Neuromuscular Function in Achilles Tendinopathy

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ABSTRACT
NEUROMUSCULAR FUNCTION IN ACHILLES TENDINOPATHY

Lauren K. Sara, DPT
Marquette University, 2021

Midportion Achilles tendinopathy (AT) is a chronic, painful condition of the long tendon that attaches the triceps surae muscle group (the soleus, medial and lateral gastrocnemius muscles), which are the primary plantar flexor muscles, to the calcaneus bone. There is incomplete understanding of the underlying pathophysiology, pain, and role of plantar flexor function (strength and fatigability) in functional impairment in AT. Deficits in plantar flexor muscle function are assumed, but evidence is sparse and inconclusive. There is no understanding of whether people with AT have deficits in neural drive to the plantar flexor muscles or altered contractile function, or the role of pain in mediating plantar flexor function in AT. The purpose of this dissertation was to evaluate plantar flexor muscle function both in persons with AT compared to healthy controls and during a common clinical test, the Single-Leg Heel Raise.

The Single-Leg Heel Raise test (SLHR) is purported to measure plantar flexor muscle strength. Study 1 challenged this notion by comparing performance in this task to the torque produced during a maximal voluntary isometric contraction, a validated test for measuring maximal strength. The lack of associations between task performance and maximal strength suggests that the SLHR is not an indicator of maximal plantar flexor strength, but rather a measure of muscular endurance.

Deficits in plantar flexor strength, power and fatigability are assumed in persons with AT. Studies 2 and 3 investigated this assumption by measuring maximal isometric, and dynamic plantar flexor strength, SLHR repetitions, and isometric fatigability in AT and controls. There were no strength or fatigability differences between groups. However, contractile function was less in people with AT, and this was correlated with pain in the Achilles tendon.

Despite similar task performance, including plantar flexor strength and fatigability, contractile function may be impaired in AT, perhaps a result of pain mechanisms. Rather than emphasizing maximal strength and fatigability alone, an integrated approach, including interventions that address both chronic pain and impaired plantar flexor contractility, are necessary when treating people with AT.
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Lauren K. Sara, DPT

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CHAPTER 1 INTRODUCTION & REVIEW OF LITERATURE

Midportion Achilles tendinopathy (AT) is a chronic, painful condition of the long tendon that attaches the triceps surae muscle group – the soleus, medial and lateral gastrocnemius muscles – to the calcaneus bone. The estimated lifetime prevalence of AT is 30% in sedentary individuals and 50% in endurance athletes (Joseph and Denegar, 2015). The widely accepted mechanism of injury is overuse of the calf muscle-tendon unit (Martin et al., 2018). However, there is incomplete understanding of the pathology as it relates to pain and functional impairment in AT. As a result, current treatment interventions are only moderately successful, and symptoms can persist for years (Van der Plas et al., 2012, Silbernagel et al., 2007a, Paavola et al., 2000, Paavola et al., 2002).

Most AT research focuses on the tendon, including histopathologic investigations (Pearce et al., 2009, de Mos et al., 2009, Burssens et al., 2013), imaging evaluations (Pingel et al., 2013, Bakkegaard et al., 2015, De Jonge et al., 2014, Gärdin et al., 2013, Pierre-Jerome et al., 2010), mechanical properties (Child et al., 2010, Arya and Kulig, 2010, Aubry et al., 2015) and biomechanical implications for the tendon (Lorimer and Hume, 2016, Intzegieanni et al., 2016, Grigg et al., 2012, Grigg et al., 2013, Dowling et al., 2014, Nuri et al., 2017). In contrast to the abundance of tendon-centric research in AT, a 2014 systematic review (Magnan et al., 2014) identified only one study (of 68 included) that identified muscle strength as a possible predisposing factor in AT. Since that time, few research studies have addressed plantar flexor muscle function, such
as muscle strength (isometric or dynamic), power or exercise-induced fatigability of the muscle in AT.

A systematic review of “muscle function” (which included any studies that evaluated strength, power, rate of force development, endurance, and work) in AT was recently completed (Hasani et al., 2021). Their extensive literature review identified 15 studies that included at least one metric of muscle function in a heterogeneous population that included both insertional and midportion AT. The metrics used to quantify muscle function included the following: peak torque during isometric and dynamic contractions; six repetition maximum; rate of force development; single-leg hop distance; soleus H-reflex; and power, work, and repetitions completed during the single-leg heel raise test. Their review found the available evidence to be conflicting for all measures of muscle function when comparing healthy controls to individuals with midportion and insertional AT. When comparing limbs in persons with insertional or midportion AT, evidence was limited-to-moderate for between-limb differences in maximal torque (greater impairments of the affected limb) but conflicting for all other measures of plantar flexor muscle function (including power, endurance, and rate of force development) (Hasani et al., 2021). The authors emphasized a need for further research evaluating plantar flexor muscle function in AT.

In addition to conflicting evidence for impaired plantar flexor strength and power, there is poor understanding of any mechanisms that may underly such changes in motor output. No studies have yet evaluated the underlying neuromuscular physiology contributing to any such changes in plantar flexor
muscle function in persons with AT. This dissertation addresses an important gap in the literature by determining whether there are deficits in plantar flexor muscle function (strength, power and fatigability) as they relate to symptoms and function in persons with midportion AT. This dissertation will also determine whether any alteration in muscle function with AT is related to neural or muscular mechanisms. The literature review that follows will incorporate anatomy, physiology and other relevant considerations that led to the development of the project Aims.

ANATOMY & PHYSIOLOGY OF THE ACHILLES TENDON AND TRICEPS SURAE

The functional role of tendon is to transmit force within the musculoskeletal system (Sara and Neumann, 2017). Human movement is the result of rotational displacement of bone about a pivot point, the joint. Control of human movement and posture is achieved through the translation of linear, muscular-produced force into rotational torque across a joint (Hunter et al., 2017). The intermediary of this process is tendon: tendon attaches between muscle and bone, passively propagating force from contractile tissue (muscle) to bone to generate joint rotation (Sara and Neumann, 2017). In contrast to skeletal muscle, which is activated by the central nervous system, tendon receives no motor supply from the central nervous system. Instead, it is a highly elastic tissue that serves to passively store and release energy and to dissipate forces within the musculoskeletal system. Unlike skeletal muscle, healthy tendon is largely

The Achilles tendon is the strongest and thickest tendon in body (Doral et al., 2010, Pierre-Jerome et al., 2010). Perhaps paradoxically, it is also one of the most frequently injured structures of the lower extremities (Joseph and Denegar, 2015). The most common Achilles tendon diagnosis is tendinopathy (Joseph and Denegar, 2015), a condition plagued by chronicity and resistance to treatment interventions (Paavola et al., 2000, Paavola et al., 2002). Limited vascular and neural supply to tendon likely contribute to slow adaptation to loading. This, in turn, translates to prolonged – and often incomplete – healing (Ackermann et al., 2009, Abate et al., 2009).

The Achilles tendon connects three muscles, together known as the triceps surae, to the calcaneus (Neumann, 2017). The triceps surae group consists of the soleus, medial and lateral gastrocnemii muscles, and the predominant motion created by these muscles is plantar flexion across the talocrural (ankle) joint. Seventy to eighty percent of maximal plantar flexor torque is generated by the triceps surae group (Murray et al., 1978, Belanger and McComas, 1981). Proximally, the gastrocnemius attaches at the posterior distal femur, while the soleus attaches along the posterior aspects of the tibia and fibula. Together, the three muscles insert into the Achilles tendon, ultimately attaching into the posterior calcaneus (Pierre-Jerome et al., 2010).

The functional importance of the gastrocnemii and soleus muscles is typically simplified in a binary manner – based on fiber type composition – into that of
power or endurance. The soleus is comprised of approximately 80% type I (slow-twitch) fibers, which is a fiber type associated with endurance activities (Schoenfeld et al., 2020, Wilson et al., 2012, Talbot and Maves, 2016, Johnson et al., 1973). The medial and lateral gastrocnemius are comprised of approximately 50% type I (slow-twitch) and 50% type II (fast-twitch) fibers (Schoenfeld et al., 2020, Johnson et al., 1973), the latter of which are associated with production of power (Fitts et al., 1991, Fitts and Widrick, 1996). The soleus is, therefore, credited with playing an important endurance role for the triceps surae group (Fitts and Widrick, 1996) and serving an important postural role for lower limb stability (Mochizuki et al., 2005). The gastrocnemius muscles, due to their proportionally greater composition of fast fibers when compared to the soleus muscle, are associated with power production (Fitts et al., 1991, Fitts and Widrick, 1996).

Some researchers have proposed that deficits within the soleus are responsible for the onset of AT (O’Neill et al., 2019, Padhiar et al., 2008). This is a particularly compelling argument given (1) the preferential atrophy of slow-twitch muscle fibers with decreased loading (Trappe et al., 2008), (2) the prevalence of AT among endurance exercises (Kujala et al., 2005), and (3) that the most common inciting factor in AT is a sudden increase or change in activity and therefore an increased load on the musculotendon complex. Currently, however, there is insufficient evidence to conclusively describe unique contributions of triceps surae muscles to AT pathophysiology.
As stated previously, the greatest torque contribution to plantar flexion – 70-80% – comes from the triceps surae group (Murray et al., 1978, Belanger and McComas, 1981). This can be attributed to the combination of a large internal moment arm and large physiologic cross-sectional area of the triceps surae muscles (Neumann, 2017). The remaining plantar flexor torque generation arises from the fibularis longus and brevis, flexor hallucis longus, flexor digitorum longus, plantaris, and tibialis posterior muscles. The antagonist muscles, the dorsiflexors, include the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and fibularis tertius (Neumann, 2017).

The triceps surae receives its motor innervation from the tibial nerve, a branch of the sciatic nerve. Bifurcation of the sciatic nerve commonly occurs at the superior angle of the popliteal space, where it divides into the tibial and common fibular nerve (Berihu and Debeb, 2015). Motor supply to the remaining plantar flexor muscles, however, is provided by a mixture of the tibial nerve (innervating the plantaris, tibialis posterior, flexor digitorum longus, and flexor hallucis longus muscles) and fibular nerve (innervating the fibularis longus and brevis muscles). The arrangement and activation of muscles crossing the talocrural joint becomes especially pertinent when considering that contractile function is assessed using electrically-evoked contractions: currently existing tools and techniques make simultaneous stimulation of all plantar flexor muscles both difficult and impractical. Methodological constraints of this technique will be addressed more thoroughly later in this dissertation.
STRENGTH, POWER & FATIGABILITY

Muscle function, in the context of this dissertation, encompasses the following variables: strength, power, fatigability, contractile properties, and neural drive. These are parameters used in this dissertation to understand neuromuscular function in people with AT.

Strength

In a laboratory setting, maximal strength is commonly measured using maximal voluntary contractions (Gandevia, 2001). This technique involves maximal-effort muscle activation while the muscle is being shortened (concentric), lengthened (eccentric), or maintained at approximately the same length (isometric activation). To ensure maximal effort, several factors are required of the researcher: familiarization to the task; real-time visual feedback of task performance for the participant; strong, verbal encouragement; ensuring each effort was perceived as “maximal” by the participant; and incentivizing maximal effort (Gandevia, 2001). Maximal strength is commonly correlated with physiological cross-sectional area of a muscle (Hunter et al., 2017). Cross-sectional area is a reflection the number of contractile proteins in parallel. Assuming maximal effort by the participant, it is proportional to maximal force potential.
**Power & Work**

Work is the product of force and displacement. When applied to joints in the body, it is the product of torque and angular displacement. Power is the *rate* of performing work: the product of force and velocity (Blanpied and Neumann, 2017). Angular power, then, is the product of torque and angular velocity. It can be calculated by multiplying the torque and velocity produced during dynamic (i.e., concentric or eccentric) maximal voluntary contractions. During isometric contractions, however, no displacement occurs. Therefore, mechanical work and power are equal to zero. Work and power are expressed as positive values for concentric activations, as force and displacement occur in the same direction. In contrast, force and displacement occur in opposite directions during eccentric activations. As such, work and power are expressed as negative values.

**Fatigability**

Performance fatigability refers to an acute decline in an objective measure of motor performance following an activity (Enoka and Duchateau, 2016). It is often quantified as either the time elapsed or repetitions completed prior to task failure (Hunter et al., 2004b). In a laboratory setting, it is commonly defined as an acute, exercise-induced loss in maximal strength or power (Enoka and Duchateau, 2008, Hunter, 2018). While both are meant to describe to muscle function, strength and fatigability are often unrelated. However, when they are associated, it is often through an *inverse* relationship, such that stronger muscles demonstrate worse endurance (i.e., are more fatigable) (Hunter et al., 2004a).
Resting Twitch Torque: a Measure of Contractile Mechanisms

Force achieved during muscle contraction is dependent upon many factors, whether at baseline or following fatiguing exercise. They include – but are not limited to – signal propagation across the neuromuscular junction, motor unit number and recruitment, excitation-contraction coupling, skeletal muscle metabolism, and cross-bridge kinetics (Toth et al., 2013, Hepple and Rice, 2016, Fitts, 1994, Fitts, 2008, Sundberg et al., 2018a). The ability of muscle to contract independent of the central nervous system can be evaluated using electrical stimulation of a muscle (or its motor nerve) while the muscle is at rest (RT). The resultant torque from such stimulation can elucidate possible mechanisms contributing to altered muscle function. This technique is limited, however, by its inability to identify which specific mechanisms are contributing to altered function within the muscle. Instead, “contractile mechanisms” refers to any mechanism distal to the point where electrical stimulation is applied.

Voluntary Activation: a Measure of Neural Drive

Voluntary activation refers to the ability to drive the muscle using the central nervous system. It is commonly measured using the Interpolated Twitch Technique, a technique that involves electrically stimulating a muscle or nerve at rest and during a maximal voluntary contraction (MVC) (Gandevia, 2001). The amount of additional torque produced by supramaximal electrical stimulation during MVCs is known as the superimposed twitch torque (SIT). Electrical stimulation is then repeated at rest, in a post-activation, potentiated state. The
amount of torque produced by electrically stimulating the resting muscle is known as the resting twitch torque (RT). Voluntary activation is the ratio of SIT to RT, expressed as a percent (Gandevia, 2001): \((1 - \text{SIT/RT}) \times 100\). This technique will be used to determine neural drive in healthy controls and in people with AT.

**PAIN PERCEPTION**

One common clinical evaluation of pain intensity is the Numeric Pain Rating Scale (NPRS). This evaluation tool utilizes an 11-point scale, where 0 is equivalent to no pain and 10 is equivalent to the worst pain imaginable. Pain can also be evaluated using algometry, which evaluates pain thresholds in response to pressure stimuli. Pressure is applied to a particular location and is increased at a constant rate. The test is complete when the participant indicates that the sensation has transitioned from being that of pressure to being painful. The outcome of interest is the corresponding pressure at which the person first experiences pain.

Pain is often the reason compelling us to seek medical intervention. In one study, 40% of the patients seeking consultation with a primary care physician listed pain as their primary complaint (Mäntyselkä et al., 2001). For this reason alone, it is an important variable to monitor in AT. Its importance is amplified when considering the inhibitory role of pain on muscle function.

Group III and IV muscle afferents respond to chemical and mechanical changes in the muscle, including nociception (Martin et al., 2008). Activation of
these afferents can impact the motor pathway, from motoneurons to the motor
cortex (Martin et al., 2008, Garland and Kaufman, 1995, Hunter, 2018). Thus,
functionally, pain can result in decrements in voluntary activation.

**PATHOPHYSIOLOGY OF MIDPORTION ACHILLES TENDINOPATHY**

AT is an overuse injury of insidious onset. It results in pain and perceived
stiffness localized within the free tendon that connects the triceps surae muscles
to the calcaneus (van Sterkenburg and van Dijk, 2011, Calder et al., 2010). AT
commonly accompanies a sudden increase or change in activity level (Martin et
al., 2018, Cook et al., 2002). Beyond this, however, the pathophysiology of AT is
poorly understood (Abate et al., 2009, Fredberg and Stengaard-Pedersen, 2008).
As discussed in the context of nomenclature (below), even the roles of
inflammation and degeneration in AT are inconclusive. Consequently, the current
diagnostic and management strategies for people with AT relies heavily upon
clinical presentation (namely, impairments and functional limitations) and less so
on the underlying pathophysiological processes (Scott et al., 2020, Abate et al.,
2009).

*Nomenclature & the Roles of Inflammation and Degeneration in Tendon
Pathology*

Terminology for Achilles tendon overuse injuries has evolved alongside improved
understanding of the pathophysiology. The evolution has reflected technological
and clinical advances. The chosen terminology is more than a nuance of
nomenclature; rather, accurate description aids in selecting optimal interventions and ensuring appropriate understanding of the chronicity and prognosis of the underlying condition (Andres and Murrell, 2008, Maffulli et al., 1998).

Overuse tendon injuries were originally termed “tendonitis” (Schanz, 1905, Clancy et al., 1976, Nelen et al., 1989). The assumed pathophysiology was inflammation of the tendon, which fit within widely-accepted models of tissue injury and recovery (Ross, 1968, Voleti et al., 2012, Broughton et al., 2006) and provided an explanation for the presence of pain (Fredberg and Stengaard-Pedersen, 2008). However, as early as the 1980’s, histopathologic evidence began to emerge that suggested an intriguing theory: despite the presence of pain, not all tendon overuse disorders involved inflammation (Perugia et al., 1986, Regan et al., 1992, Kraushaar and Nirschl, 1999, Leadbetter, 1992), thereby making the “-itis” suffix inaccurate and confusing. These experts recommended the term “tendinosis”, which was based on evidence of degeneration within the tendon. The strict definition for tendinosis, however, required that inflammation did not accompany degenerative changes (Puddu et al., 1976). Newer evidence began demonstrating that inflammation may indeed be an important part of the pathophysiology (Cetti et al., 2003, Schubert et al., 2005). From a clinical perspective, it became evident that degenerative tendons were not necessarily symptomatic (Maffulli et al., 1998, van Dijk et al., 2011, Haims et al., 2000, Miniaci et al., 1995, Docking, 2021a, Docking, 2021b), and that the magnitude of degeneration did not predict symptom severity (Khan et al., 1997, Cook et al., 2001).
It is currently recommended that “tendinopathy” be used for clinical diagnoses and that “tendinosis” and “tendonitis” be reserved only for diagnoses based on results of histopathologic analyses (Maffulli et al., 1998). It is becoming increasingly accepted that inflammation and degeneration may both be relevant fixtures of the disease process (Abate et al., 2009, Fredberg and Stengaard-Pedersen, 2008). However, consensus by tendon experts remains unchanged: the clinical terminology recommended for describing overuse tendon pathology is “tendinopathy” (Scott et al., 2020).

One final and important consideration is that of diagnostic specificity. Pathology of the Achilles tendon can involve more than the midportion of the tendon: it can include injury of the paratenon; it can be localized to the calcaneal insertion of the tendon; it can be the result of systemic disease processes, posterior ankle impingement, or neural irritation; and it can involve partial to complete tears of the tendon (Fredberg and Stengaard-Pedersen, 2008, Kearney and Costa, 2010, Martin et al., 2018, Pierre-Jerome et al., 2010).

Pathophysiologial processes, clinical presentations, and recommended interventions for these conditions vary (Kearney and Costa, 2010, Martin et al., 2018, Rees et al., 2009). Therefore, it is recommended that these conditions be considered in the differential diagnosis of midportion AT, and not as part of a larger clinical picture, as these other conditions could confound diagnosis, prognosis, and intervention in midportion AT (Martin et al., 2018). As such, this dissertation focuses specifically on midportion AT. Any subsequent reference to “Achilles tendinopathy” refers only to midportion AT unless clarified otherwise.
The hallmarks of AT include the following: tendon pain and stiffness; a stereotypical mechanism of injury; and increased tendon thickness (Cook et al., 2002). Symptom onset is gradual and insidious, and it commonly follows a sudden change in activity level. Patients commonly report pain or stiffness first thing in the morning, upon initial weight-acceptance onto their affected lower limbs. Pain is localized to the tendon and rarely refers elsewhere. Often pain-free at rest, the symptoms are typically provoked during active plantar flexion efforts.

Clinical diagnosis of AT is based on a cluster of signs and symptoms, in addition to possessing the stereotypical symptom onset (Martin et al., 2018). The “cluster” of tests recommended for clinical diagnosis of AT includes four components: thickening of the midportion of the tendon; movement of the thickened region during ankle range of motion (known as the Arc Sign) (Reiman et al., 2014); reproduction of tendon pain upon palpation; and a reduction in tendon pain on palpation when retested in ankle dorsiflexion (the Royal London Hospital Test) (Maffulli et al., 2003). Diagnosis of AT can be aided by ultrasound and magnetic resonance imaging of the tendon. However, imaging is not a gold standard for diagnosis in AT (Docking et al., 2015a). In a recent study evaluating imaging in persons with AT and healthy controls, tendon abnormalities were found to be more reflective of age, body mass index, and physical activity than of AT symptoms (Docking, 2021a). Furthermore, degenerative changes in asymptomatic tendons are common: up to 34% show histopathologic changes, despite being nonpainful (van Sterkenburg and van Dijk, 2011). Therefore, a
clinical diagnosis of “tendinopathy” is not equivalent to an imaging-based diagnosis of “tendinosis”.

**Incidence & Prevalence**

AT is one of the most common overuse injuries of the lower extremities. The estimated lifetime prevalence of AT is 30% in sedentary individuals and 50% in endurance athletes (Joseph and Denegar, 2015). Incidence rates are as high as 9% of runners each year (Kujala et al., 2005).

**Predisposing Factors in Midportion Achilles Tendinopathy**

A 2014 systematic review evaluated intrinsic and extrinsic risk factors contributing to AT (Magnan et al., 2014). The highest incidence of AT was reported in middle-aged males. However, the authors note that the sex differences findings may be skewed by differing physical activity rates among males and females included in those studies. Additional intrinsic variables identified as risk factors for developing AT include increased body weight, genetic predisposition, blood supply to the tendon, and systemic disease (such as rheumatoid arthritis, gout, thyroid and parathyroid disorders, diabetes mellitus, and lipid storage diseases). Only two extrinsic factors were identified: drugs (such as fluoroquinolone antibiotics, statins, and injected corticosteroids) and training parameters. Faulty training parameters include cold weather, poor footwear, abnormal biomechanics, and excessive training load. Only one study included in the review experimentally evaluated risk factors related to muscle
function. That study (Mahieu et al., 2006) identified two intrinsic risk factors for developing AT: insufficient plantar flexor strength and excessive dorsiflexion range of motion. However, a more recent systematic review (Hasani et al., 2021) found limited to conflicting evidence for impaired muscle function in AT when compared to healthy controls.

**Sex Differences in Midportion Achilles Tendinopathy**

Many researchers cite sex differences in AT, both in prevalence and in response to intervention (Joseph and Denegar, 2015, Paavola et al., 2000, Kvist, 1991). Many researchers question the presence of a sex difference in incidence and prevalence of AT, citing differences in physical activity between males and females included in those studies (Albers et al., 2016, Hopkins et al., 2016). Understanding sex differences in plantar flexor muscle function may help explain possible sex differences in AT. However, evidence of sex differences in plantar flexor strength and fatigability in healthy individuals is largely lacking and will be addressed in this dissertation.

**Pain & Neurovascular Considerations**

It follows from the uncertain pathophysiology of AT that the pain experienced by people with AT – and how this affects function and treatment – is also poorly understood (van Sterkenburg and van Dijk, 2011). Among asymptomatic tendons, as many as 34% are found to have histopathological changes (van Sterkenburg and van Dijk, 2011). Among persons with AT, the degree of
degeneration does not correspond to symptom severity, and the presence of inflammation is not guaranteed (Kannus and Jozsa, 1991, van Dijk et al., 2011, Cook et al., 2001, Docking et al., 2015a). In the absence of inflammation, proposed pain mechanisms are largely related to neuro-vasculature (Alfredson et al., 2003, Ackermann, 2013, Joseph and Denegar, 2015).

Neovascularization refers to a process whereby new vascular networks form, often as a component of wound healing (Brey and McIntire, 2008). Based on correlations between pain and neovascularization (Ohberg et al., 2001, Khan et al., 1999) – including improvements in pain when treating these new vessels (Alfredson and Ohberg, 2005) – some argue that the angiogenesis must be contributing to the pain experience. Similarly, neural ingrowth into the tendon itself has been identified and proposed as a contributing mechanism to pain (Andersson et al., 2007, Schubert et al., 2005, van Sterkenburg and van Dijk, 2011). However, both the role of neovascularization and neural ingrowth in AT pathophysiology and their contributions to pain are still under investigation (Rees et al., 2009, Boesen et al., 2006, Abate et al., 2009, Blackbourn et al., 2012). Finally, while their role in pain is unclear, a role for angiogenesis seems intuitive: enhanced blood supply assists in providing the optimal environment for tissue healing (Abate et al., 2009). This is particularly relevant in tendon, a connective tissue with limited vascular supply, which likely contributes to chronicity in AT (van Sterkenburg and van Dijk, 2011, Doral et al., 2010).

Pain in AT has been described both in the context of peripheral and central sensitization (Plinsinga et al., 2018, Eckenrode et al., 2019, Tompra et al.,
Peripheral sensitization refers to increased sensitivity of pain receptors to painful and non-painful stimuli, while central sensitization is increased sensitivity resulting from widespread somatosensory changes (Graven-Nielsen and Arendt-Nielsen, 2002, Plinsinga et al., 2018). Measuring sensitivity to mechanical stimuli is one method used to understand changes in peripheral and central pain sensitivity (Graven-Nielsen and Arendt-Nielsen, 2002). One such method, pressure-pain threshold (PPT) testing, measures the minimum pressure required to induce pain (Nussbaum and Downes, 1998). Evaluation of PPTs local to and remote from injured tissue can elucidate peripheral and central mechanisms, respectively, that are contributing to a painful experience (Graven-Nielsen and Arendt-Nielsen, 2002, Curatolo et al., 2001). Algometry is a reliable method for evaluating PPT both within and between sessions (Potter et al., 2006, Vanderweeën et al., 1996, Nussbaum and Downes, 1998, Frank et al., 2013) and is recommended when evaluating pain in persons with tendinopathy (Kregel et al., 2013).

Although the underlying pain mechanisms in AT are unclear, it is nevertheless important to quantify the magnitude of pain experienced by chronic pain populations and to understand the complex interactions between pain and movement that result (Merkle et al., 2018, Graven-Nielsen and Arendt-Nielsen, 2002). Pain is often assumed to serve a protective role in musculoskeletal health, such as inhibition of muscle activation to enable tissue healing. However, it can also lead to maladaptive changes within the motor system, including persistent abnormalities in motor control and muscle function, despite resolution of tissue...
injury (Merkle et al., 2020, Hodges and Smeets, 2015). Understanding the interactions between pain and performance will contribute to improved clinical management of persons with AT.

**STRENGTH & FATIGABILITY IN ACHILLES TENDINOPATHY**

AT research has largely focused on histopathology and biomechanical characteristics of the tendon (Cook et al., 2016). However, the extent of tendon abnormalities is often unrelated to symptom severity (Martin et al., 2018). Therefore, while a focus on the tendon is logical (pain is localized within the tendon), it is likely an incomplete approach. Importantly, tendon injury may result from many other intrinsic and extrinsic factors (Magnan et al., 2014). Recall that muscle is the force generator for loads expressed across the tendon. Perhaps, for this reason, insufficient strength and increased fatigability of the attached triceps surae muscles are important factors in the pathophysiology of AT.

Interestingly, a 2006 prospective study evaluating military cadets for risk factors related to Achilles tendon injury found that the most significant predictors for eventual AT diagnosis were reduced baseline plantar flexor strength and increased dorsiflexion range of motion (Mahieu et al., 2006). None of the other variables, including Achilles tendon stiffness, plantar flexion power, activity level, and anthropometrical characteristics, were significant predictors of subsequent injury in their study (Mahieu et al., 2006). While causation cannot be attributed in this type of study design, it is intriguing to consider that baseline plantar flexor strength – not tendon stiffness – was associated with AT onset. However, an
important limitation in this study was the diagnostic requirement that dorsiflexion 
*increased* the patients' perceived pain. This is in direct opposition to the 
recommended clinical cluster in AT, which requires *reduction* in tendon pain 
during ankle dorsiflexion (also known as the Royal London Hospital Test) 
(Maffulli et al., 2003, Martin et al., 2018).

Since the time of this prospective study, a 2016 Delphi study evaluated risk 
factors for developing AT (O'Neill et al., 2016). Based on consensus from tendon 
experts around the world, they concluded that muscle strength deficits increase 
the risk of developing AT and that plantar flexor strengthening interventions can 
help prevent AT onset. However, the premise of muscle strength deficits in AT 
was based, in part, on opinion or the assumptions made by review authors, 
researchers, and clinicians (O'Neill et al., 2016, Skjong et al., 2012, Murtaugh 
and Ihm, 2013). More recently, a systematic review (Hasani et al., 2021) found 
conflicting evidence for plantar flexor muscle impairment between people with AT 
and healthy controls and limited evidence for between-limb differences in 
maximal plantar flexor torque.

The potential relevance of muscle function in AT, however, cannot be 
dismissed. The highest quality evidence for treatment in AT advocates the use of 
strengthening programs (Martin et al., 2018). However, treatment interventions in 
AT are often inadequate, inefficient, or unsuccessful (Paavola et al., 2000, 
Paavola et al., 2002, Bohu et al., 2009). Addressing abnormalities in 
neuromuscular function has been proposed as an important component to 
successful intervention in AT (O'Neill et al., 2015, Debenham et al., 2016, Grigg
et al., 2013), and strength gains occasionally accompany improvement in AT symptoms (Malliaras et al., 2013b). However, it is unclear whether this is simply a byproduct of sufficiently loading the diseased tendon (Bohm et al., 2015, Hasani et al., 2021). Understanding whether – and which – muscle impairments must be addressed when treating AT would optimize treatment selection and improve prognosis.

Insufficient understanding of the underlying plantar flexor muscle function likely contributes to poor prognosis in AT. Yet, empirical evidence is inconclusive, as it pertains to the role of strength and fatigability of the plantar flexors in AT. Furthermore, there is no research that describes either the role of intramuscular impairment in the plantar flexor muscles or possible inhibition of the nervous system that innervates the plantar flexors as they contribute to AT. The skeletal contractile tissue that loads the tendon may be at least partially responsible for the relative overload of the tendon, whether through altered contractile properties or differences in activation of the muscle fibers. Understanding the basic contractile properties and neural drive to the muscle that loads the Achilles tendon during different muscle activation types and during fatiguing plantar flexor exercise will inform best strategies for prevention and rehabilitation from AT.

Clinical Evaluation of Plantar Flexor Function

In a clinical setting, plantar flexor muscle function is commonly quantified using the Single-Leg Heel Raise Test (SLHR) (Hislop et al., 2013). The SLHR is included as part of manual muscle testing. However, unlike typical manual
muscle testing, which evaluating muscle strength isometrically, the SLHR is a dynamic task performed to task failure (Hébert-Losier et al., 2009, Lunsford and Perry, 1995). As its name implies, the task involves repetitions of heel raises while standing on one leg. The number of repetitions completed is often translated into a muscle strength grade (Hislop et al., 2013).

Concerns have been raised regarding the validity of the SLHR as a measure of muscle strength when based solely on repetitions completed (Harris-Love et al., 2014, Sman et al., 2014, Haber et al., 2004, Möller et al., 2005, Silbernagel et al., 2006). As a result, many modifications have been recommended, including: performing the SLHR using specialized devices; using a weight belt; or including measurements of work or power. Differences in plantar flexor function are then reported using these new parameters. While these modifications improve the objectivity of the SLHR, it remains unclear how the SLHR can isolate itself to plantar flexor function alone.

In AT, changes in plantar flexor function are often reported through the lens of SLHR performance. This includes reporting evaluating repetitions completed (Silbernagel et al., 2001, Rabusin et al., 2019, Neeter et al., 2003, Silbernagel et al., 2007a, Silbernagel et al., 2007b), work performed (Silbernagel et al., 2001, Silbernagel et al., 2007a, Silbernagel et al., 2007b, Boesen et al., 2017) or power demonstrated (Silbernagel et al., 2007a, Silbernagel et al., 2007b) during the SLHR. Therefore, it is important to understand the advantages and disadvantages of using the SLHR to quantify plantar flexor muscle function, both at baseline (as in healthy populations) and in AT.
Clinical Interventions for Chronic Midportion Achilles Tendinopathy

Strengthening of the plantar flexor muscles via eccentric activation – activation while the muscle is simultaneously being lengthened – is commonly recommended to increase function and reduce pain with AT (Murtaugh and Ihm, 2013, Martin et al., 2018). However, the underlying mechanism for the improvements in pain, function, and efficacy over alternative strength training (often using concentric activations, where the muscle is activated while its length is shortening, or isometric activations, where the muscle is activated while being maintained at a static length) has not been established (Skjong et al., 2012). Despite the possible benefit of eccentric muscle activation, baseline muscle strength during different activation types (eccentric, concentric, and isometric) and during repeated activations that induce muscle fatigue – which form the basis of strength training programs – have not been elucidated in people with AT. Furthermore, the precise neural and contractile mechanisms that may contribute to any differences in fatigability between people with AT and controls are not known.

The frequent successes of eccentric plantar flexor muscle strengthening suggest an underlying strength deficit during lengthening muscle activations which is reversed with appropriate training. The magnitude of plantar flexor muscle strength changes, including the relationship between maximal muscle strength between concentric and eccentric activation modes and the contractile and neural mechanisms underlying these changes, have yet to be determined. Often, studies have focused on the biomechanical aspects of the tendon rather
than evaluating the intimately related muscular tissue (Chaudhry et al., 2015, Grigg et al., 2009, Rees et al., 2008). Further, even in the healthy tendon, there are inconsistencies within the literature regarding the tendon response to exercise (Svensson et al., 2016). A greater understanding of the baseline characteristics and response to fatiguing plantar flexor exercise will prove beneficial when selecting treatment techniques in AT and for prevention efforts.

**SPECIFIC AIMS**

The overarching aim of this dissertation is to characterize neuromuscular function of the plantar flexor muscles in people with AT compared with healthy controls, including during a common clinical test (the Single-Leg Heel Raise). Neuromuscular function is characterized by measurements of isometric and dynamic strength, fatigability and the contributing mechanisms. This dissertation seeks to explain the contributing contractile and neural mechanisms and the influence of pain on differences in calf muscle strength and function in people with AT and healthy controls. The hypothesis is that limbs with AT will demonstrate decreased strength of the plantar flexor muscles due to a reduction in neural drive, impaired contractile properties of the affected limb, and heightened pain sensitivity compared with both the contralateral limb and with healthy controls. The related specific aims, objectives and corresponding hypotheses are detailed below.

**Aim 1: Characterize plantar flexor muscle strength and fatigability,**

including evaluation of the neural and contractile mechanisms and pain
characteristics of the plantar flexors, during a commonly-used clinical evaluation, the Single-Leg Heel Raise Test, in young, healthy subjects. Young, healthy control participants will complete the Single-Leg Heel Raise test (SLHR). Performance in the SLHR will be compared with baseline maximal isometric strength of the plantar flexor muscles and with the reduction in maximal isometric strength following the SLHR. Electrical stimulation of the motor nerve will be used to stimulate the plantar flexor muscles that attach to the Achilles tendon to quantify 1) contractile properties of the muscle independent of volition, 2) neural drive to the muscle during maximal isometric strength contractions, both before and after fatiguing exercise. Sex differences in baseline strength and in response to fatiguing exercise will be evaluated, including any differential mechanisms contributing to performance fatigability between men and women.

**Aim 1 Hypotheses:** Performance in the SLHR will not be associated with a laboratory measure of maximal plantar flexor strength. There will be no sex differences in plantar flexor muscle fatigability, and the underlying mechanisms will contribute to similar degrees within both men and women. At baseline, however, men will demonstrate higher baseline torque levels.

**Aim 2: Determine maximal plantar flexor strength during isometric and dynamic maximal contractions, including evaluation of the neural and contractile mechanisms and pain characteristics, as they relate to AT.** Maximal isometric, concentric and eccentric strength of the plantar flexor muscles, baseline pain sensitivity, and the contractile and neural properties of the plantar flexor muscles will be compared in people with a current diagnosis of AT.
and healthy controls matched for limb dominance. Electrical stimulation of the muscle is used to stimulate the plantar flexor muscles that attach to the Achilles tendon and quantify 1) contractile properties of the muscle independent of volition, and 2) neural drive to the muscle during maximal isometric contractions.

**Aim 2 Hypothesis:** Tendinopathic limbs will demonstrate decreased strength, and this will be associated with decreased voluntary activation and heightened pain sensitivity in the affected limb compared with the contralateral limb and healthy controls.

**Aim 3:** Determine plantar flexor muscle fatigability in persons with AT compared to healthy controls, including the contributing neural and contractile mechanisms. Fatigability will be assessed using a dynamic clinical test, the Single-Leg Heel Raise, and during fatiguing isometric exercise. Fatigability will be compared between groups (i.e., in people with AT compared with healthy controls) and within groups (i.e., between limbs in people with AT). Resting twitch torque (contractile properties) of the plantar flexor muscles, voluntary activation (neural drive) to the muscle during contractions and pain responses to fatiguing exercise will be compared before and after fatiguing exercise. **Aim 3 Hypotheses:** (1) Persons with AT will show greater decrements in force following a single bout of isometric plantar flexor muscle exercise. (2) Persons with AT will complete fewer repetitions during the SLHR. (3) Persons with AT will have greater decrements in voluntary activation and will report greater magnitudes of pain in the Achilles tendon following fatiguing exercise,
and these will be associated with greater fatigability following isometric fatiguing exercise.
CHAPTER 2 : THE SINGLE-LEG HEEL RAISE TEST

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INTRODUCTION

The single-leg heel raise test (SLHR) is commonly used in clinical practice as a manual muscle test of plantar flexion strength. It is a dynamic task, assigning strength grades based on repetitions completed before task failure (Hislop et al., 2013). This approach differs from the traditional manual muscle testing approach, which involves evaluation of maximal isometric strength against resistance provided by an examiner (Hébert-Losier et al., 2009, Lunsford and Perry, 1995). While the SLHR is widely adopted in the clinic, there are several limitations for using it as a measure of antigravity plantar flexion strength. First, the repetitions required for a maximal strength grade vary widely between sources, and healthy populations vary between completing zero and 120 repetitions (Hébert-Losier et al., 2009, Jan et al., 2005). Second, task performance in the SLHR cannot be isolated to plantar flexion across the ankle. To maintain upright posture during the task, the body must appropriately respond to perturbations in three planes of motion. Lastly, and perhaps most importantly, the assertion that the SLHR correlates well with maximal isometric strength is not validated (Harris-Love et al., 2014), nor supported physiologically. In fact, the number of repetitions completed before task failure is a measure of performance
fatigability (endurance), not strength (Enoka and Duchateau, 2008, Hunter et al., 2004b).

Performance fatigability is an acute, activity-induced decline in an objective measure of motor performance over time (Enoka and Duchateau, 2016). In laboratory and clinical settings, fatigability is often quantified as an exercise-induced reduction in the maximal force or power of the exercising limb (Enoka and Duchateau, 2008, Gandevia, 2001, Hunter, 2018). For submaximal intensity tasks with a constant load -- such as body weight during the SLHR -- fatigability can be quantified as the time or number of repetitions completed before failure (Hunter et al., 2004b). Fatigability and the contributing mechanisms (e.g. neural and muscular mechanisms) vary between muscle groups, between tasks (e.g. dynamic vs isometric tasks), and between populations (Avin and Frey Law, 2011, Hunter, 2018), including between males and females (Hunter, 2016a). The SLHR purports to measure plantar flexion strength during a dynamic task. However, strength and fatigability are often not associated, possibly because the metabolic demands are quite different; in fact, in some populations, these have an inverse relationship, whereby weaker individuals exhibit a greater task duration (Hunter et al., 2004a). There is no information on 1) the relationship between maximal strength and the clinical test of SLHR; 2) the magnitude of fatigability that occurs during the SLHR; and 3) whether there are differences between males and females, as is often observed for other tasks (Hunter, 2016a, Senefeld et al., 2018b, Avin et al., 2010).
Sex differences in fatigability exist across many muscle groups and tasks, both in terms of the magnitude of fatigability and the neural and muscular mechanisms contributing to fatigability (Hunter, 2016a). Males, who are often stronger, are typically more fatigable than females (Hunter, 2016a). This is especially true during isometric tasks and is more variable with dynamic fatiguing tasks (Hunter, 2016a, Hunter, 2016b). If sex differences exist in SLHR performance, the criteria for muscle grades could differ between populations, such as between males and females. Importantly, knowledge of these will help guide clinicians when executing and evaluating the SLHR in clinic.

The purpose of this study was to determine: 1) associations between SLHR repetitions and measures of maximal plantar flexion strength, assessed as baseline maximal voluntary isometric contraction (MVIC); 2) associations between SLHR repetitions and the reduction in MVIC following the SLHR; and 3) whether sex differences exist in performance of the SLHR. We hypothesized that: 1) the number of SLHR repetitions would be poorly correlated with a measure of baseline maximal plantar flexion strength; 2) the number of SLHR repetitions would be associated with a measure of plantar flexor fatigability (measured as the reduction in maximal plantar flexor strength); and 3) males would demonstrate greater fatigability than females (measured as SLHR repetitions and the reduction in MVIC). To understand the contribution of neural mechanisms to fatigability of the plantar flexor muscles, the reduction in voluntary activation (central fatigue) was assessed with the interpolated twitch technique during MVICs before and after the SLHR (Gandevia, 2001, Senefeld et al.,
Muscular mechanisms were assessed as the change in contractile function and represented as the change in electrically-evoked involuntary contractions of the plantar flexor muscles (Gandevia, 2001).

MATERIALS & METHODS

Participants

Thirty healthy, young adults (15 males and 15 females, 19-30 years) volunteered to participate in the study. Exclusion criteria included known cardiovascular disease, neurological disease, and a history of musculoskeletal injury to the right lower extremity. Informed consent was obtained from all participants prior to participation in the study. The study protocol was approved by the Marquette University Institutional Review Board and in compliance with the Declaration of Helsinki.

All testing took place during one session by the same researcher and was performed on the right lower extremity. The study involved measures of strength (MVIC), voluntary activation and contractile properties of the plantar flexor muscles while seated in a Biodex dynamometer (Biodex System 3 Pro; Biodex Medical; Shirley, NY) before and after a single-leg heel raise task (SLHR) performed to failure. The SLHR was performed in the upright standing position on a custom-made heel raise device placed adjacent to the Biodex dynamometer (Figure 2.1B). Physical activity data were calculated based on responses to a 12-
month self-report physical activity questionnaire, the Modifiable Activity Questionnaire (MAQ) (Kriska, 1997).

**Experimental Setup**

Each participant was seated in a Biodex dynamometer to quantify forces during the MVIC and assess voluntary activation and contractile properties of the right plantar flexor muscles. The right hip and knee were flexed to 90 degrees, the thigh resting on a padded thigh support, and the foot resting on a foot plate affixed to the dynamometer (Figure 2.1A). To minimize extraneous movement and isolate exercise to the right ankle joint, straps were placed across the waist, chest, and right thigh. Two straps were used around the ankle and one around the forefoot to maintain the plantar surface of the foot in contact with the foot plate. The right ankle was placed in a neutral position, with the foot perpendicular to the shank.

**Baseline Measures**

Participants performed MVICs of the plantar flexors with two-minutes rest between trials. Each participant performed at least two trials, repeating these until no further torque increases resulted (determined as two MVICs within 5% of each other).

The right tibial nerve was stimulated using a constant-current, variable high-voltage stimulator (DS7AH; Digitimer Ltd; Hertforshire, UK) to evoke contractions to assess contractile properties at rest and during MVICs (voluntary
activation). Stimulation was applied to the right tibial nerve using a bar electrode at the medial popliteal space distal to the sciatic nerve bifurcation. Single square-wave pulses of 100µs duration (400 V, 100 Hz) were delivered with a stimulation intensity initiated at 50mA and gradually increased until a plateau was reached, such that further increases in stimulation intensity resulted in no additional increases in evoked torque (Sundberg et al., 2018b, Senefeld et al., 2018b). The plateau intensity was increased further by 10%. This stimulation intensity was used during a single pulse stimulation and double pulse of stimulation (at 100Hz) to enable assessment of contractile properties and voluntary activation, respectively, of the plantar flexor muscles.

MVICs were repeated with the addition of both a superimposed doublet stimulation (SIT, superimposed twitch) followed by a resting (potentiated) doublet stimulation (RT, resting twitch) of the tibial nerve ~2 seconds after the MVIC (Figure 2.1 C). Doublet stimulations were used for the SIT, as this has been shown to be more sensitive (Rozand et al., 2020, Oskouei et al., 2003). The forces during the SIT and RT were used in the analysis of voluntary activation and resting twitch torque (see Data Analysis). Each participant performed four MVICs with two minutes of rest between each trial.
Single-leg heel raise task

The SLHR involved repeated heel raises of the right leg while in upright standing. The SLHR task was performed using a custom-made heel raise device.
(Figure 2.1 B) that included a horizontal plate affixed above a standing surface by an upright support bar. The horizontal plate served as a visual and tactile target during the SLHR and was adjustable in both the vertical and anteroposterior dimensions. The position of the horizontal plate was selected as the maximum height achieved during a single-leg heel raise for each subject, adjusted to the dorsal ankle crease at end-range during a single-leg heel raise.

Participants were familiarized and provided instruction about on performance of the SLHR prior to the baseline measures. This included the importance of contacting the horizontal target plate at each repetition and to demonstrate slow, controlled lowering during the eccentric phase of the task. Instability as a cofounding variable was minimized by allowing use of light fingertip support in the horizontal plane.

The SLHR was standardized to a pace of one heel raise every three seconds. This was achieved using a 60 beats-per-minute audible metronome and verbal cueing of “up, down, rest” to signify three-second epochs wherein participants took one second each to raise onto their toes, lower down, then rest. Verbal encouragement was provided and the SLHR was performed until task failure, defined as two consecutive missed contacts with the horizontal target plate. Participants were blinded to the failure criteria.

Post SLHR Task Measurements

Upon task failure, the participant was returned immediately to the Biodex for post-task measurements of MVIC with a SIT followed by resting twitches two
seconds post MVIC. These measurements began at 45 ± 8 sec and were repeated at 1, 3, 5, 7, 9, and 11 mins post-SLHR.

**Electromyography (EMG)**

EMG activity of the medial gastrocnemius, lateral gastrocnemius, soleus, and tibialis anterior was recorded using bipolar EMG electrodes (Ag–AgCl, 8-mm diameter; 20 mm inter-electrode distance; Natus Medical Inc) located over the muscle bellies in accordance with recommendations by the SENIAM project (Hermens et al., 2000). In brief, electrodes were placed midway between the anatomical origin and myotendinous junction of each muscle, in alignment with the fiber direction of the respective muscle. Data were amplified (4000 Hz; Coulbourn Instruments, Allentown, PA), digitized (Power1401, Cambridge Electronic Design Limited, Cambridge, UK) and stored online using Spike2 software (Cambridge Electronic Design Limited, Cambridge, UK).

**Data and Statistical Analyses**

Thirty people volunteered to participate in this study. The data from one female and one male were removed because their MVIC torque and voluntary activation values were more than 3 standard deviations below the group means. Thus, 14 females (19-30 yrs, 21.1±2.9 yrs) and 14 males (19-26 yrs, 21.5±1.8 yrs) are included in the subsequent data and statistical analyses.

For all analyses of strength, contractile properties, and voluntary activation, “baseline” refers to the average of values that occurred during the two
baseline MVICs that yielded the greatest torque amplitudes. “Post-task” refers to the first MVIC following the SLHR.

MVIC was measured as the average of a 0.5-second window surrounding the maximum torque. Voluntary activation was calculated as the ratio of the superimposed to the resting doublet twitch (Gandevia, 2001): (1-SIT/RT)*100. The resting twitch refers to the torque amplitude of the electrically-evoked potentiated resting doublet stimulation that occurred immediately after an MVIC.

Muscle activity was quantified as the root-mean-square (RMS) value of the electromyography (EMG) signals for each the medial and lateral gastrocnemius, soleus, and tibialis anterior. Maximal baseline EMG was measured over the same 0.5-second interval as the MVIC, and this was used to normalize EMG data from the SLHR. For the SLHR, EMG data was quantified as the RMS value over a 0.5-second interval surrounding the maximal EMG activity recorded during each SLHR repetition.

Independent samples t-tests were used to compare physical characteristics, physical activity levels, number of SLHR repetitions completed, and baseline measures of strength, muscle properties and voluntary activation between males and females. Repeated-measures ANOVAs were used to evaluate changes in MVIC torque, electrically-evoked resting twitch amplitude, and voluntary activation from baseline to immediately post-SLHR, using time as the within-subjects factor and sex as the between-subject factor. Similarly, repeated-measures ANOVAs were used to evaluate changes in EMG activity from start to end of the SLHR task, using time as the within-subjects factor and
sex as the between-subjects factor. For all ANOVAs, Greenhouse-Geisser corrections were used whenever the assumption of sphericity was violated. Mediation analyses were utilized to evaluate the impact of body weight on the relationships between sex and the outcome variables (Field-Fote, 2019).

Pearson correlation was used to evaluate associations between SLHR repetitions, baseline dependent variables, and changes in dependent variables from pre- to post-task. Normality was assumed for all variables based on histograms and Q-Q plots. Significance was determined a priori at \( p < 0.05 \). Data are reported as mean ± standard deviation (SD) in the text and displayed as mean ± standard error of the mean (SEM) in the figures. All analyses were performed in IBM Statistical Package for Social Sciences (SPSS, V26).

**RESULTS**

Males and females were similar in both BMI and in self-reported physical activity levels, while males had more mass and were taller (see Table 2.1).
Table 2.1. Participant demographics & baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Males</th>
<th>Females</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>yrs</td>
<td>21.5±1.8</td>
<td>21.1±2.9</td>
<td>0.58</td>
</tr>
<tr>
<td>*Height</td>
<td>m</td>
<td>1.81±0.08</td>
<td>1.66±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*Weight</td>
<td>kg</td>
<td>79.4±10.3</td>
<td>64.0±10.8</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>kg·m(^{-2})</td>
<td>24.3±2.3</td>
<td>23.2±3.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>met·hr·wk(^{-1})</td>
<td>66.6±26.6</td>
<td>59.5±35.0</td>
<td>0.55</td>
</tr>
<tr>
<td>MVIC</td>
<td>Nm</td>
<td>148.8±36.3</td>
<td>128.1±34.1</td>
<td>0.20</td>
</tr>
<tr>
<td>RT</td>
<td>Nm</td>
<td>32.6±9.9</td>
<td>25.7±8.5</td>
<td>0.06</td>
</tr>
<tr>
<td>VA</td>
<td>%</td>
<td>91.5±8.2</td>
<td>90.9±10.2</td>
<td>0.87</td>
</tr>
<tr>
<td>SLHR</td>
<td>reps</td>
<td>32.6±6.9</td>
<td>39.4±14.8</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* \(p<0.05\); ** \(p<0.01\).

BMI, body mass index, MVIC, maximal voluntary isometric contraction; RT, potentiated resting twitch amplitude; VA, voluntary activation; SLHR, single leg heel raise.

**SLHR and MVIC**

There was no difference in the number of SLHR repetitions performed to task failure by males and females (\(p=0.14\), Figure 2.2). At baseline, there was no sex differences in MVIC torque (\(p=0.198\), Figure 2.3, “baseline”). The SLHR task resulted in 20.5% reductions in MVIC torque from baseline for all participants (time effect, \(p<0.001\)). However, there was no sex difference in the reduction of MVIC (sex effect, \(p=0.14\), males 18.6% and females 22.7%; Figure 2.3) and no interaction of sex and time (\(p=0.865\)). Normalizing MVIC torque to body weight did not change these results: baseline torque remained similar between groups (\(p=0.479\)); MVIC torque following the SLHR was not different between groups (\(p=0.808\)); and post-task reduction in MVIC was similar between males and
females \( (p=0.532) \). Furthermore, body weight did not mediate the relationship between sex and repetitions completed during the SLHR \( (p=0.206) \).

Figure 2.2. Box-and-whisker plot of single-leg heel raise (SLHR) repetitions performed by males and females. The middle line represents the median values, while the “x” represents the mean values. The left-hand box shows the pooled results for males and females. There were no sex differences in number of SLHR repetitions completed at time of task failure \( (p=0.137) \).
RMS EMG (% MVIC) amplitude of the triceps surae did not change from the start to the end of the SLHR task for males (MG: 17.3% decrease, \( p = 0.351 \); LG: 12.2% increase, \( p = 0.081 \); SOL: 1.9% decrease, \( p = 0.683 \)), but females had significant increases in all three muscles (sex and time interaction for combined triceps surae muscles, \( p = 0.029 \)). The females demonstrated increases in the MG (32.0% increase, \( p = 0.026 \)), LG (52.3%, \( p = 0.011 \)) and SOL (26.4%, \( p = 0.030 \)).
Bodyweight did not mediate the sex-differences in EMG for any of the triceps surae muscles (MG, \( p=0.176 \); LG, \( p=0.375 \); SOL, \( p=0.070 \)).

Voluntary Activation and Twitch Amplitude

There were no sex differences in baseline voluntary activation (VA, \( p=0.866 \)) or post-task reduction in VA (\( p=0.856 \)). There was a significant main effect of time: the SLHR resulted in reduced VA for all participants (9.8%).

Figure 2.4. Change in RMS EMG amplitude for each the soleus, medial and lateral gastrocnemius, and tibialis anterior muscles from the start to end of the SLHR task, as a percent of baseline MVIC. EMG for all three plantar flexor muscles increased in females (striped bars). In males (solid bars), medial gastrocnemius EMG decreased, while lateral gastrocnemius and soleus EMG remained unchanged. Tibialis anterior EMG remained unchanged in both males and females. *, interaction between sex and time, \( p<0.05 \).
decrease from baseline, p=0.012; Figure 2.5). There were similarly no sex differences in either baseline resting twitch amplitudes (RT, p=0.057) or post-task change in RT (p=0.357, Figure 2.5). There was a significant main effect of time: RT increased from pre- to post-task for all participants (17.6% increase from baseline, p<0.001, Figure 2.5).

**Associations**

The number of SLHR repetitions performed was not correlated with either the baseline MVIC (r=-0.005, p=0.979) or the percent reduction in MVIC following

![Figure 2.5 Voluntary activation (A) and resting twitch amplitude (B) before and after the SLHR task in males and females pooled. Voluntary activation decreased (p=0.01) and resting twitch amplitude increased (p<0.001) following the SLHR task for males and females (there were no sex differences in response to the SLHR). * p<0.05; ** p<0.01.]
the SLHR ($r=-0.234$, $p=0.23$). The percent reduction in MVIC was positively associated with the reduction in VA ($r = 0.841$, $p<0.001$): those who had the greatest reductions in MVIC also had the largest reductions in VA. However, the SLHR was not associated with either baseline VA ($r=0.354$, $p=0.064$), reduction in VA ($r=-0.085$, $p=0.669$), baseline RT ($r=0.054$, $p=0.786$), or the change in RT ($r=-0.104$, $p=0.597$). Baseline MVIC was not predictive of change in MVIC ($r=0.122$, $p=0.537$): those with greater MVIC torque did not necessarily have greater (or lesser) reductions in MVIC torque following the SLHR.

**DISCUSSION**

The novel findings of this study were: (1) the SLHR (number of repetitions completed at task failure) was not associated with the maximal isometric plantar flexion strength (MVIC) nor the relative reduction in maximal strength after the SLHR (fatigability of the MVIC), and (2) there were no sex differences in either SLHR repetitions completed, MVIC and fatigability of the MVIC, or associations between these variables. Additionally, our results implicate reductions in voluntary activation (i.e., neural drive) as a primary mechanism for fatigability of the MVIC after SLHR in both males and females. Collectively, our results suggest that the SLHR is not a valid measure of strength but a specific measure of dynamic-contraction lower limb fatigability that is similar in males and females.
Fatigability and Strength

The number of dynamic SLHR repetitions were not correlated with maximal isometric plantar flexion strength. From a physiological standpoint, this is expected; strength, represented in this study by brief maximal isometric voluntary efforts, is typically correlated most strongly with physiological cross-sectional area, which is indicative of the number of sarcomeres in parallel in a muscle fiber and muscle (Hunter et al., 2017). Strength is often not predicted by the ability to maintain a task for a period of time because the physiological mechanisms involved in continued task performance are quite different from those involved in generating maximal force for a brief time (Hunter et al., 2004b). Specifically, failure to maintain the requirements of task over a period of time (in this case, ~100 seconds) involves the ability of the muscle to meet the metabolic demands based on the task requirements. During dynamic fatiguing contractions, fiber velocity slows and maximal force development declines due to increased metabolites within the muscle (e.g. inorganic phosphate, hydrogen ions), thereby resulting in fatigability (Sundberg et al., 2019, Kent-Braun et al., 2012).

Furthermore, afferent feedback (group III and IV) due to increased metabolite accumulations can inhibit motor neurons in the spinal cord and reduce voluntary drive (Gandevia, 2001, Taylor et al., 2016). Thus, the physiological mechanisms most relevant to the SLHR are the ability of the muscle to meet the metabolic demands of the fatiguing task and the ability to maintain neural drive to the muscle, not the physiological cross-sectional area of the muscle.

In the clinical setting, the SLHR is thought to measure plantar flexion strength, as purported in manual muscle testing procedures (Hislop et al., 2013).
However, combined with the absence of physiological basis, the lack of association between the SLHR and maximal plantar flexion strength in young, healthy participants calls into question the construct validity of the SLHR. Importantly, our finding agrees with a prior study evaluating 43 adults with myositis (64.9 years old), where SLHR repetitions were not correlated with plantar flexion MVIC (Harris-Love et al., 2014). Concerns with the SLHR have arisen previously, including: lack of uniform testing parameters (Hébert-Losier et al., 2009, Sman et al., 2014); and limited sensitivity (specifically, an inability to differentiate outcomes between treatment groups) (Silbernagel et al., 2010). Therefore, whether for healthy or clinical populations, the SLHR is likely an invalid measure of maximal plantar flexion strength.

The plantar flexors experienced reductions in MVIC following the SLHR. However, these reductions in force were not associated with performance in the SLHR. In single-joint tasks performed to failure, maximal strength or power is expected to decrease following task failure (Kent-Braun et al., 2012). This lack of association between the SLHR and reduction in MVIC indicates that fatigability of the plantar flexors is task-dependent (Hunter, 2018), as seen in other lower limb muscle groups. For example, in young, healthy adults, the fatigability of the knee extensor muscles and involved mechanisms differed for an isometric fatiguing contraction compared with a dynamic knee extensor tasks (Senefeld et al., 2018b), because the specific demands of the task dictate the amount of fatigue and the mechanisms. A decrease in MVIC (isometric) after the SLHR may reflect a reduction in the number of active cross-bridges (Fitts, 2016, Kent-Braun et al.,
and, as we showed, a reduction in neural drive. In contrast, a slowing of velocity during the dynamic contraction fatigue of a SLHR likely reflects the limits of crossbridge speed and reduction in maximal shortening velocity of the fiber (Jones, 2010).

Importantly, the SLHR may not be limited to the ankle plantar flexor muscles. Apart from fingertip support for balance, there are no methods used to stabilize the body or surrounding joints during the SLHR. Thus, it is probable that muscles external to the plantar flexors – including foot intrinsic and extrinsic musculature (DiLiberto and Nawoczenski, 2020, Hutchison and Houck, 2018), knee extensors, frontal plane hip stabilizers, and core musculature – are additionally responsible for success (and ultimately failure) in the SLHR. The SLHR may, therefore, be best interpreted as a functional, dynamic task evaluating fatigability of the entire lower extremity.

**Mechanisms**

Our study evaluated measures representing neural and contractile mechanisms that may contribute to the reduction in MVIC strength of the plantar flexor muscles after the SLHR and variability in performance of the SLHR. Voluntary activation – assessed during the MVIC with electrically-evoked contractions – was reduced following the SLHR and was correlated with the reduction in MVIC torque, suggesting that decreased neural drive contributed to fatigability of the MVICs. Conversely, changes in resting twitch amplitude were not related to the reduction in MVIC, suggesting that contractile mechanisms
within the plantar flexor muscle group were not responsible for the loss in maximal plantar flexion force following the SLHR. This is atypical for dynamic tasks that are constrained to a single limb; typically, changes in maximal strength following dynamic fatiguing exercise are explained by contractile mechanisms, as in the knee extensor muscles (Senefeld et al., 2018b). In the case of the SLHR, this difference may highlight the whole-limb nature of this task. Without constraining neighboring joints and providing robust balance assistance, several other muscles must be innervated to enable task continuation. As a result, the burden on the central nervous system may be greater. Thus, while the SLHR fails to predict either maximal plantar flexion strength or the magnitude of the reduction in MVIC, perhaps it is best interpreted as an assessment of whole lower limb dynamic fatigability.

There were no sex differences in SLHR repetitions completed before task failure, nor were there differences in maximal strength or fatigability. The lack of sex differences in strength was surprising given that, on average, men are stronger than women -- although more so for upper limb muscles (Hunter, 2014). There were additionally no sex differences in the mechanisms driving fatigability in the SLHR, including the reduction in voluntary activation, which was similar in males and females. Neural mechanisms (i.e., voluntary activation) were similarly associated with fatigability in males and females, while contractile mechanisms (i.e., resting twitch amplitude) bore no relationship to fatigability in either males or females.
Sex differences were observed only in muscle activation levels (EMG amplitudes) during the SLHR. While males had no increase in EMG amplitudes, females had significant increases for each the soleus, medial and lateral gastrocnemius muscles. Typically, repeated submaximal contractions result in progressive increases in EMG (Enoka and Duchateau, 2008), representative of further recruitment of motor units as muscle fibers become progressively fatigued (Bigland-Ritchie et al., 1986). This was evident in the females, but it was not observed in the males, suggesting that, at least for females, the SLHR was a submaximal, fatiguing task. The relatively stable soleus and lateral gastrocnemius EMG amplitudes and the reduction in medial gastrocnemius EMG amplitude seen in male participants could indicate that the SLHR was a maximal task for their plantar flexors. However, when combined with the knowledge that their voluntary activation and MVIC torque both reduced -- and to a similar magnitude as female participants -- there is one explanation that seems more plausible: although the rate of fatigue of the dynamic contractions was similar for the males and females, they fatigued for different reasons. The EMG data indicate that males and females utilized different strategies and recruitment of muscles during the SLHR.

SLHR performance is correlated with many measures of functional relevance: joint stability, proprioception and balance (Park et al., 2019, Fujiwara et al., 2011); gait speed and use of an assistive device (Davenport et al., 2014, Brincks and Nielsen, 2012, Jung et al., 2020). This makes understanding the fatigability of the plantar flexors and surrounding, supporting musculature during
the SLHR even more critical. For instance, strengthening of intrinsic foot musculature alone improved heel raise height and repetitions completed in persons with flat feet (Hutchison and Houck, 2018). This finding supports our conclusion that SLHR performance depends upon more than just plantar flexor function, and it suggests that neuromuscular mechanisms should be investigated as they relate to fatigability of intrinsic foot muscles. To date, however, the degree to which intrinsic foot muscles contribute to SLHR performance has not been investigated, nor have the contributing roles of other muscles acting at the foot, knee, or hip joints.

There were no sex differences in SLHR repetitions completed in this study, even when accounting for differences in body weight. Total work performed, however, may have differed between males and females as a function of ankle range of motion (Lunsford and Perry, 1995). Furthermore, differences in muscle function proximal and distal to the talocrural joint may impact task performance between males and females. The role of stabilizing muscles in the SLHR, including the neuromuscular mechanisms of these muscles that contribute to task failure, would assist in identifying whether further sex differences in SLHR task performance exist and whether these need to be assessed and addressed during clinical evaluation.

**Limitations**

Maximal isometric voluntary contractions were used to assess fatigability after the SLHR, despite the dynamic nature of the task. This selection was
intentional because: (1) manual muscle testing (MMT) is traditionally performed as an evaluation of maximal *isometric* strength; and (2) assessment of voluntary activation during maximal dynamic contractions in this setting is not yet a reliable technique. Furthermore, there was ~45 seconds of delay in measuring post-task maximal strength and contractile properties assessed in the dynamometer. Any pre- to post-task differences, therefore, reflect the time of measurement and were not precisely immediately post-task. Finally, lack of a familiarization session could have impacted MVIC torque (Gandevia, 2001). However, it is unlikely that the groups would have been differentially impacted by the lack of a familiarization session. Furthermore, young to middle-aged adults do not exhibit sex differences in activation (Hunter et al., 2006, Sundberg et al., 2018b) and typically require minimal practice to achieve optimal activation in a session with no prior familiarization (Hunter et al., 2008).

Testing in the isokinetic dynamometer (Biodex) utilized a flexed-knee position, while the SLHR utilizes a straight-knee position. This could affect interpretations of relative muscle contributions in the SLHR when compared to MVICs. However, no such comparisons were made between tasks. Importantly, while the change in knee position may result in altered PF torque, this would not impact the relationship between the SLHR and MVIC torque: the approximate 85% reduction in PF torque that occurs from 0 degrees to 90 degrees knee flexion (Landin et al., 2015) would simply be as though a constant multiplier were added to the equation evaluating correlation between SLHR reps and MVIC torque, which would not impact the detection of a relationship between these
variables. Finally, neither sex, BMI category, nor physical activity level impact the relationship between ankle angle and peak PF muscle activity (Hébert-Losier et al., 2011). Thus, the choice of testing position in the Biodex is unlikely to have impacted the between-group findings in this study.

**Conclusions**

The SLHR is a poor predictor of maximal plantar flexor strength in young, healthy males and females. As a test of repetitions to failure, the SLHR is well-suited to evaluate performance fatigability. However, as a task whose performance is dependent upon several factors - including coordination and stabilization of proximal and distal muscles and joints - the SLHR more likely evaluates dynamic fatigability of the lower extremity. Additionally, there were no sex differences in the number of SLHR repetitions, nor were there sex differences in maximal baseline plantar flexor strength or plantar flexor fatigability. Based on differences in muscle activation patterns, males and females likely utilize different strategies to succeed in the SLHR.

**Clinical Relevance**

The results of this study reveal a critical limitation in current interpretation of the SLHR: the lack of association between SLHR repetitions and MVIC diminishes the validity of using the SLHR as a clinic-based evaluation of plantar flexor strength. Furthermore, the lack of relationship between SLHR repetitions and reduction in plantar flexion MVIC suggests that the cause of task failure of the
SLHR may not be specific to the plantar flexor muscles. Instead, this task may be best interpreted as a task of dynamic lower extremity fatigability rather than strength or fatigability specific to the primary plantar flexor muscles involved in the task. Modifications have previously been suggested to improve the psychometric properties of the SLHR, including construction of various specialized devices, addition of linear encoders, utilization of a metronome, and addition of a weight belt (Haber et al., 2004, Möller et al., 2005, Sman et al., 2014, Silbernagel et al., 2006). However, the same limitations exist for these modified protocols: number of repetitions to failure cannot predict plantar flexor strength, and the SLHR task is not specific to the plantar flexor muscles. Thus, to evaluate maximal plantar flexor strength in clinic, new clinical measures need to be developed.
CHAPTER 3: PLANTAR FLEXOR STRENGTH IN ACHILLES TENDINOPATHY

INTRODUCTION

Midportion Achilles tendinopathy (AT) is an overuse injury commonly attributed to deficient plantar flexor muscle function (Mahieu et al., 2006, O'Neill et al., 2016). The premise of weak or fatigable plantar flexor muscles in people with AT is largely based on two factors: (1) insidious onset commonly accompanies a sudden increase or change in activity level (Martin et al., 2018, Cook et al., 2002); and (2) strength gains often – but not always (Silbernagel et al., 2007a, Silbernagel et al., 2001) – accompany improvements in symptoms and function following rehabilitation (Malliaras et al., 2013a, Alfredson et al., 1998). However, the empirical evidence supporting impaired neuromuscular function is sparse and largely inconclusive (Martin et al., 2018, Hasani et al., 2021).

Maximal voluntary contractions (MVCs) are commonly used to quantify maximal force-generating capacity of limb muscles (Gandevia, 2001). These involve maximal-effort muscle activation with a fixed joint position (isometric MVCs) or changing joint position (concentric and eccentric MVCs). These voluntary contractions are the result of neural drive to the muscle and the force-generating capacity of the muscle (i.e., contractility). Thus, weakness associated with impaired function, such as may occur in people with AT, could be due to lower neural drive, muscle atrophy, or an inability of the available muscle to contract. Understanding the contribution of neural drive and muscular contractility
to alterations in neuromuscular function, particularly weakness, may inform treatment selections (Russell et al., 2012, Ochala, 2010). Whether any muscle weakness associated with AT is due to impaired neural drive or low muscle contractility is not known.

Muscle contractility can be evaluated using electrical stimulation of a resting muscle (Senefeld et al., 2018a). The amount of torque generated from electrically stimulating a resting muscle (known as resting twitch, RT) provides insight into the muscle’s ability to contract and its contractile behavior independent of activation of the nervous system (Heyters et al., 1994, Allen et al., 1995, Booth and Thomason, 1991). Neural drive, or voluntary activation, refers to the ability of the central nervous system to activate a muscle. It can be quantified using the Interpolated Twitch Technique (Gandevia, 2001, Shield and Zhou, 2004). This technique involves electrically stimulating a muscle during a maximal effort contraction (i.e., an MVC) and then at rest, immediately following the MVC, during its potentiated state. Voluntary activation is calculated as the ratio of the torque produced in response to the stimulation during the MVIC (known as a superimposed twitch, SIT) to the torque produced in the potentiated, resting state twitch (RT) (Gandevia, 2001): Voluntary Activation (VA) = 100*(1-SIT/RT). Thus, this technique evaluates the magnitude of additional torque that could be generated during a maximal-effort contraction when the muscle, motor nerve or motor cortex are stimulated.

There are other factors that potentially confound muscle function and the ability to activate optimally during tasks that require maximal strength. Pain for
example, can influence effort and activation in clinical populations (Briani et al., 2018, Barker et al., 2004, Merkle et al., 2020, Hodges and Smeets, 2015) and potentially could contribute to altered activation of the plantar flexor muscles in people with AT. Activation of group III and IV motor afferent nerves, for example, can result in inhibition of motoneurons and reduce voluntary activation (Hunter, 2018, Salomoni et al., 2016). Such somatosensory feedback is likely imperative to protect exercising muscle (Amann et al., 2009, Blain et al., 2016). However, in chronic pain populations, such inhibition could result in muscle atrophy (Barker et al., 2004) and persistent abnormalities in neuromuscular function (Briani et al., 2018, Bennell et al., 2008).

No study has yet evaluated either the neural drive or contractile function of the plantar flexor muscles or their contribution to potential deficits in strength in people with AT. To understand neural drive and contractile function of the plantar flexor muscle we used the interpolated twitch technique and electrically evoked twitch contractions, respectively. We also assessed the role of pain in influencing neural drive and contractile function in AT, as this is poorly understood. Thus, the purpose of this study was to determine the following in persons with AT: 1) maximal plantar flexion strength and power during isometric and dynamic contractions; 2) neural drive during maximal effort contractions and contractile function based on electrically-evoked contractions at rest; and 3) whether pain, neural drive, and contractile mechanisms contribute to differences in maximal strength in people with AT.
MATERIALS & METHODS

Participants

Fourteen participants with tendinopathy (10 males, 4 females; 18-49 yrs) and 14 controls (7 males, 7 females; 18-32 yrs) volunteered to participate in the study. Inclusion criteria included the following: gradual, insidious onset of pain and/or stiffness at the midportion of the Achilles tendon, which had become chronic (i.e., persisted for at least 3 months (Scott et al., 2011); and healthy controls without history of either pain or stiffness in the Achilles tendon region. AT diagnosis was a clinical diagnosis based on the following: gradual, insidious onset of symptoms; pain and/or stiffness localized to the midportion of the Achilles tendon; pain with palpation of the midportion of the tendon; a positive Arc Sign; and a positive Royal London Hospital Test (Martin et al., 2018). Exclusion criteria included diabetes (Baskerville et al., 2018), thyroid disorders (Oliva et al., 2013), cardiovascular disease, neurological disease, known contraindications to exercise, and any acute injury, bursitis, insertional tendinopathy, or osteoarthritis in either lower extremity. Informed consent was obtained from all participants prior to participation in the study. The study protocol was approved by the Marquette University Institutional Review Board and in compliance with the Declaration of Helsinki.

All testing took place during two sessions and was led by the same researcher. The first session included completion of clinical measurements and self-report outcome measures (including the Tampa Scale of Kinesiophobia
(TSK) (French et al., 2007); the Foot and Ankle Ability Measure (FAAM), including both the sport and activities of daily living (ADL) subscales (Martin et al., 2005); and the Victoria Institute of Sport Assessment-Achilles Questionnaire (VISA-A) (Robinson et al., 2001). Familiarization to the following was provided during the first session: the Biodex, electrical stimulation protocol (for voluntary activation and contractile properties) and PPT. The second session involved: evaluation of isometric MVCs with electrical stimulation (for neural and muscular properties); concentric and eccentric MVCs; PPT; and body composition (using Dual X-Ray Absorptiometry). Physical activity data were calculated based on responses to a 12-month self-report physical activity questionnaire, the Modifiable Activity Questionnaire (MAQ) (Kriska, 1997).

All testing was completed for both lower extremities. The order of limbs was randomized every session. Within a given session, testing was completed on one leg before performing identical testing of the contralateral limb (during the same session). The study involved measures of maximal strength (both isometric and dynamic), pressure-pain threshold (PPT), voluntary activation and contractile properties of the plantar flexor muscles while seated in a Biodex dynamometer (Biodex System 3 Pro; Biodex Medical; Shirley, NY).

**Experimental Setup**

Each participant was seated in a Biodex System 3 Pro dynamometer. The test position involved a straight knee (0 degrees flexion) with a trunk angle of 55 degrees. The trunk recline was utilized to minimize any hamstring discomfort and
sciatic nerve tension during testing. The thigh rested on a padded thigh support, and the foot rested on a foot plate affixed to the dynamometer (Figure 3.1). To minimize extraneous movement and isolate exercise to the ankle joint, straps were placed across the waist, chest, and thigh. Two straps were used around the ankle and one around the forefoot to maintain the plantar surface of the foot in contact with the foot plate during strength testing. For PPT measurements, the ankle straps were removed to access the Achilles tendon, and the ankle was placed in a neutral position, with the foot perpendicular to the shank.

**Baseline Measures**

Participants performed maximal voluntary isometric contractions (isometric MVCs) of the plantar flexors with two-minutes rest between trials. Each participant performed at least two baseline isometric MVC trials, repeating these until there was no further increase in torque by >5%.

The ipsilateral tibial nerve was stimulated with a bar electrode and a constant-current, variable high-voltage stimulator (DS7AH; Digitimer Ltd; Hertforshire, UK) to evoke contractions to assess contractile properties at rest and during isometric MVCs to assess voluntary activation. Stimulation was applied to the ipsilateral tibial nerve using a bar electrode at the medial poplitical space distal to the sciatic nerve bifurcation. Single square-wave pulses (400 V, 100µs duration) were delivered with a stimulation intensity initiated at 50mA and gradually increased until a plateau was reached, such that further increases in stimulation intensity resulted in no additional increases in evoked torque.
(Senefeld et al., 2018b, Sundberg et al., 2018b). The plateau intensity was increased further by 10% to ensure supramaximal stimulation during assessment of contractile properties and voluntary activation of the plantar flexor muscles.

Figure 3.1. Experimental setup of a participant in the Biodex System3 Pro dynamometer used for plantar flexor strength measurements. Participants were given visual feedback on a monitor. Surface electromyography (EMG) was recorded for the medial and lateral gastrocnemius, soleus, and anterior tibialis muscles. Electrical stimulation was positioned over the tibial nerve.
Pressure-pain thresholds (PPTs) were measured using an algometer (Somedic SenseLab AB, Sweden) with a 1cm² probe tip at an application rate of 30 kPa/s while the participant was seated in the dynamometer (Figure 3.2 A). Algometry is a reliable method for evaluating pressure-pain thresholds (PPTs) both within and between sessions (Potter et al., 2006, Vanderweeën et al., 1996, Nussbaum and Downes, 1998, Frank et al., 2013). PPT is defined as the minimum pressure required to induce pain (Nussbaum and Downes, 1998). Evaluation of PPTs both local and remote to injured tissue provides valuable information about central compared to peripheral mechanisms contributing to a painful experience (Graven-Nielsen and Arendt-Nielsen, 2002, Curatolo et al.,

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**Figure 3.2. PPT measurement locations.** A, Pressure-pain thresholds were measured twice at each of three locations: Achilles tendon, medial gastrocnemius, and upper trapezius (marked with an “x”). B, Tendon measurements were completed using the pinch handle attachment of the Somedic Algometer.
PPT familiarization involved practice repetitions over the nailbed of the left 2\textsuperscript{nd} digit and included emphasis that the measurement was not a test of pain tolerance but rather the point at which the pressure sensation was first perceived as painful. Measurements were completed at three sites: (1) the Achilles tendon, using the pinch handle 4 cm proximal to the calcaneal insertion; (2) the ipsilateral medial gastrocnemius, measured at the midpoint between its lateral and medial margins along the location of largest calf girth; and (3) the upper trapezius, along its superior margin halfway between the seventh cervical vertebrae and the acromion process (see Figure 3.2). For all PPT measurements, the probe tip was maintained in a position orthogonal to the tissue being tested. Participants pressed a button when the pressure sensation was first perceived as painful (Rakel et al., 2014). Two measurements were completed at each measurement site, and the average of the two measurements was used in subsequent analyses. Measurement order was randomized for each leg, participant, and session.
Isometric MVCs were repeated with the addition of a superimposed doublet stimulation (SIT, superimposed twitch) followed by a resting (potentiated), 100 Hz doublet stimulation (RT, resting twitch) of the tibial nerve at ~2 seconds after the isometric MVC (Figure 3.3). Doublet stimulations were used for the SIT, as this has been shown to be more sensitive than a single stimulation (Rozand et al., 2020, Oskouei et al., 2003). The forces during the SIT and RT were used in the analysis of voluntary activation and resting twitch torque (see Data Analysis). Each participant performed four isometric MVCs with two minutes of rest between each trial.

Figure 3.3. Representative torque data from a male participant during maximal voluntary isometric contraction (isometric MVC). Measurements included: superimposed twitch (SIT) and resting twitch (RT).
**Dynamic Strength**

Concentric MVCs were performed at five velocities: 30, 60, 90, 120, and 150 deg/s. Velocities faster than 150 deg/s were not utilized, because pilot testing revealed that most healthy participants could not reach a velocity plateau at those target velocities within their available ankle range of motion. Eccentric MVCs were completed at three velocities: 30, 60, and 90. During pilot testing, eccentric velocities greater than 90 deg/s resulted in no further change in torque (i.e., participants reached a torque plateau by 90 deg/s). Concentric and eccentric MVCs were completed using each participant’s available range of motion. Familiarization included four repetitions of concentric MVCs and four repetitions of eccentric MVCs at 60 deg/s. Test contractions included four repetitions of maximal-effort contractions at each of the velocities listed above. Order of velocity was randomized for each limb of every participant. Participants were given one minute rest between each set of maximal-effort contractions. Strong verbal encouragement and visual feedback were provided for every strength measurement in the study, including familiarization repetitions.

**Data and Statistical Analyses**

The best of four efforts was used for each of the maximal strength efforts (isometric, concentric, and eccentric MVCs). Isometric MVC was measured as the average of a 0.5-second window surrounding the maximum torque but preceding the superimposed electrical stimulation. Concentric and eccentric MVCs were measured as the instantaneous peak torque during dynamic
contractions. Peak power was calculated as the product of instantaneous peak torque and the velocity at time of peak torque. Voluntary activation was calculated as the ratio of the superimposed twitch (SIT) torque to the resting doublet twitch (RT) during the MVIC (Gandevia, 2001): (1-SIT/RT)*100. The resting twitch refers to the torque amplitude of the electrically-evoked, potentiated resting doublet stimulation that occurred immediately after an MVIC.

Independent samples t-tests were used to compare physical characteristics, physical activity levels, and kinesiophobia between groups. Multivariate analyses of covariance (MANCOVAs) were used to evaluate the between-group effects of AT diagnosis on the dependent variables (strength, voluntary activation, and resting twitch amplitude), with covariates of biological sex and age. Mediation analyses were performed to evaluate effects of AT on PPT and any subsequent effects of PPTs on strength, neural drive, and resting twitch amplitude. Repeated-measures ANCOVAs were used to compare the more and less affected (or unaffected) limbs of persons with AT using a similar approach: outcome variables of strength, neural drive, and resting twitch; mediation analysis using pressure-pain thresholds. For all ANOVAs, Greenhouse-Geisser corrections were used whenever the assumption of sphericity was violated.

Regression analyses were completed to assess the contributions of muscle properties, neural drive, and pain to maximal isometric strength. Normality was assumed for all variables based on histograms and Q-Q plots. Significance was determined a priori at p < 0.05. Data are reported as mean ±
standard deviation (SD) in the text and displayed as mean ± standard error of the mean (SEM) in the figures. All analyses were performed in IBM Statistical Package for Social Sciences (SPSS, V26).

RESULTS

Subjects

Seven of the 14 AT participants who participated had unilateral AT, while seven had bilateral AT. Thus, limbs were divided into “more affected” and “less affected” when completing within-group analyses. Limbs were matched for dominance for between-group analyses (comparing the more affected limb in AT to control limbs). In the more affected AT limbs, symptom duration ranged between 3 and 240 months. Despite attempts at matching based on age and sex, the AT group was older and had a greater proportion of males than the control group (Table 3.1). Consequently, age and sex were used as covariates in statistical analyses (see above) and torque data were normalized to body weight. There was insufficient power to analyze interactions between sex and group and differences between more affected, less affected, and unaffected limbs in AT.
Table 3.1. Demographics of the test groups: control; AT group, more affected limb; and AT group, less affected limb.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>AT more affected</th>
<th>p-value, C vs AT</th>
<th>AT less affected</th>
<th>p-value more vs less</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14 [7 male]</td>
<td>14 [10 male]</td>
<td>0.26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>23.6±5.5</td>
<td>31.0±11.1</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.48±0.11</td>
<td>1.52±0.09</td>
<td>0.31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>67.4±13.0</td>
<td>87.7±21.3</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>24.1(10.5)</td>
<td>27.5(11.2)</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lean mass (%)</td>
<td>72.3(9.3)</td>
<td>69.6(10.6)</td>
<td>0.48</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)*</td>
<td>22.9±2.0</td>
<td>28.5±7.1</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MAQ (met·hr/wk)</td>
<td>35.1(26.2)</td>
<td>59.6(53.6)</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TSK</td>
<td>32.9(6.9)</td>
<td>36.6(9.7)</td>
<td>0.29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Symptom duration (mos)</td>
<td>0 (0.0)</td>
<td>66.9 (67.0)</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FAAMadl (%)*</td>
<td>99.2(1.6)</td>
<td>82.1(18.9)</td>
<td>0.005</td>
<td>93.3(10.9)</td>
<td>0.067</td>
</tr>
<tr>
<td>VISA-A (%)*§</td>
<td>99.2(2.9)</td>
<td>63.0(17.9)</td>
<td>&lt;0.001</td>
<td>78.1(20.5)</td>
<td>0.048</td>
</tr>
<tr>
<td>FAAMsport (%)*§</td>
<td>98.1(3.0)</td>
<td>61.7(16.7)</td>
<td>&lt;0.001</td>
<td>86.5(14.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p<0.05 between groups; §p<0.05 within AT group

Self-Reported Pain and Disability

Pain and disability were significantly greater in the more affected AT limb, whether when compared to controls or to the less affected AT limb, based on each the FAAM activities of daily living subscale, the FAAM sport subscale, and the VISA-A (Table 3.1). Kinesiophobia did not differ between groups (range of values: AT, 26-54; controls, 25-46).

Isometric Plantar Flexor Strength

Isometric MVC torque of the plantar flexor muscles was not different between AT and controls, whether normalized to body weight (AT: 1.65(0.59))
Nm/kg; C: 1.77(.030) Nm/kg; p=0.472; Figure 3.4) or considered in isolation with body weight as a covariate (AT: 140.45(47.70) Nm; C: 120.47(36.64) Nm; p=0.954). There were no group differences when controlling for sex (p=0.171). In persons with AT, isometric MVC torque was not different between the more affected and less affected limbs (less affected AT: 151.59 (45.83); p=0.534).

![Bar chart showing maximal isometric plantar flexor torque, normalized to body weight.](image)

**Figure 3.4. Maximal isometric plantar flexor torque, normalized to body weight.** There were no differences either between the more affected limb in AT and the matched-dominance limb in controls (p=0.472) or the more and less affected limbs in AT participants (p=0.534).

**Dynamic Strength & Power of the Plantar Flexor Muscles**

Concentric and eccentric MVC torque was not different between groups at any of the dynamic velocities, whether pooled across different velocities (p=0.127) or at individual velocities (Table 3.2; Figure 3.5) when controlling for age and sex. There was a main effect of velocity for both torque (p=0.028) and power (p<0.001). Power was not different between groups when analyzed
collectively across velocities ($p=0.838$) or at individual velocities (Table 3.3; Figure 3.6) when controlling for age and sex.

When comparing the more and less affected limbs in AT, there were no differences in concentric and eccentric MVC torque ($p=0.598$) or power ($p=0.966$). When analyzed at individual velocities, the findings were similar: maximal dynamic (concentric and eccentric) plantar flexor strength was not different between more affected and less affected (or unaffected) limbs in AT. There was a main effect of velocity on both torque ($p<0.001$) and power ($p<0.001$).

Table 3.2. Peak plantar flexor torque during concentric and eccentric velocities. Comparisons between groups (control versus more-affected AT) and within the AT group (more versus less affected limb) are included.

<table>
<thead>
<tr>
<th>Velocity (deg/s)</th>
<th>Control</th>
<th>AT more affected</th>
<th>AT less affected</th>
<th>C vs AT more</th>
<th>AT more vs less</th>
</tr>
</thead>
<tbody>
<tr>
<td>-90</td>
<td>2.14(0.63)</td>
<td>1.93(0.79)</td>
<td>1.91(0.75)</td>
<td>0.235</td>
<td>0.949</td>
</tr>
<tr>
<td>-60</td>
<td>1.80(0.33)</td>
<td>1.59(0.57)</td>
<td>1.84(0.79)</td>
<td>0.427</td>
<td>0.345</td>
</tr>
<tr>
<td>-30</td>
<td>1.87(0.74)</td>
<td>1.45(0.51)</td>
<td>1.83(0.81)</td>
<td>0.057</td>
<td>0.147</td>
</tr>
<tr>
<td>30</td>
<td>1.51(0.26)</td>
<td>1.24(0.54)</td>
<td>1.28(0.49)</td>
<td>0.148</td>
<td>0.808</td>
</tr>
<tr>
<td>60</td>
<td>1.22(0.26)</td>
<td>1.01(0.42)</td>
<td>1.02(0.41)</td>
<td>0.181</td>
<td>0.974</td>
</tr>
<tr>
<td>90</td>
<td>0.99(0.27)</td>
<td>0.83(0.35)</td>
<td>0.89(0.34)</td>
<td>0.308</td>
<td>0.700</td>
</tr>
<tr>
<td>120</td>
<td>0.88(0.20)</td>
<td>0.73(0.30)</td>
<td>0.76(0.30)</td>
<td>0.246</td>
<td>0.809</td>
</tr>
<tr>
<td>150</td>
<td>0.85(0.23)</td>
<td>0.75(0.28)</td>
<td>0.72(0.28)</td>
<td>0.474</td>
<td>0.784</td>
</tr>
</tbody>
</table>
Table 3.3. Peak plantar flexor power during concentric and eccentric velocities. Comparisons between groups (control versus more-affected AT) and within the AT group (more versus less affected limb) are included.

<table>
<thead>
<tr>
<th>Velocity (deg/s)</th>
<th>Control</th>
<th>AT more affected</th>
<th>AT less affected</th>
<th>C vs AT more</th>
<th>AT more vs less</th>
</tr>
</thead>
<tbody>
<tr>
<td>-90</td>
<td>-3.06(0.81)</td>
<td>-2.75(1.16)</td>
<td>-2.81(1.12)</td>
<td>0.324</td>
<td>0.889</td>
</tr>
<tr>
<td>-60</td>
<td>-2.10(0.45)</td>
<td>-1.87(0.76)</td>
<td>-1.87(0.79)</td>
<td>0.197</td>
<td>0.998</td>
</tr>
<tr>
<td>-30</td>
<td>-1.13(0.26)</td>
<td>-0.97(0.39)</td>
<td>-0.94(0.41)</td>
<td>0.110</td>
<td>0.821</td>
</tr>
<tr>
<td>30</td>
<td>0.77(0.18)</td>
<td>0.64(0.28)</td>
<td>0.67(0.25)</td>
<td>0.246</td>
<td>0.783</td>
</tr>
<tr>
<td>60</td>
<td>1.26(0.30)</td>
<td>1.06(0.43)</td>
<td>1.06(0.43)</td>
<td>0.239</td>
<td>0.989</td>
</tr>
<tr>
<td>90</td>
<td>1.58(0.46)</td>
<td>1.29(0.58)</td>
<td>1.34(0.56)</td>
<td>0.259</td>
<td>0.810</td>
</tr>
<tr>
<td>120</td>
<td>1.63(0.53)</td>
<td>1.35(0.74)</td>
<td>1.39(0.74)</td>
<td>0.383</td>
<td>0.897</td>
</tr>
<tr>
<td>150</td>
<td>1.73(0.69)</td>
<td>1.49(0.95)</td>
<td>1.37(0.93)</td>
<td>0.351</td>
<td>0.738</td>
</tr>
</tbody>
</table>
Figure 3.5. Plantar flexor torque-velocity relationship, normalized to body weight. There were no differences either between the more affected limb in AT and the matched-dominance limb in controls (p=0.127) or the more and less affected limbs in AT participants (p=0.598).

Figure 3.6. Maximal plantar flexor power at each dynamic velocity, normalized to body weight. There were no differences either between the more affected limb in AT and the matched-dominance limb in controls (p=0.838) or the more and less affected limbs in AT participants (p=0.966).
Voluntary Activation & Contractile Function

Resting twitch amplitude, a measure of contractile function, was significantly different between groups when controlling for age and sex (C: 0.48(0.07) Nm/kg; more affected AT: 0.38(0.12) Nm/kg; p=0.001; Figure 3.7). Resting twitch amplitude was not different between limbs in persons with AT (less affected AT: 0.44(0.12) Nm/kg; p=0.267). There were no differences in voluntary activation between groups, controlling for age and sex (p=0.546), or between limbs (p=0.351; C: 81.74(20.32)%; more affected AT: 82.32(20.01)%, less affected AT: 88.51(13.90)%; Figure 3.8).

Figure 3.7. Plantar flexor resting twitch amplitude, normalized to body weight, in people with AT compared to healthy controls. Resting twitch torque was lower in the more affected limb in AT compared to the matched-dominance limb in controls (p=0.001). There were no differences between the more and less affected limbs in AT participants (p=0.267). *p<0.01
Upper trapezius PPTs were higher in the more affected limb in AT when compared with controls (AT: 327.86(184.60) kPa; control: 189.82(73.31) kPa; \( p = 0.015 \); Figure 3.9). This difference remained significant whether adjusting for age \( (p=0.019) \), sex \( (p=0.033) \) or physical activity \( (p=0.046) \). However, it was not significant when adjusting for body weight alone \( (p=0.202) \) or for the combined variables of physical activity, age, sex and body weight \( (p=0.393) \). There were no differences in calf \( (AT: 258.86(156.51) \text{ kPa}; \text{ control: } 197.14(109.53) \text{ kPa}; \ p = 0.238) \) or Achilles tendon PPTs \( (AT: 268.18(136.78) \text{ kPa}; \text{ control: } \)
229.86(97.26) kPa; \( p=0.401 \), respectively; Figure 3.9), even when controlling for sex, age, body weight, and physical activity (calf, \( p=0.934 \); Achilles tendon, \( p=0.650 \)). The more and less affected limbs in AT were not different at the upper trapezius (less affected AT: 334.25(181.44), \( p=0.927 \)), calf (less affected AT: 285.21(158.22), \( p=0.661 \)) or Achilles tendon (less affected AT: 300.82(142.74), \( p=0.542 \)).

**Predictors of Isometric MVC Strength**

Predictors for isometric MVC strength included in the regression analysis were: RTA, VA, and upper trapezius PPT. Because local pain levels (Achilles...
tendon and calf PPTs) did not differ between groups, only upper trapezius PPTs were included in this analysis.

In healthy controls, the set of predictors (RTA, VA, and upper trapezius PPT) significantly contributed to isometric MVC: $F(3,10)=3.93, p=0.043$. However, when controlling for other predictors, VA was the only predictor of isometric MVC in controls, $t(10)=2.70, p=0.022$. The proportion of variance uniquely explained by VA ($sr^2$) in healthy controls was 0.33. The set of three predictors also significantly contributed to isometric MVC in the more affected limb in AT: $F(3,10)=9.11, p=0.003$. When controlling for other predictors, only RTA significantly predicted isometric MVC in the more affected limb in people with AT: $t(10)=4.65, p=0.001$. The proportion of variance uniquely explained by RTA ($sr^2$) in the more affected limbs of persons with AT was 0.58. In the less affected limb in AT, the set of predictors significantly contributed to isometric MVC: $F(3,10)=7.29, p=0.007$. When controlling for the other predictors, both VA ($t(10)=2.29, p=0.045$) and RTA ($t(10)=2.98, p=0.014$) were significant predictors of MVC torque in the less affected limb in people with AT. The proportional variance uniquely explained by these predictors, in the less affected AT limb, were as follows: $sr^2=0.16$ for VA and $sr^2=0.28$ in RTA.

DISCUSSION

This is the first study to evaluate the neural and muscular contributions to maximal strength in people with AT. We showed that the contribution differed between healthy controls and people with AT, despite similar maximal isometric,
concentric, and dynamic plantar flexor strength between groups and legs. People with AT had lower involuntary evoked twitch amplitude than controls, both in the more- and less-affected AT limbs. Accordingly, the twitch amplitude was associated with MVIC strength in people AT, indicating contractile function predicted their strength. In contrast, voluntary activation, thus neural drive, was the largest predictor of plantar flexor MVIC in healthy controls. Furthermore, systemic pain perception differed between groups, because persons with AT had elevated pressure-pain thresholds of the upper trapezius, despite similar pressure-pain thresholds at the Achilles tendon and medial gastrocnemius muscle.

**Strength in AT**

There were no differences in maximal plantar flexion strength, whether between limbs in persons with AT or between AT and healthy controls. While strength differences are commonly assumed in tendinopathy (O’Neill et al., 2016), a recent systematic review (Hasani et al., 2021) found conflicting evidence for impaired plantar flexor muscle strength in people with AT compared with healthy controls. When comparing between limbs in persons with AT, Hasani et al. (2021) concluded that there was limited to moderate evidence for decreased plantar flexor strength in the affected limb in people with AT. Supporting these conclusions, we showed the plantar flexor strength and power in people with AT was not impaired at any velocity.
Strength values obtained in this study were within normative ranges reported for healthy adults in their second through fourth decades (McKay et al., 2017, Danneskiold-Samsøe et al., 2009). Voluntary activation data similarly were within expected ranges for the plantar flexor muscles (Shima et al., 2002). Together, these suggest that participants provided maximal effort during measurements for maximal isometric plantar flexor strength and were appropriately familiarized to the task.

Neural and Muscular Factors in AT

Voluntary activation was the best predictor of isometric MVC torque in healthy controls. However, this index of neural drive had a lesser influence on isometric MVC torque with greater symptom severity: at the proportional variance in isometric MVC uniquely explained by VA decreased from 0.33 in healthy controls, to 0.28 in the less-affected limb in AT, to 0.01 in the more affected limb in AT. In contrast, muscular (contractile) mechanisms were the best predictor of isometric MVC torque in the more affected limb in AT. Muscular mechanisms played an increasingly prominent role in predicting isometric MVC as symptom severity increased: the proportional variance in isometric MVC that was uniquely explained by RT increased from 0.02 in controls, to 0.28 in the less-affected limb, to 0.58 in the more affected limb in AT.
Pain Pressure Thresholds in AT

Persons with AT had greater upper trapezius PPT when compared to healthy controls, while PPTs at the calf and Achilles tendon were not different. Thus, persons with AT were less sensitive to pain than controls in a region of the body not involved in the AT injury. These findings suggest a difference in systemic pain modulation, despite similar local pain modulation. However, it is important to note the apparent trend of higher PPTs at all sites – perhaps not limited to the upper trapezius – in persons with AT. While not significant at the Achilles tendon and medial gastrocnemius, this could simply be the result of insufficient power to detect group differences at these sites. Importantly, a trend toward greater PPTs globally could be a reflection of increased body weight and increased number of male participants in the AT group, rather than a reflection of meaningful differences in PPTs between AT and controls.

Altered central pain processing in AT has been previously described (Eckenrode et al., 2019, Tompra et al., 2016), based on lower pressure-pain thresholds when measured at a remote site. In contrast, Plinsinga et al. (2018) found no differences in PPTs at either their remote site (the lateral elbow) or over the affected tendon when comparing AT to controls (Plinsinga et al., 2018). However, neither of these studies limited their test group to midportion AT; they included insertional AT (Tompra et al., 2016, Eckenrode et al., 2019, Plinsinga et al., 2018), persons with lateral ankle pain and persons with heel pain (Tompra et al., 2016). The heterogeneity of findings suggests that AT may be too multifactorial to simplify into central versus peripheral processes.
Often, the impact of pain on motor output is thought to be inhibitory, whereby pain inhibits motor pathways (Hodges and Moseley, 2003). However, the relationship between pain and motor output can be far more complex (Hodges, 2011), including a redistribution of motor commands within and between muscles. Such a complex relationship could explain why maximal plantar flexor torque was similar between groups, despite diminished contractile function in people with AT: perhaps, in response to pain, motor commands are redistributed to optimize recruitment of agonist muscles innervated by the superficial fibular nerve. It is not possible to make a definitive conclusion regarding this theory, however, as the fibularis muscles and superficial fibular nerve were not evaluated in this study.

In this study, persons with AT reported being highly active per the MAQ, including in activities commonly associated with onset of AT (such as running and jumping sports). One possible explanation for continued participation – and at such high levels, no less – is that central pain mechanisms dampen any pain-related signaling, effectively “protecting” these people from symptoms (a phenomenon previously reported, (Rio et al., 2018)). In this way, the decreased sensitivity to pain observed in this study (measured by increased upper trapezius pressure-pain thresholds) may have enabled people with AT to continue participating in activities, even if those activities result in further damage to the Achilles tendon. However, reduced sensitivity to painful stimuli, while advantageous in the short term (i.e., for enabling continued participation in activities), could prove detrimental in the long run, resulting in constant re-injury
to the tendon and possibly resulting in eventual tendon rupture (Río et al., 2018, Noback et al., 2018).

**Limitations**

Possible neural and muscular mechanisms for any differences in strength with AT were investigated during isometric contractions only. The interpolated twitch technique is not well-validated during dynamic contractions (Klass et al., 2007, Rozand et al., 2017), thereby limiting our application to the eccentric and concentric contractions. This does not change comparisons between groups or limbs. However, neural drive and muscular mechanisms cannot be assumed to behave identically during dynamic as during isometric contractions.

Diagnosis in this study was based upon clinical evaluation. While imaging can provide confirmation of pathologic changes within the tendon (Puddu et al., 1976, Maffulli et al., 1998), it does not correlate well with symptoms (Docking et al., 2015a, van Dijk et al., 2011, Cook et al., 2001, Rompe et al., 2007). Importantly, variability in the quality of the Achilles tendon, when evaluated based on imaging findings, is partially explained by age, BMI, and physical activity (Docking, 2021a, Kannus and Jozsa, 1991). Thus, in this study, any identified differences in tendon quality as assessed via imaging may simply be a byproduct of the older, heavier AT group.

Supramaximal stimulation is an important prerequisite when evaluating neural drive and contractile mechanisms. However, complete activation of all plantar flexor muscles would require simultaneous stimulation of the superficial
fibular nerve and tibial nerve, while avoiding activation of the deep fibular nerve. Even proximity of the stimulating electrode to either the sciatic or deep fibular nerve can result in inadvertent stimulation of the antagonist muscles. This is particularly problematic at higher (supramaximal) stimulation intensities. Therefore, there is a potential that supramaximal stimulation levels resulted in inadvertent activation of dorsiflexors. As this would impact controls and persons with AT similarly, however, it is unlikely this would change the between-group results as reported in this study.

The control and AT groups in this study were not matched for age, body weight, or sex. However, analyses were unchanged when normalizing torque to body weight and when adding age and sex as covariates. This applied for all between-group measurements, including MVCs, VA, RT, and PPT.

Finally, this study cannot attribute cause and effect to the altered muscular mechanisms (impaired RT) or differences in systemic pain modulation (elevated upper trapezius PPT) seen in persons with AT. Further research – and alternative study designs – would be required to establish causation.

Conclusions

Plantar flexor strength and power differences cannot be assumed in persons with AT, regardless of whether these are evaluated isometrically, concentrically, or eccentrically. Despite similar maximal strength and power, however, there were underlying impairments within the triceps surae muscle group of people with AT compared with controls. These findings suggest that
prognosis in AT may not depend upon making gains in plantar flexor strength or power, a finding echoed by a recent systematic review (Hasani et al., 2021). Instead, symptom resolution may be contingent upon normalizing function of the triceps surae, not emphasizing strength and power of the entire plantar flexor group.
CHAPTER 4: PLANTAR FLEXOR FATIGABILITY IN ACHILLES TENDINOPATHY

INTRODUCTION

Midportion Achilles tendinopathy is an overuse condition resulting in pain and stiffness localized to the middle of the tendon (between 2 and 6 centimeters proximal to the calcaneal insertion). It is commonly assumed either to be caused by or to result in endurance deficits of the plantar flexor muscles. However, the role of fatigability in AT – and the contributing mechanisms – are poorly described.

Fatigability can be understood as either performance fatigability or perceived fatigability (Enoka and Duchateau, 2016). Perceived fatigability is a symptom measured by self-report. In contrast, performance fatigability is an objective measure that quantifies the decline in motor performance over time. It can be quantified as the number of repetitions completed prior to task failure (Hunter et al., 2004b), such as number of heel-raise repetitions completed in the Single-Leg Heel Raise test (Hislop et al., 2013). In a laboratory setting, fatigability is often measured as an acute reduction in either force or power following fatiguing exercise (Enoka and Duchateau, 2008, Gandevia, 2001). Fatigability can be evaluated in response to isometric or dynamic exercise.

In clinical and research settings, the Single-Leg Heel Raise test (SLHR) is recommended for evaluating activity limitations and prognosis in AT (Martin et al., 2018). The SLHR was designed for the purpose of measuring plantar flexor
strength within physical therapy manual muscle testing protocol (Hislop et al., 2013). However, when performed as originally designed and instructed, it lacks sufficient construct validity (Harris-Love et al., 2014, Hébert-Losier et al., 2009, Sara et al., 2021).

Mechanisms contributing to fatigability include contractile properties (measured as the electrically-evoked twitch torque in a resting muscle) and neural drive (voluntary activation measured using the interpolated twitch technique) (Gandevia, 2001). These mechanisms differ in their contribution to fatigability between populations, muscle groups, and tasks (Avin and Frey Law, 2011, Senefeld et al., 2018b, Hunter et al., 2004a). In people with AT, it is possible that the contributions of the neural and contractile mechanisms that lead to reductions in force in response to a fatiguing task could differ to healthy controls. We reported in aim 2 (chapter 3), for example, that people with AT were similar in maximal strength and power to that of healthy controls, but that contractile function was lower and was associated with pain perception. The impact of pain and the effects on motor output during repeated voluntary fatiguing contractions are not known in people with AT. Furthermore, the contribution of the neural and contractile mechanisms to fatigability is not understood in people with AT.

The purpose of this study was to evaluate performance fatigability of the plantar flexors with two different tasks (1) a dynamic and clinically-based task (SLHR) that involves repetitions completed during to failure, and (2) in response to a single bout of maximal isometric contractions. Contractile properties, neural
drive, and pain were quantified to understand the mechanisms of plantar flexor fatigability in people with AT.

**MATERIALS & METHODS**

*Participants*

Twenty-eight participants volunteered to participate in this study (14 with AT, 14 controls; see Table 4.1). Inclusion criteria included the following: gradual, insidious onset of pain and/or stiffness at the midportion of the Achilles tendon, which had persisted for at least 3 months; and healthy controls without history of either pain or stiffness in the Achilles tendon region. AT diagnosis was a clinical diagnosis based on localized tendon pain 2-6 cm proximal to the calcaneal insertion, a positive Royal London Hospital Test (Maffulli et al., 2003), thickening at the midportion of the tendon, and a positive Arc Sign (Reiman et al., 2014). Exclusion criteria included known cardiovascular disease, neurological disease, and any acute injury, bursitis, insertional tendinopathy, or osteoarthritis in either lower extremity. Informed consent was obtained from all participants prior to participation in the study. The study protocol was approved by the Marquette University Institutional Review Board and in compliance with the Declaration of Helsinki.

All testing took place during three sessions and was performed on both lower extremities. All data collection was led by the same researcher (LKS). The first session involved familiarization, clinical measurements, and self-report
outcome measures evaluating pain, disability, and fear of movement (Foot and Ankle Ability Measure (FAAM) (Martin et al., 2005); Victoria Institute of Sport Assessment-Achilles Questionnaire (VISA-A) (Robinson et al., 2001), and Tampa Scale of Kinesiophobia (TSK) (French et al., 2007)). Physical activity data were calculated based on responses to a 12-month self-report physical activity questionnaire, the Modifiable Activity Questionnaire (MAQ) (Kriska, 1997). The second session involved performance of the single-leg heel raise (SLHR) to task failure. The third session evaluated performance during the isometric fatiguing exercise task. In brief, the third session involved measures of maximal isometric strength (MVIC), voluntary activation and contractile properties of the plantar flexor muscles, perceived pain, rating of perceived exertion (RPE) and pain-pressure thresholds (PPTs) while seated in a Biodex dynamometer (Biodex System 3 Pro; Biodex Medical; Shirley, NY) before, during, and after a maximal-effort isometric fatiguing protocol performed for four minutes. The order of the second and third sessions was randomized.

**Single-Leg Heel Raise**

The SLHR was completed as is done in clinic (Hislop et al., 2013) and as is described in chapter 2, with participants performing as many SLHR repetitions as possible prior to task failure. This involved repeated heel raises while standing on one leg. Participants completed these at a standardized pace of one heel raise every three seconds using the assistance of an audible metronome and
verbal cueing. Participants were provided light fingertip support in the horizontal plane to assist with maintaining balance during the task.

Setup and familiarization were completed earlier in the same session. Setup involved positioning a horizontal target plate to the maximum height achievable by each participant during a single-leg heel raise. Practice repetitions were performed using the metronome. Once proficiency was demonstrated during task familiarization, the SLHR was completed. Task failure was defined as two consecutive missed repetitions of the target plate and/or inability to continue at the prescribed pace. The number of repetitions prior to failure was recorded.

*Isometric Fatiguing Exercise Task: Experimental Setup*

Participants were seated in a Biodex System 3 Pro dynamometer with the knee in neutral extension (0 degrees) and the trunk reclined 35 degrees. The trunk position was chosen to minimize the influence of hamstring tightness and sciatic nerve tension of the test limb. The test foot was positioned on a foot plate affixed to the dynamometer (Figure 3.1). To minimize extraneous movement and isolate exercise to the ankle joint, straps were placed across the waist, chest, and ipsilateral thigh. Two straps were used around the ankle and one around the forefoot to maintain the plantar surface of the foot in contact with the foot plate. The test ankle was placed in a neutral position (0 degrees), with the foot perpendicular to the shank. The order of limbs was randomized every session. PPTs were measured at the Achilles tendon, ipsilateral medial gastrocnemius,
and upper trapezius. Testing order for PPTs was randomized every session for each limb.

**Baseline Measures**

Preliminary testing involved MVICs of the plantar flexors with two-minutes rest between trials. Each participant performed at least two trials, repeating these until no further torque increases resulted (determined as two MVICs within 5% of each other). The highest torque achieved during these repetitions was used to establish a torque target for the electrical stimulation procedure that followed.

The ipsilateral tibial nerve was stimulated using a constant-current, variable high-voltage stimulator (DS7AH; Digitimer Ltd; Hertfordshire, UK) to evoke contractions at rest and during MVICs. Stimulation was applied to the ipsilateral tibial nerve using a bar electrode at the medial popliteal space distal to the sciatic nerve bifurcation. Single square-wave pulses (400 V, 100µs duration) were delivered with a stimulation intensity initiated at 50mA and gradually increased until a plateau was reached, such that further increases in stimulation intensity resulted in no additional changes in evoked torque (Senefeld et al., 2018b, Sundberg et al., 2018b). The plateau intensity was increased further by 10% to achieve a supramaximal stimulation. This stimulation intensity was used during a single pulse stimulation and double pulse of stimulation (at 100Hz) to enable assessment of contractile properties and voluntary activation, respectively, of the plantar flexor muscles.
MVICs were repeated four times with the addition of both a superimposed
doublet stimulation (SIT, superimposed twitch) and a post-activation, resting
(potentiated) doublet stimulation (RT, resting twitch) of the tibial nerve ~2
seconds after the MVIC. Doublet stimulations were used for the SIT, as this has
been shown to be more sensitive (Rozand et al., 2020, Oskouei et al., 2003). The forces during the SIT and RT were used in the analysis of voluntary
activation and resting twitch torque (see Data Analysis). Two minutes of rest
were provided between each repetition of MVIC with electrical stimulation.

Perceived Pain and Exertion

The Numeric Pain Rating Scale was used to evaluate perceived calf and
Achilles tendon pain, where 0 is no pain and 10 is the worst pain imaginable. The
10-point Borg Rating of Perceived Exertion (RPE) Scale was used to evaluate
perceived exertion in the exercising calf and tendon. Participants were
familiarized to both measurement scales during the familiarization session.
Reference scales were posted below the feedback monitor during all sessions. At
the start of the second session, participants were asked to rate baseline pain and
RPE. They were also instructed to consider the maximum calf pain and RPE
experienced during the fatiguing task and that these would be recorded
immediately following the fatiguing task. Achilles tendon pain was reported every
minute during the fatiguing task.
**Pressure-Pain Thresholds**

Pressure-pain threshold (PPT) refers to the minimum pressure required to induce pain (Nussbaum and Downes, 1998). PPTs were measured using an algometer (Somedic SenseLab AB, Sweden) with a 1cm² probe tip at an application rate of 30 kPa/s. Algometry is a reliable method for evaluating pressure-pain thresholds (PPTs) both within and between sessions (Potter et al., 2006, Vanderweeën et al., 1996, Nussbaum and Downes, 1998, Frank et al., 2013). Evaluation of PPTs both local and remote to injured tissue provides valuable information about central compared to peripheral mechanisms contributing to a painful experience (Graven-Nielsen and Arendt-Nielsen, 2002, Curatolo et al., 2001) and is recommended for inclusion in tendinopathy populations (Kregel et al., 2013).

PPT familiarization involved practice repetitions over the nailbed of the left 2nd digit and included emphasis that the measurement was not a test of pain tolerance but rather the point at which the pressure sensation was first perceived as painful. Measurements were completed before and after fatiguing exercise at three sites: (1) the Achilles tendon, using the pinch handle 4 cm proximal to the calcaneal insertion; (2) the ipsilateral medial gastrocnemius, measured at the midpoint between its lateral and medial margins along the location of largest calf girth; and (3) the upper trapezius, along its superior margin halfway between the seventh cervical vertebrae and the acromion process. For all PPT measurements, the probe tip was maintained in a position orthogonal to the tissue being tested. Participants pressed a button when the pressure sensation
was first perceived as painful (Rakel et al., 2014). Two measurements were completed at each measurement site during each timepoint (i.e., at baseline and immediately following the fatiguing exercise task). The average of the two measurements was used in subsequent analyses. Measurement order was randomized for each leg, participant, and session.

Figure 4.1. Representative torque data from a male AT participant during the intermittent MVIC task. The task involved four sets of fourteen MVICs, the first of which included electrical stimulation during (SIT) and after (RT) the MVIC. An additional MVIC with stimulation was completed immediately following the task.

*Isometric Fatiguing Exercise Task*

Participants were familiarized to the isometric fatiguing exercise prior to initiating the task. This included instruction, demonstration, and practice repetitions at a submaximal level with sample verbal cues and encouragement. The task was not initiated until the participant could demonstrate several repetitions, including a repetition with mock stimulation, without error.
The fatiguing exercise involved four, 1-minute sets of 14 repetitions of intermittent MVICs while seated in the Biodex dynamometer. The intermittent MVICs were performed in a 2:2 duty cycle: 2 seconds of maximal contraction followed by 2 seconds of rest, repeated for 13 repetitions without stimulation. MVICs with superimposed and resting electrical stimulations were performed before each 13-repetition set and again at the end of the 4-minute task, for a total of 14 MVIC repetitions per set with one immediate post-task MVIC. Therefore, a total of 57 MVICs (52 without stimulation; 5 with stimulation) were completed during the 4-minute task (see Figure 4.1). The repetitions that included electrical stimulation included an additional 4 seconds of rest following the resting stimulation. During these 4 seconds, the participants were asked (1) whether the MVIC during electrical stimulation was a maximal attempt, and (2) what their perceived tendon pain was at that time (per NPRS). Strong verbal encouragement was provided for every repetition and real-time visual feedback was provided using a feedback monitor.

**Data and Statistical Analyses**

For all analyses of strength, contractile properties, and voluntary activation, “baseline” refers to the values that correspond to the baseline MVIC that yielded the greatest torque amplitudes. “Post-task” refers to the MVIC immediately following completion of the isometric fatiguing exercise. All torque measurements (including MVIC and RT at all timepoints) were normalized to body weight.
MVIC was measured as the average of a 0.5-second window surrounding the maximum torque. Voluntary activation was calculated as the ratio of the superimposed to the resting doublet twitch (Gandevia, 2001): \((1 - \text{SIT}/\text{RT}) \times 100\). Resting twitch refers to the torque amplitude of the electrically-evoked potentiated resting doublet stimulation that occurred immediately after an MVIC. Fatigability was quantified as the reduction in MVIC from baseline to immediately following the isometric fatiguing exercise task.

Independent samples t-tests were used to compare physical characteristics, physical activity levels, SLHR repetitions, and Kinesiophobia between groups. Analysis of covariance was used to evaluate group differences in the following baseline variables, controlling for sex and age: MVIC torque, electrically-evoked resting twitch amplitude (RT), voluntary activation (VA), pain, RPE, and PPT. Repeated-measures analysis of variance (RM-ANOVA) was used to evaluate those same variables between limbs in persons with AT. RM-ANOVA was used to evaluate changes in MVIC torque, RT, VA, pain, RPE, and PPT across the fatiguing exercise, using time as the within-subjects factor and diagnosis as the between-subject factor, controlling for age and sex between groups. Greenhouse-Geisser corrections were used whenever the assumption of sphericity was violated. Mediation analyses were utilized to evaluate the impact of pain on the relationships between diagnosis and muscle function (MVIC, VA, and RT) (Field-Fote, 2019).

Regression analysis was used to evaluate which variables (PPT, VA, RT) predict fatigability in the isometric fatiguing task. Normality was assumed for all
variables based on histograms and Q-Q plots. Significance was determined a priori at p < 0.05. Data are reported as mean ± standard deviation (SD) in the text and displayed as mean ± standard error of the mean (SEM) in the figures. All statistical analyses were completed using IBM Statistical Package for Social Sciences (SPSS, V26).

RESULTS

Participants

Seven of the 14 AT participants who participated had unilateral AT, while seven had bilateral AT. For within-group analyses, limbs in persons with AT were divided into “more affected” and “less affected” limbs. Limbs were matched for dominance for between-group analyses (comparing the more affected limb in AT to control limbs). The AT group was older, heavier, and included a greater proportion of male participants, despite attempts at matching based on age and sex (Table 1). Consequently, age and sex were used as covariates in statistical analyses (see above) and torque data were normalized to body weight. There was insufficient power to analyze interactions between sex and group and differences between more affected, less affected, and unaffected limbs in AT.

The AT group scored lower (worse pain and function) on the FAAM (both ADL and Sport subscales) and the VISA-A. The more-affected limb scored lower (greater disability) on the VISA-A and Sport subscale of the FAAM, when compared to the less-affected limb. (Table 1)
Table 4.1. Demographics of the test groups: control; AT group, more affected limb; and AT group, less affected limb.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>AT more affected</th>
<th>p-value, C vs AT</th>
<th>AT less affected</th>
<th>p-value more vs less</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14 [7 male]</td>
<td>14 [10 male]</td>
<td>0.26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>23.6±5.5</td>
<td>31.0±11.1</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.48±0.11</td>
<td>1.52±0.09</td>
<td>0.31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>67.4±13.0</td>
<td>87.7±21.3</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>24.1(10.5)</td>
<td>27.5(11.2)</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lean mass (%)</td>
<td>72.3(9.3)</td>
<td>69.6(10.6)</td>
<td>0.48</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)*</td>
<td>22.9±2.0</td>
<td>28.5±7.1</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MAQ (met·hr/wk)</td>
<td>35.1(26.2)</td>
<td>59.6(53.6)</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TSK</td>
<td>32.9(6.9)</td>
<td>36.6(9.7)</td>
<td>0.29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FAAMAdl (%)*</td>
<td>99.2(1.6)</td>
<td>82.1(18.9)</td>
<td>0.005</td>
<td>93.3(10.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>VISA-A (%)*§</td>
<td>99.2(2.9)</td>
<td>63.0(17.9)</td>
<td>&lt;0.001</td>
<td>78.1(20.5)</td>
<td>0.048</td>
</tr>
<tr>
<td>FAAMsport (%)*§</td>
<td>98.1(3.0)</td>
<td>61.7(16.7)</td>
<td>&lt;0.001</td>
<td>86.5(14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SLHR repetitions</td>
<td>58.5(35.6)</td>
<td>48.1(22.2)</td>
<td>0.40</td>
<td>52.7(31.0)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*p<0.05 between groups; §p<0.05 within AT group

Fatigability: Single-Leg Hell Raise Test

Three participants (one control female, one AT female, one AT male) did not complete the SLHR task. Therefore, results from this task are based on 13 control limbs, 12 AT limbs, and 12 AT control limbs. There were no differences in SLHR repetitions completed between AT and control or the more and less affected limbs in AT (Table 1).

Fatigability: Isometric Contractions

There were no differences in fatigability (i.e., the reduction in MVIC) between groups, measured as the interaction between group and time (Figure
There was no main effect of group on MVIC torque (p=0.096). There was a significant main effect of time for all groups (p=0.001): increased time in the fatiguing exercise task resulted in decreased MVIC torque for all participants.

Voluntary Activation, and Resting Twitch Amplitude

The trends observed for the MVIC were similar for voluntary activation (Figure 4.3): there were no interactions between group and time (p=0.866) and no main effect of group (p=0.779), but there was a main effect of time (p=0.006); increased time in the fatiguing task resulted in decreased voluntary activation for both groups. In contrast, while there were no interactions between group and

![Figure 4.2](image.png)
time for RT (p=0.637), there was a main effect of group (Figure 4.4, p=0.001): RT torque was lower in AT at all time points compared to controls.

When comparing between limbs in people with AT, there were no differences in any variables across time (interactions between limb and time: MVIC: p=0.909; VA: p=0.937; RT: p=0.998). There were no main effects of limb (more versus less affected limb in AT) on any of these variables (MVIC: p=0.226; VA: p=0.773; RT: p=0.335). There was a main effect of time on all variables (MVIC: p<0.001; VA: p=0.003; RT: p<0.001): increased time in the fatiguing task resulted in similar between-limb reductions in MVIC and VA and similar changes in RT.

![Graph showing voluntary activation change over time](image)

**Figure 4.3. All groups demonstrated reductions in neural drive over time (p=0.006).** The change in neural drive (quantified as Voluntary Activation using the Interpolated Twitch Technique) was not different between groups (p=0.866).
For all participants, RT increased between the start of the task and the first minute \((p<0.001\)) , then decreased between minutes 1 and 4 \((p<0.001)\). There were no changes in RT between minutes 0 and 4. There was no interaction between group and time \((p=0.641)\).

![Graph showing RT over time](image)

**Figure 4.4. RT was lower in AT compared to controls at all time points \((p=0.001)\).** Collectively, the three groups experienced an increase in RT between minutes 0 and 1 \((p<0.001)\), followed by a decrease from minutes 1 to 4 \((p<0.001)\). There was no change between minutes 0 and 4 \((p=0.108)\). Analyzed separately, from minutes 1 to 4, there was no change in RT in controls \((p=0.185)\), but a significant decrease in RT in both AT limbs \((p<0.001)\). This difference was different between controls and AT \((p=0.003)\).

**Pain**

Pressure-pain thresholds (PPTs) measured at the upper trapezius were larger in people with AT when compared to controls (Figure 4.5; interaction between PPT location and group, \(p=0.011\)). PPTs were not different between
groups when measured at the Achilles tendon (Figure 4.6; \( p=0.720 \)) or medial gastrocnemius (Figure 4.7; \( p=0.615 \)). There was no influence of time on PPTs (\( p=0.444 \)): PPTs were not different between baseline and immediately following the fatiguing exercise at any measurement location (medial gastrocnemius: \( p=0.688 \); Achilles tendon: \( p=0.823 \); upper trapezius: \( p=0.856 \)). Within the AT group, there was no difference in PPTs between limbs when analyzed collectively (\( p=0.695 \)), and there were no interactions between limb, time, and PPT location (\( p=0.609 \)).

Baseline Achilles tendon pain (per the Numeric Pain Rating Scale, NPRS) was not different between groups when assessed at rest (AT: 0.29(0.47); Control: 0.00(0.00); \( p=0.228 \)). Baseline calf pain (NPRS) also did not differ between groups (AT: 0.00(0.00); Control: 0.29(0.73); \( p=0.308 \)). Maximum calf pain reported during fatiguing exercise was not different (AT: 3.2(2.5); Control: 2.5(3.1); \( p=0.145 \)). However, the maximum Achilles tendon pain reported during fatiguing exercise was greater in the more affected AT limb compared to controls (AT: 1.57(1.74); Control 0.00(0.00); \( p<0.001 \)). There were no differences between the more and less affected limbs in the AT group, whether baseline calf (AT Control: 0.00(0.00), \( p=1.0 \)), baseline Achilles tendon (AT Control: 0.29(1.07), \( p=1.0 \)), maximum calf pain (AT Control: 3.4(2.8), \( p=0.833 \)) or maximum Achilles tendon pain experienced during the fatiguing exercise (AT Control: 1.3(1.6), \( p=0.654 \)). The maximum rating of perceived exertion (RPE) in the exercising calf and tendon was not different between groups (AT: 7.3(3.0); Control: 8.1(2.2); \( p=0.67 \)) or within the tendinopathy group (AT Control: 7.3(2.9); \( p=1.0 \)).
Baseline upper trapezius PPT and maximum Achilles tendon pain (NPRS) were positively correlated in the more affected limb in AT ($r=0.559$, $p=0.058$). There was no relationship in the less affected limb in AT ($r=0.104$, $p=0.724$) and could not be computed in controls (Achilles tendon pain was 0 for all control participants). Upper trapezius PPT was also positively correlated with medial gastrocnemius PPT ($r=0.867$, $p<0.001$) and Achilles tendon PPT ($r=0.747$, $p=0.002$) in AT. These correlations were not as strong in the less affected limb in AT (medial gastrocnemius: $r=0.816$, $p<0.001$; Achilles tendon: $r=0.700$, $p=0.005$) and were absent in controls (medial gastrocnemius: $r=0.505$, $p=0.066$; Achilles tendon: $r=0.518$, $p=0.058$).

Baseline upper trapezius PPT and maximum reported Achilles tendon pain (per NPRS) were used in mediation analyses, as these were the only pain variables that differed between groups. Baseline upper trapezius PPT mediated the relationship between group and the reduction in RT ($r=-0.321$, $p=0.038$): greater upper trapezius PPT predicted greater reductions in RT torque between minutes 1 and 4 of the fatiguing task. Baseline upper trapezius PPT did not mediate the relationship between group and either the reduction in MVIC ($p=0.319$) or the reduction in VA ($p=0.989$). Maximum Achilles tendon pain (per NPRS) did not mediate the relationship between group and any of the outcome measures: reduction in MVIC ($p=0.308$), change in RT ($p=0.107$), and reduction in VA ($p=0.524$). When evaluated only in the people with AT (both limbs), maximum reported Achilles tendon mediated the change in MVIC ($r=-0.411$, $p=0.030$): higher upper trapezius pressure pain thresholds predicted greater
reductions in RT torque, and higher perceived tendon pain predicted greater reductions in MVIC torque.

Figure 4.5. Upper trapezius PPTs were higher in AT compared to controls at all time points (p=0.011). Upper trapezius PPTs did not differ between limbs in AT (p=0.919) and did not change following fatiguing isometric exercise (p=0.856).

Figure 4.6. Achilles tendon PPTs were not different between groups (p=0.720) or between limbs (p=0.630). Achilles tendon PPTs did not change across time (p=0.823)
Predictors of Fatigability

The following variables were included in regression analyses to evaluate the extent to which they predicted fatigability, measured as the reduction in MVIC torque: maximum Achilles tendon pain during exercise (per NPRS); maximum calf pain during exercise (per NPRS); pressure-pain thresholds (PPTs) at the medial gastrocnemius, Achilles tendon, and upper trapezius; rating of perceived exertion; change in voluntary activation; and change in resting twitch amplitude. As a set, these variables predicted fatigability in the combined group of participants (p=0.029). However, only the reduction in voluntary activation...
predicted fatigability when considered in isolation ($r=0.598$, $p<0.001$). No other variables predicted plantar flexor fatigability.

When the three groups were analyzed separately, the result was the same: reduction in voluntary activation was the only variable to predict fatigability (AT: $r=0.586$, $p=0.028$; control: $r=0.607$, $p=0.021$; AT Control: $r=0.627$, $p=0.016$). While not significant, the relationship between change in voluntary activation and RT differed in direction between groups: a negative relationship was found in the more affected limb in AT ($r= -0.373$, $p= 0.189$), no relationship in the less affected limb in AT ($r= +0.061$, $p= 0.836$), and a positive relationship was found in controls ($r= +0.209$, $p= 0.473$). There was no relationship between the change in RT and the change in MVIC for any of the groups (AT: $r=0.271$, $p=0.348$; Control: $r=0.386$, $p=0.173$; AT Control: $r=0.288$, $p=0.318$).

When the three groups were analyzed together, there was a negative correlation between baseline Achilles tendon PPT and the change in RT between minutes 1 and 4 of isometric fatiguing exercise ($r= -0.457$, $p=0.002$). When the three groups were analyzed separately, this relationship was absent in controls and in the less-affected limb of AT (Control: $r= -0.232$, $p=0.425$; AT Control: $r= -0.167$, $p=0.569$). However, when the more affected limbs in AT were analyzed alone, the relationship was strengthened ($r= -0.782$, $p=0.001$): larger pressure-pain thresholds at the Achilles tendon predicted greater reductions in resting twitch amplitude as a result of exercise.
DISCUSSION

Summary of Findings

There were no differences in fatigability between AT and controls, whether when measured using a common clinical test, the SLHR, or a laboratory-based test of isometric fatiguing exercise. Voluntary activation, which is indicative of neural drive, was the greatest predictor of fatigability from the isometric task in all groups. Contractile function (RT torque) was reduced in the more affected limb in AT compared to controls at all time points throughout the isometric fatiguing contraction. Pain also differed between groups: perceived pain in the Achilles tendon (per NPRS) was higher in the AT group; and central pain sensitivity was lower (increased upper trapezius PPTs) in the AT group.

Fatigability

Fatigability was not different between groups or limbs, whether measured as the acute reduction in MVIC following isometric exercise or for a dynamic task as the number of repetitions completed in the SLHR.

Based on the findings from Aim 1, it is unsurprising that the SLHR did not detect group differences. When implemented as in clinic, the SLHR has inherent limitations that cannot be ignored. Not least of these is a questionable construct validity (Hébert-Losier et al., 2009, Harris-Love et al., 2014). Future work should address nuances of muscle function in the SLHR, including evaluating neural
drive and contractile mechanisms related to task failure in people with AT compared to healthy controls.

A recent case-control study evaluated strength and endurance in people with AT (O’Neill et al., 2019). They reported impaired endurance of the plantar flexor muscles in persons with AT. Their endurance task measured total work performed during 20 repetitions of maximum-effort contractions. However, since their AT group had decreased maximal plantar flexor strength at baseline, and the study constrained number of repetitions to 20, the work performed by the AT group would necessarily be lower. Importantly, this would not be the result of worse endurance, but simply due to limited per-contraction force in the AT group compared to healthy controls.

*Reductions in Neural Drive and Contractile Function as Mechanisms of Fatigability* Voluntary activation decreased for all participants across the fatiguing isometric task, indicating reduced neural drive, commonly termed central fatigue (Gandevia, 2001). The magnitude of reduction in voluntary activation was correlated with the magnitude of reduction in MVIC (fatigability), and this was similar between groups.

People with AT had reduced resting twitch torque in their more affected limb at all time points when compared to controls. All three groups demonstrated an increase in RT between baseline and minute one of the fatiguing isometric exercise. This increase in electrically-evoked torque was likely a result of the stretch-shortening cycle effect, which has been demonstrated in response to isometric contraction (Fukutani et al., 2015, Svantesson et al., 1994). After that
time, RT remained unchanged in controls but decreased in both limbs in the AT group. Thus, contractile function in both limbs in the AT group may have been more affected by fatiguing exercise than controls.

Interestingly, in unilateral upper extremity tendinopathies, motor deficits have been recorded in both upper extremities (Bisset et al., 2006). These findings could explain why persons with AT had altered contractility of the triceps surae muscles bilaterally.

**Effect of Pain on Motor Output**

Pain mediated the effect of diagnosis on motor output: presence of tendinopathy alone did not predict group differences; instead, pain played a mediating role in the effect of tendinopathy on motor output. Specifically, when evaluated at a location remote from the Achilles tendon (the upper trapezius), decreased sensitivity to painful stimuli (a higher PPT) correlated with greater reductions in resting twitch amplitude. Similarly, larger pressure-pain thresholds at the Achilles tendon predicted greater reductions in resting twitch amplitude during fatiguing exercise. Greater reductions in MVIC (i.e., greater fatigability) were correlated with higher perceived Achilles tendon pain during fatiguing exercise.

**A Comprehensive Look at Pain and Contractile Function in AT**

People with AT had reduced resting twitch torque at all time points when compared to controls. Resting twitch torque, a measure of involuntary torque
production, decreased from the first to last minute in the fatiguing isometric exercise task. This reduction was correlated with pain sensitivity both locally and systemically (based on pressure-pain thresholds in the Achilles tendon and upper trapezius, respectively): lower pain sensitivity was correlated with a greater reduction in RT. In contrast, when people in the AT group experienced Achilles tendon pain, it affected their maximal voluntary isometric strength: increased perceived pain resulted in greater decrements in muscle force. However, the decrements in force were not different from that demonstrated in the control group.

The findings of this study suggest an unusual phenomenon in AT, a sort of “inattention” to pain, perhaps enabled by central desensitization. Despite impaired contractile mechanisms and Achilles tendon pain, people with AT demonstrated similar exercise-induced reductions in torque as the controls and similar neural drive. This may result from an ability to ignore the pain and tissue damage, thanks to decreased pain sensitivity. It seems that these patients do not consciously and voluntarily change their behavior based on pain. Rather, involuntary processes may be responsible for the reduction in contractility, perhaps in an effort to protect the injured tissue. Then, redistributing motor command to agonist muscles (those not innervated by the tibial nerve) could help reduce fatigue while enabling continued task performance (Blain et al., 2016, Amann, 2012).

These unusual findings were specific to the AT group; no such relationships existed in controls. The protective pain mechanisms that are
expected to impede motor function during fatiguing exercise or with injury may not be functioning in AT as they do in healthy controls. This, in turn, could help explain chronicity in AT: continued activity participation could result from constant re-injury to the already injured tendon. This could implicate an important role for patient education and activity modification (Martin et al., 2018, Silbernagel et al., 2007b). However, based on findings of central desensitization, reliance on symptom monitoring may not be sufficient to protect the tendon from further injury.

Limitations

This study utilized electrical stimulation of the tibial nerve for evaluation of neural drive and contractile properties. The plantar flexors, however, receive innervation from both the tibial and superficial fibular nerves. As such, generalizability of findings from neural drive and contractile properties to reflect function of all plantar flexor muscles is imperfect. However, under existing methodology, it is both difficult and impractical to simultaneously stimulate both motor nerves while avoiding stimulation of the antagonist muscles (the dorsiflexors).

As in chapter 3, diagnosis was based on clinical presentation, not on tendon quality as assessed using imaging. However, while imaging can assist in diagnosing degeneration in the tendon (i.e., Achilles tendinosis) (Puddu et al., 1976, Maffulli et al., 1998), tendon quality does not correlate well with symptoms (Docking et al., 2015a, Kannus and Jozsa, 1991, van Dijk et al., 2011). In fact,
tendon changes are correlated with age and BMI (Docking, 2021a, Kannus and Jozsa, 1991). Therefore, degenerative changes would be more likely in the tendinopathy group, which was older and heavier. Thus, any correlations between symptom and tendon quality could be merely spurious and coincidental.

Despite attempts at matching based on age, body weight, and sex, the control and AT groups were not matched. In order to address this, all measures of MVIC torque and resting twitch torque were normalized to body weight. Also, statistical analyses included covariates of age and sex. Heel raise repetitions were not normalized to body weight. However, despite being heavier, the AT group performed similarly in the SLHR task, suggesting that any normalization would perhaps favor the AT group.

Conclusions

Fatigability was similar between people with AT and healthy controls, whether when evaluated in response to a lab-based isometric fatiguing exercise task or as number of repetitions performed in a dynamic clinical task, the SLHR. In both groups, fatigability was predicted by neural drive. However, people with AT had impaired muscle contractility, which – unlike in healthy controls – also contributed to their fatigability. In people with AT, fatigability and muscle contractile function were related to pain, suggesting an important role of pain in mediating function in AT in both lower extremities. These findings suggest that a comprehensive approach – involving activity modification and addressing pain
and contractile function in the plantar flexors – may be necessary to resolve symptoms and return these patients to their prior level of function.
CHAPTER 5: CONCLUSIONS & FUTURE DIRECTIONS

PURPOSE

The primary aims of this dissertation were to evaluate plantar flexor muscle function, including strength, power, and fatigability, in people with midportion Achilles tendinopathy (AT). This required first evaluating the validity and utility of a common clinical test, the Single Leg Heel Raise (chapter 2). The Single-Leg Heel Raise test (SLHR) was subsequently used in combination with measures of maximal plantar flexor strength (both isometric and dynamic), power, and isometric fatigability to evaluate differences in plantar flexor muscle function between people with AT and healthy controls (chapters 3 and 4). Each chapter evaluated the contributing role of neural drive and contractile mechanisms on plantar flexor muscle function. As AT is a chronic condition characterized by pain in the tendon, chapters 3 and 4 additionally evaluated pain and its contributions to plantar flexor muscle function.

STRENGTH & FATIGABILITY BETWEEN GROUPS

Whether evaluated as maximal isometric or dynamic strength, isometric fatigability, or dynamic fatigability, plantar flexor muscle function did not differ between people with AT or healthy controls. Differences in maximal strength and fatigability were also absent between limbs in people with AT: the more and less affected limbs were equally strong and fatigable. These findings did not support the hypotheses from Aims 2 and 3, which predicted worse strength and
fatigability in the more affected limb when compared to either healthy controls or the less affected limb.

THE SINGLE-LEG HEEL RAISE TEST

As was hypothesized in Aim 1, there was no relationship between maximal isometric plantar flexor strength and performance in the SLHR, measured as repetitions completed prior to task failure. Surprisingly, the SLHR was also poorly associated with plantar flexor fatigability, measured as the acute reduction in maximal plantar flexor force following the SLHR. Specifically, the SLHR did not result in similar degrees of plantar flexor fatigability among participants. Therefore, it was not surprising that SLHR performance was similar between people with AT and healthy controls (chapter 4). These findings suggest an important limitation in interpretation of SLHR performance, at least in regards to its original design.

One limitation of the SLHR is its inability to truly isolate itself to plantar flexor function. Certainly, no other muscles can perform the ankle plantar flexion required to complete a heel raise. However, strength of intrinsic foot musculature is critical to dynamic ankle function (Hashimoto and Sakuraba, 2014, McKeon et al., 2015): the ability to translate forces across the talocrural joint into extension at the metatarsophalangeal joints requires coordination with and stabilization of the foot. Importantly, the ability to reach the terminal ankle flexion in a heel raise requires ankle supination, and thus contributions from intrinsic and extrinsic muscles of the foot and ankle. In one study, 36% of the variance in heel raise
height was attributed to midfoot peak power (DiLiberto and Nawoczenski, 2020), suggesting an important limitation in attributing SLHR performance to plantar flexor function alone.

In contrast to the SLHR, laboratory-based measures of muscle function can often be isolated to specific joint regions. For example, when testing maximal strength in a laboratory setting, constraints are often applied to neighboring joint regions. This limits the contributions being made by other muscle groups. Importantly, it restricts participants from using compensatory behaviors to achieve a task. As such, performance can be attributed directly to the joint region of interest. The SLHR requires the participant to independently stabilize neighboring joint regions and thus does not share this same advantage.

The mean number of repetitions completed by healthy control participants was similar to that reported in a study evaluating normative SLHR in healthy controls (Hébert-Losier et al., 2017). This study also developed models to estimate the number of heel-raise repetitions expected by biological sex and decade of life, assuming a BMI of 24.2 and a moderate physical activity level. Based on this model, the median number of heel-raise repetitions completed by males in chapter 2 (Aim 1) were similar to that estimated for young males in their second decade. However, the range of heel-raise repetitions completed by young females in chapter 2 was higher than that estimated by the model for females in their second decade. However, this difference may be attributed to a slightly lower BMI among participants in chapter 2 or possible differences in physical activity levels between these cohorts.
SEX DIFFERENCES IN PLANTAR FLEXOR FUNCTION

Male sex has been identified as an intrinsic risk factor for developing AT (Magnan et al., 2014). The rationale for sex differences in AT, however, is poorly understood. This dissertation sought to first investigate sex differences in plantar flexor function in healthy controls (Aim 1), as this could contribute to possible sex differences in plantar flexor function in AT. Isometric plantar flexor strength and performance in the SLHR did not differ between healthy males and females (chapter 2). Similarly, comparisons in plantar flexor function between people with AT and healthy controls were not different when controlling for sex. If prevalence of AT indeed differs between males and females, whereby males are more frequently affected (Joseph et al., 2014, Kvist, 1991) – a notion debated among clinicians and researchers (Albers et al., 2016, Hopkins et al., 2016), the findings of this dissertation suggest that this would not be the result of differences in plantar flexor function. However, it is important to consider that Aims 2 and 3 studies lacked sufficient power to empirically evaluate sex differences in plantar flexor function among persons with AT.

BILATERAL CHANGES IN MUSCLE FUNCTION IN AT

It is interesting to note that, in contrast to the hypotheses in Aims 2 and 3, people with AT had similar muscle function in both limbs. Such bilateral motor and sensory changes in unilateral tendinopathies have been reported previously (Heales et al., 2014). While the results of this dissertation support the findings in
the systematic review completed by Heales et al. (2014), however, caution must be taken when interpreting between-limb differences as reported in chapters 3 and 4. Specifically, the “control” limb in people with AT was asymptomatic in only 50% of the participants. In the other half of AT participants, the “control” limb was simply less affected than the test limb. As such, the data from participants with bilateral tendinopathy symptoms may have contaminated the between-limb results in people with AT. Nevertheless, tendon pathology is common in the contralateral, asymptomatic limb of unilateral AT (Docking et al., 2015b, Rabello et al., 2020), so even an AT cohort that was purely unilateral in symptoms could have presented with heterogeneity in muscle function and pain.

**NEURAL DRIVE AND CONTRACTILE FUNCTION**

Neural drive to the plantar flexor muscles did not differ between groups in any Aims of this dissertation. In Aim 1 (chapter 2), males and females had similar reductions in neural drive following the SLHR, and this was associated with fatigability from the task. The hypotheses in Aim 1 were supported by this finding. In Aims 2 and 3 (chapters 3 and 4), people with AT and healthy controls had similar neural drive at baseline and in response to fatiguing exercise. As in Aim 1, neural drive predicted fatigability in Aim 3, and it was the only predictor of fatigability in all three groups (more and less affected limbs in AT and healthy controls.

Despite similar plantar flexor strength and fatigability and similar neural mechanisms, contractile function differed between groups: compared with
controls, people with AT had decreased resting twitch amplitudes at rest in their more affected limbs (chapter 3). These differences in contractile function, however, were not accompanied by differences in maximal isometric strength between groups. Instead, the contributions of neural and contractile mechanisms differed between people with AT and healthy controls: in controls, maximal strength was predicted by neural drive but not by contractile function; in the more affected limb in AT, maximal strength was predicted by contractile function, but not by neural drive; and in the less affected limb in AT, maximal strength was predicted by a combination of neural drive and contractile function.

People with AT also experienced reductions in resting twitch amplitudes in response to fatiguing isometric exercise (chapter 4). Interestingly, the fatiguing exercise resulted in reductions in resting twitch amplitudes in both limbs in people with AT. These remained unchanged in healthy controls. This suggests deficits within the contractile mechanisms in both limbs of people with AT. However, the reduction in resting twitch amplitude was not related to the reduction in maximal strength (fatigability). These findings suggest an impairment within the triceps surae muscles (impaired contractile function) that may be compensated for by other plantar flexor muscles. This type of compensation would enable people with AT to demonstrate similar external torque production as healthy controls, despite decreased contribution of the triceps surae in generating internal force.

An alternate explanation for differences in resting twitch amplitude in AT (both at baseline and in response to fatiguing exercise) despite similar maximal
strength measures relates to tendon elasticity. Elasticity of tendon is predicted using the linear region of a stress-strain curve, which depicts the relationship between force applied on a tendon and the resulting tissue deformation (Kelc et al., 2013). The Achilles tendon is less stiff (i.e., more elastic) in people with AT (Finnamore et al., 2019, Morgan et al., 2018). Perhaps the reduction in stiffness is not readily apparent during maximal contractions, as the muscle-generated force would be high enough to bring the tendon into the linear region of the stress-strain curve. Resting slack in the tendon, known as the toe region, would be fully taken up as the collagen fibrils uncrimp (Kelc et al., 2013). However, in contrast to maximal contraction, resting twitch amplitudes occur at around 20% of the maximal isometric torque. As such, it is conceivable that this level of force is insufficient to bring the tendon out of the toe region and into the linear region of the stress-strain relationship, thereby resulting in reduced force propagation from the muscle through the tendon and, therefore, reduced external torque generation. Analysis of tendon elasticity – and evaluation of whether this correlates with reduced resting twitch amplitudes in AT – would help elucidate whether this is the case. If so, resting twitch amplitudes could prove to be beneficial when quantifying tendon elasticity in this clinical population, particularly as a way to translate changes in tendon elasticity into a clinically relevant, functional outcome measure (namely, joint forces).

The studies contained within this dissertation used resting twitch amplitude to evaluate contractile properties. However, there are many additional variables related to resting electrical stimulation that may be of interest, such as
rate of force development, rate of force relaxation, and changes in muscle activity (as measured using electromyography). Analyzing these additional variables may provide further understanding of differences in maximal strength and fatigability between groups.

**PAIN AND ITS INTERACTIONS WITH MUSCLE FUNCTION IN AT**

People with AT had decreased central pain sensitivity: upper trapezius pressure-pain thresholds (PPTs) were higher in people with AT compared to healthy controls (chapter 3). Furthermore, in people with AT, lower baseline pain sensitivity was associated with greater reductions in contractile properties: those with higher pressure-pain thresholds at the upper trapezius and Achilles tendon had greater reductions in resting twitch amplitude with fatiguing exercise (chapter 4). These findings, though counter-intuitive, may implicate pain desensitization as a perpetuating factor in AT chronicity. It is conceivable that decreased pain sensitivity enables continued participation in motor tasks, even if those same tasks result in further damage to the musculotendinous unit. If this were the case, greater degrees of tissue damage (in this case, measured by impaired contractile function) would be associated with decreased pain sensitivity. Though theoretical, this idea supports the relationship between decreased pain sensitivity and impaired contractile function observed in this dissertation (chapter 4). As addressed in chapter 3, however, the unusual pressure-pain threshold results could simply be the result of a heavier AT group comprised of more males than the control group.
Despite the inverse – and somewhat counterintuitive – relationship between pain sensitivity (PPT) and contractile function, Achilles tendon pain (per NPRS) was positively correlated with fatigability in people with AT. Among people with AT, those who reported higher levels of Achilles tendon pain from fatiguing exercise also demonstrated greater reductions in maximal torque (fatigability). However, the magnitude of fatigability was not different from healthy controls. Thus, despite greater maximum tendon pain predicting greater fatigability, people with AT, on average, performed similarly to healthy controls during fatiguing isometric exercise.

Decreased pain sensitivity predicted greater reductions in contractile function, while increased pain predicted greater fatigability. However, the change in MVIC (degree of fatigability) was not correlated with the change in resting twitch amplitude (contractile function), nor was pain sensitivity correlated with fatigability. Definitive statements about the underlying processes cannot be made based on results of this dissertation alone. The relationship between Achilles tendon pain (NPRS) and fatigability implies that a symptom monitoring approach could be beneficial in people with AT. Yet, decreased sensitivity to pain (PPT) and its correlation to impaired contractility suggest that that symptom monitoring alone is insufficient. Similarly, tracking motor performance alone is likely insufficient; impairments in contractile function did not translated into increased fatigability in people with AT.

When considering each of these variables – pain sensitivity (PPT), tendon pain (NPRS) resulting from fatiguing exercise, contractile function, and fatigability
– and the relationships between them, the impact of pain on motor function in AT is complex. Only when the patient recognizes pain – as evidenced by self-reported pain on the NPRS – do they modify their voluntary behavior (as evidenced by greater reductions in MVIC). Yet, impairments in contractile function underly their motor performance. The theory of motor adaptation posed by Hodges (2011) may explain the seeming inconsistencies within these findings (Hodges, 2011). Using this theoretical framework, redistribution of muscle activity would be warranted to protect the injured tendon. By redistributing motor commands to agonist plantar flexor muscles (namely, the fibularis muscles, innervated by the superficial fibular nerve), the body could optimize motor output, despite impairments in contractile function in the muscles innervated by the tibial nerve.

Ultimately, the findings from this dissertation identify a complicated interaction between motor function and pain in persons with AT: limitations in contractile function do not necessarily result in appreciable differences in plantar flexor strength and fatigability, and perceived pain in the tendon does not predict reductions in contractile function. Furthermore, it is unclear whether adaptations in motor function are due to pain or whether they precede pain in people with AT. Either way, these long-term changes in motor function could prove detrimental to symptoms and function if not addressed with appropriate interventions. If redistribution of motor activity (Hodges, 2011) explains these changes, it may also be the key to effective and efficient treatment in AT. Certainly, symptoms and muscle function are important outcomes to monitor during clinical
management in AT. However, rather than prioritizing improvements in force, power, or fatigability, the muscle parameter of interest may actually be motor control.

LIMITATIONS

An important limitation in each aim relates to study power and the number of participants; each study included only 14 participants per group. As such, the ability to detect small, between-group differences was limited. Importantly, insufficient statistical power can lead to type II error: concluding there are not group differences when differences indeed exist (Schreffler 2020). In contrast, the risk of type I error (false positive, or concluding there are not group differences when differences indeed exist) is a risk associated with very large sample sizes.

An additional limitation of this study relates to multiple comparisons. By virtue of the large number of variables being analyzed – and for such a small sample size – there is a risk of inflating type I error (falsely concluding there are group differences when differences do not exist). However, many of the variables presented in this thesis were not different between-groups. As explained above, this could have resulted from insufficient power to detect group differences. Of those variables that were different between groups, the effect sizes, calculated as Cohen’s $d$, exceeded 0.74: baseline resting twitch amplitude, $d=0.824$, power=0.987; baseline upper trapezius PPT, $d=0.748$, power=0.967; post-task upper trapezius PPT, $d=0.787$, power=0.979.
A recent study recommended subgroupings of patients with AT in an effort to identify heterogeneity among persons with AT (Hanlon et al., 2021). These groupings were as follows: activity-dominant, psychosocial-dominant, and structure-dominant. The participants included in aims 2 and 3 were perhaps most representative of the activity-dominant subgroup – a group characterized by their young age, continued high activity levels, and mild symptoms. As a result, the findings may not translate to the entire population of persons with AT, but rather primarily the subgrouping of activity-dominant AT patients.

**SUMMARY**

This body of work has contributed to the field in several important ways: by describing neuromuscular function of the plantar flexor muscles during a common clinical evaluation tool, the Single-Leg Heel Raise test; by evaluating neuromuscular function of the plantar flexor muscles in people with AT; and by combining measures of pain alongside measures of motor function in people with AT. Importantly, many of the tools and techniques utilized in these studies have not been previously utilized in people with AT or as they relate to performance in the Single-Leg Heel Raise test. Future work should focus on additional evaluation of neuromuscular function in AT, including: during other forms of fatiguing exercise; alongside evaluation of tendon elasticity; and by evaluating additional properties of contractile function, such as rate of torque development and relaxation. Finally, future work should take into consideration both the subgroupings that may exist within AT and the importance of sufficient sample
size to enhance study power, both of which will contribute to greater external validity of future research studies.
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