 (3.2)*	59 (95.2)	1 (1.6)
	Variance	1121.80	2 (3.2)*	58 (93.5)	2 (3.2)
	Contrast	2.71	1 (1.6)*	59 (95.2)	2 (3.2)
Supraspinatus	Width (mm)	0.52	2 (3.2)	53 (85.5)	7 (11.3)*
	Echogenicity	23.30	1 (1.6)*	59 (95.2)	2 (3.2)
	Variance	766.19	4 (6.5)*	56 (90.3)	2 (3.2)
	Contrast	1.69	6 (9.7)*	54 (87.1)	2 (3.2)

Notes. Tendon width is measured in millimeters (mm). MDC = Minimal detectable change.
* Indicates the number of participants who exceeded MDC in the hypothesized direction.

3.4.3 Transfer Technique and QUS Markers

When total TAI part 1 scores were entered as outcomes in regression models, TAI scores did not predict baseline or post-transfers QUS ($p>.05$). Weight was the only variable to correlate with QUS variables: at baseline, participants with higher weight exhibited reduced biceps variance ($\beta=-.449$, $p<.01$) and contrast ($\beta=-.321$, $p<.05$); and supraspinatus width ($\beta=.357$, $p<.05$), echogenicity ($\beta=-.331$, $p<.05$), and contrast ($\beta=-.359$, $p<.05$). Higher weight also predicted greater acute increases in biceps width ($\beta=.124$, $p<.01$). Gender showed a relationship, with males exhibiting reduced post-transfers biceps contrast ($\beta=.168$, $p<.05$) and supraspinatus echogenicity ($\beta=.156$, $p<.05$). No other relationships were observed when TAI total scores were included in the models.

All participants received a score of 2 for item 11 (Table 5), which precluded statistical analysis of this item. The lack of variability in item 8 scores (all but one participant received a score of 2; Table 5) introduces variance in and violates the outlier assumption of regression tests; thus, this item was not analyzed. Three individuals received “N/A” for item three (transferring

over the rear wheel; Table 5). These individuals were using power wheelchairs at the time of testing (although they self-reported using a manual chair for the majority of mobility), which do not have a large rear wheel like manual wheelchairs. “N/A” responses in these cases were transformed to a 2, indicating they did not transfer over the rear wheel during both transfers. Twenty-seven participants received “N/A” for item 4 (removing obstructions such as armrests or clothing guards; Table 5). Individuals would have received this response if they did not have an “obstruction” to remove, or if their “obstruction” was non-removable. No notes were taken indicating why the individual received the “N/A” response. This item was eliminated from the analysis to maintain the sample size and preserve statistical power.

Items 1, 2, 3, 6, 7, 9, 10, 12, 13, and 14 were entered into backwards elimination linear-regression models to determine which items were related to QUS markers (Step 1). Results of these models found baseline biceps width correlated with items 9 and 14; baseline biceps echogenicity with item 9; baseline supraspinatus echogenicity with item 6; baseline supraspinatus variance with item 3; and baseline supraspinatus contrast with item 9 ($p<.10$). Relationships were also observed between TAI items and post-transfers QUS variables: items 1, 9, and 13 with biceps width; items 7, 12, and 13 with biceps echogenicity; items 7 and 12 with biceps variance; items 2, 3, and 10 with supraspinatus width; and items 10 and 13 with supraspinatus echogenicity ($p<.10$). These items were entered into forced entry regression models with demographic risk factors (Step 2). No relationships were observed between TAI items and baseline supraspinatus width, post-transfers biceps contrast, or post-transfers supraspinatus variance and contrast; thus, no further analysis was performed using these variables.

Table 8. Correlations of baseline biceps tendon quantitative ultrasound measures with demographics and Transfer Assessment Instrument items using multiple linear-regression.

				B 95% CI			
	IV	*B*	*SE B*	*Lower*	*Upper*	*β*	*p*
Width*	Constant	2.971	1.769	-0.574	6.517		.099
	Injury Duration	0.031	0.016	-0.002	0.063	.232	.065
	Weight	0.011	0.012	-0.012	0.035	.133	.338
	TAI 09	-0.533	0.282	-1.098	0.031	-.238	.064
	TAI 14	0.758	0.577	-0.398	1.915	.163	.194
	Gender	-0.369	0.574	-1.518	0.781	-.086	.523
	Injury Level	0.378	0.441	-0.505	1.262	.109	.395
Echogenicity†	Constant	131.151	30.907	69.212	193.090		<.001
	Injury Duration	-0.614	0.332	-1.279	0.051	-.241	.070
	Weight	-0.357	0.239	-0.836	0.122	-.216	.141
	TAI 09	8.531	5.514	-2.519	19.582	.198	.128
	Gender	5.928	11.067	-16.251	28.108	.072	.594
	Injury Level	-9.258	8.579	-26.451	7.935	-.139	.285
	Tendon Distance	0.735	0.896	-1.061	2.531	.114	.416
Variance‡	Constant	2877.685	783.364	1307.790	4447.581		.001
	Injury Duration	-9.546	8.791	-27.164	8.073	-.140	.282
	Weight	**-18.071**	**6.058**	**-30.211**	**-5.932**	**-.410**	**.004**
	TAI 10	328.330	196.305	-65.073	721.733	.208	.100
	Gender	54.768	285.179	-516.744	626.280	.025	.848
	Injury Level	-141.712	218.590	-579.776	296.532	-.080	.519
	Tendon Distance	26.965	23.507	-20.145	74.075	.156	.256
Contrast¥	Constant	8.323	2.226	3.862	12.785		<.001
	Injury Duration	-0.044	0.023	-0.091	0.003	-.230	.067
	Weight	-0.033	0.017	-0.067	0.001	-.266	.060
	TAI 09	0.833	0.550	-0.268	1.935	.183	.135
	Gender	1.055	0.787	-0.523	2.632	.170	.186
	Injury Level	-0.290	0.602	-1.498	0.917	-.058	.632
	Tendon Distance	-0.057	0.064	-0.184	0.071	-.118	.376

Notes. Gender referenced to male, injury level to paraplegia. Significant predictors (p<.05) are bolded.

* $F(6,55)=2.323$, $p=.045$, $R^2=.202$, Adj. $R^2=.115$.

† $F(6,55)=2.157$, $p=.061$, $R^2=.190$, Adj. $R^2=.102$.

‡ $F(6,55)=3.073$, $p=.012$, $R^2=.251$, Adj. $R^2=.169$.

¥ $F(6,55)=3.456$, $p=.006$, $R^2=.274$, Adj. $R^2=.195$.

When baseline QUS was entered as the dependent variable (Table 8, Table 9), biceps width was greater in those who used unsafe hand positioning, although the relationship only trended toward significance (item 9; $p<.10$). No subject characteristics or TAI items correlated with biceps echogenicity, variance, or contrast. Trends were observed in correlations between supraspinatus variance and transferring over the rear wheel (item 3; $p<.10$), and supraspinatus contrast and hand positioning (item 9; $p<.10$).

When post-transfers biceps QUS was the dependent variable (Table 10): participants with higher weights, who positioned their wheelchairs close to the mat table (item 1; $p<.05$), and who did not use proper arm positioning (item 13; $p<.05$) exhibited wider tendons after transfers. Post-transfers echogenicity was lower in those who did not scoot to the front of the chair prior to transferring or use proper arm positioning (items 7 and 13; $p<.05$); gender also influenced post-transfers echogenicity, with females exhibiting brighter tendons ($p<.05$). When examining post-transfers supraspinatus QUS (Table 9): wider tendons were observed in those who did not use proper trailing hand positioning (item 10; $p<.05$), did not position their chair so they could clear the rear wheel (item 3; $p<.05$), and who angled their chair between 20 and 45 degrees with respect to the target surface (item 2; $p<.05$). Participants who did not use proper arm positioning exhibited darker supraspinatus tendons post-transfers (item 13; $p<.01$).

Table 9. Correlations of baseline supraspinatus tendon quantitative ultrasound measures with demographics and Transfer Assessment Instrument items using multiple linear-regression.

				B 95% CI			
		B	*SE B*	*Lower*	*Upper*	*β*	*p*
Echogenicity*	Constant	138.702	24.743	89.117	188.288		<.001
	Injury Duration	-0.421	0.282	-0.987	0.145	-.188	.142
	Weight	-0.444	0.227	-0.900	0.011	-.306	.056
	TAI 06	5.764	3.458	-1.165	12.694	.212	.101
	Gender	-6.277	9.858	-26.033	13.480	-.086	.527
	Injury Level	-2.435	7.736	-17.938	13.067	-.042	.754
	Tendon Distance	0.176	1.139	-2.107	2.460	.024	.878
Variance†	Constant	1997.833	778.555	425.548	3550.118		.014
	Injury Duration	-10.778	9.873	-30.590	9.033	-.148	.280
	Weight	6.558	7.459	-8.409	21.526	.152	.383
	TAI 03	-224.126	129.239	-483.464	35.212	-.239	.089
	Gender	117.827	334.930	-554.259	789.912	.052	.726
	Injury Level	-243.781	244.684	-734.774	247.213	-.139	.324
	Tendon Distance	-31.370	37.353	-106.325	43.584	-.141	.405
Contrast‡	Constant	6.813	1.362	4.082	9.543		<.001
	Injury Duration	-0.015	0.0156	-0.047	0.016	-.119	.341
	Weight	-0.022	0.013	-0.049	0.004	-.270	.097
	TAI 09	0.500	0.278	-0.056	1.057	.232	.077
	Gender	-0.382	0.547	-1.478	0.714	-.092	.488
	Injury Level	-0.455	0.431	-1.319	0.410	-.137	.297
	Tendon Distance	-0.055	0.064	-0.182	0.073	-.130	.396

Notes. Gender referenced to male, injury level to paraplegia.

* $F(6,55)=1.859$, $p=.105$, $R^2=.169$, Adj. $R^2=.078$.

† $F(6,55)=1.154$, $p=.344$, $R^2=.112$, Adj. $R^2=.015$.

‡ $F(6,55)=2.424$, $p=.038$, $R^2=.209$, Adj. $R^2=.123$.

Table 10. Prediction of post-transfers quantitative ultrasound measures of the biceps tendon by demographics and Transfer Assessment Instrument items while controlling for baseline ultrasound measures.

				B 95% CI			
DV	*IV*	*B*	*SE B*	*Lower*	*Upper*	*β*	*p*
Biceps Width*	Constant	0.400	0.674	-0.952	1.752		.165
	Baseline	0.910	0.045	0.818	1.002	.878	<.001
	Injury Duration	0.004	0.006	-0.008	0.015	.029	.493
	Weight	0.010	0.004	0.001	0.018	.109	.022
	TAI 01	0.164	0.079	0.005	0.323	.092	.043
	TAI 09	-0.168	0.099	-0.367	0.031	-.072	.096
	TAI 13	-0.329	0.162	-0.653	-0.004	-.096	.047
	Gender	-0.029	0.215	-0.460	0.402	-.006	.893
	Injury Level	0.022	0.153	-0.285	0.329	.006	.886
Biceps Echogenicity†	Constant	-29.510	16.561	-67.743	3.723		.081
	Baseline	0.885	0.051	0.754	0.957	.903	<.001
	Injury Duration	0.057	0.133	-0.209	0.324	.024	.668
	Weight	-0.054	0.092	-0.240	0.131	-.035	.560
	TAI 07	4.571	1.794	0.971	8.171	.135	.014
	TAI 12	-2.378	1.660	-5.708	0.953	-.081	.158
	TAI 13	9.545	3.249	3.026	16.065	.158	.005
	Gender	10.399	4.536	1.298	19.501	.133	.026
	Injury Level	-0.428	3.243	-6.935	6.078	-.007	.895
	Tendon Distance	0.635	0.375	-0.118	1.389	.104	.097
Biceps Variance§	Constant	-525.959	671.832	1873.483	821.564		.437
	Baseline	0.855	0.101	0.652	1.058	.804	<.001
	Injury Duration	-0.816	6.494	-13.842	12.209	-.011	.900
	Weight	3.069	5.018	-6.996	13.134	.065	.543
	TAI 07	135.262	92.520	-50.309	320.834	.133	.150
	TAI 12	-140.947	85.493	-312.425	30.531	-.161	.105
	Gender	309.835	216.160	-123.727	743.398	.132	.158
	Injury Level	87.322	163.022	-239.659	414.304	.046	.594
	Tendon Distance	1.409	19.604	-37.911	40.730	.008	.943

Table 11. Prediction of post-transfers quantitative ultrasound measures of the supraspinatus tendon by demographics and Transfer Assessment Instrument items, while controlling for baseline ultrasound measures.

				B 95% CI			
DV	*IV*	*B*	*SE B*	*Lower*	*Upper*	*β*	*p*
Width*	Constant	0.733	0.456	-0.183	1.648		.114
	Baseline	**0.886**	**0.049**	**0.788**	**0.984**	**.896**	**<.001**
	Injury Duration	0.007	0.005	-0.004	0.017	.067	.194
	Weight	0.003	0.003	-0.004	0.010	.048	.366
	TAI 02	**0.139**	**0.062**	**0.014**	**0.264**	**.112**	**.030**
	TAI 03	**-0.148**	**0.066**	**-0.280**	**-0.016**	**-.106**	**.029**
	TAI 10	**-0.226**	**0.086**	**-0.398**	**-0.054**	**-.131**	**.011**
	Gender	-0.047	0.164	-0.376	0.281	-.015	.7474
	Injury Level	-0.135	0.127	-0.389	0.119	-.052	.292
Echogenicity†	Constant	7580	16.207	-24.913	40.074		.642
	Baseline	**0.883**	**0.060**	**0.763**	**1.004**	**.915**	**<.001**
	Injury Duration	-0.012	0.132	-0.276	0.252	-.006	.928
	Weight	0.169	0.108	-0.048	0.387	.121	.125
	TAI 13	**-9.921**	**3.512**	**-16.963**	**-2.880**	**-.183**	**.007**
	Gender	6.247	4.781	-3.338	15.832	.089	.197
	Injury Level	-0.026	3.511	-7.065	7.014	.000	.994
	Tendon Distance	0.100	0.516	-0.936	1.135	.014	.847

Notes. DV = Dependent Variable. IV = Independent Variable. TAI # = Transfer Assessment Instrument item.
* $F(8,53)=56.207$, $p<.001$, $R^2=.895$, Adj. $R^2=.879$.
† $F(7,54)=34.718$, $p<.001$, $R^2=.818$, Adj. $R^2=.795$.

3.5 DISCUSSION

Transfers have been identified as one causative factor in the development of shoulder pain and injury in wheelchair users.[7, 16, 26] However, there is limited evidence that describes how transfers and transfer technique affect the health of shoulder tendons. The present study investigated the effects of a repeated-measures protocol on ultrasonographic markers for biceps and supraspinatus tendinopathy. Further analysis determined whether subject characteristics and transfer technique were associated with these markers at baseline, or with changes in these

markers after transfers. In accordance with hypotheses, relationships were observed between transfer technique, bodyweight, and markers for tendinopathy at baseline and after transfers.

Biceps thickness – a marker for tendinopathy[132] – was found to acutely increase after transfers. Increases were similar in magnitude to a previous study investigating ultrasonographically-measured biceps tendon changes after a wheelchair sporting event.[134] Similar to a previous study investigating propulsion,[111] no significant changes were observed in supraspinatus measures. These observations may indicate more stress is placed on the biceps tendon, which aids in humeral stabilization during abduction.[139] Alternatively, biceps tendon QUS may be more sensitive when detecting reactive changes. Imaging the supraspinatus transversely allows for more repeatable QUS measures, yet collagen fiber orientation is easier to view in a longitudinal orientation compared to transverse. Mean differences in biceps width did not exceed the standard error of measurement or minimal detectable change (MDC) reported by Collinger, et al.[133] (Table 7). MDC was surpassed by 16 participants, or 25%; thus, changes for other participants may be due in part to error. Thirteen individuals (21%) exhibited increases in tendon width greater than the reported MDC, indicating a response occurred in a subset of this sample. Further testing will help determine the clinical meaning of these responses. Pairing ultrasound with other physiological measures of tendinopathy, such as inflammatory cytokines, may provide a more comprehensive understanding of shoulder pathology in this population.

Changes in the biceps and supraspinatus tendons may have been influenced by transfer ability and subject characteristics. These factors may have introduced variability in the tendon responses to the transfer activity that yielded no overall mean differences between baseline and post-transfers QUS values. By using linear-regression and controlling for baseline tendon characteristics, the influence of technique and subject characteristics on tendon responses could

be elucidated. When including TAI total scores, overall transfer technique was not found to be related to ultrasound markers at baseline, nor changes in response to the transfer protocol. Individuals may perform different skills that, when combined, yield the same TAI score. The various TAI skills influence upper limb biomechanics more than others;[88] thus, different skills may affect tendon responses more than others.

Relationships were found when TAI total score was removed from regression models and replaced with specific TAI items. Items that required the user to move closer to the transfer surface and use stable and safe arm and hand positions were related to greater changes in QUS markers after transfers. These skills stabilize the shoulder and arm, and reduce the lever-arm through which forces are applied.[88] While these techniques were found to influence changes, they were not observed at baseline. It is possible that these skills acutely influence tendon responses within this testing environment – performing multiple transfers onto a level mat table with a time limit – but not necessarily in real-world situations. However, it is also possible that these changes represent pre-clinical damage that could contribute to tendinopathy without intervention. Longitudinal testing is needed to determine if acute changes associated with transfer skills manifest as chronic tendinopathy. It was unclear as to why other skills did not relate to QUS markers. It is possible that certain techniques (e.g. placing the feet on the floor or scooting forward in the seat prior to transferring) have greater benefits/detriments to other upper limb soft tissues, such as elbow ligaments or peripheral nerves.[140, 141] Ultrasonographic analysis of other upper limb tissues may reveal such relationships.

Bodyweight was one of the most consistent predictors of baseline pathological ultrasound markers in this sample. These findings contribute to the growing body of evidence that suggests reducing bodyweight can prevent upper-extremity injury in this population.[16, 22, 107, 140

Individuals with more mass must place higher loads on their joints to transfer, so it follows that repeated exposure would manifest as tendinopathy. Greater bodyweight was associated with greater increases in biceps tendon width, but not other biceps or supraspinatus measures. Heavier individuals may load the biceps tendon to a magnitude that approaches physiological capacity, resulting in a potentially pathological response. Transfer skills did not appear to vary with weight in this sample. It is possible that using certain strategies may help offset the deleterious effects of body mass on the biceps tendon; for example, shifting some of the load to the feet by placing them on the floor prior to the transfer (item 6).[26, 81] Utilizing assistive technologies such as transfer boards can also help to redistribute upper-extremity loading and are recommended when appropriate.[16, 26]

There is a need to develop and test evidence-based wheelchair mobility training and assessment tools.[91, 142] This is exemplified in the current sample, as only one skill was completed by all individuals (Table 5). A recent randomized-controlled trial found that structured transfer training during inpatient rehabilitation, using the TAI as a framework, resulted in improvements in transfer quality one year after discharge.[142] The present study has identified a relationship between transfer skills and shoulder pathology, and a previous investigation found similar results with respect to the median nerve.[140] Longitudinal testing is necessary to determine how transfer quality impacts the development of upper limb pathology, and whether transfer training using the TAI can delay its progression.

3.5.1 Limitations

Transfers were paced using a metronome, and participants were required to transfer using a standardized setup. These factors allowed a degree of control over transfer speed and

environment, yet could have affected participants' natural transfer ability and skills. The fatiguing nature of the activity may have induced changes in their transfer skills/quality that were different than those observed during baseline TAI testing. The standardized setup limits generalizability to other environments such as a bathroom, bed, or car. Images were only performed on the non-dominant shoulder, yet biomechanical and electromyographical differences have been noted between leading and trailing arms.[124] The study design allowed for the non-dominant shoulder to trail or lead an equal number of transfers, accounting for these differences. Subjects in this sample were independent and most were athletes, which is not reflective of the SCI population as a whole and may affect generalizability; however, it is possible tendon responses in a less active population may be amplified from disuse. Power analyses indicated a sample size of 77 would be provide sufficient study power yet data from only 62 were included. A lack of power could potentially introduce Type 2 error and limit the ability to detect significant differences. Finally, this study was cross-sectional in nature and thus it cannot be concluded that these factors delay pathology. Further investigations are needed to understand how transfers in different environments affect longitudinal development of upper limb soft tissue injury.

3.6 CONCLUSIONS

Repeated transfers caused increases in biceps tendon thickness in a subset of individuals, measured using ultrasound, yet no changes were observed in the supraspinatus tendon. Changes in biceps tendon thickness after transfers were influenced by subjects' weight. Certain skills were associated with changes in biceps and supraspinatus tendons; specifically, those promoting a

body position closer to the target surface, and facilitating stable and safe shoulder and hand positions. Results indicate a relationship between bodyweight, transfer technique and shoulder tendinopathy. Reducing weight and improving transfer quality may attenuate the development or progression of shoulder pathology, yet longitudinal testing is needed to confirm this assertion. Further testing is needed to determine the clinical meaning of the observed responses.

4.0 ULTRASOUND MEDIAN NERVE CHANGES AFTER WHEELCHAIR TRANSFERS IN INDIVIDUALS WITH PARAPLEGIA: RELATIONSHIPS WITH SUBJECT CHARACTERISTICS AND TRANSFER SKILLS

4.1 ABSTRACT

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Objective: To evaluate the effects of repeated transfers on ultrasound markers for carpal tunnel syndrome (CTS) in people with spinal cord injuries, and relate changes to subject characteristics and transfer skills.

Design: Cross-sectional, repeated-measures.

Setting: Research laboratory and national wheelchair sporting events.

Participants: A convenience sample of 30 wheelchair users with non-progressive paraplegia were recruited via research registries and at the 2013 National Veterans Wheelchair Games and 2014 Paralyzed Veterans of America Buckeye Games. Participants were over 18 years old and could complete transfers independently within 30 seconds without use of their leg muscles.

Methods: Demographic questionnaires and physical examinations for CTS were completed. Quantitative ultrasound techniques were used to measure changes in the median nerve after a repeated-transfers protocol. The Transfer Assessment Instrument (TAI) was completed to quantify transfer ability.

Main Outcome Measurements: Median nerve cross-sectional area at the level of the pisiform (PCSA) and swelling ratio (SR), transfer quality and skills via the TAI.

Results: PCSA increased after repeated-transfers ($p<.025$). Participants who used safe hand positions had a lower baseline SR ($\beta=-.728$; $p<.01$). Those with higher body weight had a lower baseline SR provided they performed higher-quality transfers. Those who scooted to the front of the seat prior to transferring (TAI item 7; $\beta=.144$; $p<.05$) and who weighed more ($\beta=.142$; $p<.05$) exhibited greater increases in CSA in response to transfers.

Conclusions: An acute increase was observed in median nerve CSA at the pisiform after repeated wheelchair transfers. Changes were greater in those with higher body weight and those not performing certain transfer skills correctly (according to the TAI). It is possible these factors contribute to chronic injury and possibly CTS.

Key words: ultrasonography, median nerve, cumulative trauma disorders, spinal cord injuries, wheelchairs

4.2 BACKGROUND

Carpal tunnel syndrome (CTS) is the most frequently diagnosed compressive mononeuropathy.[143] It is caused by compression of the median nerve as it passes through the

carpal tunnel beneath the flexor retinaculum.[143] CTS is characterized by numbness, paresthesia, pain, and nocturnal symptoms in the distribution of the median nerve in the hand.[143] Symptoms can be caused by increases in carpal tunnel pressure – induced by extreme wrist angles and thickening of the sheaths around tendons within the tunnel – or disruptions in the ability of the nerve to glide normally during joint range of motion. Inflammation also plays a role, affecting carpal tunnel flexor tendons and nerve gliding.[144] Thus, certain populations exposed to forceful and repetitive hand motions have a higher risk for development of CTS.[144] Performing force-generating tasks while wrists are in non-ergonomic positions has been linked to development of median mononeuropathies.[25] As wheelchair activities such as transfers require the generation of large upper limb forces, they have been implicated in the development of CTS in people with spinal cord injury (SCI).[25]

Between 236,000 to 327,000 individuals live with SCI in the United States.[145] People with SCI rely on their upper-extremities for mobility and participation in daily activities. A diagnosis of CTS in a wheelchair user can increase functional impairment, with a potential detriment to quality of life.[6] CTS prevalence in SCI is between 40% and 66%[1, 20, 25, 146] – higher than both general and working populations[147, 148] – and increases with time after injury.[1, 20, 25, 146] As life expectancies for people with SCI continue to increase[145], it is important to reduce risk factors for developing the disorder.

Diagnosing CTS involves a careful history, physical examination, nerve conduction, and often includes electromyography.[149] Ultrasonography as a diagnostic tool in CTS is becoming more widely used due to its low cost, noninvasiveness, short exam time, and portability.[150] Ultrasound allows for the visualization of carpal tunnel anatomy as well as real-time assessment of dynamic changes within the carpal tunnel. Recent studies have observed measurable changes

in median nerve characteristics after stressful activities.[24, 151-153] In two of these studies, changes were greater in those with CTS.[24, 151]

In this study, we aimed to identify the effects of independent transfers on ultrasonographic markers of CTS in people with paraplegia. In addition, we sought to develop a better understanding of how subject characteristics and transfer techniques impact the median nerve during transfers. It was hypothesized that 1) repeated transfers would cause acute changes in quantitative ultrasound (QUS) markers for CTS; and 2) baseline QUS and changes in QUS would relate to subject characteristics (e.g. duration of wheelchair use, body weight) and transfer skills/quality measured by the transfer assessment instrument (TAI).

4.3 METHODS

4.3.1 Participants

Wheelchair users with SCI were recruited in response to flyers and research registries, at the 2013 and 2014 National Veterans Wheelchair Games, and at the 2014 Paralyzed Veterans of America Buckeye Games. Prior to enrollment, subjects provided written informed consent. Ethical approval was obtained through the Institutional Review Board prior to data collection. Subjects were included in the study if they were older than 18 years of age, had non-progressive paraplegia for at least one year prior to the start of the study, used a manual wheelchair over 40 hours per week, and were able to transfer to-and-from their chair within 30 seconds with or without assistive equipment. Individuals were excluded from this study if they self-reported having arm pain that prevented transfers, having use of their leg muscles during transfers, or

having a recent history of cardiopulmonary problems or pressure sores that could be exacerbated by repeated transfers.

An *a priori* power analysis was performed to determine sample size, using pre- and post-activity CSA reported by Altinok, et al.[151] The effect sizes in that study were large; however, based on the authors' previous experience and differences in methodology, a power analysis was performed using a medium effect size.

4.3.2 Baseline Questionnaires and Examinations

Subject demographics such as age, gender, race/ethnicity, and duration of wheelchair use were collected with a general demographics questionnaire. Body weight was collected using a wheelchair scale (Befour, Inc., Saukville, WI, USA), and determined by subtracting wheelchair weight from combined subject and wheelchair weights. The Brigham and Women's Carpal Tunnel Questionnaire (CTQ) was then completed.[154] The CTQ is divided into two subscales that assess severity of CTS symptoms and functional consequences. Subscales are graded and averaged, with final scores resting between 1 and 5. Higher scores represent greater severity of symptoms or functional impairment from CTS.

A physical exam of the wrist was performed by a physiatrist to test for the presence of CTS symptoms. The examiner was blinded to demographic and pain/symptom questionnaire information. This exam utilized a set of clinically-guided manual tests to evaluate degree of CTS symptoms: thenar muscle atrophy, thumb abduction weakness, impaired sensation to pin-prick between the 2nd and 5th digits along the median nerve distribution, Tinel's Sign, and Phalen's test.[155] Each test was graded either 0 (symptom absent), 1 (equivocal), or 2 (symptom present). Higher scores represent greater clinically-graded median neuropathy. The distribution of findings

across the sample was highly skewed; thus, participants were dichotomized into those with absence (score of 0) or presence (score of 1 or greater) of physical examination findings.

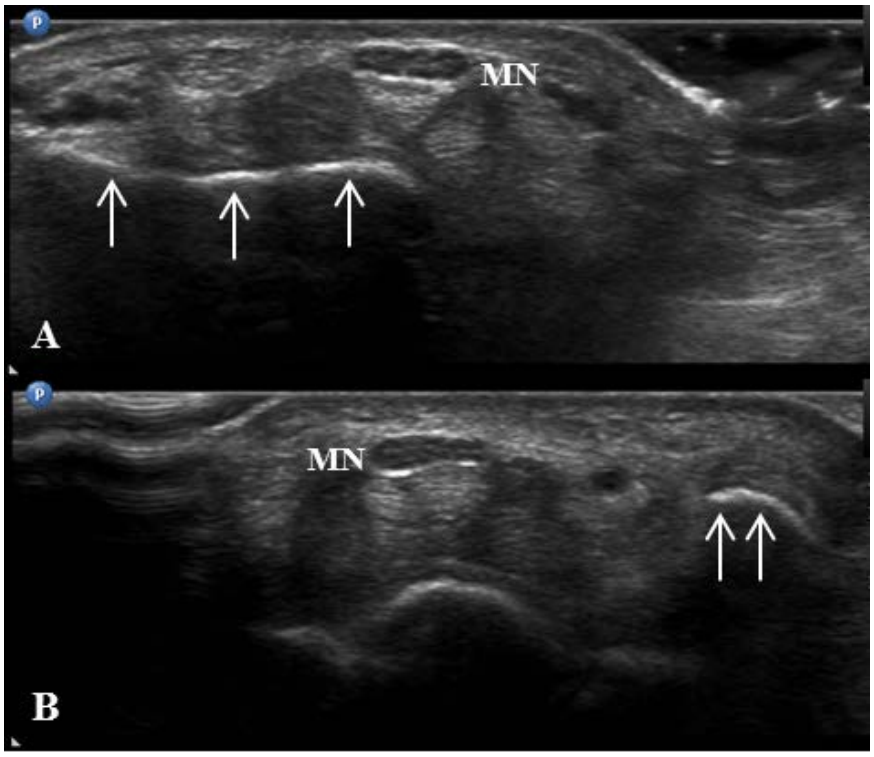


Figure 3. Cross-sectional images of hypoechoic median nerve (M) at the levels of the distal-radius (A) and pisiform (B). Vertical arrows indicate the respective bony landmarks identified during the imaging protocol.

4.3.3 Quantitative ultrasound Examination

A previously designed QUS protocol[156] was used to measure ultrasonographic changes in the median nerve in response to repeated transfers. A single evaluator imaged the median nerve at the levels of the pisiform and distal-radius (Figure 3). This evaluator was blinded to clinical findings and transfer quality. This standardized measurement technique has high reproducibility and reliability when taking multiple measurements of the median nerve.[156] Images were collected

in the non-dominant wrist in order to isolate the effects of hand dominance on the development of CTS. Subjects sat upright in their wheelchairs with their elbows flexed at 90°; their forearms were supinated and supported with a cushion. Images were collected while the wrist was in a neutral position and the fingers relaxed. The probe was positioned in the transverse plane, perpendicular to the palmar side of the wrist. A single image was recorded at each level before (baseline) and immediately after (post-transfers) a repeated-transfer protocol; the time between cessation of the activity and commencement of the imaging protocol was not recorded.

Focal enlargement of the median nerve in the wrist is commonly present in individuals with CTS.[157] One of the best discriminatory criteria is enlargement at the level of the pisiform bone, measured via cross-sectional area (CSA).[150, 157] The pisiform location represents the inlet of the carpal tunnel; increased CSA of the nerve proximal to the tunnel may indicate swelling caused by compression within the tunnel itself.[151, 158-160] Another consistent finding is an increased swelling ratio (SR), which is defined as the ratio of the median nerve CSA at the pisiform level (PCSA) in comparison to the CSA at the distal-radius level.[150] While SR was not included in a recent evidence-based guideline for ultrasonographic diagnosis of CTS[157], it has been shown to be a reliable parameter that is sensitive and specific for CTS diagnosis.[150, 151] In addition, activity-induced changes in SR have been related to presence of CTS symptoms in people with SCI and able-bodied individuals.[24, 151]

Median nerve images were analyzed using a previously described protocol.[156] Each image was loaded in a random fashion into a custom MATLAB program, which blinds the evaluator to subject ID and time point. A boundary trace of the median nerve was performed to determine CSA. SR was calculated by dividing CSA at the pisiform level by CSA at the distal-radius level. A single investigator collected and analyzed each image. Depth, frequency, and

focus were held constant between subjects and time points, while gain was modified to capture the best image possible.

4.3.4 Transfer Assessment Instrument

Transfer technique was measured using the Transfer Assessment Instrument (TAI).[90, 91] The TAI is able to quantitatively and reliably measure the safety and quality of transfers in wheelchair users, and was recently biomechanically validated.[88] The TAI contains two parts. Part 1 is comprised of 15 items that are scored during the transfer, with one of the following responses: yes (1 point), no (0 points), or non-applicable (removed item). Each item represents a transfer skill, with "yes" or "no" applied depending on whether or not the individual performed the skill. Non-applicable is given in situations where the skill cannot be performed; for example, if an individual does not have an armrest, they cannot be given a score for removing it prior to the transfer (item 4). Scores are summed, multiplied by 10, and then divided by the number of applicable items. TAI Part 1 items are listed in Table 1. Part 2 is completed after the 4 transfers are performed and is scored on a Likert scale ranging from 0 to 4 (strongly disagree to strongly agree). After calculating an average score for each item in part 2, the final score of the TAI is the average of the part 1 and part 2 scores. Items included in the assessment are related to wheelchair position, feet placement, flight movement, handgrip, landing ability, position of the weight-bearing arm, and proper use of transfer devices or assistance.[90, 91] When grading the TAI, the evaluator was blinded to subject characteristics, clinical findings, and ultrasonographic measurements.

4.3.5 Repeated Transfers Protocol

All transfers were performed using the subjects' own wheelchairs. Participants first performed 4 transfers to-and-from a height-adjustable mat table; these were graded by a physical therapist using the TAI. The first 2 transfers were to-and-from the mat table positioned level to their wheelchair seats. The second 2 transfers were to-and-from the mat table set 2 inches higher than their wheelchair seats. Participants then completed a repeated-transfers protocol, which consisted of 18 transfers to-and-from the mat table. Eighteen was determined as an approximate number of transfers a wheelchair user completes in one day.[85] Movement from one surface to the other was considered one transfer (i.e. wheelchair to mat table, mat table to wheelchair). Each participant was given 15 seconds to complete a single transfer, controlled by metronome. The first and last set of 6 transfers were to-and-from a mat table at a height level with the wheelchair seat. The middle set of 6 transfers were to-and-from a mat table that was 2 inches higher than the wheelchair seat. A one-minute break was given between each set of transfers to allow for recovery. At the end of the final set of transfers, the subject rated their perceived level of exertion during the entire transfer protocol using a Borg scale.

4.3.6 Statistical Analysis

Significance was set *a priori* to $p<.05$, with trends reported as $p<.10$. All analyses were run using SPSS 22 (SPSS, Inc., Chicago, IL). Normality was assessed using the Shapiro-Wilk test, and presence of outliers using graphical techniques. Pearson's *r* was calculated to determine how demographics correlated with transfer quality and skills. Paired *t*-tests were performed to test hypothesis 1 and determine if differences between baseline and post-transfers QUS variables

were significant; a Bonferroni correction was applied to account for multiple tests (α=.05/2=.025).

Two aspects of transfers were analyzed for their effects on baseline and post-transfers QUS markers, overall quality (TAI part 1 total score) and specific transfer skills (TAI item scores). For baseline testing, multiple-linear regression models (forced entry) were built with TAI part 1 total scores and subject characteristics (weight, age, presence/absence of physical examination findings, and gender[1, 20, 22, 25, 113, 146]) as independent variables, and baseline SR and CSA as dependent variables. When post-transfers QUS variables were entered as dependent variables, baseline QUS was also included as an independent variable. Weight and age were not transformed; raw values were entered into regression models to test for correlations.

TAI item scores from the two level transfers (to and from the mat table) were summed giving a score of 0, 1, 2, or N/A for each item. Subjects were placed in groups based on their score. It was decided to dichotomize scores because of the disproportionate group sizes at baseline (Table 13). For most items, individuals who completed the skill during both transfers (score of 2) were considered the successful group, while those with 0 and 1 were grouped together. The distributions for items 9 and 10 necessitated dichotomization depending on whether the skill was not performed (0) or performed on one or both transfers (1 and 2). Items with highly disproportionate group sizes (≥90:10) and proportions of "N/A" responses greater 33% were not considered for analysis. Remaining items were tested for multicollinearity by calculating Kendall's tau-b (τ-b). Multiple linear-regression models (backward elimination) determined which TAI items (independent variables) best predicted baseline and post-transfers QUS variables (dependent variables). Items with p-values less than .10 in these *a priori* analyses were included in final models to test hypotheses. Linear-regression models (forced entry) were

then built to test if TAI item(s) and subject characteristics predicted baseline or post-transfers QUS.

Because of the unexpected findings, secondary analyses were performed to analyze the interaction between weight and overall transfer quality (TAI part 1 total scores) in baseline and post-transfers QUS. Multiple linear-regression models (forced entry) with duration of injury, gender, weight, TAI part 1 total scores, and the weight/TAI interaction as dependent variables were built with baseline SR and post-transfers CSA as dependent variables.

4.4 RESULTS

4.4.1 Participants

Thirty individuals with paraplegia participated in this study. Average age, weight, and duration of injury of the sample were 42.2±13.2 years, 80.7±23.4 kilograms, and 15.4±10.9 years, respectively. Twenty-seven were male and 3 were female. Ten participants were African-American/Black, 17 were Caucasian/White, 2 were Hispanic, and 1 was Multiracial. CTQ symptom severity and functional status scores averaged 1.36±0.5 and 1.10±0.2, respectively, with a median physical examination score of 2 (ranging from 0 to 8). The median Borg scale score for the entire transfer protocol was 7 (ranging from 6 to 11).

4.4.2 Median Nerve Changes

Median nerve CSA at the pisiform significantly increased after repeated transfers ($p<.025$; Table 12). Significant differences were not observed in SR or CSA at the distal-radius.

Table 12. Descriptive and t-test statistics for median nerve quantitative ultrasound measures.

	Baseline	Post-Transfers	*t*	*df*	*p*
CSA - radius	11.97 (2.18)	12.10 (2.37)	-.882	29	.385
CSA - pisiform	11.49 (2.48)	11.89 (2.59)	-2.763	29	.010*
Swelling Ratio	0.97 (.15)	0.99 (.15)	-1.497	29	.145

Notes. CSA = Cross-sectional area

4.4.3 Ultrasound Markers, Transfer Skills, and Subject Characteristics

Subjects were required to perform independent transfers at fixed heights, so TAI items 5 and 15 were removed. Over 90% of participants performed items 8, 11, 13, and 14. Items 3 and 7 were highly correlated (τ-b=.841, $p<.001$); as item 3 only applies to manual wheelchair users, this item was removed to reduce effects of multicollinearity in regression models. Final items used in multiple-regression models included 1, 2, 6, 7, 9, 10, and 12 (Table 13).

Table 13. Distribution of raw and dichotomized Transfer Assessment Instrument item scores.

Item Number and Description	Baseline				Dichotomized	
	0	1	2	N/A	0	1
1. The subject's wheelchair is within 3 inches of the target on which he/she is transferring	10	0	20	0	10 (33.3)	20 (66.7)
2. The angle between the subject's wheelchair and the surface to which he/she is transferring is approximately 20-45 degrees.	8	0	22	0	8 (26.7)	22 (73.3)
3. The subject attempts to position his/her chair to perform the transfer forward of the year wheel (i.e., does not attempt to transfer over the rear wheel)	9	0	21	0	9 (30.0)	21 (70.0)
4. If possible, subject removes his armrest or attempts to take it out of the way.	9	0	9	12	-	-
5. The subject performs a level or downhill transfer, whenever possible.	0	0	0	30	-	-
6. The subject places his/her feet in a stable position (on the floor if possible) before the transfer.	16	3	11	0	19 (63.3)	11 (36.7)
7. The subject scoots to the front edge of the surface before he/she 8. transfers (moves his buttocks to the front 2/3 of the seat)	8	1	21	0	9 (30.0)	21 (70.0)
8. Hands are in a stable position prior to the start of the transfer.	1	1	28	0	2 (6.7)	28 (93.3)
9. A handgrip is utilized correctly by the leading arm (when the handgrip is within the individual's base of support).	11	14	5	0	11 (36.7)	19 (63.3)
10. A handgrip is utilized correctly by the trailing arm (when the handgrip is within the individual's base of support).	15	13	2	0	15 (50.0)	15 (50.0)
11. Flight is well controlled.	0	0	30	0	0 (0.0)	30 (100.0)
12. Head-hips relationship is used (the head moves in the opposite direction of the hips to make the transfer easier to perform).	18	1	11	0	19 (63.3)	11 (36.7)
13. The leading arm is correctly positioned (i.e. not extremely internally rotated, and abducted 30-45 degrees)	1	0	29	0	1 (3.3)	29 (96.7)
14. The landing phase of the transfer is smooth and well controlled (i.e. hands are not flying off the support surface and subject is sitting safely on the target surface).	3	0	27	0	3 (10.0)	27 (90.0)
15. If an assistant is helping, the assistant supports the subject's arms during the transfer.	0	0	0	30	-	-

Higher TAI part 1 scores (β=.152, $p<.05$) and body weight (β=.142, $p<.05$) were related to greater post-transfers PCSA. Based on this finding, we hypothesized that body weight may moderate the effects of transfer quality on post-transfers CSA. The interaction between TAI scores and body weight was not significant ($p>.10$); visual inspection of the scatterplots revealed little relationship between TAI scores and acute changes in PCSA (Figure 4). The weight/TAI

interaction was significant with respect to baseline SR (β=-.386; p<.05), and inspection of the graph revealed participants with greater weight had lower SR if they had better transfer quality (Figure 5). Transfer quality and baseline SR were inversely related, although this relationship only trended toward significance (β=-.407, p<.10). Physical examination findings did not correlate with QUS measures (p>.05).

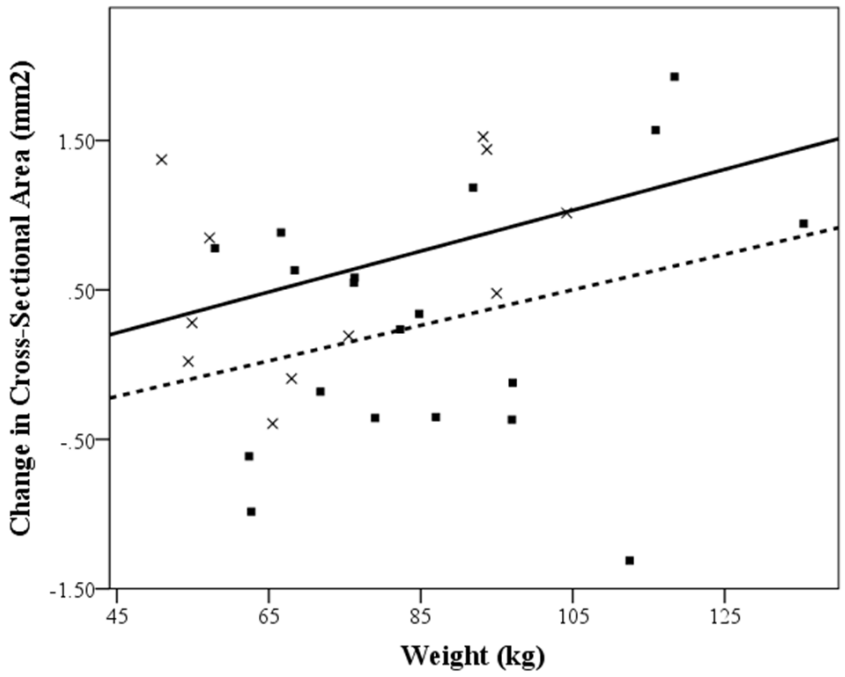


Figure 4. Scatterplot representing the interaction between body weight and transfer quality (TAI part 1 scores) on changes in cross-sectional area. To visualize the interaction, subjects were split into low and high transfer quality groups using a cutoff of 7.36.[90, 91] The high-quality group is represented by the "x" symbol and a solid line (R^2=0.158), and the low-quality group by the box symbol and a dotted line (R^2=0.091).

Correlational analysis between transfer skills and QUS variables found a relationship between items 6 and 9 and baseline SR (p<.10), and item 7 and post-transfers PCSA (p<.05). These items were included in their respective post hoc models along with demographic factors.

Post hoc analyses found body weight (β=-.554, p<.01), and completion of TAI items 9 (β=-.728, p<.01) and 6 (β=.369, p<.05) were related to baseline SR. When controlling for baseline PCSA, completion of item 7 predicted greater post-transfers PCSA (β=.145, p<.05). No factors correlated with baseline CSA or changes in SR.

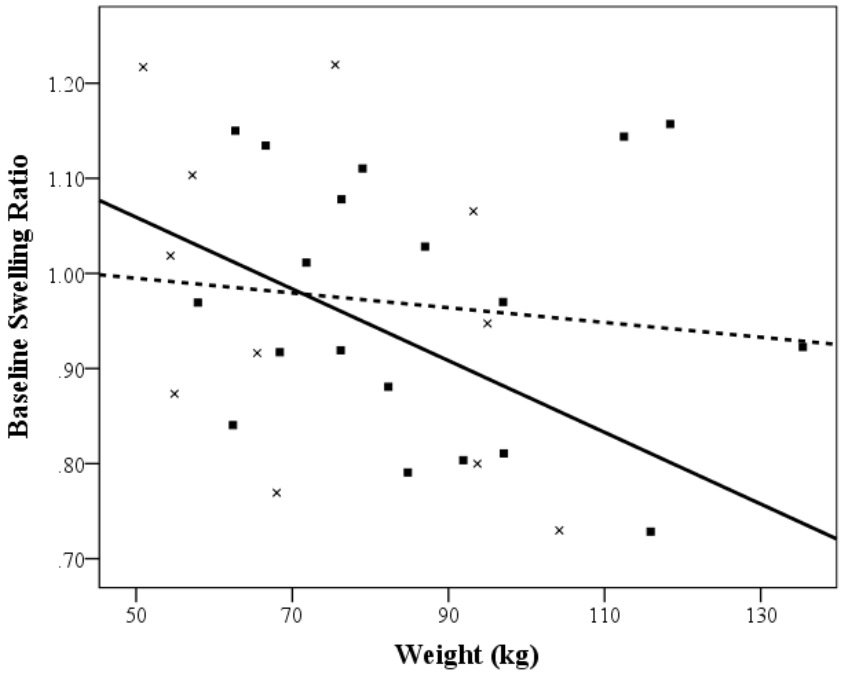


Figure 5. Scatterplot representing the interaction between body weight and transfer quality (TAI part 1 scores) on baseline swelling ratio. To visualize the interaction, subjects were split into low and high transfer quality groups using a cutoff of 7.36. This value was generated from the average TAI score of samples from two independent reliability studies.[90, 91] The high-quality group is represented by the "x" symbol and a solid line (R^2=0.184), and the low-quality group by the boxes and a dotted line (R^2=0.015).

4.5 DISCUSSION

Wheelchair transfers have been implicated as a contributing factor in the progression of CTS in people with SCI.[10, 12] Yet a direct link between transfers and upper limb injury has not been

reported in the literature. Previous studies have primarily relied on biomechanical analysis of potentially injurious aspects of transfers, such as wrist kinetics and kinematics.[124] The present study found repeated transfers to be associated with acute increases in nerve size at the carpal tunnel inlet – a marker for CTS indicating compression.[157] Of perhaps greater importance were the relationships found between injury markers and specific transfer techniques and body weight. These findings not only strengthen evidence that independent transfers contribute to CTS, but highlight certain techniques and subject characteristics and thus offer potential interventions.

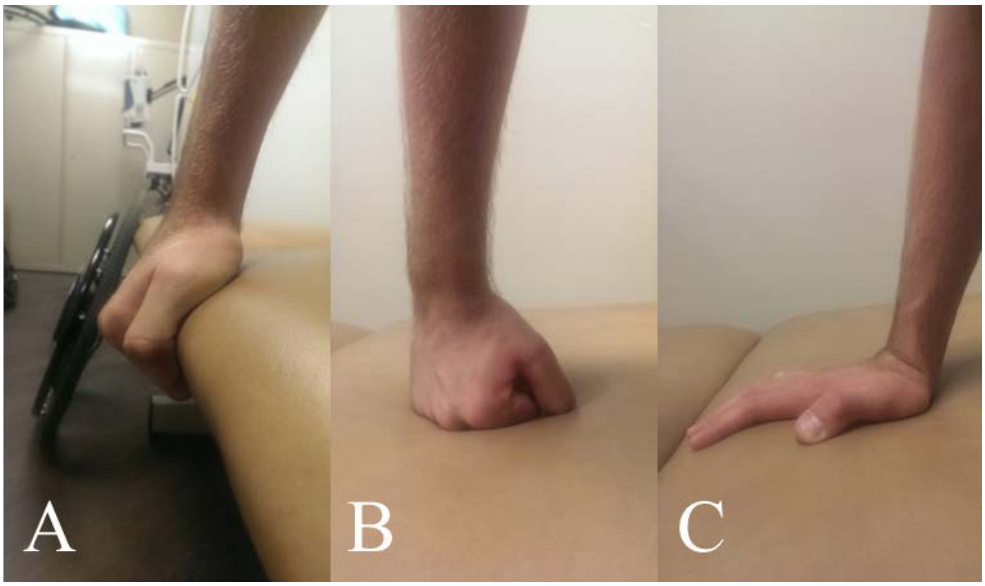


Figure 6. Images of proper (A) and improper (B and C) hand positions and use of handgrips. The safest position (A) is closest to neutral with a firm grip on the surface. Unsafe positions are less stable (B) or facilitate wrist extension and median nerve excursion under the transverse carpal ligament and over the carpal bones (C).

The observed relationship between proper use of handgrips (TAI item 9) and injury markers was as expected. This skill implies the individual placed their leading hand in a position such that their wrist is stabilized and closer to neutral (Figure 6), which can protect the median

nerve by reducing entrapment.[161] Larger nerves were observed at baseline in those who placed their feet on the floor during the transfer. This was not anticipated, as the feet can relieve upper limb loading during the transfer.[81] However, placing the feet on the floor can also extend the distance between the trunk and pivot point, increasing moment of inertia. Greater wrist/hand activity is also likely needed to move the trunk into a position where the feet can be placed on the floor and moved into the right position. To conserve angular momentum, individuals who used this skill may have to spend more time bearing weight during the transfer than those with smaller bases of support. Transfer timing was not evaluated in the current setup, so any potential relationship with foot placement could not be established.

Item 7 describes scooting forward to the front of the surface prior to transferring, which reduces the time and distance of upper limb loading. It was thought this skill would reduce impact on the median nerve, yet the opposite reaction was observed. Like placing feet on the floor, the "scoot" requires the user to lift his or her body weight to the front of the chair. This extra lift could compound acute effects of the transfer itself. Scooting also reduces the distance between the user's leading wrist and trunk, potentially increasing wrist extension and range of motion and amplifying the nerve response.[161, 162] No relationship was observed between a scoot and other TAI items that may be protective of the wrist, such as safe wrist positioning (items 9 and 10). Transfer interventions targeting multiple skills that optimize wrist position and loading may attenuate the effects of transfers, however this remains to be tested.

The literature suggests a positive relationship between body weight and median neuropathy in wheelchair users with SCI.[20, 22] In the present study weight was positively related to changes in CSA, indicating participants with more mass experienced greater nerve responses to transfers. Additional analysis found that participants with greater body weight exhibited lower

SR provided they had higher TAI scores, while weight affected CSA change regardless of TAI score. It appears that while weight has an acute impact on the nerve, the chronic effects may be offset by better transfer quality. These findings strengthen evidence that maintaining a proper body weight can help prevent or delay the development of median neuropathy.[113] Use of transfer assistive devices (such as transfer boards) can also reduce loading and potentially prevent pathology.[16] Weight is influenced by many factors including anthropometrics and body composition; measurement of Body Mass Index or central adiposity in place of total mass may provide a more conclusive analysis.

4.5.1 Limitations

Only one rater imaged the median nerve of all subjects. While this protocol optimizes reliability[156], inclusion of images made by an additional investigator may have improved accuracy of the measurements. Although changes in median nerve measures were significant, the group's average change in size was small. For individuals who were heavier and did not use specific skills, this change was often larger; however, this study was not able to determine a clinically-meaningful change. This study used a standardized setup and only included a mat table. While this was done to allow more control over the study, the setup limits generalizability of the results to other surfaces, heights, and objects. Participants may have adjusted their natural transfer technique mid-protocol to compensate for fatigue or match the metronome speed; this would have occurred after the initial grading of the TAI, which were used in regression analyses. Subjects in the present study performed 18 consecutive transfers; although this frequency is not akin to everyday-life, the protocol was designed to examine median nerve changes after a stressful transfer activity. There was also a disproportion of males to females in this study.

Differences in CTS prevalence have been noted to exist between genders[20, 148], as have differences in median nerve responses to activity.[153] Thus, it is possible a stronger relationship existed but was unable to be observed due to the small sample of females.

Many of the subjects were tested at wheelchair sporting events. It is possible these individuals were more active than the average wheelchair user with SCI, and prior training could amplify the median nerve response to activity. However, literature suggests activity levels and upper-limb pain are similar between the two populations.[128, 129, 163] After factoring in the similar proportion of athletes (56.7%) to non-athletes (43.3%) in the present sample, effects of prior training likely had a negligible impact on generalizability of the results.

Future studies should include neurophysiological testing to determine physiologic impact of activity. Evaluating nerve changes in the same individual after performing different skills would also provide more control and strengthen the study's conclusions. Finally, longitudinal testing is necessary to determine whether transfers and transfer skills training could reduce chronic injury.

4.6 CONCLUSIONS

Repeated wheelchair transfers resulted in acute increases in median nerve size – a marker for CTS. Median nerve changes were greater in those who scooted forward on the seat prior to transferring and those who weighed more. Proper hand positioning and utilization of hand grips by the leading arm was associated with less nerve swelling, and better overall transfer quality seemed to alleviate the negative consequences of higher body weight on the median nerve. Clinicians should consider training wheelchair users to use handgrips properly during the

transfer, as defined by the TAI. Further investigation is necessary to determine whether utilization of TAI skills deters longitudinal development of CTS.

5.0 MICRODIALYSIS TO MEASURE CHANGES IN GLENOHUMERAL JOINT INFLAMMATORY CYTOKINES AFTER UPP-EXTREMITY ACTIVITY: A PILOT STUDY

5.1 ABSTRACT

The repetitive and forceful nature of wheelchair use can contribute to rotator cuff pathology, potentially because of an upregulation of inflammatory mediators that can degrade the structural integrity of the tendons. The first objective was to test a novel method of measuring inflammatory cytokines in the glenohumeral joint (GHJ) and how they change after intense, upper-extremity activity (wheelchair propulsion and transfers). The secondary objective was to correlate inflammatory cytokines with ultrasound measures of pathology and with injurious propulsion biomechanics. Six able-bodied veterans were recruited for this pilot study who were over 18 years old, were not being treated with steroids, did not have any cardiopulmonary issues, were not pregnant, and did not have any upper-extremity dysfunction that could prevent wheelchair use. One individual with SCI was recruited who met the aforementioned inclusion criteria and the following: used a wheelchair for the majority of mobility, over one year post-injury, no current/recent history of pressure sores, had a quick-release axle, and could independently transfer without the use of their leg muscles. A microdialysis catheter was inserted into the posterior GHJ space under ultrasound guidance. Quantitative ultrasound (QUS) images

and microdialysis samples were collected, then participants completed an intense wheelchair propulsion and transfer protocol. QUS images and microdialysis samples were collected immediately after activity, 30-minute post-activity, and 60-minutes post-activity. In three (out of seven) participants, the microdialysis catheter failed and prevented sample collection. As well, only three cytokines could be reliably collected in all subjects: interleukin-8 (IL-8), IL-1 receptor antagonist (IL-1RA), and RANTES. At baseline, IL-1RA was correlated with age (r = .991, p = .003) and RANTES with BMI (r = .905, p = .095). RANTES (p < .05, η^2 = .615) and IL-1RA (p < .05, η^2 = .728) significantly changed after activity. A darker post-activity supraspinatus tendon was associated with greater increases in IL-8 (r = -.973, p < .05) and IL-1RA (r = -.912, p < .10); the same relationships were found in the biceps tendon (IL-8: r = -.958, p < .05; IL-1RA: r = -.994, p < .01). Greater exercise-induced changes in RANTES were correlated with smaller propulsive forces (r = -.948, p = .052). Results from this study suggest that BMI and age are associated with inflammatory markers in the shoulder joint. Furthermore, an acute inflammatory response occurs during wheelchair activities that may be influenced by propulsion biomechanics. The inflammatory biochemical response may influence the progression of rotator cuff tendinopathy. Longitudinal testing with a larger sample size would yield a better understanding of how cytokines interact with age and BMI to contribute to rotator cuff pathology. Different methodologies need to be explored to improve data collection, such as use of serial blood draws or an aspiration technique.

5.2 BACKGROUND

Shoulder pain is highly prevalent among manual wheelchair users with SCI, with an estimated prevalence of between 30% and 73%.[117] Pain is attributed to their reliance upon their upper-extremity to perform most activities of daily living. Propulsion and transfers promote independence and mobility, but repeatedly expose the soft tissues of the shoulder to loads that contribute to pathology.[16]

Rotator cuff pathology is a complex phenomenon. Normally, exposure to overload initiates a cascade of biochemical changes that are designed to promote tendon healing.[34] Chronic exposure, however, can lead to alterations in cellularity, vascularization, and extracellular matrix that reduce the ability of a tendon to withstand load.[164, 165] This repetitive microtrauma can lead to degeneration, and ultimately culminate in a tear.[34, 165] Investigation in rats has revealed that overuse – from repetitive, forceful activity – leads to an upregulation of inflammatory cytokines in the exposed soft tissues.[51, 54, 56] Such overuse can negatively influence tendon mechanics, illustrated by an altered Young's modulus and reduced load to failure.[50] In humans, rotator cuff tendinopathy is associated with an upregulation of several systemic inflammatory cytokines, including interleukins-1 beta (IL-1β), -6, -8, and -10.[59]

Inflammatory cytokines have been observed in the glenohumeral joint (GHJ) synovial membrane and fluid, and appear to relate to rotator cuff tear severity.[166-168] Osawa, Shinozaki, and Takagishi observed higher levels of IL-1β in the synovial fluid of patients who underwent rotator cuff repair; samples were collected during surgery and compared with patients who had non-rotator cuff shoulder lesions.[166] Gotoh, et al. performed a histological analysis to determine mRNA expression of IL-1β and its receptor antagonist, IL-1RA, in samples of the GHJ synovium collected during rotator cuff surgery. Patients with full- and partial-thickness tears

were compared with samples from controls collected during shoulder surgery for other (non-rotator cuff) pathologies. This group found that expression of both cytokines was higher in full-thickness tears compared with partial-thickness tears, and both groups were higher than controls.[167] Cytokine expression was inversely related to pain in the patients with rotator cuff tears.[168] GHJ inflammatory cytokines appear to be associated with rotator cuff pathology, yet this has not been tested in non-pathological tendons.

Microdialysis allows for the *in vivo* detection of inflammatory mediators in a variety of soft tissues.[69] A fluid is pumped through a catheter with a perforated membrane, which is placed within the tissue of interest. This technique allows the passive diffusion of molecules from the interstitial space surrounding the membrane into the fluid flowing through the catheter. Inflammatory mediators have been found to increase following exercise in the Achilles peritendinous space[79, 169], as well as alterations in extracellular matrix turnover in pathological tendons.[43] More recently, the microdialysis technique has been developed and applied in the synovial membrane and intra-articular space of the knee.[170] Helmark, et al. observed exercise-induced increases in intra-articular IL-6, -8, and -10, and tumor necrosis-alpha (TNF-α) in women with osteoarthritis.[73]

Quantitative ultrasound (QUS) allows for the non-invasive measurement of different markers that indicate pathology. Tendon width and echogenicity attempt to quantify intratendinous edema, a hallmark of tendinopathy. A healthier tendon will contain a higher collagen content and less fluid; thus, it would be thinner and brighter (i.e. greater echogenicity). Both markers have been previously applied to better understand the acute responses of the rotator cuff tendons to wheelchair use.[111, 134] Participants in a study by van Drongelen, et al. exhibited darker, wider biceps tendons after a wheelchair sporting event. Greater decrements in

echogenicity were associated with higher levels of shoulder pain and greater lengths of play. Collinger, et al. found that participants with a longer duration of wheelchair use and more baseline tendinopathy exhibited darker biceps tendons after an intense, standardized wheelchair activity. These studies suggest wheelchair propulsion acutely impacts fluid accumulation within the biceps tendon, which acts alongside the rotator cuff to stabilize the humerus within the GHJ.

Few groups have studied the association between GHJ inflammation and rotator cuff pathology.[166, 167, 171, 172] To date, none have attempted to answer the same question in individuals without a rotator cuff tear, or how shoulder overuse influences the relationship. The objective of this study was to investigate how an intense upper-extremity activity influences GHJ inflammatory cytokines, and how cytokines in turn affect rotator cuff pathology. In this way, a better understanding of how highly repetitive and forceful activities influence rotator cuff pathology can be developed. An intense wheelchair activities protocol was hypothesized to cause an acute increase in GHJ inflammatory cytokines, measured using microdialysis. Furthermore, greater increases in exercise-induced cytokines would correlate with higher propulsive forces and stroke frequencies, and with QUS measures of biceps and supraspinatus pathology.

5.3 METHODS

5.3.1 Participants

A convenience sample of able-bodied Veterans was recruited using flyers posted in the local Veterans Affairs hospital. Subjects were included if they were over 18 years old; not being treated with steroids; were not pregnant; and did not have a generalized inflammatory condition,

upper extremity pain that would limit their ability to use a wheelchair, a history of shoulder fractures/dislocations that had not fully healed, or cardiopulmonary problems that could be exacerbated by strenuous physical activity. Able-bodied Veterans were recruited to test the protocol and gather data before recruiting wheelchair users with SCI.

The subjects with SCI would meet additional criteria: a non-progressive SCI with residual paralysis that occurred more than one year ago; use of a wheelchair for the majority of mobility (≥40 hours/week); could independently transfer to and from a surface within 30 seconds without the use of their leg muscles; had a quick-release axle for attachment of the SmartWheel to the chair; and had no recent or current history (within the past 3 months) of pressure ulcers.

5.3.2 Study Protocol

All procedures occurred during a single, 5-hour visit. Subjects provided informed consent, which was approved by the local VA ethical committee. All procedures occurred on the non-dominant shoulder to control for the effects of handedness. First, subjects' shoulders were examined for seven different clinical ultrasound signs for shoulder pathology, according to the Ultrasound Shoulder Pathology Rating Scale (USPRS; further details of each test are located in Section 2.3.2). A microdialysis catheter was then inserted into the posterior GHJ space using the procedure described below. A 60-minute resting period followed the insertion protocol; this timeframe was chosen to allow any insertion-related inflammation to subside and return to basal levels.[169] Subjects were instructed to use their arm as little as possible during the remainder of the protocol when they were not exercising. Baseline microdialysis samples and QUS images of the biceps and supraspinatus tendons were collected after the resting period.

Participants then completed an intense wheelchair activities protocol. A force- and moment-sensing handrim was attached to the chair under the non-dominant arm, opposite a wheel with identical handrim and tread pattern. They propelled their wheelchair at self-selected maximal effort around a 15-meter figure-8 course, stopping in the center after every turn (Figure 7). Three, four-minute intervals were completed. They then performed three sets of six back-and-forth transfers onto a mat table; a bathroom scale was placed at their feet to monitor how much bodyweight they were offloading onto their legs. The goal of this wheelchair activities protocol was to stress the shoulder joint via repetitive activity.

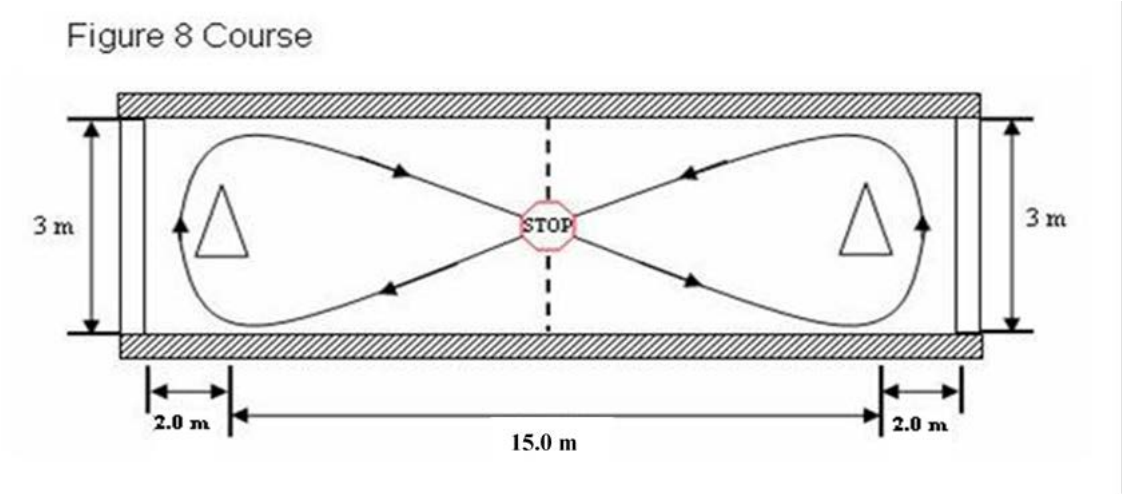


Figure 7. Figure-8 course for propulsion trials. Arrows indicate direction of travel. Triangles indicate turning points, and the stop sign indicates stopping point.

Microdialysis samples and QUS images were collected immediately after the wheelchair activities protocol, and every 30 minutes thereafter during a 60-minute rest period. Subjects were contacted 7 and 30 days after their participation and asked a series of questions to monitor potential side effects of the protocol.

5.3.3 Microdialysis Procedure

After the ultrasound examination, the subject lay on a height-adjustable mat table with their non-dominant arm toward the ceiling. A physician, highly experienced in joint injections, imaged the posterior joint space using a curvilinear ultrasound probe to determine the best needle pathway to enter the joint; this location was marked on the skin with a surgical marker. Once the entry location was demarcated, sterile procedures akin to a central line insertion were followed.[173] More information about the sterile procedures is detailed in Appendices A.1 and A.2. Under ultrasound guidance, the physician injected a 50:50 solution of 1.0% lidocaine and 0.5% bupivacaine to anesthetize the shoulder to reduce any discomfort for the subject.

A needle with a splitable introducer was guided into the posterior joint space, again using ultrasound (Figure 8). The needle was removed and replaced with a microdialysis catheter (MDialysis, Inc., North Chelmsford, Massachusetts, USA). The catheter has a 1-centimeter membrane with 100 kDa diameter pores that allow the passive diffusion of inflammatory molecules into the perfusion fluid that is pumped through the catheter. The introducer was then removed, leaving the catheter in place, and a surgical dressing with chlorhexidine gluconate sponge was adhered to the skin to secure the catheter. All sterile barriers were removed once the dressing was in place.[173]

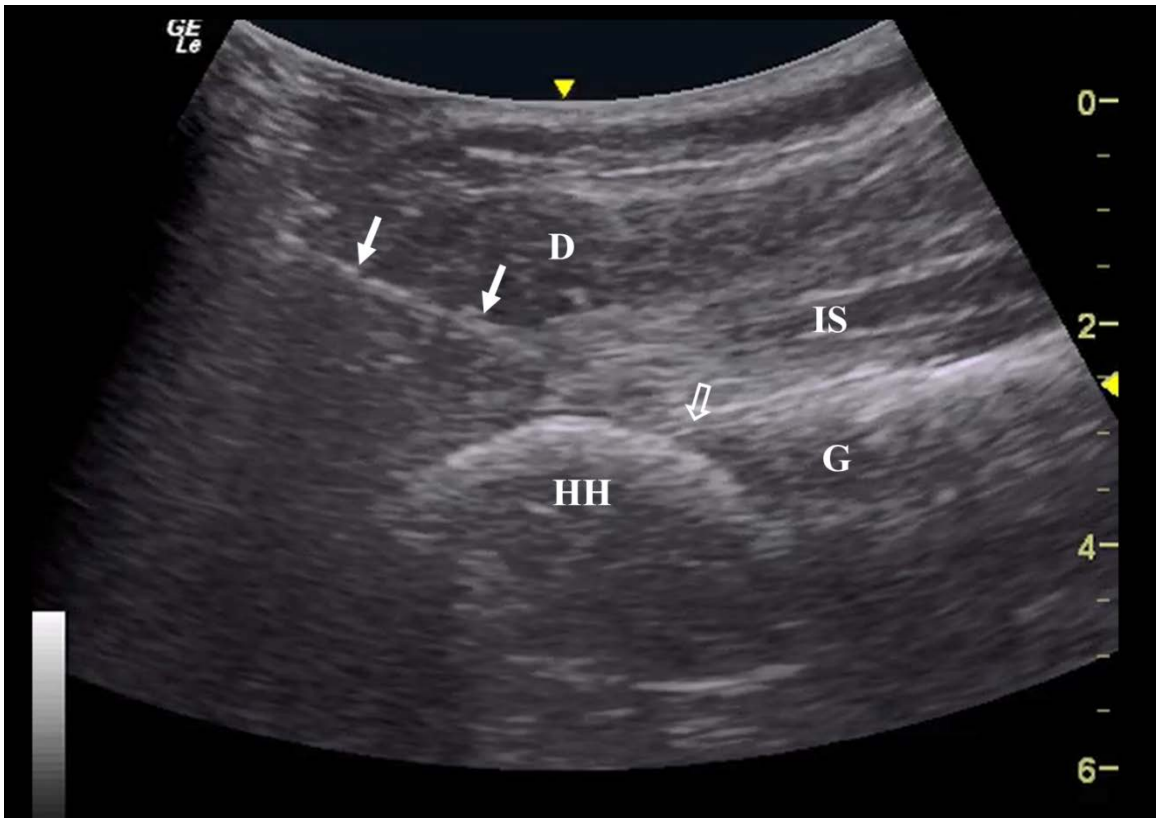


Figure 8. Microdialysis catheter position within the posterior glenohumeral joint. White arrows=introducer/needle. Empty arrow=needle tip. G=glenoid. HH=humeral head. D=deltoid muscle.

A high-precision perfusion pump was connected to the catheter and turned on to begin the 5-minute flushing procedure. The perfusion fluid was pumped through the catheter at a flow rate of two µL/minute, which was collected in a microvial. Perfusion fluid is an isotonic solution that mimics the interstitial fluid of peripheral tissues: 147 mmol/L NaCl, 4 mmol/L KCl, 2.3 mmol/L $CaCl_2$. Dextran 60 is added to the fluid to prevent loss of perfusion fluid during the exercise protocol.[169] The flow rate was chosen to optimize diffusion through the membrane while ensuring enough dialysate could be collected for analysis. The remainder of the catheter was secured to the skin with tape and the pump was secured to the subject's back using a custom-built harness (Figure 9).

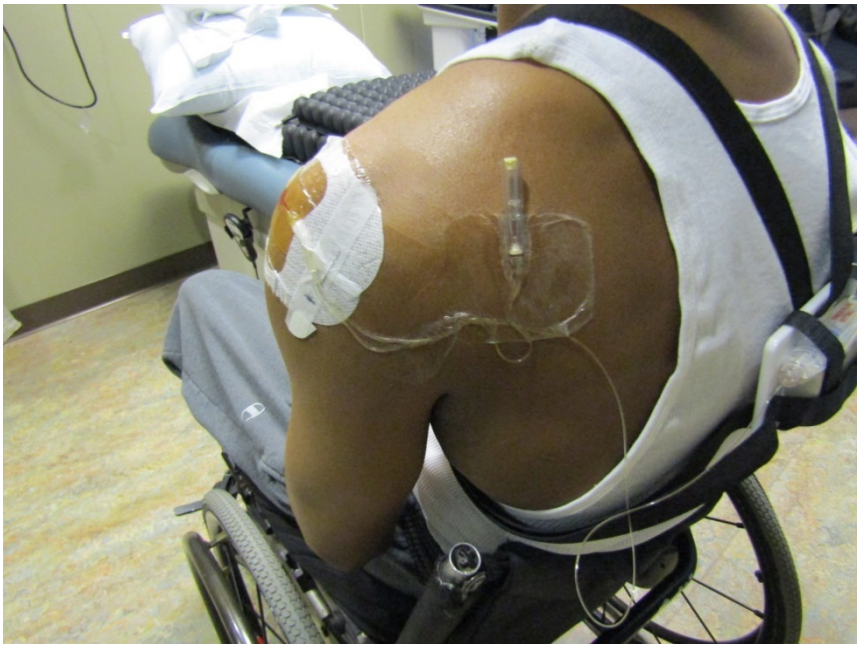


Figure 9. Microdialysis pump, catheter, and microvial setup.

5.3.4 Sample Collection and Analysis

Microdialysis dialysate samples were collected every 30 minutes when possible, and immediately stored at -80 degrees Celsius until they were transported for analysis to the University of Pittsburgh Cancer Proteomics Facility. They were kept on dry ice within an insulated container during transportation. Samples were analyzed for inflammatory cytokines via Luminex (Luminex Corporation, Austin, Texas, USA), a bead-array cytometric analyzer, using a Milliplex Human Cytokine Panel (Millipore, Billerica, Massachusetts, USA). This particular panel analyzes each sample for 27 different inflammatory cytokines, which are listed in Appendix C.1. 30 µL of dialysate were analyzed, and samples with less than 30 µL were diluted to reach that concentration. Sample volumes and dilutions are included in Appendix Section C.2. The Luminex procedure is comparable with ELISA for many inflammatory cytokines.[174]

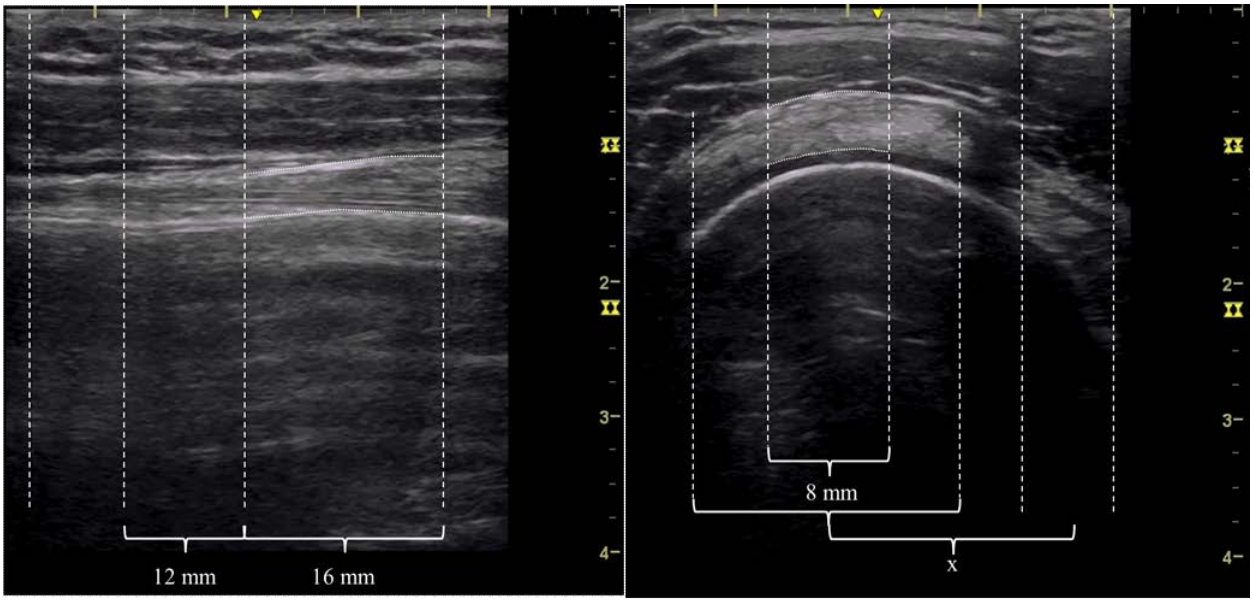


Figure 10. Quantitative ultrasound images of the biceps (left) and supraspinatus (right) tendons. The region of interest (ROI) is calculated from the center of the interference pattern, either 12mm for the biceps tendon or a variable distance for the supraspinatus tendon ("x"). "X" is determined when the user defines the visible portion of the tendon, and is held constant throughout the rest of the analysis using the center of the interference pattern as a reference.

5.3.5 Quantitative Ultrasound

The QUS protocol described in Section 3.3.3 was used to measure biceps and supraspinatus tendon width and echogenicity. These two measures are associated with inflammation and edema[132], which are hallmarks of tendinopathy. However, a different ultrasound machine was used in the current study (Logiq e, GE Medical Systems Co., Jiangsu, China). The linear probe was smaller (50.0x10.0mm versus 38.4x5.0mm), which required altering the original MATLAB code and marker design[175] (created by Dr. Jen Collinger) to accommodate the differences in probe dimensions and pixel density. Specifically, the skin marker length and ROI width were scaled down approximately 20% to accommodate for differences in probe lengths; the width of

the marker was scaled down 50% to accommodate for differences in probe widths. The original pixel conversion algorithm was modified to accommodate the new pixel density. Images with the new ultrasound machine are shown in Figure 10.

5.3.6 Biomechanical Analysis

Handrim kinetic data were collected using the SmartWheel, a modified wheel that senses three-dimensional forces and moments imparted onto the handrim.[176] Data were collected at 240 Hz during the first and last minute of each of the three intervals. Each stroke during the straightaway portion of the figure 8 (Figure 7) was analyzed.[111] Although participants propelled for three intervals, only data from the second and third intervals were analyzed; the first was omitted to account for learning effects. Data were filtered with an 8th order Butterworth low pass filter (20 Hz cutoff frequency).[107] Parameters of interest included stroke frequency and peak resultant force (FR).[176] FR is calculated using Equation 5.1, where Ft and Fr are tangential and radial forces, respectively. Propulsive forces and stroke frequencies are influenced by speed[107], thus were normalized to velocity.

$$FR = \sqrt{Ft^2 + Fr^2 + Fz^2} \qquad \text{[Eq. 5.1]}$$

5.3.7 Statistical Analysis

All analyses were performed using SPSS v23.0 (IBM, Inc., Armonk, New York, USA). Because of the small sample size, p-values of <.05 were considered significant and no corrections for multiple tests were applied. Trends of p<.10 were also reported. Cytokine concentrations at each

time point were plotted to show temporal changes in each. Normality was assessed using the Shapiro-Wilk test. A repeated-measures analysis of variance was used to determine significance of changes in cytokines after the activity. Although the sample size was small, analysis of variance is appropriate if the variables are normally distributed and a Hyun-Feldt correction is applied.[177] Post hoc analyses for the ANOVAs were conducted to examine changes at each time point with respect to baseline; Bonferroni corrections were applied. Following the within-subjects tests, cytokine changes were correlated with QUS changes and biomechanical variables by calculating Pearson's *r*.[178] Percentage changes were calculated by subtracting the time-specific value from baseline, then dividing by baseline.

5.4 RESULTS

5.4.1 Participants and Study Power

Six able-bodied Veterans and one wheelchair user with SCI participated in the present study; demographic information is presented in Table 14. No participants reported any side effects, including signs of infection, 30 days after participation. The microdialysis membrane failed within the joint after insertion in three participants, which prevented collection of dialysis fluid (Table 14). Complications during testing of the first participant prevented the collection of the last sample. For this subject, an intent-to-treat technique was used to preserve the sample size for within-subjects analyses by using 30-minute biochemical concentrations for the 60-minute value.[179]

With usable data from only four subjects, this study was underpowered to detect significant correlations between cytokines changes and propulsion biomechanics. A power analysis using an α of 0.05, β of 0.80, and correlation coefficient of 0.4 revealed a sample size of 26 would be required to achieve significance. The correlation coefficient was derived from the relationship between peak FR and IL-8 post activity changes (See Appendix B.3).

Table 14. Subject demographics and baseline cytokine concentrations (pg/mL).

Subject #	Age	Weight	Sex	Race	RANTES	IL-8	IL-1RA
1	57	30.2	M	W	324.15	11.01	18.43
2	55	26.8	M	W	NA	NA	NA
3	37	33.5	M	W	696.98	4.53	12.18
4	29	27.3	M	AsA	150.53	5.49	9.86
5	62	25.9	M	AfA	NA	NA	NA
6	50	25.2	F	AfA	210.88	14.41	16.93
7*	33	19.6	M	AfA	NA	NA	NA

Notes. W=white. AsA=Asian-American. AfA=African-American. NA=not available.
*Participant with level T3/4 paraplegia, 18.1 years since injury.

5.4.2 Self-Reported Pain and Clinically-Graded Pathology

None of the able-bodied subjects reported any usual shoulder pain (0 out of 10). However, at least one ultrasonographic sign of pathology were noted in all subjects, with supraspinatus tendinopathy and cortical irregularity being the most common (Table 14). The subject with SCI reported an average level of shoulder pain of five out of ten, yet no signs of pathology were noted (Table 14).

Table 15. Ultrasound Shoulder Pathology Rating Scale individual item scores per subject.

ID	Biceps Grade	Supraspinatus Grade	Supraspinatus Impingement	Subscapularis Impingement	Cortical Irregularity	Joint Effusion	Bursal Thickness	Total USPRS
1	0	0	0	0	1	0	0	1
2	1	1	0	0	1	0	1	4
3	0	0	0	0	1	0	1	2
4	0	1	0	0	1	0	0	2
5	3	3	0	0	2	1	1	10
6	0	2	0	0	2	0	0	4
7*	0	0	0	0	0	0	0	0

*Participant with SCI

5.4.3 Glenohumeral Joint Cytokines and Activity

Only three of the twenty-seven analytes were detectable by the assay across all participants: RANTES, IL-8, and IL-1RA. Baseline IL-1RA concentrations were higher in older participants (r = .991, p = .003; Figure 11). Baseline RANTES concentrations were higher in participants with higher BMI (r = .905, p = .095; Figure 12).

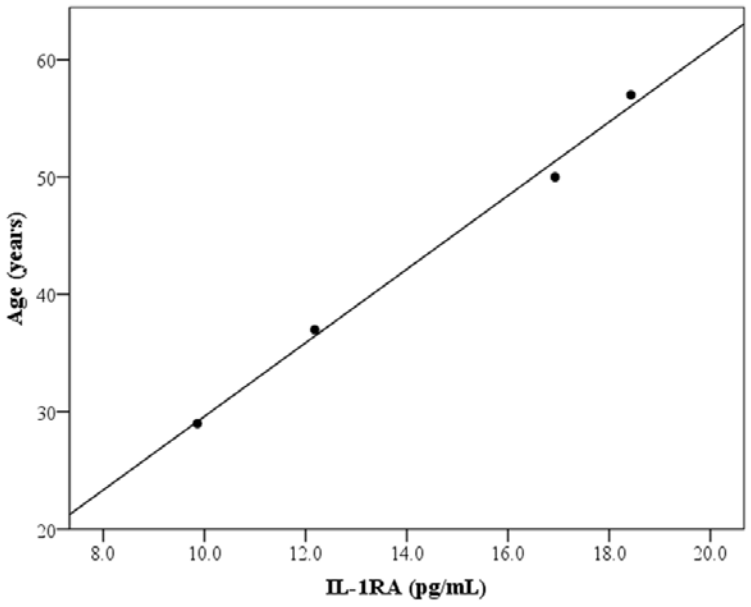


Figure 11. Scatterplot depicting the positive, linear relationship between interleukin-1RA and age (R^2=.982).

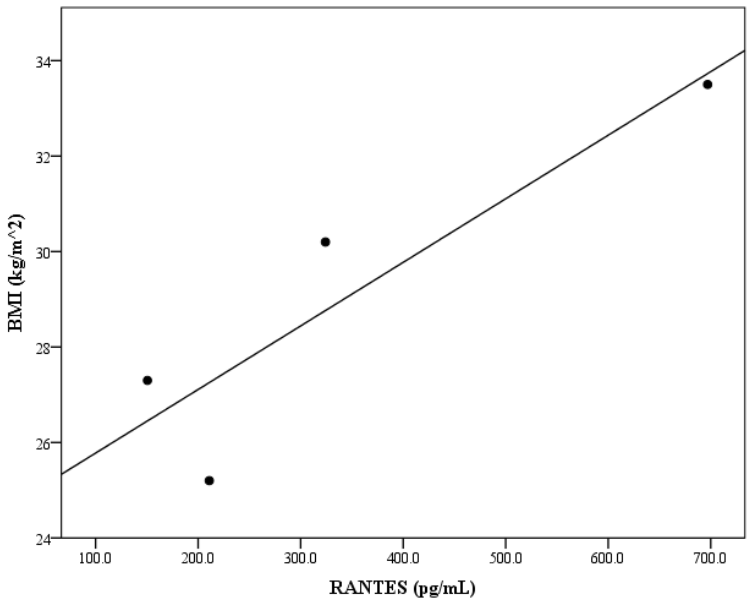


Figure 12. Scatterplot depicting the linear relationship between body mass index (BMI) and baseline RANTES concentrations (R^2=.819).

Changes in RANTES (F = 4.78, p = .029, η^2 = .615) and IL-RA (F = 8.03, p = .007, η^2 = .728) were significant across all time points; changes in IL-8 were not significant (p > .05). Figure 13 shows each subject's individual response to the wheelchair activity. IL-1RA concentrations were greater than baseline immediately after and 30 minutes after the activity (p < .05). RANTES concentrations were greater than baseline immediately after the activity (p < .05), but at no other time point (p > .05). Changes in IL-8 and IL-1RA were correlated immediately after activity (r = .979, p = .021) and after 60 minutes of rest (r = .999, p = .001).

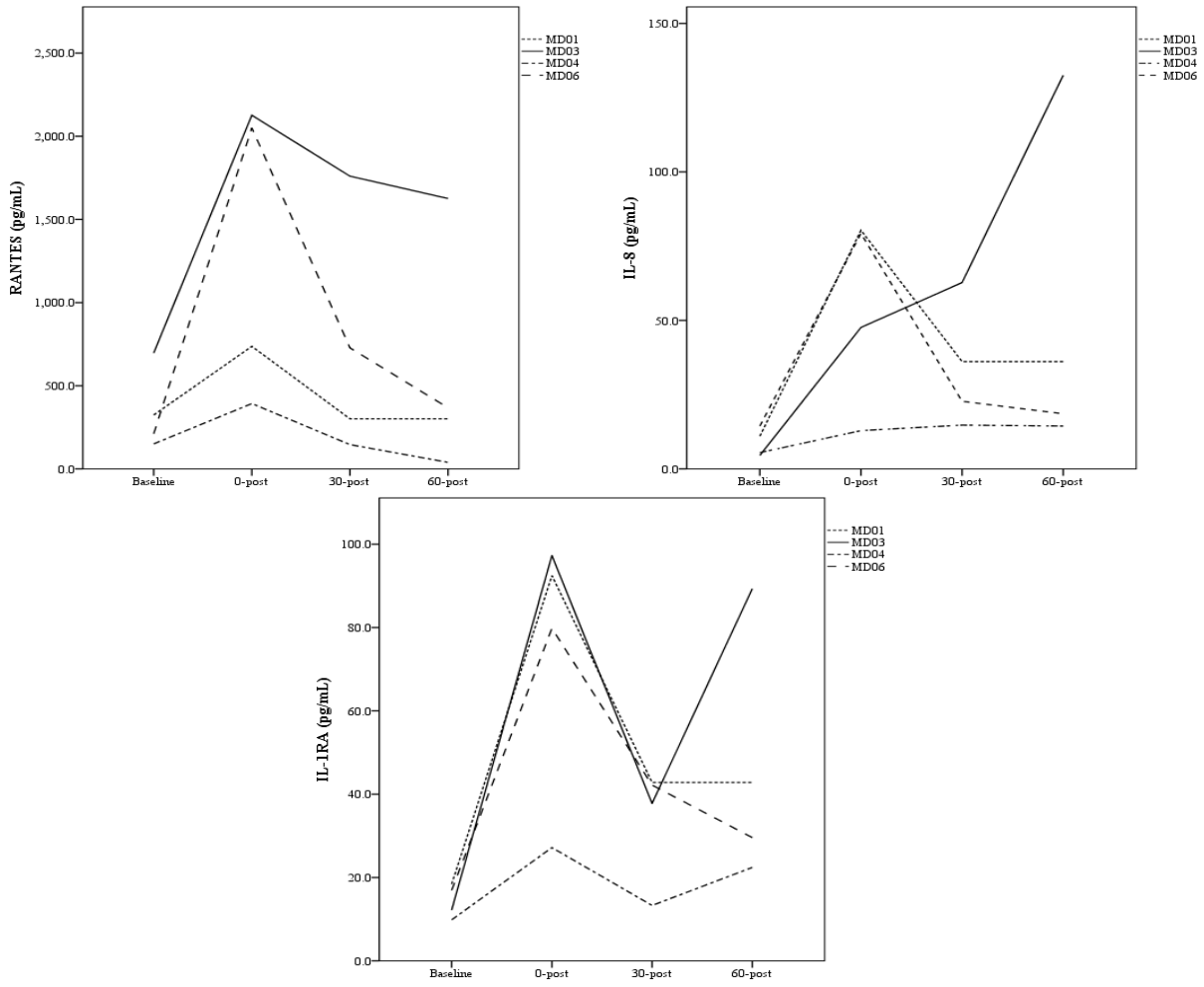


Figure 13. Subject-specific changes in RANTES, IL-8, and IL-1RA after intense wheelchair activities between baseline, immediately post-activity, 30-minutes post-activity, and 60-minutes post-activity.

5.4.4 Cytokine Changes and Propulsion Biomechanics

Subject-specific biomechanical variables are described in Table 16. The correlation between post-activity RANTES changes and normalized peak FR approached significance (r = -.948, p = .052; Figure 14). No other relationships were observed.

Table 16. Subject-specific propulsion biomechanical variables.

Subject #	Peak FR (N)	Stroke Frequency (strokes/s)	Average Velocity (m/s)
1	105.02	0.84	0.83
3	139.96	1.06	1.17
4	153.17	0.89	1.39
6	66.85	0.70	0.81
Mean (SD)	116.25 (38.7)	0.87 (0.15)	1.05 (0.3)

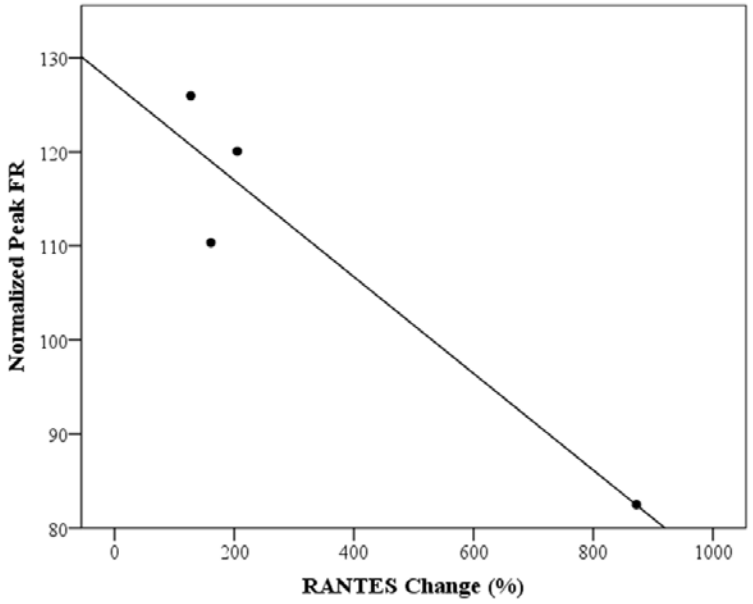


Figure 14. Scatterplot depicting the inverse linear relationship between peak resultant force (FR), normalized to velocity, and post-activity changes in RANTES concentrations, normalized to baseline (R^2=.898).

5.4.5 Cytokines and Ultrasound Markers for Pathology

At baseline a brighter supraspinatus tendon was correlated with greater RANTES concentrations (r = .928, p = .072). A brighter, wider tendon was also associated with smaller IL-8 concentrations, yet the correlations were not significant (width: r = .793, p = .207; echogenicity:

r = -.729, p = .271). Immediately after the wheelchair activity, a darker supraspinatus tendon was associated with greater increases in IL-8 (r = -.973, p = .027) and IL-1RA (r = -.912, p = .088). The linear relationships are presented in Figure 15. A darker biceps tendon was also associated with greater increases in IL-8 (r = -.958, p = .042) and IL-1RA (r = -.994, p = .006). Greater increases in IL-8 (r = .828, p = .172) and IL-1RA (r = .831, p = .169) were related to wider supraspinatus tendons, but the correlations were not significant. Total USPRS score was correlated with greater increases in RANTES after activity (r = .951, p = .049; Figure 16), but none of the QUS measures.

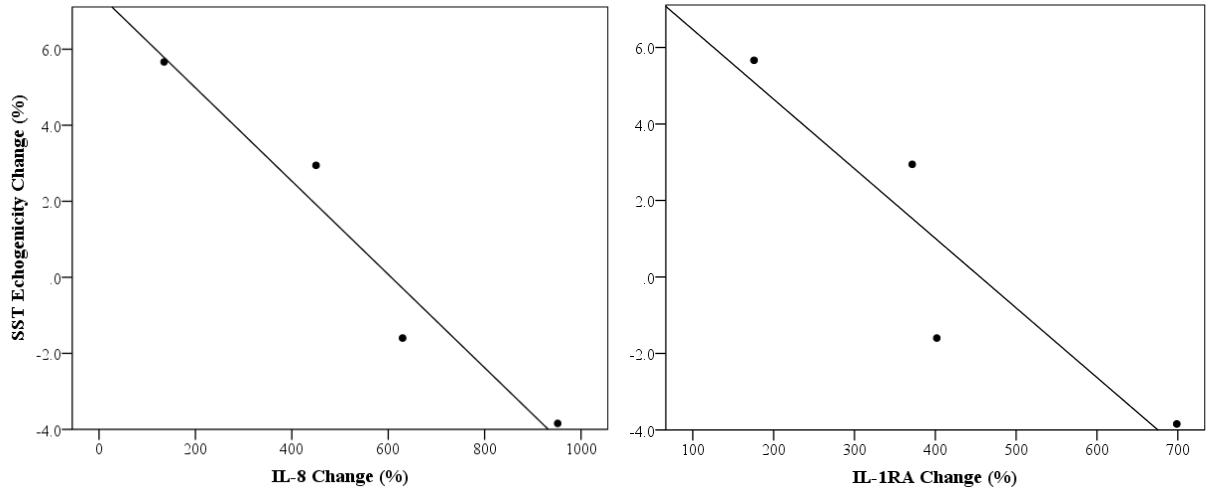


Figure 15. Scatterplot of the linear relationships between activity-induced changes in supraspinatus tendon (SST) echogenicity and interleukins-8 and -1RA (IL-8 and IL-1RA). Changes in SST echogenicity were correlated with IL-8 (R^2=.947) and IL-1RA (R^2=.833).

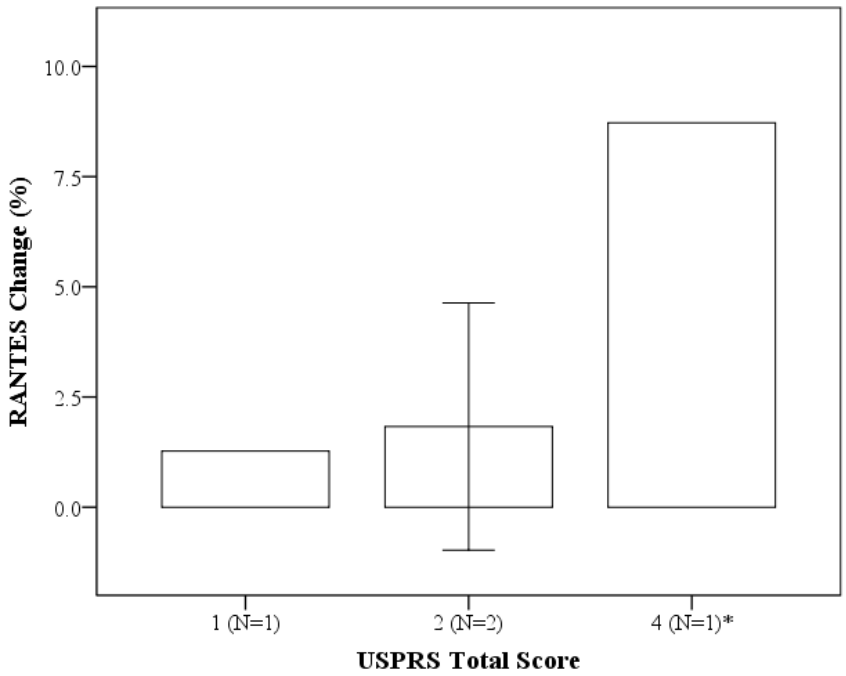


Figure 16. Bar graph depicting activity-induced changes in RANTES concentrations in subjects with differing pathology grades, measured using the USPRS. *Outlying subject in Figure 14.

5.5 DISCUSSION

The present study tested a novel, *in vivo* method of quantifying GHJ inflammatory cytokines using microdialysis. This technique allowed for continuous measurement of inflammatory cytokines during and after a stressful wheelchair activities protocol. To our knowledge, this is the first study to establish concentrations of RANTES and IL-1RA in soft tissue using microdialysis so it is difficult to establish the validity of those measurements. However, similar concentrations of IL-8 have been reported recently in the masseter muscle of the jaw, and the intra-artciular space and (extra-articular) synovial membrane of the knee in osteoporotic women.[73, 180] The strong relationship that was observed between BMI and baseline RANTES concentrations

provides evidence of the validity of our measurements, as this cytokine is released by adipose tissue and associated with obesity.[181] The measurements were further validated by the strong, positive correlation between RANTES changes and USPRS scores. The primary finding was that changes in RANTES and IL-1RA were observed after wheelchair propulsion and transfers. Furthermore, cytokine changes were related to clinically-relevant ultrasound measures of shoulder pathology and propulsive forces.

Large increases in the inflammatory cytokines were observed in all subjects immediately after the activity. Exercise is known to induce acute pro- and anti-inflammatory responses, thus this response was expected.[182] The immediate influx of cytokines could have been caused by an activity-induced increase in blood flow to the area[183], cellular responses to stress, or a combination of both. It is also possible that the correlations between tendon QUS parameters and cytokine changes can be attributed to commensurate fluctuations in blood flow.[184] However, the lack of a relationship between exercise-induced changes in RANTES concentrations and QUS parameters suggests another mechanism. IL-8 has been hypothesized to induce angiogenesis in response to exercise[185], and a systemic upregulation of this chemokine is associated with radiologic signs of rotator cuff degeneration.[59] Excessive neovascularization can lead to venous congestion – a mismatch of arterial and venous pressures caused by the growth of new vessels – which attenuates the clearance of inflammatory mediators.[186] It is possible that tendons became darker after exercise because of this occlusion. As vessels emptied and pressures normalized during the resting period, the tendon became brighter while still appearing inflamed.

The only cytokine to correlate with propulsion biomechanics was RANTES; an inverse relationship was noted, which was opposite of our hypothesis. This was also the only cytokine that did not correlate with QUS measures. It is possible that RANTES is secreted in response to

stress in an effort to heal the tendon. In a rat model of Achilles tendon rupture, intratendinous RANTES concentrations were found to stimulate an inflammatory response that promoted the healing process.[187] In vitro investigations have examined the influence of platelet-rich plasma (PRP) on the expression of several cytokines, including RANTES and IL-8. PRP therapy modulates angiogenesis and low-grade inflammation to modify the pathological state of the tendon, and has moderate success in the rotator cuff.[188] These studies found that pathological tendon cells synthesize high levels of RANTES in response to PRP treatment, while IL-8 secretion was reduced.[189] Thomas, et al. conducted an in vitro study to examine how RANTES and IL-8 respond to cyclical stretching in bronchial epithelial cells and observed opposite responses; while IL-8 increased after stretching, RANTES decreased.[190] Although it is a pro-inflammatory cytokine, RANTES may promote soft-tissue healing. This may explain the observations made by Sowa, et al. in a sample of people with low-back pain, who reported smaller RANTES activity-induced changes in those with had greater mobility.[191] Although greater changes were observed in participants with more clinically-graded pathology, the sample size was too small to build a more comprehensive model that would elucidate how pathology and propulsive forces interact. Further exploration into the role of this cytokine in in vivo models is necessary to better understand its role in the tendinopathic pathway and response to stressful activity.

The results were promising, yet outcomes of this study suggest the microdialysis technique is not appropriate for measuring GHJ intra-articular cytokines. We were unable to determine the reason why no fluid was collected in some of the subjects, and less than 60 µL was collected in others. The catheter membrane is delicate and even a small fracture will cause the perfusion fluid to leak into the joint. It is likely that the bony environment of the GHJ was too

harsh for use in participants with a smaller joint space. Cellular debris may also have infiltrated the small pores, potentially slowing collection. Scanning electron microscopy of the catheters revealed some may have malformations that may affect collection.[192]

Most microdialysis studies have not placed the catheter inside a joint, but instead in soft tissues such as adipose or muscle. Felländer-Tsai, et al.[193] inserted a microdialysis catheter into the knee joint synovial space, under athroscopic control, to test the metabolic response to irrigation after surgery. Helmark, et al. later redeveloped the technique by inserting two catheters intra- and extra-articularly.[170] This group then used their method to evaluate exercise-induced responses of IL-6, -8, and -10, and tumor necrosis factor-α (TNF-α).[73] Subjects in the aforementioned studies were resting with little movement during the sampling period; exercise was performed prior to catheter insertion. In our approach, we inserted the catheter into the posterior joint space while the joint was fully adducted and internally rotated. During the following resting period, the subjects reverted to their natural posture. The physician also noted smaller joint spaces in the two able-bodied participants whose catheter malfunctioned. It is possible that when these subjects externally rotated and abducted their shoulders back to neutral, the high contact forces between the glenoid and humeral head[194] fractured the catheter. Helmark removed the catheters after the baseline resting period and prior to exercise, and then inserted another set of catheters immediately after exercise.[73] Cytokine concentrations increased in both the exercise and non-exercise groups in a similar manner. The observed response was likely caused by tissue trauma during the insertion process; thus, a similar approach may not yield meaningful results.[195]

Concentrations of many of the hypothesized cytokines were too low to be detected by the assay. Because the microdialysis technique relies on passive diffusion, the membrane molecular

cutoff and pump flow rate both affect molecular recovery. A previous group has used a similar flow rate and had success using a custom-made catheter with a larger molecular cutoff (3000 kDa).[73] The catheters that were used in the present study, however, were those with the largest commercially-available cutoff (100 kDa). Increasing the pore size also reduces membrane durability; considering the durability issues with the 100 kDa catheters in the GHJ, a larger cutoff would not be appropriate. Additionally, relative recovery was not established so the exact concentrations in the space outside of the catheter cannot be determined.[169] Several groups have quantified relative recovery for various cytokines, yet none with the same catheter and flow rate used in the present study.[79, 169, 170, 192] Sampling directly from the synovial fluid or utilizing serial blood draws may overcome these limitations and yield higher biochemical concentrations for each candidate marker. These techniques would also allow for the identification of additional relevant biochemical markers, such as adiponectin or substance P.

5.5.1 Limitations

There were a few limitations to this study. The sample with analyzable data was small and consisted of able-bodied Veterans, which limits generalizability to the SCI population. We were unable to determine if the catheter moved during the protocol because the CHG patch in the sterile dressing prevented a clear image of the catheter; we chose to maintain the sterile barrier to reduce the risk of infection. Movement of the catheter away from the joint would promote the collection of intramuscular cytokine concentrations. Most other widely-studied pro-inflammatory markers (e.g. TNF-α, IL-1β, IL-6, IL-10) could not be reliably collected to better understand the inflammatory pathway. As well, the first subject's true cytokine concentrations values after 60 minutes of rest were not available because of the missing sample; it is possible that the true

response of this subject would alter the results. Implantation of a microdialysis catheter initiates an inflammatory reaction.[70] A 60-minute post-insertion rest period was included in an attempt to control for this.[70] However, during the wheelchair activity protocol, movement of the tissues around the catheter may have caused an inflammatory response that was not representative of the activity itself. As well, lidocaine and bupivacaine have been found to affect cytokine responses to inflammatory stimuli.[196, 197] Although anesthetic was not introduced into the joint, there is a possibility that the observed cytokine response was influenced by its presence.

5.6 CONCLUSION

Wheelchair activities caused an acute increase in inflammatory cytokines in able-bodied Veterans. Subjects that propelled with greater force and stroke frequency exhibited a sustained elevation in these inflammatory mediators. Furthermore, a relationship exists between inflammatory changes in the supraspinatus tendon and IL-8. It is possible that chronic exposure to these inflammatory mediators via wheelchair activities could accumulate to influence supraspinatus tendon health. The microdialysis technique is not appropriate for use in the GHJ during activity because of complications with the membrane and cytokine concentrations below the assay's detection range. The small sample size prevented a more comprehensive analysis to determine the exact relationships between wheelchair activities, rotator cuff tendon health, and joint inflammation.

6.0 CONCLUSIONS

The first study described the correlation between transfer technique, ultrasound markers for shoulder pathology, and self-reported transfer-related pain. Participants who weighed less and transferred using more ergonomic techniques exhibited healthier shoulders, with particular respect to the supraspinatus tendon. Better technique was also correlated with less shoulder pain during transfer activities. These associations were observed after controlling for several subject characteristics that were associated with pathology. Results from this cross-sectional investigation indicate that utilizing more ergonomic techniques may prevent the development of shoulder pathology and ameliorate the pain caused by transfers.

The second study continued the narrative by investigating the acute effects of transfers and technique on quantitative ultrasound markers of biceps and supraspinatus tendon pathology. An acute increase in biceps tendon width – a marker for inflammation – was observed in response to a repeated-transfers protocol. Utilizing proper shoulder and hand positioning was protective of both tendons, while higher bodyweight was associated with wider biceps tendons. It is apparent that utilizing certain transfer techniques can be protective of the shoulder tendons, which could translate into better overall shoulder health.

The third study applied a similar methodology to determine whether transfers and different techniques had a similar effect on the median nerve. An acute increase in median nerve CSA – a marker for median mononeuropathy – was observed after transfers. Participants who

utilized improper arm and hand positions exhibited more nerve swelling at baseline. Participants who weighed more and scooted to the front of the wheelchair prior to transferring exhibited greater nerve CSA after transfers. The results of these three studies suggest that higher bodyweight has a deleterious effect on the response of the upper-extremity soft tissues to transfers. Furthermore, proper shoulder, arm, and hand positioning can potentially protect these tissues from injury.

The final study sought to further understand how wheelchair activities contribute to shoulder tendon overuse pathology. An acute increase in inflammatory cytokines was observed in the GHJ after an intense wheelchair propulsion and transfer protocol. Greater changes in IL-8 and -1RA were correlated with darker biceps and supraspinatus tendons after activity. This observation suggests that wheelchair propulsion and transfers causes an acute chemical response that is associated with tendon edema. Smaller RANTES changes were associated with more forceful propulsion strokes, indicating a relationship between propulsion technique and inflammation. The catheters failed in three out of seven subjects, including the subject with SCI, which essentially disqualifies microdialysis for use in the GHJ. A larger sample size would have allowed a more thorough analysis of how age, BMI, and wheelchair technique influence cytokines and their manifestation as tendinopathy. Ideally, a model could be built to predict whether an individual will develop tendinopathy. This model would utilize basal cytokine concentrations and subject characteristics, and could potentially be used by clinicians to prevent rotator cuff dysfunction in their patients with SCI.

Measurement of inflammatory cytokines appears to yield valuable information in the study of rotator cuff tendinopathy and understanding the mechanisms that lead to pathology. However, another modality that limits invasiveness and optimizes collectability must be applied

and tested. One possibility is sampling directly from the GHJ synovial fluid via aspiration, potentially applying a lavage technique. This method has been used to establish a relationship between soft-tissue pathology and cytokine concentrations in the knee.[198-200] Limitations exist for this technique as well; for example, serial measurements within one testing session could likely not be collected without compromising joint health. However, given the results of our microdialysis study, the aspiration technique could be used in a longitudinal study as a sensitive method to detect how individuals respond to a wheelchair skills intervention.

Results from the four presented studies suggest that there is a relationship between wheelchair propulsion, transfers, and upper-extremity soft-tissue pathology. Furthermore, repetitive wheelchair activities may cause an upregulation of inflammatory cytokines that contribute to overuse pathology of the rotator cuff. Throughout each study, bodyweight was associated with ultrasound and biochemical markers. In addition to amplifying joint loads, systemic inflammation from obesity may also contribute to pathology. Providing individuals with information to help manage their weight may be an additional method of preventing upper-extremity soft-tissue degeneration. Technique also appeared to be a contributing factor to the deleterious soft-tissue changes that were observed in the shoulder and carpal tunnel. By teaching their patients to use more ergonomic wheelchair techniques – such as proper hand/arm positions during transfers and propelling with less force – clinicians may help delay the development of pain and pathology and the associated detriments in quality of life and independence. Further testing may lead to the development of a model to predict an individual's susceptibility to developing tendinopathy using subject characteristics and cytokine information.

APPENDIX A

A.1 PROTOCOL CHECKLIST

#	Item	Start Time	Complete?
2	Prepare rooms for testing the night before		
3	Prepare rooms the morning of		
Subject Arrives			
4	Upon subject arrival, start consent process		
5	Perform USPRS and physical exam		
6, 7	Catheter insertion procedure		
8	Pump setup, insert microvial 1		
Insertion procedure complete, begin data collection			
8	Biomarker collection 1 (-60 minutes)		
8	Questionnaires		
8	QUS marker placement		
8	Biomarker collection 2 (-30 minutes)		
8	Weigh subject		
8	Biomarker 3 collection, QUS 1 (-00 min)		
8, 9	Wheelchair activities protocol		
9	Biomarker 4 collection, QUS 2 (+00 min)		
9	Biomarker 5 collection, QUS 3 (+30 min)		
9	Biomarker 6 collection, QUS 4 (+60 min)		
9	Biomarker 7 collection, QUS 5 (+90 min)		
10	Catheter removal procedure		
Subject Departs			
10	Post-protocol cleanup		

Preparation:

NSH	Prepare the following the night before: Study packet: • Study checklist • CLIP checklist • Informed consent and HIPAA • Documentation of informed consent • Research answering form • Respective inclusion/exclusion form • Payment forms (25$, 50$, 200$, vendor sheet) • General questionnaire • USPRS • Borg scale • Infection questionnaire • Comment sheet • ASIA scale (SCI only) • WUSPI (SCI only) • TAI (SCI only) • ISCIPDS (SCI only) 3 Pillows Rolling supply table Sterile supplies • 2 Sterile kits • 2 Individual ChloraPrep cleaners (not from sterile kit) • 2 Small sterile drape 3 Non-sterile caps, masks, pairs of gloves Microdialysis supplies • 1 Catheter package • 1 Introducer package • 7 Microvials • 1 Microvial rack • 1 Syringe and perfusion fluid • 1 Pump and harness • 7 Microvial labels (labeled: -60, -30, B, 0, 30, 60, 90) SmartWheel • Attach to wheelchair • Charge SmartWheel batteries • Ensure SmartWheel connects to computer • Charge SmartWheel laptop Ultrasound machine with linear and curvilinear probes • Machine with power cord and linear probe moved to alternate exam room • Cart remains in procedural room Reconfigure exam table/ultrasound setup for optimum scanning	___________ ___________
NSH	Prepare the following the morning of: Confirm SmartWheel is connecting and recording data Transfer mat table is level with wheelchair Figure-8 runway with cones, turn signs	___________ ___________ ___________

	Randomize fatigue protocol (flip coin) Exam room and table cleaned/sterilized	_____ _____

Consent:

Secondary investigator	Consent form and HIPAA signed, dated, timed Documentation of informed consent Inclusion/exclusion criteria form	_____ _____ _____
Secondary investigator	Payment form	
Secondary investigator	Make copy of consent for participant	
Secondary investigator	Guide subject to exam room for USPRS	

USPRS:

NSH	Ultrasound machine with power cord and linear probe moved to next (non-procedural) room Probe set to LINEAR INSERTION preset Adjust if necessary	
KO	Stand behind subject, scan 7 check points: • Biceps tendon • Supraspinatus tendon • Greater tubercle irregularities • Subacromial impingement • Subcoracoid impingement • Bursal thickness • Joint effusion	
Non-sterile assistant	Record scores	

Insertion:

NSH	Probe set to CURVILINEAR INSERTION preset Depth set to 6cm, adjust if necessary	
Non-sterile assistant(s)	Wash hands Don non-sterile face mask, gloves, and cap	
KO	Instruct participant to lie down in a lateral recumbent position hugging him/herself with the side of interest toward the ceiling Scan shoulder and mark area of entry with surgical marker Instruct participant not to move the shoulder	
KO, NSH Non-sterile	Wash hands, use (sterile) towel in gown packaging to dry Don sterile gloves, cap, mask, and gown – KO followed by NSH	

Assistant	Non-sterile assistant ties the back of the gowns, opens sterile kit	
KO Non-sterile Assistant	Bupivicaine is prepared Non-essential items are removed from kit and placed aside Essential items: • Drape • ChloraPrep x4 • 25G 2.0” needle • 25G 3.5” needle • 5cc syringe • 18G drawing needle • Lidocaine vial • Needle rest • 4x4 gauze • Sterile probe cover and gel Non-sterile assistant opens introducer package, drops introducer into tray Non-sterile assistant opens catheter package, KO grabs catheter kit and places onto tray	
Non-sterile Assistant	Scrub shoulder with ChloraPrep prior to draping	
KO Non-sterile Assistant	Keeping marked area in the center of the fenestration, place drape over subject Clean fenestrated area 3 times with ChloraPrep	
Non-sterile assistant NSH	Put non-sterile gel on probe Place probe cover over probe, tie with rubber bands	
KO	Time out: check subject’s name, date of birth, allergies, side of interest	
KO Non-sterile assistant	Draw necessary volume of Lidocaine Non-sterile assistant opens Bupivicaine bottle for KO to draw without breaking the sterile field	
KO Non-sterile assistant	Anesthesia is injected using 3.5 inch needle (KO) Ultrasound pictures and video taken to confirm needle tip is adjacent to joint capsule (assistant) Labeled “ins_anest_needle”	
KO NSH	Introducer is inserted Target area is just under the shoulder capsule, lateral to GHJ labrum Probe location is marked on the skin using surgical marker	
Non-sterile assistant	Pictures and videos of needle tip are collected Labeled “ins_intro_needle”	
KO NSH	Stylet is removed from introducer very carefully Catheter is inserted into introducer very carefully	
Non-sterile assistant	Pictures and videos of catheter/introducer are collected Labeled “ins_intro_cath”	
KO NSH	Once catheter tip placement is confirmed, apply downward force on catheter while NSH peels the introducer Perform with extreme caution, making sure catheter tip does not move Attempt to visualize catheter on ultrasound screen	
Non-sterile assistant	Take videos and pictures of catheter tip if possible Labeled “ins_cath_tip”	

KO NSH	Gel and blood is removed with gauze (NSH) Loop is made with catheter for slack to allow for movement during exercise (KO) Tegaderm is applied (NSH)	
NSH Non-sterile assistant	While drape is removed, prepare microdialysis syringe with perfusion fluid (NSH) Insert a microvial (NSH) Attach the syringe to the pump and turn on the pump (NSH) Wait for sequential green lights to confirm pump is on and the flushing sequence has begin Set timer for 15 minutes after pump is turned on, record time	
NSH Non-sterile assistant	Attach the pump to the subject using the harness (NSH) Apply tegaderm to remainder of catheter, with enough slack to allow for movement during activity (NSH) Throw away used and unused supplies	

Post-Insertion:

NSH Secondary investigator	-60-minutes PRE: After 15 minutes, pump sequence will end Watch for change in green light pattern on pump Start timer for 30 minutes after flushing sequence ends and record time (SI) Ask subject to remain seated without moving arm of interest Place QUS markers (NSH)	_____ _____ _____
NSH	Go through questionnaires while subject is resting	_____
Secondary investigator	Prepare SmartWheel and computer Prepare transfer mat table Move ultrasound machine to runway	_____ _____ _____
NSH Secondary investigator	-30-minutes PRE: After 30 minutes, remove microvial 1 and store in -80 freezer (NSH) Replace with microvial 2 before storing (NSH) Restart 30-minute timer and record time (SI) Move subject to runway in wheelchair (NSH/SI)	 _____ _____ _____ _____
NSH Secondary investigator	Prepare Borg scale and TAI (SI) Prepare SmartWheel computer and make sure it is connected (SI) Instruct subject how to navigate the figure-8 and transfer table (NSH)	_____ _____ _____
NSH Secondary investigator	Baseline: After 30 minutes, remove microvial 2 and store in -80 freezer (SI) Replace with microvial 3 before storing (SI) Begin 30-minute timer and record time (SI) Take QUS, label “qus_base” (NSH)	 _____ _____ _____ _____
NSH Secondary investigator	Brief introduction to wheelchair use for abled-bodied subjects: • Instruct subject not to use leg muscles when transferring, and place feet on scale • Perform two back-and-forth transfers for practice, providing feedback • Instruct subject how to safely propel, do a turn, start and stop,	

	and use the handrim on the SmartWheel (no tire) • Propel twice slowly along the runway, providing feedback Begin fatigue protocol Propulsion: • Timer (SI) • Record number of laps (SI) • SmartWheel data collection (NSH) • Rename data folders (NSH) Transfers: • Timer (SI) • Record scale value (NSH) • TAI (NSH) Complete Borg scale after each Record time of completion (SI)	_____ _____ _____ _____ _____ _____ _____
NSH Secondary investigator	0-minutes POST: Perform QUS at runway, label "qus_+00" (NSH) Remove microvial 3 and store in -80 freezer (SI) Replace with microvial 4 before storing (SI) Restart 30-minute timer and record time (SI)	_____ _____ _____ _____
NSH Secondary investigator	Return with subject to exam room using wheelchair (NSH) Return ultrasound machine to exam room (NSH) Breakdown runway and transfer mat table (SI) Confirm biomechanics data was collected and store SmartWheel computer in file cabinet (SI)	_____ _____ _____ _____
NSH Secondary investigator	30-minutes POST: After 30 minutes, remove microvial 4 and store in -80 freezer (SI) Replace with microvial 5 before storing (SI) Begin 30-minute timer and record time (SI) Take QUS, label "qus_+30" (NSH)	_____ _____ _____ _____
NSH Secondary investigator	60-minutes POST: After 30 minutes, remove microvial 5 and store in -80 freezer (SI) Replace with microvial 6 before storing (SI) Begin 30-minute timer and record time (SI) Take QUS, label "qus_+60" (NSH)	_____ _____ _____ _____
NSH Secondary investigator	90-minutes POST: After 30 minutes, remove microvial 6 and store in -80 freezer (SI) Take QUS, label "qus_+90" (NSH)	_____ _____

Catheter Removal

NSH Secondary investigator	Don non-sterile gloves (both) Prepare bandage and gauze	
NSH	Remove tegaderm (NSH) Place tegaderm in biohazard bin (SI) Remove catheter and place on drape for inspection (NSH) Scrub area with ChloraPrep (NSH) Apply bandage with gauze (SI)	

Post-Protocol

NSH Secondary investigator	Clean exam rooms Return supplies to file cabinet Sanitize applicable surfaces Sanitize probes and machine Ensure microvials are properly labeled and secured in freezer	_____ _____ _____ _____ _____
NSH	Return data and equipment to HERL • SmartWheel • Ultrasound machine (if data has not been removed) • Study packet	 _____ _____ _____
NSH	Remove data from SmartWheel computer Remove data from Ultrasound machine Store on VA network	_____ _____ _____

Microdialysis Supplies

- Catheter package (x1)
- Introducer package (x1)
- Microvials (x8)
- Microvial rack (x1)
- Syringe and needle (x1)
- Perfusion fluid (x1)
- Pump with battery
- Harness
- Microvial labels (x8)
    - -60
    - -30
    - -00
    - +00
    - +30
    - +60
    - +90

Sterile Supplies

- Sterile gowns (x2)
- Sterile caps (x2)
- Sterile gloves (x2 pairs)
- Sterile masks (x2)
- Fenestrated drape (x1)
- Chloraprep (x4)
- 25G 2.0” needle (x1)
- 25G 3.5” needle (x1)
- 5cc syringe (x2)
- 18G drawing needle (x1)
- Lidocaine vial (x1)
- Needle rest (x1)
- 4x4 gauze (x4)
- Sterile probe cover, rubber bands, gel (x1)

Gowning and Gloving Procedure

1. Set up kit, gloves, and gown
    a. Prepare a trash can so you can quickly discard non sterile trash
    b. Set up so you will not have to touch anything non-sterile
2. Wash hands
3. Without touching anything, dry hands using sterile towel provided in the kit
4. With the help of an assistant, put on gown (see image below)
    a. Place hands under folded portion of the gown (sleeves) and unfold, allowing it to fall in front of you
    b. Do not touch anything with the front of the gown or sleeves
    c. Place elbows by your side and arms out front to prevent accidental breaking of the field
    d. Have assistant stand behind you and secure the gown, without touching the front
    e. Tie the gown
5. Put on gloves using procedure described below, careful not to come in contact with anything non-sterile
6. Prepare drape
    a. Fold in half so fenestration is a half-circle
    b. Peel back fenestration sticker
    c. Place on subject so insertion site is in the center of the fenestration
    d. Unfold drape with the help of an assistant, who only touches the non-sterile side

Sterile Gowning Procedure

1. DRY HANDS.

2. PICK UP GOWN.

3. LET GOWN UNFOLD.

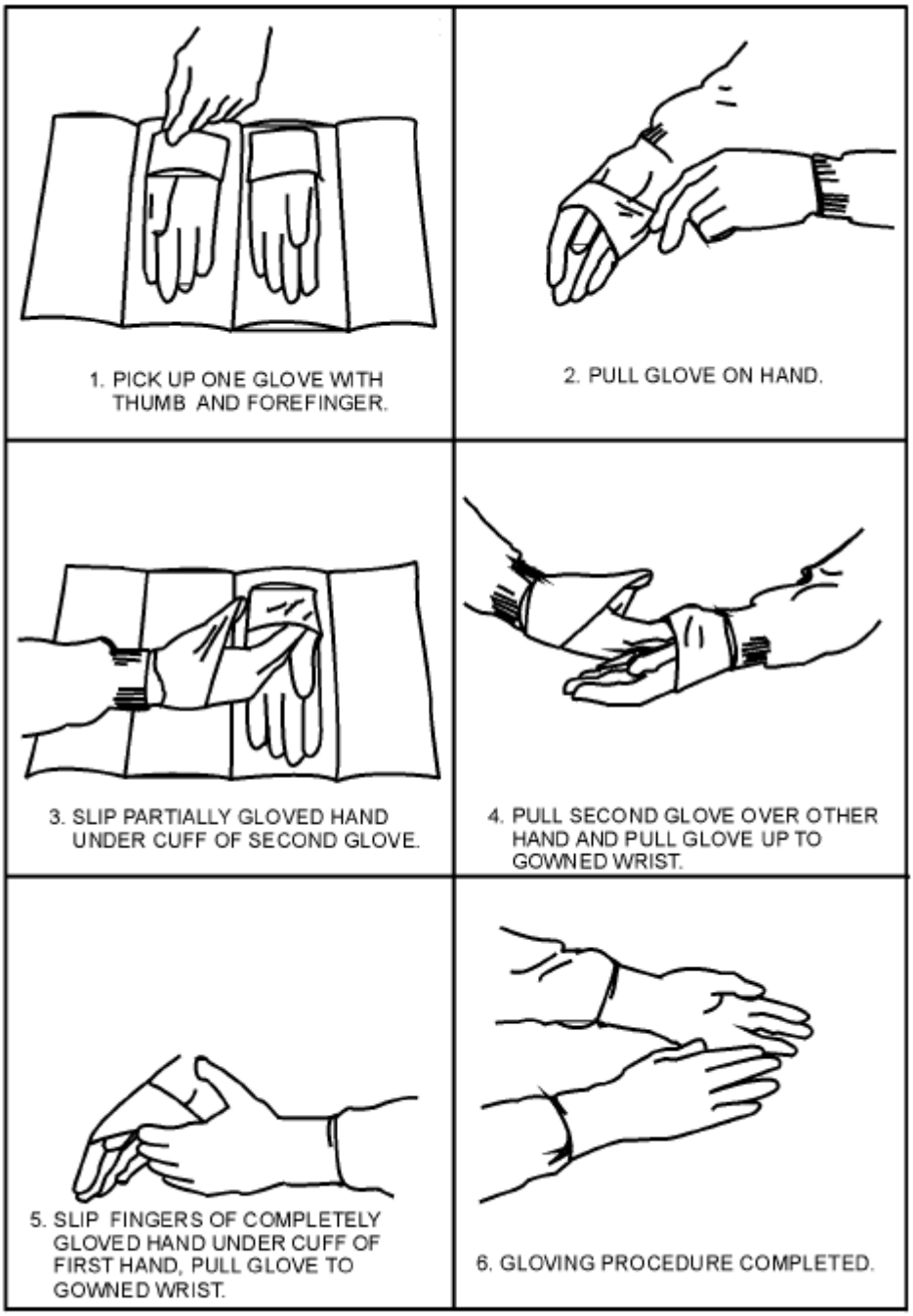
4. OPEN TO LOCATE SLEEVE / ARMHOLES.

5. SLIP ARMS INTO SLEEVES.

6. HOLD ARMS OUT AND SLIGHTLY UP.

7. CIRCULATOR PULLS GOWN ON.

Sterile Gloving Procedure



A.2 CATHETER INSERTION STERILITY CHECKLIST

Patient ID (Last Name and last 4 SS#) _____ **Unit** _____
Insertion Date: ___/___/____ Time: _____ Guide wire change ____ Yes ____ No
Amount of time to insert line: _____ hour (s) _____ minute (s) Urgent/Emergency ____ Yes ____ No
Type of Catheter: Single Double Triple Quad Swan PICC Dialysis Introducer
Other _____
Insertion Site: LSC RSC LIJ RIJ LFEM RFEM LCEPH RCEPH LBRACH RBRACH
Other _____
Number of punctures/attempts _____ Ultrasound used ____ Yes ____ No

Observations **Document Name & Title →**	**Please document **Name** and **Title** of person inserting and assisting with line insertion (i.e. intern, resident, fellow, attending MD, IV team RN). Inserter 1		Inserter 2		Circulator 1		Other		Other		**Comments**
Hand Hygiene (15 sec hand wash or alcohol hand rub)	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	
Head Cover	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	
Face mask	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	
Sterile Gloves	**YES**	**NO**	**YES**	**NO**							
Sterile Gown	**YES**	**NO**	**YES**	**NO**							
Full Body Drape	**YES**	**NO**									
Chloraprep (back and forth scrub technique used)	**YES**	**NO**									
Sterile Technique Maintained	**YES**	**NO**									
If ultrasound used, sterile probe cover applied	**YES**	**NO**	**NA**								
Catheter lumens (aspirated, flushed, capped & connected without compromising sterile field)	**YES**	**NO**									
Sutured/Sterile dressing applied (Bio patch/sterile	**YES**	**NO**									

impregnated dressing applied)				

Instructions for completing check sheet.

1. Hand hygiene: Inserter and circulator used alcohol hand rub or a 15 second hand wash prior to central line insertion.
2. Head Cover: Inserter and circulator applied a cap that covers all hair.
3. Face Mask w/ shield: Inserter and circulator donned a face mask with face shield prior to procedure.
4. Sterile gloves: Inserter applies sterile gloves after hand hygiene.
5. Sterile gown: Inserter dons sterile gown prior to procedure.
6. Full Body Drape: Sterile field must extend at least 3 feet from the insertion site.
7. Chloraprep: Chloraprep applied in a back and forth scrub motion for skin prep.
8. If an Ultrasound is used, document if probe cover was used.

If Ultrasound was not used, mark N.A. in comments.

9. Sterile Technique maintained. If there are any major breaks in sterile technique, insertion should be disrupted. Document details about breaks in comments as necessary.
10. Catheter lumens aspirated, flushed and capped/connected without compromising sterile field.
11. Reprepped/Sterile dressing applied. Biopatch only applies for central lines other than triple lumen catheters.

APPENDIX B

BIOMECHANICS, QUANTITATIVE ULTRASOUND, AND CYTOKINE CORRELATION MATRICES

B.1 CHANGES IN CYTOKINES

Table 17. Correlation matrix of each cytokine concentration immediately after activity.

	IL-8	RANTES	IL-1RA
IL-8	-	-.137 (.863)	.979 (.021)
RANTES	-	-	-.069 (.931)
IL-1RA	-	-	-

Table 18. Correlation matrix of each cytokine concentration after 30 minutes of rest.

	IL-8	RANTES	IL-1RA
IL-8	-	-.186 (.814)	.689 (.311)
RANTES	-	-	.614 (.386)
IL-1RA	-	-	-

Table 19. Correlation matrix of each cytokine concentration after 60 minutes of rest.

	IL-8	RANTES	IL-1RA
IL-8	-	.715 (.285)	.979 (.021)
RANTES	-	-	.685 (.315)
IL-1RA	-	-	-

B.2 QUANTITATIVE ULTRASOUND AND CYTOKINES

Table 20. Correlation between quantitative ultrasound parameters and IL-8

	Baseline	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
SST Width	.793 (.207)	.828 (.172)	.894 (.106)	.810 (.190)
SST Echogenicity	-.729 (.271)	-.973 (.027)	-.051 (.949)	-.563 (.437)
LHBT Width	.095 (.905)	-.680 (.320)	-.241 (.759)	.348 (.652)
LHBT Echogenicity	-.357 (.643)	-.958 (.042)	.804 (.196)	.152 (.848)

Notes. SST = supraspinatus tendon. LHBT = long head of the biceps tendon.

Table 21. Correlation between quantitative ultrasound parameters and RANTES

	Baseline	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
SST Width	-.767 (.233)	-.597 (.403)	-.270 (.730)	.169 (.831)
SST Echogenicity	.928 (.072)	.307 (.693)	.589 (.411)	-.182 (.818)
LHBT Width	.157 (.843)	.120 (.880)	-.448 (.552)	.675 (.325)
LHBT Echogenicity	.862 (.138)	-.034 (.966)	.246 (.754)	.140 (.860)

Notes. SST = supraspinatus tendon. LHBT = long head of the biceps tendon.

Table 22. Correlation between quantitative ultrasound parameters and IL-1RA

	Baseline	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
SST Width	.350 (.650)	.831 (.169)	.423 (.577)	.833 (.167)
SST Echogenicity	-.469 (.531)	-.912 (.088)	.685 (.315)	-.572 (.428)
LHBT Width	.552 (.448)	-.523 (.477)	-.835 (.165)	.318 (.682)
LHBT Echogenicity	-.237 (.763)	-.994 (.006)	.913 (.087)	.140 (.860)

Notes. SST = supraspinatus tendon. LHBT = long head of the biceps tendon.

B.3 BIOMECHANICS AND CYTOKINES

Table 23. Correlation between biomechanical parameters and IL-8

	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
Normalized Peak FR	.401 (.599)	.471 (.529)	.415 (.585)
Normalized Stroke Frequency	.711 (.289)	.215 (.785)	.190 (.810)

Notes. FR = resultant force.

Table 24. Correlation between biomechanical parameters and RANTES

	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
Normalized Peak FR	-.948 (.052)	-.730 (.270)	-.154 (.846)
Normalized Stroke Frequency	-.136 (.864)	-.018 (.982)	.386 (.614)

Notes. FR = resultant force.

Table 25. Correlation between biomechanical parameters and IL-1RA

	+00 Post-Activity	+30 Post-Activity	+60 Post-Activity
Normalized Peak FR	.301 (.699)	.068 (.932)	.446 (.554)
Normalized Stroke Frequency	.559 (.441)	.635 (.365)	.180 (.820)

Notes. FR = resultant force.

APPENDIX C

MULTI-ANALYTE KIT CYTOKINES

C.1 LIST OF ANALYZED CYTOKINES

1. Fibroblast Growth Factor 2 (FGF-2)
2. Eotaxin
3. Granulocyte Colony-Stimulating Factor (G-CSF)
4. Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)
5. Interferon gamma (IFNg)
6. Interleukin-10
7. Interleukin-12
8. Interleukin-13
9. Interleukin-15
10. Interleukin-17
11. Interleukin-1 Receptor Antagonist
12. Interleukin-9
13. Interleukin-1 beta
14. Interleukin-2
15. Interleukin-4
16. Interleukin-5
17. Interleukin-6
18. Interleukin-7
19. Interleukin-8
20. Gamma-Induced Protein 10 (IP-10)
21. Monocyte Chemoattractant Protein-1 (MCP-1)
22. Macrophage Inflammatory Protein 1 alpha (MIP-1A)
23. Macrophage Inflammatory Protein 1 beta (MIP-1B)
24. Tumor Necrosis Factor alpha (TNF-a_
25. Vascular Endothelial Growth Factor (VEGF)
26. Platelet-Derived Growth Factor AB/BB (PDGF-AB/BB)
27. Regulated on Activation, Normal T-Cell Expressed and Secreted (RANTES)

C.2 COLLECTED CYTOKINE VOLUMES AND DILUTIONS

Table 26. Sample volumes and dilutions for each subject and time point.

Subject ID	Sample Number	Volume (µL)	Dilution
1	-00	30	1
	+00	30	1
	+30	30	1
	+60	30	1
3	-00	30	1
	+00	30	1
	+30	30	1
	+60	30	1
4	-00	3	10
	+00	5	6
	+30	6	5
	+60	3	10
6	-00	1	30
	+00	1	30
	+30	1	30
	+60	1	30

APPENDIX D

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