6-21-2017

Muscle strength and control characteristics are altered by peripheral artery disease

Molly Schieber

Ryan Hasenkamp

Iraklis Pipinos

Jason Johanning

Nicholas Stergiou

See next page for additional authors

Authors

Molly Schieber, Ryan Hasenkamp, Iraklis Pipinos, Jason Johanning, Nicholas Stergiou, Holly DeSpiegelaere, Jung Chien, and Sara Myers

Muscle strength and control characteristics are altered by peripheral artery disease

Molly N. Schieber, BS, Ryan M. Hasenkamp, MS,a Iraklis I. Pipinos, MD, PhD, Jason M. Johanning, MD, Nicholas Stergiou, PhD, Holly K. DeSpiegelaere, BSN, RN, Jung H. Chien, PhD, and Sara A. Myers, PhD

ABSTRACT

Objective: Peripheral artery disease (PAD), a common manifestation of atherosclerosis, is characterized by lower leg ischemia and myopathy in association with leg dysfunction. Patients with PAD have impaired gait from the first step they take with consistent defects in the movement around the ankle joint, especially in plantar flexion. Our goal was to develop muscle strength profiles to better understand the problems in motor control responsible for the walking impairment in patients with PAD.

Methods: Ninety-four claudicating PAD patients performed maximal isometric plantar flexion contractions lasting 10 seconds in two conditions: pain free (patient is well rested and has no claudication symptoms) and pain induced (patient has walked and has claudication symptoms). Sixteen matched healthy controls performed the pain-free condition only. Torque curves were analyzed for dependent variables of muscle strength and motor control. Independent t-tests were used to compare variables between groups, and dependent t-tests determined differences between conditions.

Results: Patients with PAD had significantly reduced peak torque and area under the curve compared with controls. Measures of control differed between PAD conditions only. Load rate and linear region duration were greater in the pain condition. Time to peak torque was shorter in the pain condition.

Conclusions: This study conclusively demonstrates that the plantar flexor muscles of the PAD patient at baseline and without pain are weaker in patients with PAD compared with controls. With the onset of claudication pain, patients with PAD exhibit altered muscle control strategies and further strength deficits are manifest compared to baseline levels. The myopathy of PAD legs appears to have a central role in the functional deterioration of the calf muscles, as it is evident both before and after onset of ischemic pain. (J Vasc Surg 2017;66:178-86.)

Peripheral artery disease (PAD) is a prevalent vascular disease affecting 8.5 million people in the United States.[1] The most common presentation of PAD is intermittent claudication, a condition in which when the patient walks, the metabolic demands of the lower limbs exceed the limited supply of blood, causing ischemia and

exercise-induced discomfort and pain in the exercising leg. Chronic lower limb ischemia and ischemia-reperfusion introduce biochemical and histologic changes in the muscles of the affected legs, producing the well-described myopathy of PAD.[2-4] Involved in this myopathy are dysfunctional mitochondria bioenergetics, increased oxidative damage, and fiber type shifting from type II to type I.[2-9] The myopathic changes are associated with decreased quality of life,[10] leg function,[11,12] poor health outcomes, and mortality in patients with PAD.[12,13] Furthermore, the functional effects of the myopathy are most clearly seen in the gait alterations[14-22] that claudicating patients demonstrate from the first step they take before they experience any exercise-induced ischemia or pain.[14-16,18,19] The altered gait profile found in PAD patients presents as decreased muscle power contributions at the ankle, knee, and hip joints. Among these findings, the compromised biomechanics at the ankle joint are the most consistent deficits seen in patients with PAD compared with controls.[15,18,21,22] These alterations include a lack of controlling the downward, plantar flexion motion of the foot on heel strike,[19] decreased ankle power generation during push-off,[22] decreased plantar flexion impulse,[16] decreased energy output during the push-off phase of gait,[15] and altered ankle angle variability.[14] These findings equate to an overall reduced ability for patients with PAD to propel themselves forward during the late stance phase of gait and are present from the first step the patients take while they become exacerbated after the onset of claudication pain. Thus, submaximal muscle performance, common in most functional tasks such as gait, has been quantified in detail in patients with PAD. Previous investigations have also shown that patients with PAD have significantly reduced maximal lower extremity strength compared with controls,[7,23-25] but limited work has investigated muscle strength beyond measurement of peak maximal output. A peak maximal lower extremity strength measurement represents one value in time and alone provides limited insight to the sequence of functions and mechanics that correspond to normal gait or the muscle contraction abilities as a whole in these patients. Incorporating variables beyond peak maximal strength that reflect the collaboration between muscle and nerve during a contraction, such as torque generated over time and torque variability, may provide a better understanding of the motor control deficits at the ankle contributing to gait dysfunction in these patients.

Our objective was to develop a detailed strength profile of the ankle plantar flexors in patients with PAD before and after the onset of claudication pain and to compare it with that of non-PAD controls. We hypothesized that patients with PAD have decreased strength output and altered control of the plantar flexor muscles.

METHODS

Participants.

The study was approved by the Institutional Review Boards at the Veterans Affairs Medical Center of Nebraska and Western Iowa and the University of Nebraska

Medical Center. Informed consent was obtained from all participants before data collection.

PAD group.

Ninety-four claudicating patients who were evaluated and diagnosed with PAD in the vascular surgery clinic of the two institutions were recruited (Table I). All patients with PAD were screened and evaluated by one of two board-certified vascular surgeons. Diagnosis of PAD was based on medical history, physical examination, significantly decreased resting ankle-brachial index (#0.9), and computed or standard arteriography. Symptomatic claudication in at least one lower extremity during walking was required for inclusion. Exclusion criteria included ambulation-limiting cardiac, pulmonary, neuromuscular, or musculoskeletal conditions; rest pain; and history of previous revascularization.

Control group.

Sixteen controls of similar age and anthropometric characteristics were recruited through convenience sampling in the community (Table II). Control subjects were screened in a manner similar to subjects with PAD, were excluded for the same criteria, and were required to have an ankle-brachial index >0.9 and no subjective or objective ambulatory dysfunction.

Experimental procedure and data collection.

Muscle strength was examined through isometric dynamometry using a Biodex (System 4.0; Biodex Medical Systems, Shirley, NY). Isometric contractions are a well-established and reliable technique that is better tolerated by patients compared with an isokinetic measurement.[25] All subjects were secured in the Biodex and were positioned so that the ipsilateral thigh was braced and supported with a knee angle of 30 degrees, which allowed maximum contribution of the gastrocnemius.[26] The ankle was positioned at 90 degrees, allowing maximum torque recruitment at the ankle. To isolate the plantar flexor muscles, the contralateral thigh, waist, and chest were secured. The ankle was secured to the Biodex attachment with the axis of rotation of the dynamometer aligned with the subjects' malleoli.

All control subjects walked on a treadmill for 3 minutes as a warm-up. Patients with PAD walked for a maximum of 3 minutes or less if pain forced them to stop and then rested until they were free of pain. Before testing, subjects were allowed to perform submaximal trial-repetitions to get comfortable with the Biodex. Patients with PAD performed pain-free and pain-induced conditions. During each condition, two repetitions of maximal plantar flexion contraction for a duration of 10 seconds[26] were performed on the more diseased leg of PAD patients with bilateral disease or the symptomatic leg of patients with unilateral disease. Two repetitions provide a more representative sample than a single repetition and are well tolerated by the patients. Controls performed only the pain-free condition with the dominant leg. Each subject was instructed to push as

quickly and as hard as possible throughout the entire repetition. During the pain-free condition, patients and controls rested for 1 minute between each repetition. This rest period served to prevent the onset of claudication pain in subjects with PAD and to limit the effect of fatigue in controls. After performing two repetitions of plantar flexion in the pain-free condition, subjects were unstrapped from the Biodex, concluding the testing for controls. Subjects with PAD were tested again in the pain condition, after claudication pain was induced by walking on a treadmill at 2 mph and a 10% incline until the subject reached a moderate level of pain that persisted. Immediately, subjects again performed two maximal contractions of plantar flexion for 10 seconds each but were given only 5 seconds of rest between repetitions.

Table I. Demographics of peripheral artery disease (PAD) subjects

Ankle-brachial index	
Range	0.19-0.9
Mean	0.54 ± 0.19
Disease duration, months	54.4 ± 57.5
Smoking	
Never	0
Current	58.5
Former	41.5
Coronary artery disease	33.0
Obesity	40.4
Diabetes	33.0
Dyslipidemia	77.7
Hypertension	79.8

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as %.

Data analysis.

Each isometric plantar flexion was collected at 100 Hz in the Biodex, and the resultant torque time series was imported into MATLAB (MathWorks, Natick, Mass) to calculate dependent variables from custom scripts (Supplementary Figs 1-3, online only). The linear region of each torque curve was identified for a more detailed analysis of torque control during the maximal contraction. The linear region was determined as the region in the torque curve that showed a trend of constant slope. Collectively, these dependent variables provide a clear picture about the ability to control force output during muscle contractions (Fig 1):

1. Area under the curve: total area under the torque curve. This measure is representative of work performed during the contraction.

2. Peak torque: average torque produced during the linear region of the contraction.

3. Time to peak torque: amount of time it takes to reach the start of the linear region. This measure indicates the functional ability of the muscle to produce and to maintain maximal torque quickly.

4. Linear region duration: amount of time during the contraction that the linear region is maintained. This timing measure is representative of fatigue during maximum contraction.

5. Standard deviation during the linear region: calculated during the defined linear region to create a measure of variability. This represents an ability to control a constant muscle contraction.

6. Load rate: the rate of torque applied during the first second of the contraction. This timing measure indicates the ability to produce torque rapidly and is indicative of muscle power.

Table II. Baseline characteristics of peripheral artery disease (*PAD*) and control subjects

Characteristics	PAD	Control	*P*
No. in group	94	16	
Age, years	63.7 ± 7.0	65.2 ± 7.9	.49
Body mass, kg	89.7 ± 20.0	86.7 ± 13.5	.57
Body height, m	1.74 ± 0.10	1.78 ± 0.05	.23

Data are reported as mean ± standard deviation.

Statistical analysis.

Means and standard deviations for each variable were calculated. Two independent t-tests were used to compare PAD conditions independently with controls, and one dependent t-test was used to compare PAD pain free vs PAD pain. A repeated-measures analysis of variance was used to perform linear trend analysis. Statistical comparisons were performed using SPSS 22.0 software (IBM Corp, Armonk, NY), and the significance level was set at .05.

RESULTS

Group means for age (P ¼ .49), body mass (P ¼ .57), and height (P ¼ .23) were not different between patients with PAD and controls, verifying that the groups were well matched (Table II).

In comparisons of PAD with controls, both peak torque and area under the curve are greater in controls than in PAD pain-free and pain conditions (Table III, Fig 2). No other variables were statistically different between both PAD conditions and the control group.

Five variables were significant in comparisons between PAD pain-free and PAD pain conditions (Table III, Fig 2). Peak torque, area under the curve, and time to peak torque are all greater in the PAD pain-free condition. Load rate is larger and the linear region is longer in the PAD pain condition. Thus, exercise-induced ischemic pain further reduced strength and changed motor control in the plantar flexors of patients with PAD.

Standard deviation during the linear region yielded no significant comparisons. The linear region of each torque curve was divided into three equal tertile regions for further analysis. Trend analysis revealed a decreasing linear trend for torque variability about the linear region, from beginning to end, in PAD conditions only (Table IV).

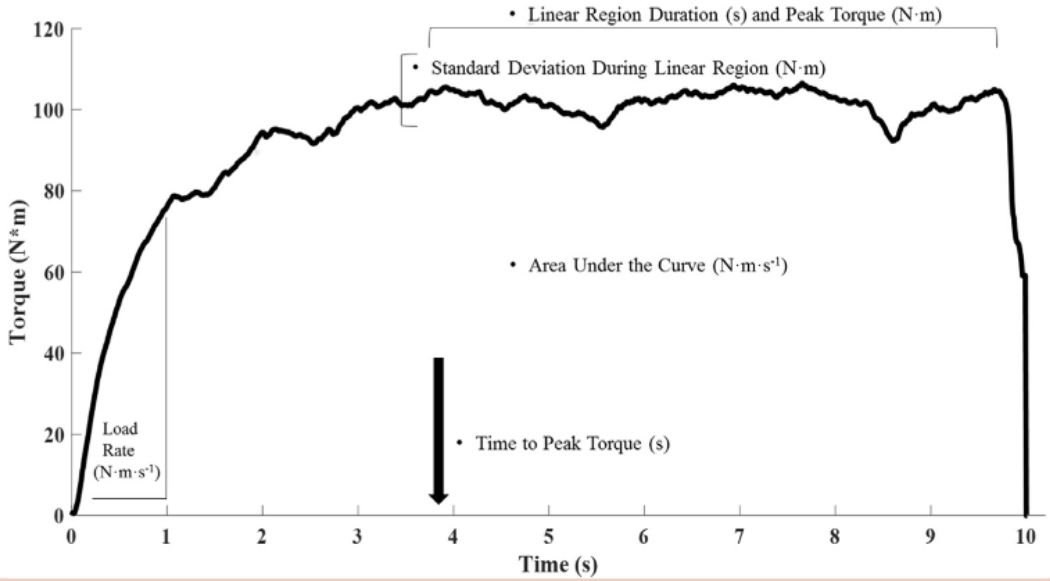


Fig 1. A representative strength curve from the control group with the six calculated dependent variables: area under the curve, linear region duration, peak torque, time to peak torque, standard deviation of torque during the linear region, and load rate.

Table III. Group means for each dependent variable

Variable	Control	PAD PF	PAD P		*P*
Area under the curve, N · m · s^{-1}	858.7 ± 237.0	682.4 ± 274.0	601.5 ± 265.4	C vs P	<.001[a]
				C vs PF	.01[a]
				P vs PF	<.001[a]
Peak torque, N · m	98.2 ± 27.6	81.4 ± 32.6	69.1 ± 28.7	C vs P	<.00[a]
				C vs PF	.04[a]
				P vs PF	<.01[a]
Time to peak torque, seconds	3.74 ± 1.22	3.91 ± 1.39	3.09 ± 1.17	C vs P	.06
				C vs PF	.67
				P vs PF	<.001[a]
Standard deviation during linear region, N · m	3.04 ± 1.53	2.75 ± 2.00	2.54 ± 1.41	C vs P	.23
				C vs PF	.49
				P vs PF	.23
Linear region duration, seconds	5.80 ± 1.42	5.00 ± 1.77	5.85 ± 1.77	C vs P	.91
				C vs PF	.06
				P vs PF	<.001[a]
Load rate, N · m · s^{-1}	197.1 ± 140.8	147.9 ± 88.2	168.3 ± 88.0	C vs P	.44
				C vs PF	.19
				P vs PF	.04[a]

C, Control; *P*, pain; *PAD*, peripheral artery disease; *PF*, pain free.
Data are reported as mean ± standard deviation.
[a]Indicates a significant difference ($P < .05$) between groups.

DISCUSSION

The purpose of this study was to create a more detailed strength profile of the ankle plantar flexors to gain insight into the contribution of the ankle to the identified gait abnormalities in patients with PAD.[14-22] Measures of maximal strength and motor control were measured while subjects performed isometric ankle plantar flexions with and without claudication pain and were compared with controls. Our findings support our hypothesis that significant differences exist in muscle strength profiles between controls and patients with PAD. As expected, previously reported findings for reduced ground reaction forces and joint powers[15,16,18] coincide with the significant differences found for area under the curve and peak torque of the plantar flexors in all comparisons. Specifically, patients with PAD exhibited reduced area under the curve and peak torque production compared with controls. The strength differences between controls and PAD when subjects perform a 10-second isometric test immediately after rest and before any exercise-induced ischemia/pain confirm that the weakness in the PAD ankle plantar flexors is related to the well-described myopathy of PAD.[2,4,9,11,27,28] Furthermore, the introduction of ischemic claudication symptoms altered the motor control strategies of the ankle plantar flexors, producing significant differences between PAD conditions.

Table IV. Results of linear trend analysis within each linear region section

Group	Beginning third (N · m)	Middle third (N · m)	End third (N · m)	*P*
Control	2.13 ± 0.97	2.13 ± 1.45	2.03 ± 1.10	.756
PAD PF	1.90 ± 1.35	1.54 ± 1.19	1.47 ± 1.44	.001[a]
PAD P	1.71 ± 1.05	1.53 ± 0.92	1.47 ± 1.18	.041[a]

P, Pain; *PAD*, peripheral artery disease; *PF*, pain free.
Data are reported as mean ± standard deviation.
[a]Indicates a significant difference ($P < .05$).

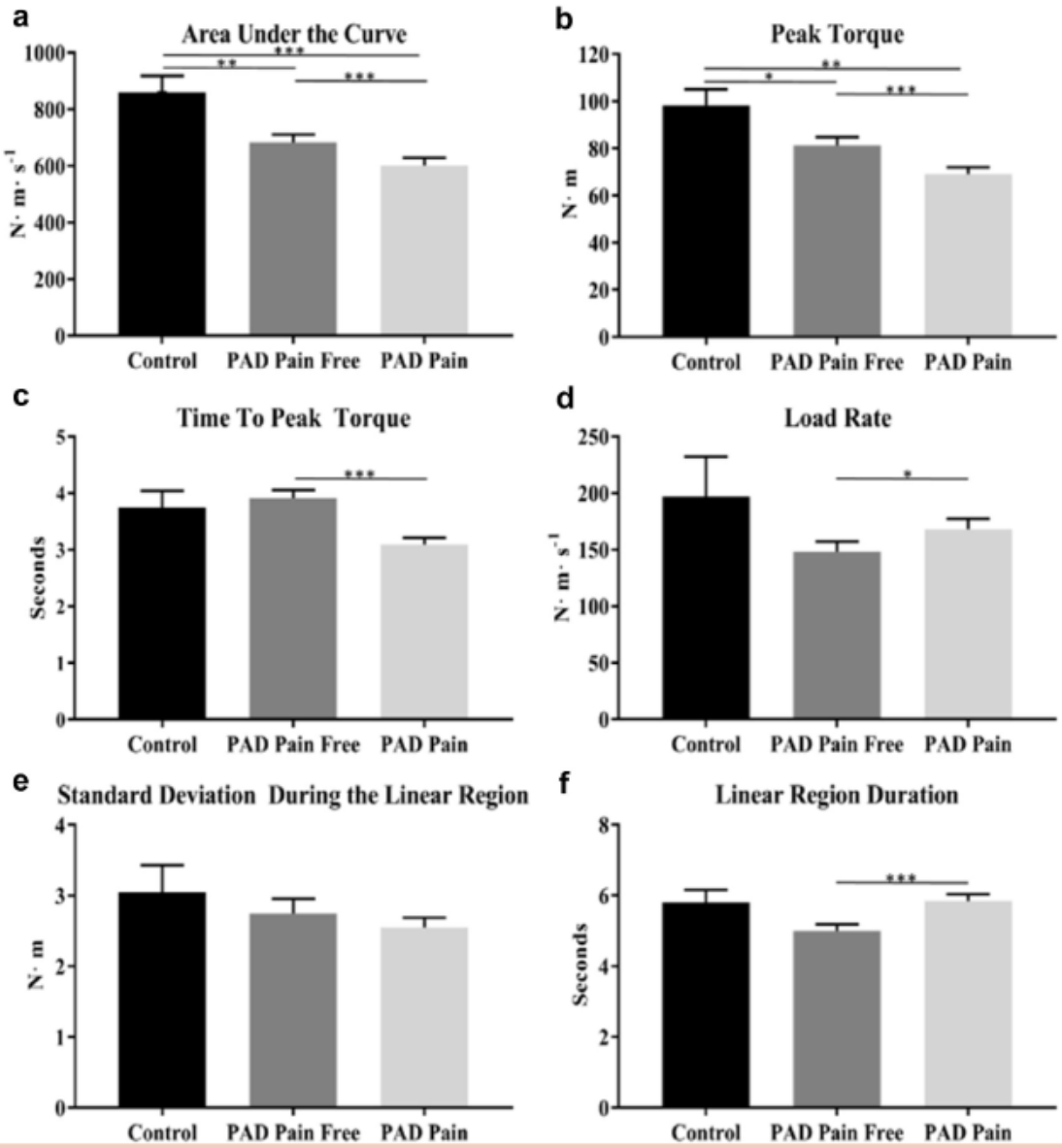


Fig 2. Mean and standard deviation graphs for **(a)** area under the curve, **(b)** peak torque, **(c)** time to peak torque, **(d)** load rate, **(e)** standard deviation during the linear region, and **(f)** linear region duration. *PAD*, Peripheral artery disease. Significance denoted as $^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .001$.

Our data demonstrate that the plantar flexor muscles of PAD patients have significant functional deficits. These deficits appear related to the neuropathy and myopathy previously described by our group[2-4,11,27,2]8 and others.[5,6,29-31] Our work demonstrates that there are functional tests, including the maximal isometric plantar flexion test we are describing in this paper, that can measure and stratify the degree of impairment in the legs of patients with PAD. Such measurements can be used as diagnostic tools to assess the severity of PAD in each individual patient but also potentially to predict and guide therapy, depending on the patient's presentation. Our group is currently evaluating multiple parameters of this myopathy as predictors of outcomes after standard therapies (revascularization or supervised exercise) but also in

an effort to understand whether therapeutic measures can improve these deficits and to what extent.

Decreased area under the curve.

Area under the curve is a measure of angular impulse during a contraction and is indicative of work; the smaller area found in patients with PAD indicates that they are unable to reach or to maintain a similar level of torque output during the same amount of time as controls. Our results show a decreased total area in PAD torque curves at the ankle plantar flexors and a decreased capacity to complete the same amount of work as controls. The difference between controls and patients with PAD in pain-free conditions was exacerbated in pain conditions.

Decreased peak torque.

Similarly, peak torque is highest in controls and lowest in the PAD pain condition. Our results demonstrate a true deficit in strength at the ankle plantar flexors in patients with PAD before the onset of pain. These findings further document the strength decreases associated with PAD that could potentially contribute to gait deficits during intermittent claudication by reducing total propulsive forces during push-off.

Works from other groups are in agreement with our finding of reduced strength in the plantar flexor muscles of patients with PAD.7,12,24 Gerdle et al24 found that patients with PAD produced lower peak torque and less contractile work than controls during submaximal endurance testing of the plantar flexors.24 The methodology was different in the study of Gerdle et al24; subjects performed a set of 30 nonfatiguing isokinetic contractions at 180 degrees/s and a set of 200 fatiguing isokinetic contractions at 60 degrees/s.24 Other work by Regensteiner et al7 showed reduced levels of strength in the plantar flexors in patients with PAD that correlated with total calf cross-sectional area and type II fiber cross-sectional area.7 Strength testing in the study of Regensteiner et al7 was performed during two sets of five maximal-effort isokinetic contractions at 60 degrees/s in pain-free conditions. The single highest torque for the gastrocnemius and anterior tibial muscles was used for analysis.7 However, in a similar study, Scott-Okafor et al25 tested strength at the ankle, knee, and hip but found differences only at the dorsiflexors compared with individuals without PAD.25 Similar to this study, Scott-Okafor et al25 used isometric testing but tested plantar flexor strength with the knee at a 90-degree angle, whereas Regensteiner et al7 tested the ankle with the knee fully extended and this study tested the ankle with slight flexion of 30 degrees at the knee. The gastrocnemius crosses both the knee and the ankle joint; therefore, for a given ankle plantar flexion torque, the contribution of the gastrocnemius is dependent on the position of the knee. A more flexed knee decreases the overall plantar flexion torque output by minimizing the contribution of the gastrocnemius, the main contributor in plantar flexor contractions,32 and is likely the main reason that Scott-Okafor et al25 were not able to see the decrease in torque during plantar flexion. Collectively,

decreased strength about the ankle in patients with PAD is a common finding, and this study adds to that conclusion.

Measures of motor control at plantar flexors.

To our knowledge, this is the first study to investigate muscle strength beyond a measurement of the peak maximal force in patients with PAD. Measures of rate, standard deviation, and timing (including time to peak torque, standard deviation during linear region, linear region duration, and load rate) represent muscle motor control because they assess the ability of a subject to produce a maximal contraction and detail changes in the quality of the contraction during the course of the trial. The differences found in these measures were only in comparisons between PAD conditions. Our data did not demonstrate differences between PAD patients and controls.

Increased load rate in pain conditions.

A larger load rate indicates rapid torque production during the first second of the isometric contraction. A steeper slope during the first second of contraction would represent this on the torque curve. Load rate increased in pain conditions for PAD, indicating that the onset of pain altered the initial approach to the contraction to perform more work. It appears that induction of pain produces motor adjustments that lead to the observed faster load rates. It is possible that pain input from sensory endings may change the motor output into the symptomatic muscle, leading to increased recruitment of motor units during the first second of the contraction. Another possibility is that once symptoms have been induced, the neuromuscular system is sensitized and responds quicker to the nerve impulses for contraction. Irrespective of the underlying mechanism, the capacity of the myopathic tissues to perform more work is not maintained throughout the contraction because our data demonstrated decreased overall area under the curve in pain conditions.

Time to peak torque.

Time to peak torque was measured to assess whether timing differences existed in maximal torque generation in an isometric contraction. PAD pain reached peak torque quicker than in pain-free conditions, which is likely associated with the concurrent decrease in peak torque observed in the pain condition. Specifically, the PAD patients more quickly reach the level of peak torque while in pain because the peak torque is lower than in the pain-free condition and they are able to arrive faster to it. Although a quicker response may be the product of a neuromuscular system that is more sensitive to nerve impulses, when it is combined with the finding of lower peak torque and area under the curve, it indicates that the presence of symptoms exacerbates the deficit in torque output capabilities in patients with PAD.

Linear region duration and standard deviation.

Linear region duration was significantly longer in the PAD pain condition compared with baseline. It appears that because torque generation is of a lower

magnitude in the pain condition, the patients spend more time trying to maintain their torque output because of an inability to generate more.

Standard deviation of the entire linear region elicited no significant comparisons. Because of the large variance within this variable, we investigated variability in maintenance of torque further by dividing the linear region of each curve into three equal tertiles. Linear trend analysis revealed that variability about the linear region decreased in PAD and did not change in controls. Neuro-muscular fatigue is known to affect motor output during an isometric contraction by increasing the amount of variability as a contraction progresses.[33] Controls exhibit no trend because a healthy neuromuscular interaction involves recruitment of more motor units to maintain torque within a 10-second contraction, whereas the decreasing variability in PAD is an example of less activity within the muscle. Myopathic fiber type shifting from type II to type I[2,9] and the neuropathy in PAD muscle that has been shown to decrease conduction velocities and amplitude corroborate this trend.[29-31]

Possible mechanisms for the strength and motor control deficits at the ankle.

This study confirmed the significant deficits in strength that have been found in the ankle plantar flexors of patients with PAD previously.[7,15,16,21,22,25] During gait, the leg of a patient with PAD is unable to generate normal power and to produce normal positive work for push-off, indicated by reduced ankle plantar flexion torque and power compared with adults without PAD.[7,15,16,18] This gait deficit is present both before and after the onset of claudication pain.16 Patients with PAD also have a reduced ability to produce work during walking, independent of walking speed.[15] The deficits in strength and ability to produce work with the plantar flexor muscles are likely key contributors to the gait deficits that have been documented in patients with PAD.

Our findings are the result of maximal isometric strength assessments, which are independent of blood flow, and demonstrate that deficits in patients with PAD relative to controls reflect the metabolic myopathy and neuropathy that are present in the muscles of patients with PAD.[2,4,5] The effects of neuropathy in patients with PAD have been found to include decreased nerve conduction velocities and decreased amplitude and increased duration of motor unit action potential.[29-31] The myopathy in patients with PAD involves defective mitochondrial bioenergetics, oxidative damage, myofiber degeneration, and fibrosis of the affected skeletal muscles.[2-6,11,27,28,34,35] Increased oxidative damage in PAD muscle is associated with deterioration of the size and shape of myofibers in the gastrocnemius with preference for type II myofibers, whereas type I fibers persist and are less damaged.[9] Type II fibers are high-energy consumers and are used in short explosive movements, such as the isometric contraction.[36] The change in myofiber type in the gastrocnemius in connection with defective mitochondria and neuropathy demonstrates possible underlying mechanisms for the deficits we are demonstrating in maximal torque generation and performance of effective work at the plantar flexor muscles in patients with PAD relative to controls. It is evident from our data that the onset of claudication pain affects motor control at the ankle in patients with

PAD. It is probable that during exercise-induced ischemia, fatigue, pain, and an increased workload from restricted bioenergetics would alter the control of a muscle contraction, especially at a maximal intensity for 10 seconds. To our knowledge, no work with similar measures of motor control in the ankle plantar flexors currently exists to compare our results with other populations and pathologic processes.

The parameters we have described allow quantitation of the degree of neuromuscular impairment present in the legs of claudicating patients. These parameters delineate the collaboration between muscle and nerve during leg contraction and allow an objective assessment of the neuromuscular health of the leg of each patient at baseline and the way it responds to different treatment modalities. If a patient improves walking distances after treatment, knowledge of whether the improvement is or is not reflected in muscle strength and performance can help us understand how treatments raffect the performance of different muscle groups. Of particular interest would be the possibility that after treatment, a patient increases the ability to walk either without a measurable change (or even deterioration) in the performance of the neuromuscular system or with a measurable improvement of certain “unexpected” muscle groups. Based on these examples, it becomes obvious that there are many and exciting opportunities for expanding our understanding of the pathophysiologic mechanisms involved in PAD but also for taking advantage of these mechanisms to modify current treatments and to propose new ones.

Control group size and the use of an isometric measurement instead of isokinetic are possible limitations of this study. Isokinetic testing is more reflective of function because strength is measured through a range of motion rather than in a static position. However, the differences reported here provide insight into the functional capacity of the muscle. Furthermore, an isometric test was tolerable for our patients in the pain condition and still allowed measurement of the changes that occur because of pain.

CONCLUSIONS

Our findings conclusively confirm that the plantar flexor muscles of the PAD patient have a significant functional impairment compared with controls. Impairments in strength were present at baseline, providing more evidence for the impact of myopathy and neuropathy of PAD on the skeletal muscle of claudicating patients. With the onset of claudication pain, patients with PAD have further decrease in peak strength and altered muscle control strategies at the ankle compared with base-line levels. The ankle joint is of primary importance to proper gait mechanics and patterns, especially during the push-off phase in late stance, and thus the deficits we describe have important clinical implications for restoring function. Future biomechanics research in PAD populations should examine the use of strength deficits as predictors of surgical and exercise outcomes.

AUTHOR CONTRIBUTIONS

Conception and design: MS, RH, IP, JJ, NS, SM

Analysis and interpretation: MS, RH, IP, SM

Data collection: RH, HD, JC

Writing the article: MS, RH, IP, JJ, SM

Critical revision of the article: MS, RH, IP, JJ, NS, HD, JC, SM

Final approval of the article: MS, RH, IP, JJ, NS, HD, JC, SM

Statistical analysis: MS

Obtained funding: IP, JJ, NS, SM

Overall responsibility: SM

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statisticsd2016 update: a report from the American Heart Association. Circulation 2016;133:e38.

2. Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, et al. The myopathy of peripheral arterial occlusive disease: part 2. Oxidative stress, neuropathy, and shift in muscle fiber type. Vasc Endovasc Surg 2008;42:101-12.

3. Pipinos II, Judge AR, Zhu Z, Selsby JT, Swanson SA, Johanning JM, et al. Mitochondrial defects and oxidative damage in patients with peripheral arterial disease. Free Radic Biol Med 2006;41:262-9.

4. Pipinos II, Judge AR, Selsby JT, Zhu Z, Swanson SA, Nella AA, et al. The myopathy of peripheral arterial occlusive disease: part 1. Functional and histomorphological changes and evidence for mitochondrial dysfunction. Vasc Endovascular Surg 2008;41:481-9.

5. Makris KI, Nella AA, Zhu Z, Swanson SA, Casale GP, Gutti TL, et al. Mitochondriopathy of peripheral arterial disease. Vascular 2007;15:336-43.

6. Kemp GJ. Mitochondrial dysfunction in chronic ischemia and peripheral vascular disease. Mitochondrion 2004;4: 629-40.

7. Regensteiner JG, Wolfel EE, Brass EP, Carry MR, Ringel SP, Hargarten ME, et al. Chronic changes in skeletal muscle histology and function in peripheral arterial disease. Circulation 1993;87:413-21.

8. Steinacker JM, Opitz-Gress A, Baur S, Lormes W, Bolkart K, Sunder-Plassmann L, et al. Expression of myosin heavy chain isoforms in skeletal muscle of patients with peripheral arterial occlusive disease. J Vasc Surg 2000;31:443-9.

9. Koutakis P, Weiss DJ, Miserlis D, Shostrom VK, Papoutsi E, Ha DM, et al. Oxidative damage in the gastrocnemius of patients with peripheral artery disease is myofiber type selective. Redox Biol 2014;2:921-8.

10. Evans NS, Liu K, Criqui MH, Ferrucci L, Guralnik JM, Tian L, et al. Associations of calf skeletal muscle characteristics and peripheral nerve function with self-perceived physical functioning and walking ability in persons with peripheral arterial disease. Vasc Med 2011;16:3-11.

11. Koutakis P, Miserlis D, Myers SA, Kim JK, Zhu Z, Papoutsi E, et al. Abnormal accumulation of desmin in gastrocnemius myofibers of patients with peripheral artery disease: associations with altered myofiber morphology and density, mitochondrial dysfunction and impaired limb function. J Histochem Cytochem 2015;63:256-69.

12. McDermott MM, Liu K, Tian L, Guralnik JM, Criqui MH, Liao Y, et al. Calf muscle characteristics, strength measures, and mortality in peripheral arterial disease: a longitudinal study. J Am Coll Cardiol 2012;59:1159-67.

13. Thompson JR, Swanson SA, Haynatzki G, Koutakis P, Johanning JM, Reppert PR, et al. Protein concentration and mitochondrial content in the gastrocnemius predicts mortality rates in patients with peripheral arterial disease. Ann Surg 2015;261:605-10.

14. Myers SA, Johanning JM, Stergiou N, Celis RI, Robinson L, Pipinos II. Gait variability is altered in patients with peripheral arterial disease. J Vasc Surg 2009;49:924-31.

15. Wurdeman SR, Koutakis P, Myers SA, Johanning JM, Pipinos II, Stergiou N. Patients with peripheral arterial disease exhibit reduced joint powers compared to velocity-matched controls. Gait Posture 2012;36:506-9.

16. Scott-Pandorf MM, Stergiou N, Johanning JM, Robinson L, Lynch TG, Pipinos II. Peripheral arterial disease affects ground reaction forces during walking. J Vasc Surg 2007;46: 491-9.

17. Scherer SA, Bainbridge JS, Hiatt WR, Regensteiner JG. Gait characteristics of patients with claudication. Arch Phys Med Rehabil 1998;79:529-31.

18. Koutakis P, Pipinos II, Myers SA, Stergiou N, Lynch TG, Johanning JM. Joint torques and powers are reduced during Journal of Vascular Surgery Schieber et al 185 Volume 66, Number 1 ambulation for both limbs in patients with unilateral claudication. J Vasc Surg 2010;51:80-8.

19. Celis R, Pipinos II, Scott-Pandorf MM, Myers SA, Stergiou N, Johanning JM. Peripheral arterial disease affects kinematics during walking. J Vasc Surg 2009;49:127-32.

20. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. Vasc Med 2001;6: 31-4.

21. Chen S, Pipinos II, Johanning JM, Radovic M, Huisinga JM, Myers SA, et al. Bilateral claudication results in alterations in the gait biomechanics at the hip and ankle joints. J Biomech 2008;41:2506-14.

22. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. J Vasc Surg 2010;52:340-7.

23. McDermott MM, Criqui MH, Greenland P, Guralnik JM, Liu K, Pearce WH, et al. Leg strength in peripheral arterial disease: associations with disease severity and lower-extremity performance. J Vasc Surg 2004;39: 523-30.

24. Gerdle B, Hedberg B, Angquist KA, Fugl-Meyer AR. Isokinetic strength and endurance in peripheral arterial insufficiency with intermittent claudication. Scand J Rehabil Med 1986;18: 9-15.

25. Scott-Okafor HR, Silver KK, Parker J, Almy-Albert T, Gardner AW. Lower extremity strength deficits in peripheral arterial occlusive disease patients with intermittent claudication. Angiology 2001;52:7-14.

26. Biodex Medical Systems, Inc. Biodex user manual Pro 4.0. Shirley, NY: Biodex Medical Systems; 2013.

27. Ha DM, Carpenter LC, Koutakis P, Swanson SA, Zhu Z, Hanna M, et al. Transforming growth factor-b1 produced by vascular smooth muscle cells predicts fibrosis in the gastrocnemius of patients with peripheral artery disease. J Transl Med 2016;14:1.

28. Weiss DJ, Casale GP, Koutakis P, Aikaterini NA, Swanson SA, Zhu Z, et al. Oxidative damage and myofiber degeneration in the gastrocnemius of patients with peripheral arterial disease. J Transl Med 2013;11:1.

29. Ugalde V, Wineinger MA, Kappagoda CT, Kilmer DD, Pevec WC, Rosen WS, et al. Sensory axonopathy in mild to moderate peripheral arterial disease. Am J Phys Med Rehabil 1998;77:59-68.

30. Weber F, Ziegler A. Axonal neuropathy in chronic peripheral arterial occlusive disease. Muscle Nerve 2002;26:471-6.

31. England JD, Regensteiner JG, Ringel SP, Carry MR, Hiatt WR. Muscle denervation in peripheral arterial disease. Neurology 1992;42:994-9.

32. Landin D, Thompson M, Reid M. Knee and ankle joint angles influence the plantarflexion torque of the gastrocnemius. J Clin Med Res 2015;7:602.

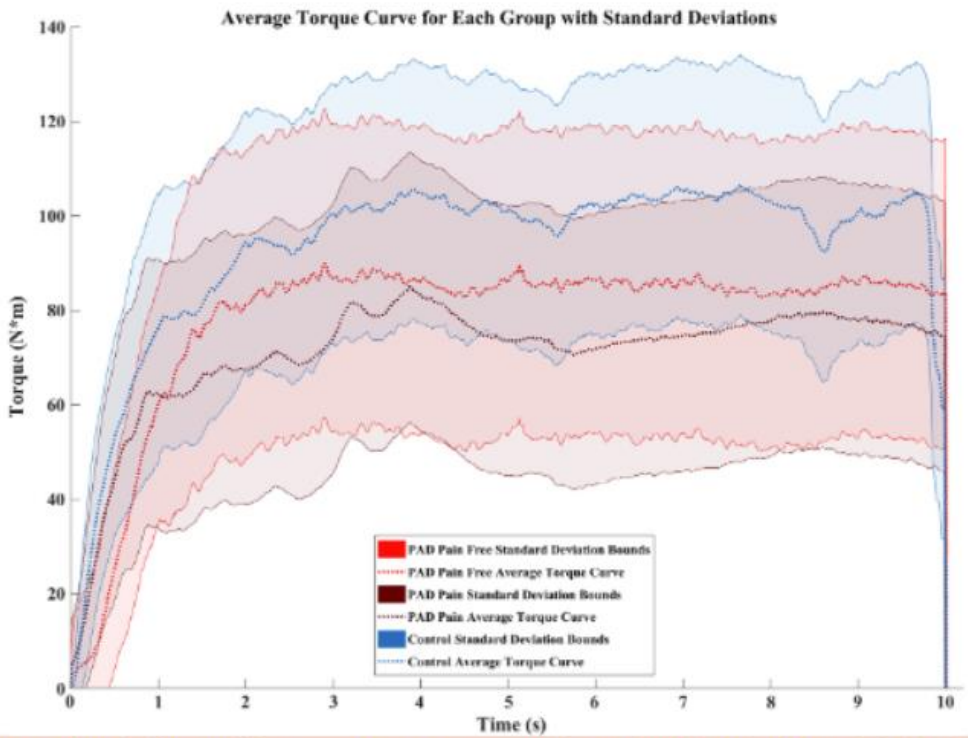
33. Pethick J, Winter SL, Burnley M. Fatigue reduces the complexity of knee extensor torque fluctuations during maximal and submaximal intermittent isometric contractions in man. J Physiol 2015;593(Pt 8):2085-96.

34. Pipinos II, Shepard AD, Anagnostopoulos PV, Katsamouris A, Boska MD. Phosphorus 31 nuclear magnetic resonance spectroscopy suggests a mitochondrial defect in claudicating skeletal muscle. J Vasc Surg 2000; 31: 944-52.

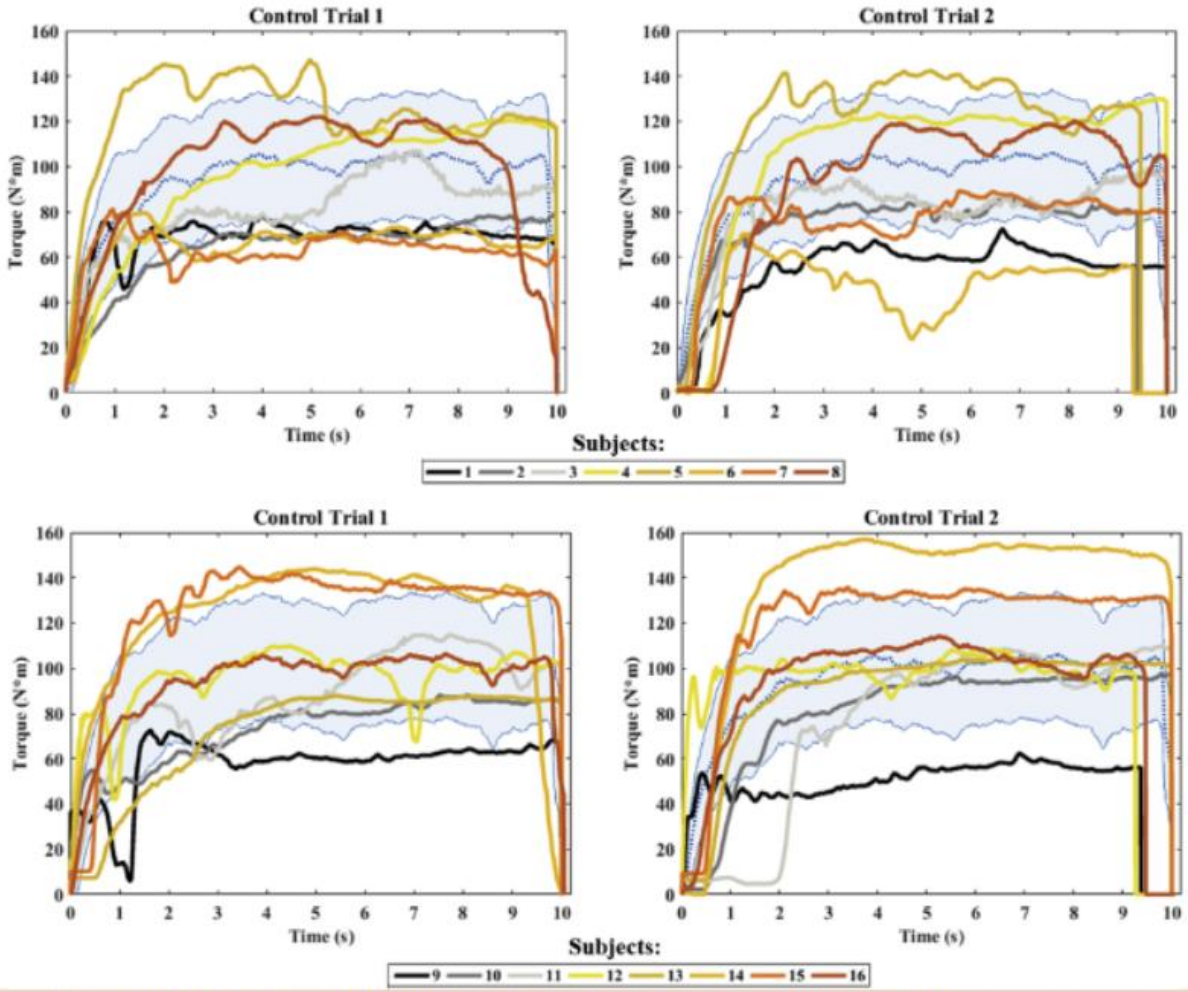
35. Judge AR, Dodd SL. Xanthine oxidase and activated neutrophils cause oxidative damage to skeletal muscle after contractile claudication. Am J Physiol Heart Circ Physiol 2004;286:H252-6.

36. Winter DA. Biomechanics and motor control of human movement. New York: John Wiley & Sons; 2009.

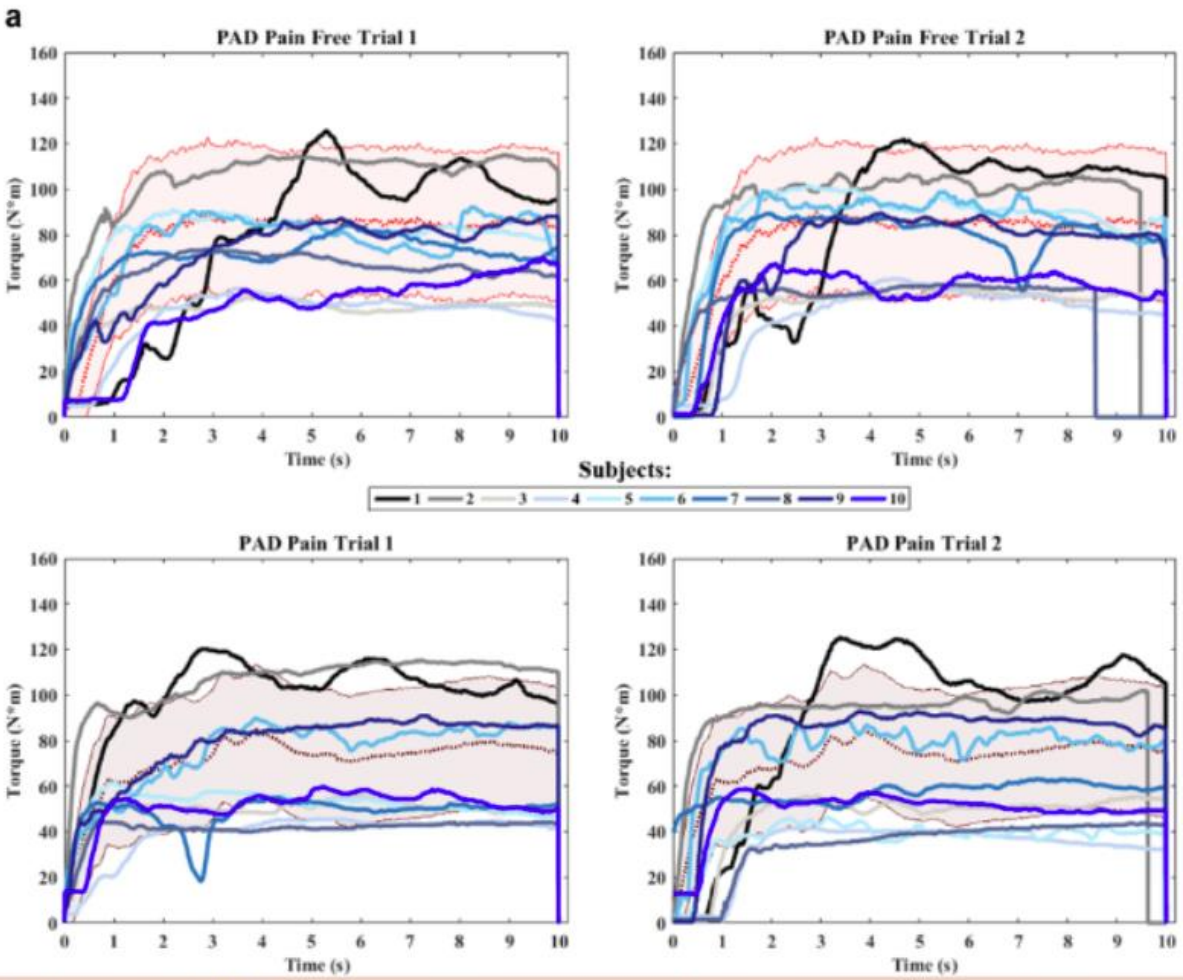
Additional material for this article may be found online at www.jvascsurg.org



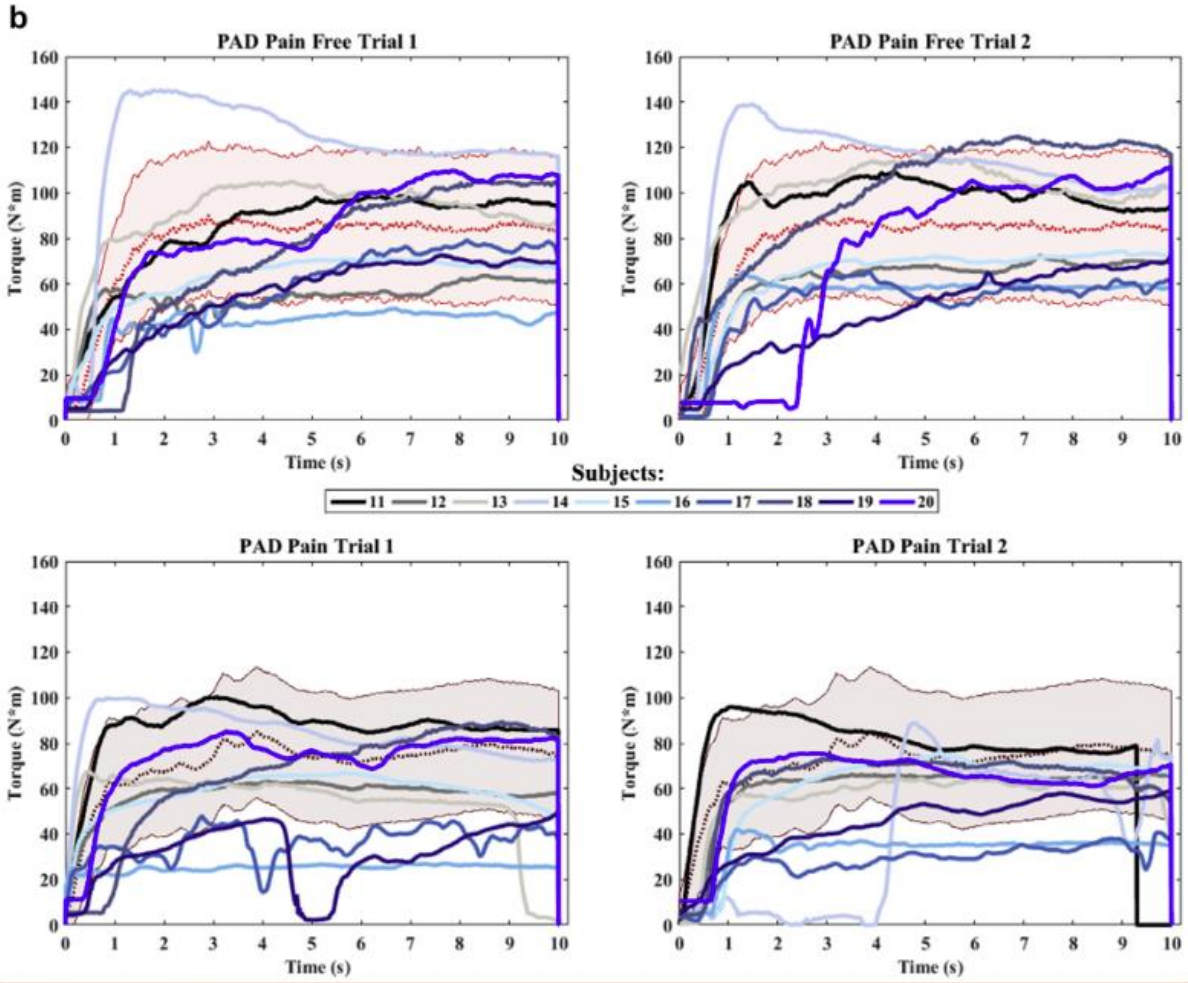
Supplementary Fig 1 (online only). Average torque curves with standard deviation bounds for both groups and conditions. *PAD*, Peripheral artery disease.



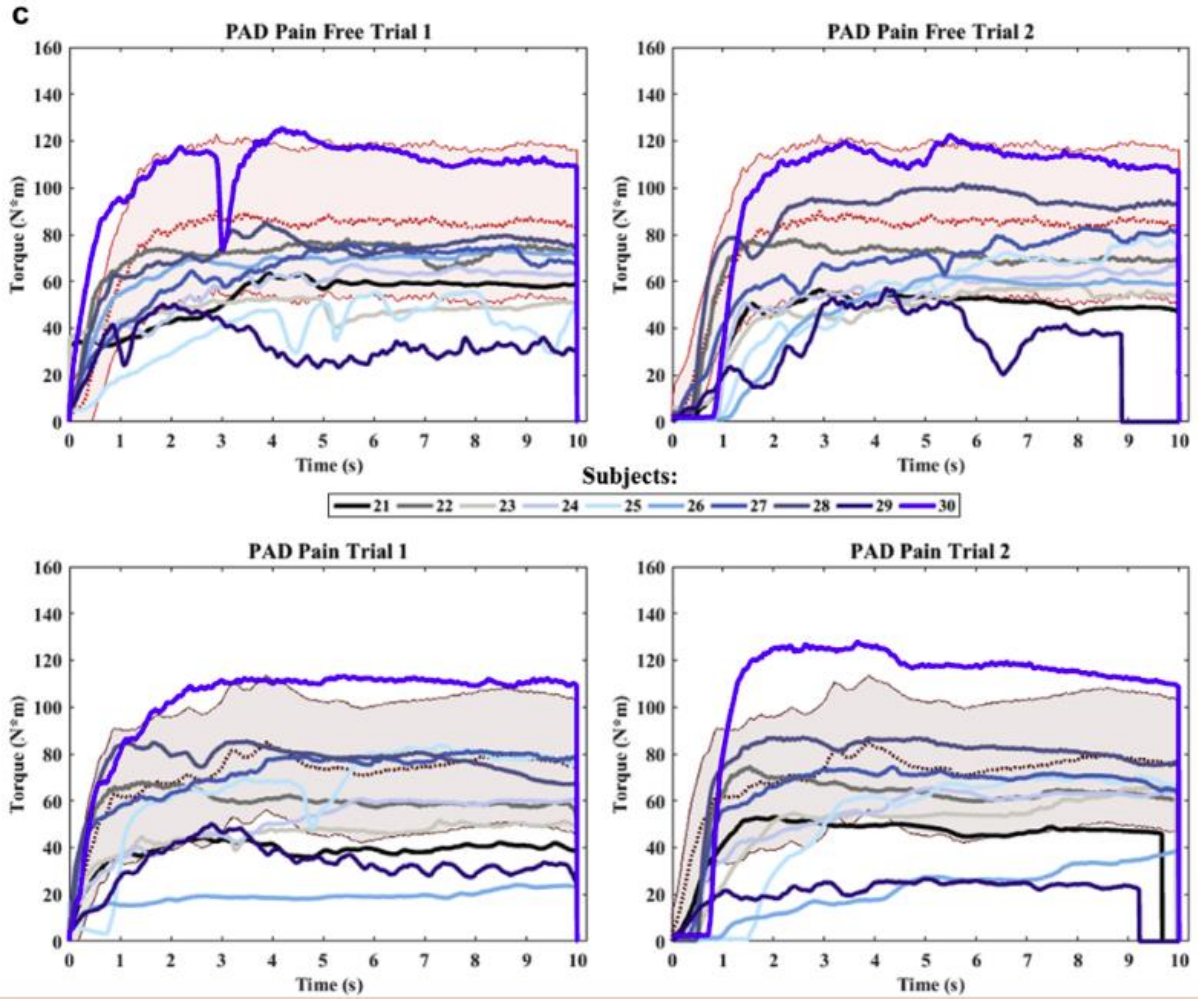
Supplementary Fig 2 (online only). Individual torque curves for control subjects 1 to 16.



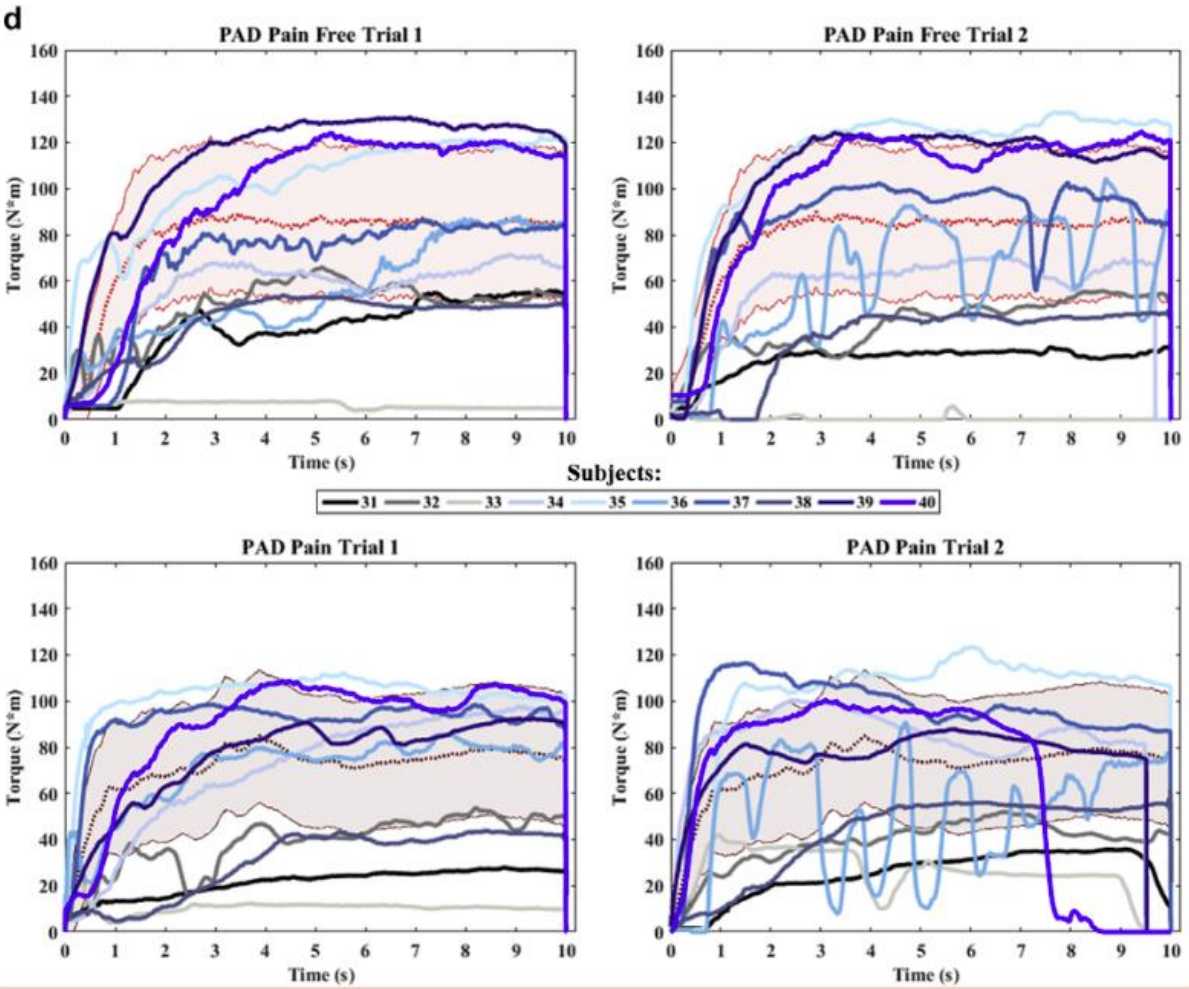
Supplementary Fig 3 (online only). Individual torque curves of all peripheral artery disease (*PAD*) subjects in each trial and in pain-free and pain conditions: **(a)** subjects 1 to 10; **(b)** subjects 11 to 20; **(c)** subjects 21 to 30; **(d)** subjects 31 to 40; **(e)** subjects 41 to 50; **(f)** subjects 51 to 60; **(g)** subjects 61 to 70; **(h)** subjects 71 to 80; **(i)** subjects 81 to 90; and **(j)** subjects 91 to 94.



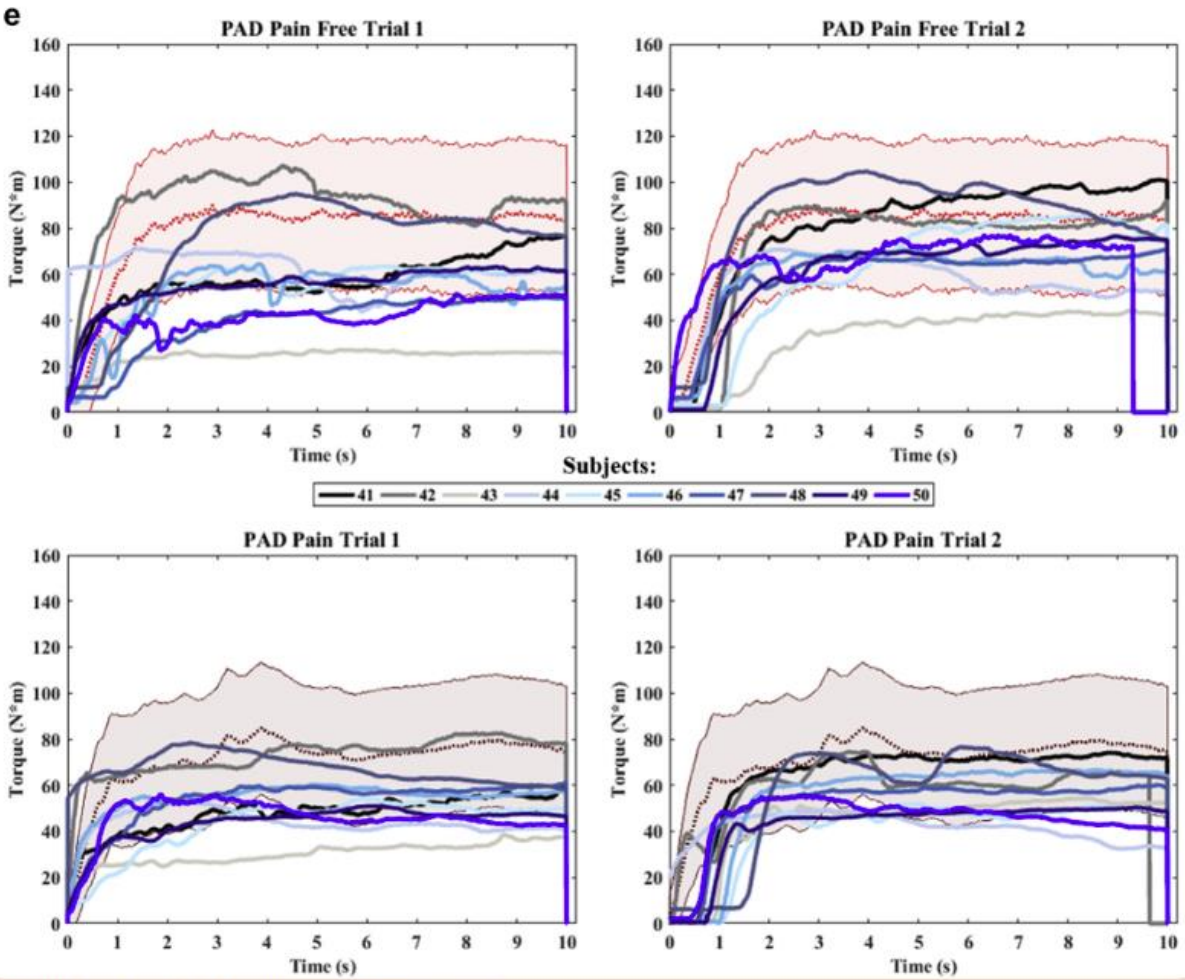
Supplementary Fig 3 (online only). Continued.



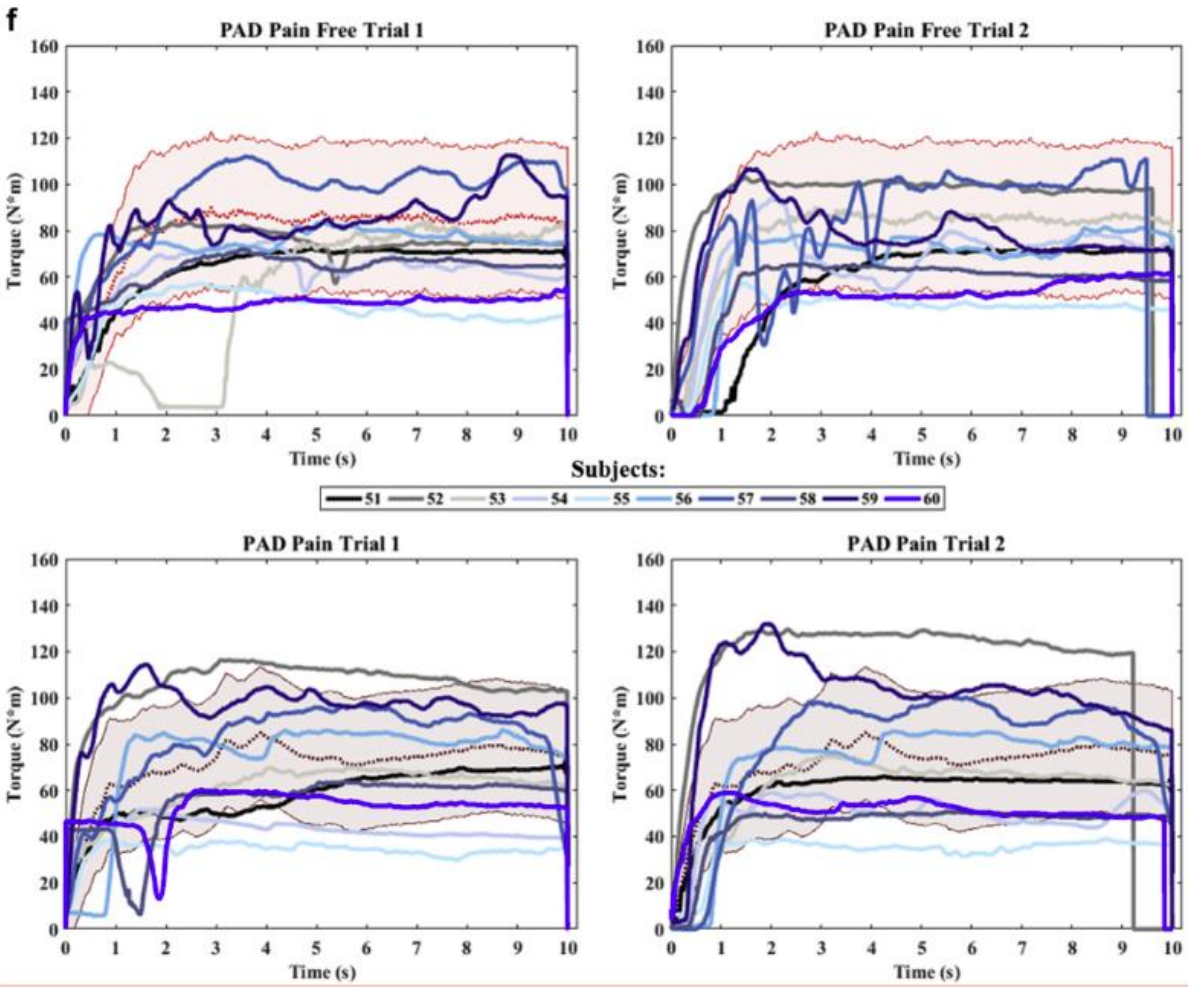
Supplementary Fig 3 (online only). Continued.



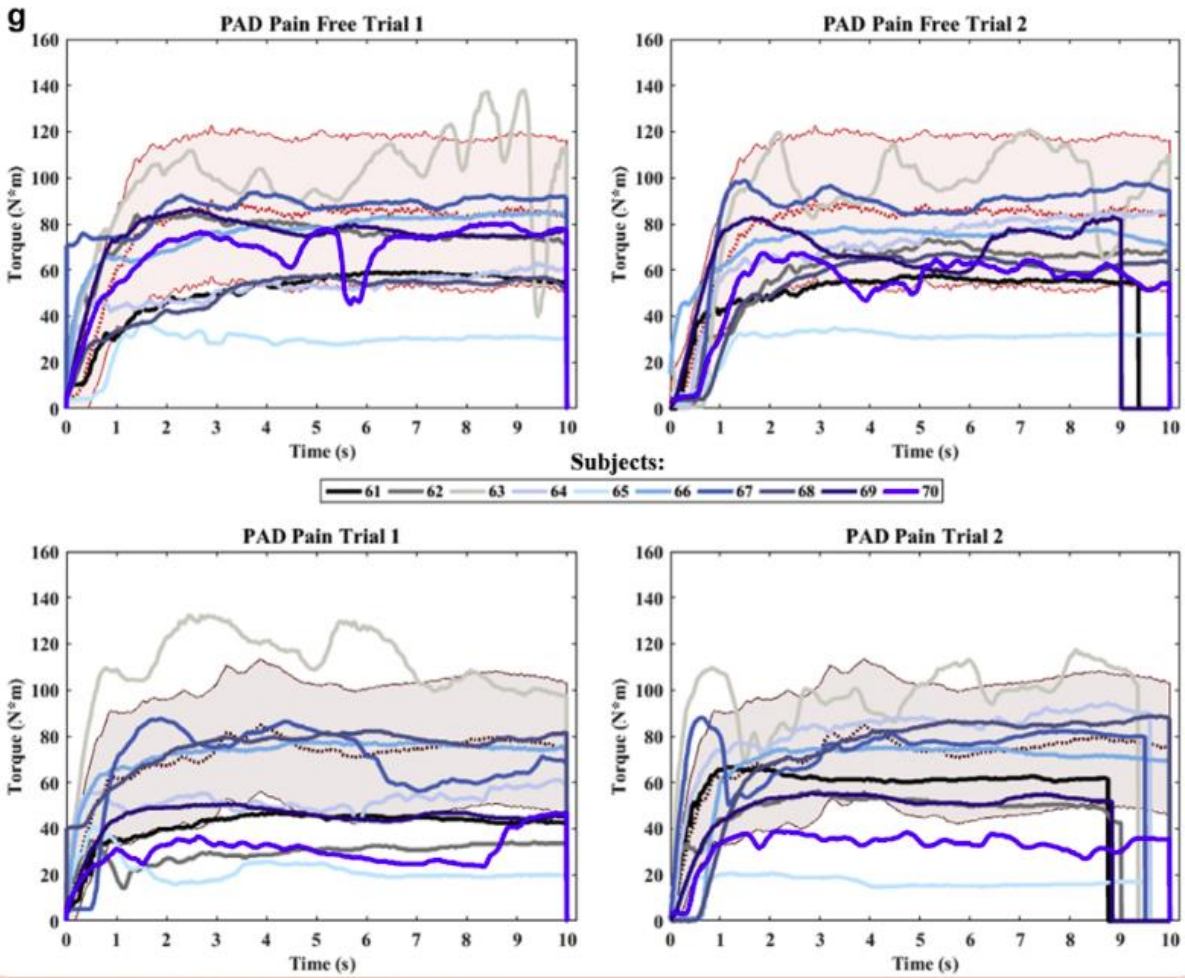
Supplementary Fig 3 (online only). Continued.



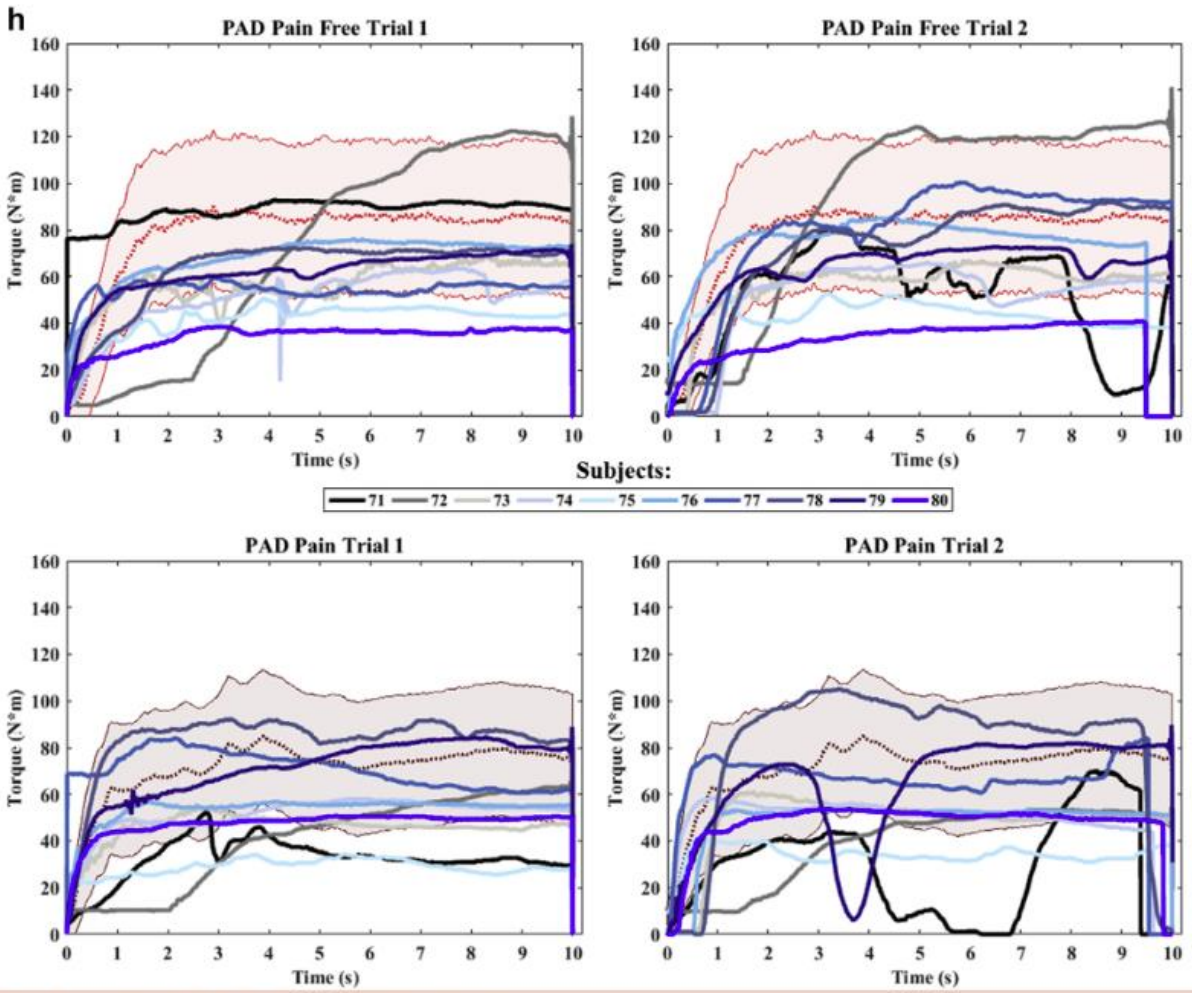
Supplementary Fig 3 (online only). Continued.



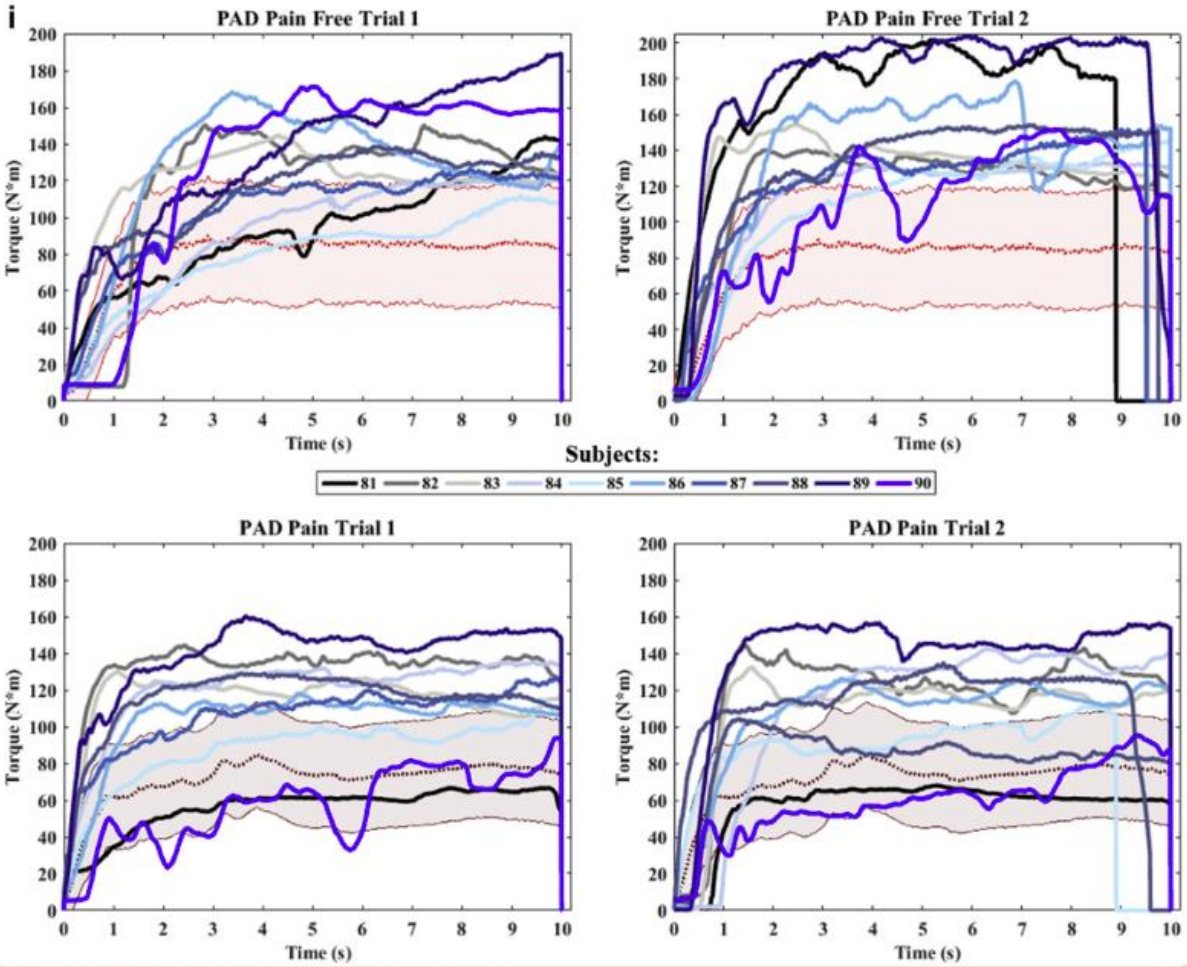
Supplementary Fig 3 (online only). Continued.



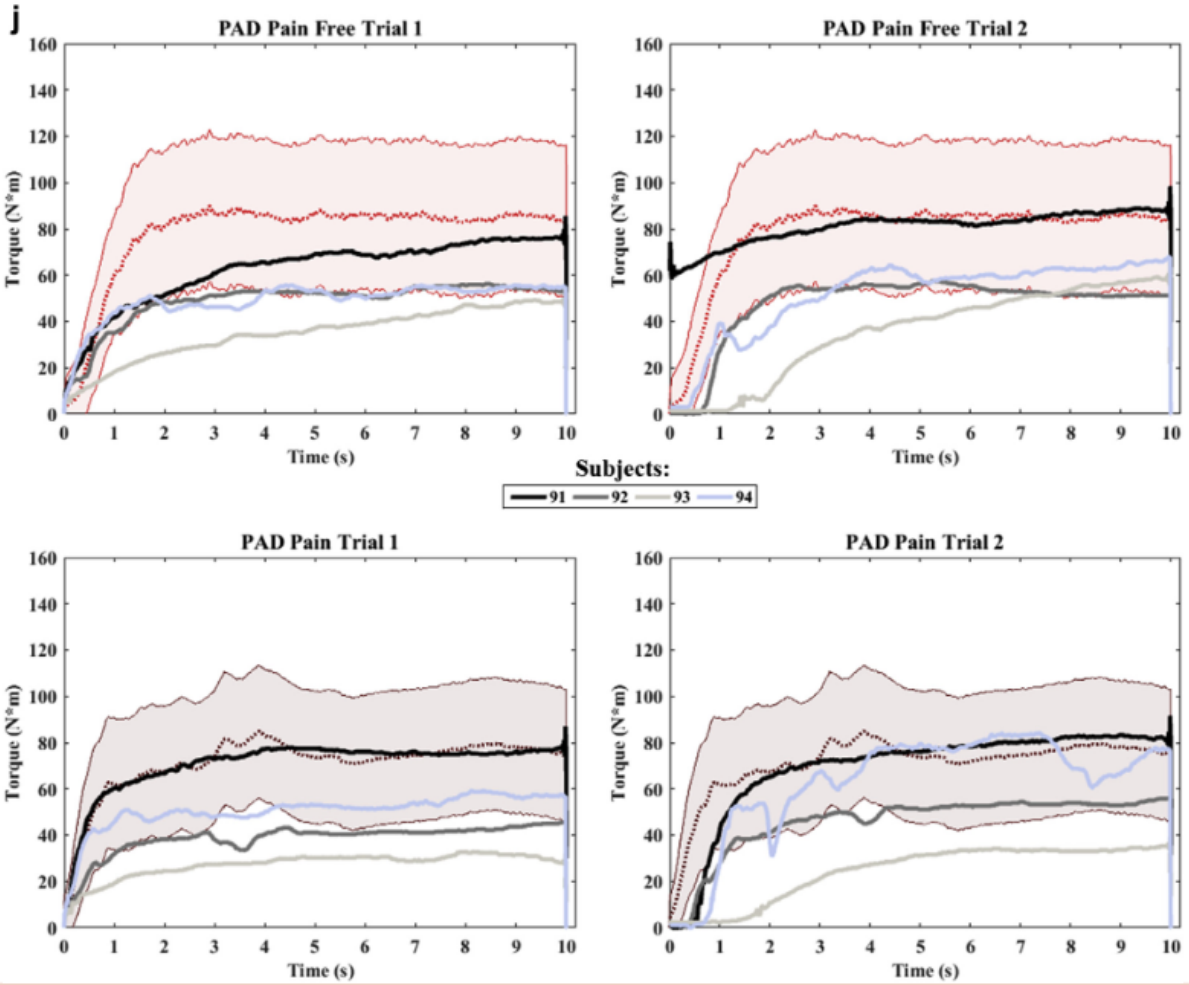
Supplementary Fig 3 (online only). Continued.



Supplementary Fig 3 (online only). Continued.



Supplementary Fig 3 (online only). Continued.



Supplementary Fig 3 (online only). Continued.