Neural Excitability Alterations After Anterior Cruciate Ligament Reconstruction

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Context: Neuromuscular dysfunction is common after anterior cruciate ligament reconstruction (ACL-R). However, little is known about quadriceps spinal-reflex and descending corticomotor excitability after ACL-R. Understanding the effects of ACL-R on spinal-reflex and corticomotor excitability will help elucidate the origins of neuromuscular dysfunction.

Objective: To determine whether spinal-reflex excitability and corticomotor excitability differed between the injured and uninjured limbs of patients with unilateral ACL-R and between these limbs and the matched limbs of healthy participants.

Design: Case-control study.

Setting: Laboratory.

Patients or Other Participants: A total of 28 patients with unilateral ACL-R (9 men, 19 women; age = 21.28 ± 3.79 years, height = 170.95 ± 10.04 cm, mass = 73.18 ± 18.02 kg, time after surgery = 48.10 ± 36.17 months) and 29 participants serving as healthy controls (9 men, 20 women; age = 21.55 ± 2.70 years, height = 170.59 ± 8.93 cm, mass = 71.89 ± 12.70 kg) volunteered.

Main Outcome Measure(s): Active motor thresholds (AMTs) were collected from the vastus medialis (VM) using transcranial magnetic stimulation. We evaluated VM spinal reflexes using the Hoffmann reflex normalized to maximal muscle responses (H : M ratio). Voluntary quadriceps activation was measured with the superimposed-burst technique and calculated using the central activation ratio (CAR). We also evaluated whether ACL-R patients with high or low voluntary activation had different outcomes.

Results: The AMT was higher in the injured than in the uninjured limb in the ACL-R group ($t_{27} = 3.32$, $P = .003$) and in the matched limb of the control group ($t_{55} = 2.05$, $P = .04$). The H : M ratio was bilaterally higher in the ACL-R than the control group ($F_{1,55} = 5.17$, $P = .03$). The quadriceps CAR was bilaterally lower in the ACL-R compared with the control group ($F_{1,55} = 10.5$, $P = .002$). The ACL-R group with low voluntary activation (CAR < 0.95) had higher AMT than the control group ($P = .02$), whereas the ACL-R group with high voluntary activation (CAR ≥ 0.95) demonstrated higher H : M ratios than the control group ($P = .05$).

Conclusions: The higher VM AMT in the injured limbs of ACL-R patients suggested that corticomotor deficits were present after surgery. Higher bilateral H : M ratios in ACL-R patients may be a strategy to reflexively increase excitability to maintain voluntary activation.

Key Words: knee, quadriceps muscles, voluntary activation, transcranial magnetic stimulation

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Key Points
- Active motor thresholds (AMTs) were higher in the injured limbs of patients with anterior cruciate ligament reconstruction (ACL-R) than in the uninjured limb and in the matched limb of the control participants.
- Quadriceps spinal reflexes were greater in both limbs of the ACL-R patients than in the control participants.
- Patients with ACL-R and quadriceps-activation failure in the injured limb had higher AMTs than control participants did.
- Patients with ACL-R who maintained voluntary quadriceps activation greater than 0.95 demonstrated corticomotor excitability that was similar to and spinal-reflex excitability that was greater than those measures in the control participants.
- Researchers need to determine whether therapeutic strategies that increase spinal-reflex excitability and decrease AMT in ACL-R patients with voluntary-activation deficits will improve voluntary activation in these patients.

Anterior cruciate ligament (ACL) ruptures occur in approximately 250 000 Americans per year,[1] resulting in knee instability and loss of function.[2] Surgical ACL reconstruction (ACL-R) and therapeutic rehabilitation are often pursued to stabilize the knee and improve physical performance. Unfortunately, many patients demonstrate persistent neuromuscular alterations for years after ACL-R.[3–5] Models have detected a shift in knee-joint loading patterns after ACL-R, which may be consistent with atypical cartilage loading and thinning.[6]

Researchers[7,8] have proposed that compromised lower extremity neuromuscular function after acute knee injury contributes to aberrant knee biomechanics or a stiffened knee strategy that may impair energy attenuation at the knee and increase the risk of developing posttraumatic osteoarthritis.

Specifically, quadriceps-activation failure has been reported in ACL-deficient (ACL-D) limbs and in patients who have undergone ACL-R.[5] The central activation ratio (CAR)[9] measures voluntary activation and provides a gross estimation of the number of motor units that can be recruited and the extent to which those motor units can maximize firing frequency.[10] A CAR of less than 95% during a maximal open chain knee extension is defined as *quadriceps-activation failure*.[11,12] Persistent quadriceps-activation failure may limit the strength gains that can be elicited with traditional therapeutic exercise. The ability to regain quadriceps strength is critical for optimizing clinical outcomes after ACL-R. Specifically, quadriceps strength predicts 61% of the variance in self-reported disability after ACL-R,[13] which reflects the importance of developing therapeutic methods that can improve voluntary quadriceps activation and strength after ACL-R.

Researchers[14–18] have begun to develop new methods to improve voluntary activation, yet the best way to target neuromuscular deficits after ACL-R remains unclear. Muscle contraction can be initiated through the excitation of spinal-reflex pathways or descending corticomotor tracts.[19,20] Determining whether these influential neural pathways (reflexive pathways and corticomotor tracts) function differently in ACL-R patients is critical for developing interventions and therapeutic techniques that can best improve rehabilitation outcomes. The quadriceps Hoffmann reflex (H-reflex) is a measure of spinal-reflex excitability. The H-reflex, which is modulated by both presynaptic and postsynaptic central nervous system inhibitory mechanisms, provides an estimate of the percentage of the motor-neuron pool that can be activated reflexively.[21] Corticomotor motor thresholds, which can be measured while the muscle is resting or during a submaximal muscle contraction, estimate the excitability of intracortical synapses in the primary motor cortex and descending interneuronal relays of the spinal cord.[22]

Experimental knee effusion in healthy participants demonstrated inhibition of spinal-reflex–excitability pathways,[21,23] which resulted in impaired gait and landing mechanics.[24,25] Previous knee-effusion studies have been useful in developing the evidence base behind theoretical models that have touted the involvement of spinal-reflex inhibition in the pathogenesis of voluntary-activation failure and clinical muscle weakness after ACL-R.[26] Whereas Rosenthal et al[27] reported that spinal-reflex excitability increased in the first 3 months after ACL-R, investigations that compared spinal–reflex-quadriceps excitability in ACL-R patients and healthy control participants have been limited. Heroux and Tremblay[28] reported that corticomotor excitability was altered in ACL-D patients, but research exploring how the corticomotor-excitability tracts are affected in ACL-R patients is lacking. Inadequate excitation of descending corticomotor tracts may negatively affect voluntary activation, which could limit muscle-strength development. Understanding how both spinal-reflex and corticomotor pathways are affected in ACL-R patients compared with healthy control participants will improve our understanding of the mechanism that may be important for identifying therapeutic targets and intervention strategies to improve voluntary activation and muscle strength after ACL-R.

Although voluntary-activation failure has been reported after ACL-R,[4,29] some data have indicated that a proportion of ACL-R patients regain normal voluntary quadriceps activation after ACL-R.[3,30] We do not know whether spinal-reflex excitability or corticomotor excitability are affected differently in ACL-R patients who demonstrate voluntary quadriceps-activation failure than in those who reestablish or maintain voluntary activation equal to or greater than 95%.[12] Lepley et al[31] recently reported that voluntary quadriceps activation and spinal-reflex excitability predicted 47% of the variance in quadriceps strength in ACL-R patients. Evaluating how spinal-reflex– and corticomotor-excitability pathways are affected in ACL-R patients with and without voluntary-activation deficits may provide critical information about how to best maintain voluntary quadriceps activation after ACL-R. Understanding how spinal-reflex excitability and corticomotor excitability differ in ACL-R patients who maintain high voluntary quadriceps activation may provide specific targets for improving the efficacy of therapeutic interventions for patients who cannot regain normal activation after ACL-R. Therefore, the primary purpose of our study was to determine whether spinal-reflex excitability and corticomotor excitability differed between the injured and uninjured limbs of patients with ACL-R and between those limbs and the matched limbs of healthy control participants. Second, we explored whether spinal-reflex excitability and corticomotor excitability differed among ACL-R patients who demonstrated acceptable levels of voluntary quadriceps activation (CAR $\geq$ 0.95), ACL-R patients who exhibited voluntary quadriceps activation failure (CAR $<$ 0.95), and healthy control participants. Third, we explored the role that ACL graft type may play in these neuromuscular outcome measures after ACL-R.

METHODS

A case-control design was used to evaluate the differences between limbs (injured, uninjured) and between groups (ACL-R, control). The outcome measures (ie, spinal-reflex excitability, corticomotor excitability, and voluntary activation) were evaluated in all participants. Volunteers were excluded from the study if we could not elicit spinal-reflex–excitability or active motor threshold (AMT) corticomotor-excitability measurements. The matched injured limb in the control group was assigned according to the limb dominance of the injured limb of an ACL-R counterpart. Therefore, if the dominant limb of an ACL-R participant was injured, the dominant limb of a matched control participant was designated as the "injured match." *Limb dominance* was identified as the limb with which the participant was more comfortable kicking a ball.[32] All outcomes were measured in a single 2-hour data-collection session. The order in which injured and uninjured limbs were tested and the order of spinal-reflex– and corticomotor-excitability testing were randomized; voluntary activation was always performed last so that the spinal-reflex and corticomotor outcome measures were

Table 1. Demographics and Bilateral Evaluation of Neuromuscular Outcome

Variable	Anterior Cruciate Ligament Reconstruction	Control
	Group	
Participants, n(%)	28(68)	29(69)
	Mean ± SD	
Anterior cruciate ligament-injured limb, % left	21 ± 75	Not applicable
Age, y	21.28 ± 3.79	21.55 ± 2.70
Height, cm	170.95 ± 10.04	170.59 ± 8.93
Mass, kg	73.18 ± 18.02	71.89 ± 12.70
Time since surgery, mo	48.10 ± 36.17	Not applicable
Tegner Activity Scale score (range, 0–10)	5.92 ± 2.03	6.00 ± 1.39
International Knee Documentation Committee score (range, 0–100)	84.12 ± 9.70[a]	99.60 ± 1.00
Injured quadriceps maximal voluntary isometric contraction, Nm/kg of body weight	2.68 ± 0.78[b]	3.13 ± 1.07
Bilateral evaluation of neuromuscular outcomes		
Injured central activation ratio	0.88 ± 0.12[c]	0.96 ± 0.03
Uninjured central activation ratio	0.88 ± 0.12[c]	0.95 ± 0.05
Injured active motor threshold	45.14 ± 15.22[d,e]	37.50 ± 12.70
Uninjured active motor threshold	38.35 ± 14.39	37.03 ± 10.69
Injured Hoffmann reflex-to-muscle response ratio	0.27 ± 0.12[f]	0.19 ± 0.10
Uninjured Hoffmann reflex-to-muscle response ratio	0.28 ± 0.16[f]	0.20 ± 0.15

[a] Indicates different from control group ($P < .001$).
[b] Indicates trend toward difference compared with control group ($P = .07$).
[c] Indicates lower than control group ($P = .02$).
[d] Indicates greater than the uninjured limb of the anterior cruciate ligament reconstruction group ($P = .003$).
[e] Indicates greater than the control group ($P = .04$).
[f] Indicates greater than the control group ($P = .02$).

not affected by the voluntary-activation testing.[33] Sample size was estimated using pooled grand volitional activation means from ACL-R patients (89.3%) and healthy matched controls (95.6%) published in a systematic review.[14] Volitional activation was used to power the study because it has been the most commonly published measure of neuromuscular function in ACL-R patients.[14] We used a within-group variability of 5%, which is the typical voluntary-activation variability in healthy participants within our laboratory (Table 1). We estimated needing 10 ACL-R and 10 healthy patients to detect a voluntary-activation mean difference of 6.3 using an α level of .05 and power of 80%. We oversampled to account for differences in variability for the main outcome measures of voluntary activation, spinal-reflex excitability, and corticomotor excitability (AMT) between limbs and between groups and to allow us to analyze differences in the main outcome measures between secondary subgroups (high and low voluntary activation and graft types).

Participants

A total of 62 people recruited from the university community volunteered for the study. We could not elicit H-reflexes in 4 healthy control participants and 1 ACL-R participant, who were excluded from the study. Twenty-eight participants with a history of unilateral ACL-R and 29 healthy individuals serving as controls participated (Table 1). Exclusion criteria were a neurologic or muscular disorder; history of cranial surgery, migraine, seizure, or concussion in the 6 months before the study; prescription of medications that may alter neural excitability (stimulants, antidepressants); or pregnancy. Exclusion criteria for the ACL-R participants were a history of knee surgery other than ACL-R, multiple ligament ruptures, or any other lower

extremity musculoskeletal injury in the 6 months before the study. All ACL-R participants were cleared by an orthopaedic surgeon for full involvement in all activities without any restrictions. Healthy participants did not have previous knee injuries or lower extremity orthopaedic surgery. All participants were instructed not to consume caffeine on the day they were tested. They completed an International Knee Documentation Committee (IKDC) form and a Tegner Activity Scale questionnaire (Table 1) in a quiet room where an investigator (A.S.L.) was present to explain the forms and answer questions if necessary. The IKDC form is a valid and reliable tool for evaluating self-reported function after knee injury.[34] The Tegner Activity Scale, which has demonstrated acceptable reliability in assessing the level of physical activity in ACL-injured patients,[35] was used to represent the level of activity at the time of testing for each participant. All ACL-R participants reported the date of surgery and the type of graft that was used for reconstruction. All participants provided written informed consent, and the institutional review board at the University of Toledo approved the study.

Instrumentation

Torque signal was collected on a Biodex System III dynamometer (Biodex Medical Systems, Shirley, NY) with a 16-bit, 1.25-MS/s analog-to-digital conversion board (model USB-6251; National Instruments, Austin, TX) and displayed to participants on a 55-cm LCD monitor. During spinal-reflex and corticomotor data collection, analog-to-digital electromyography (EMG) signal conversion was processed with a 16-bit converter (model MP150; BIOPAC Systems Inc, Goleta, CA). Acqknowledge software (version 4.2.0; BIOPAC Systems Inc) interfaced with a 200-V maximum-stimulus isolation adaptor (STMISOC; BIOPAC

Systems Inc) was used to visualize the signals and to manipulate the stimulus used for reflex testing. The EMG signals were sampled at 2000 Hz with amplification set at a gain of 1000 (model EMG100C; BIOPAC Systems Inc). A square-wave stimulator (model S88 telefactor; Grass Technologies, Warwick, RI) and a stimulus isolation unit (model SIU8T; Grass Technologies) were used for voluntary-activation testing, and a magnetic stimulator unit (Magstim Rapid[2]; Magstim Co, Wales, UK) with a double-cone coil was used to stimulate the motor cortex for corticomotor-excitability testing.[13]

Corticomotor Excitability

Participants were seated in the dynamometer with the knee and hip joints positioned at 90° and 85° of flexion, respectively. Bilateral shoulder and lap restraints were used to secure participants in the dynamometer to limit excess movement.[36] In addition, the distal shank of the test limb was secured into the dynamometer arm using a hook-and-loop strap. Two 10-mm pregelled silver/silver chloride EMG electrodes (BIOPAC Systems Inc) were positioned 1.75 mm apart over the muscle belly of the vastus medialis. A Lycra (Invista, Wilmington, DE) swim cap was placed on the participant's head, and the optimal stimulating position was determined using published methods and was marked on the swim caps.[37] The coil was then secured using a flexible camera mount (Manfrotto Co, Cassola, Italy). Participants were provided visual torque feedback and instructed to maintain a contraction at 5% of their maximal voluntary isometric contraction (MVIC) while transcranial magnetic stimulation (TMS) was applied.[13,38] *Active motor threshold*, defined as the lowest TMS intensity required to evoke a measureable motor-evoked potential (≥ 100 µV) in 5 of 10 trials, was collected for each participant.[39] The AMT is reported as a percentage of maximal magnetic stimulator output (2 T).

Spinal-Reflex Excitability

We instructed participants to lie supine on a padded plinth and used the same EMG electrode configuration as for corticomotor testing of the vastus medialis. A 2-mm shielded disc-stimulating electrode (model EL254S; BIO-PAC Systems Inc) was positioned over the femoral nerve, and a 5-cm, round, self-adhesive dispersive electrode (Dura-Stick II; Chattanooga Group Inc, Hixson TN) was placed over the hamstrings. Peak-to-peak H-reflex amplitudes were determined by increasing the stimulus intensity in increments of 2 V until peak-to-peak H-reflex amplitudes plateaued. Three maximal H-reflexes were recorded, averaged, and normalized to 3 maximal muscle-response (M-response) amplitudes (H : M ratio). Maximal M-responses were determined after identifying the H-reflex by continuing to increase the stimulus until the peak-to-peak amplitude of the M-response plateaued.

Voluntary Activation

Participants were positioned in the dynamometer as described for corticomotor excitability testing. Voluntary quadriceps activation was assessed using the superimposed-burst (SIB) technique and quantified using the CAR.[10] Two 7 × 13-cm, self-adhesive electrodes (Dura-Stick II) were positioned on the distal rectus femoris and proximal rectus femoris, which is the electrode configuration that has been reported to exogenously excite the most muscle with our stimulation procedures.[40] A square-wave stimulator and a stimulation isolation unit with a 100-millisecond train of 10 stimuli at 100 pulses per second, pulse duration of 0.6 milliseconds, and 0.01-millisecond pulse delay were used for voluntary-activation testing.[16] Norte et al[41] demonstrated acceptable reliability with this measure (intraclass correlation coefficient = 0.85).

Stimulation of the participants was automated using a custom computer software program (Visual Basic Editor; Microsoft Corp, Redmond, WA).[42] After a graded warm-up (25%, 50%, and 75% of perceived MVIC),[16,32,40] preliminary MVIC trials were performed at least 60 seconds apart until participants were unable to exceed the torque production from the previous trial. A torque-based triggering system was used to optimize the precision of the timing in which the SIB was applied to the quadriceps during the MVIC.[42] The mean torque value of the last 2 practice trials was used as a threshold that each participant had to exceed before an electrical stimulus would be triggered automatically. We encouraged participants to exert an effort at which torque production would reach a blue line that was displayed on the LCD screen at 10% above the threshold value or the previously recorded MVIC. They were provided visual feedback of real-time torque production. The automated trigger delivered the SIB when torque production exceeded the threshold value and subsequently dropped by 1 Nm.[42] The use of the automated-trigger program ensured that the participant had reached a maximal-force production that was equivalent to that in previously recorded MVIC trials (threshold value) and was not continuing to increase force (1-Nm drop) before SIB application (Figure). In addition to the visual feedback, we provided strong oral encouragement to participants.

Data Analysis

Before CAR analysis, torque data was low-pass filtered at 150 Hz using a second-order Butterworth filter. Torque samples were extracted from immediately before the application of the SIB and at the point of peak torque after SIB; CAR was then calculated as in the Figure.

An investigator (A.S.L.) recorded the percentage of 2 T from the magnetic stimulator as AMT.[43,44] Similarly, 3 peak-to-peak H-reflexes and M-responses were extracted using Acqknowledge software. The H-reflex and M-response waveforms were averaged separately. Averaged maximal H-reflexes were normalized to averaged maximal M-responses and reported as H : M ratios.[45]

Statistical Analysis

We used independent-samples t tests to evaluate differences in demographics between the ACL-R and control groups. Separate 2 × 2 analyses of variance (ANOVAs) with repeated measures on limb were calculated to determine differences between limbs in the entire ACL-R group and the control group for all outcome measures. Independent-samples t tests and paired-samples t tests[46] were performed to determine differences between groups and between limbs in the presence of an interaction,

$$CAR = \left(\frac{MVIC}{MVIC + SIB} \right) \times 100$$
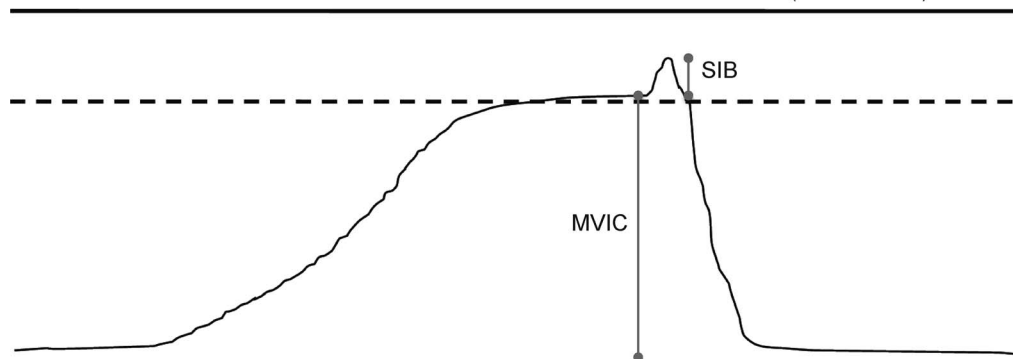
Figure. Voluntary-activation measurement (central activation ratio [CAR]). The dashed line represents the threshold or the maximal voluntary isometric contraction (MVIC) produced during the last of the preliminary trials when investigators were confident that participants were producing an MVIC. The solid horizontal line represents 110% of the average MVIC, which was used to encourage maximal effort during testing. During testing trials, participants were instructed to produce enough force to reach the solid horizontal line, which the participants did not know was greater than their force-generation capacity. The automatic triggering system was armed when torque output reached the dashed threshold line. If the participant's torque dropped by 1 Nm after the torque output exceeded the threshold, the automated stimulus was delivered to the quadriceps muscle. The need to drop by 1 Nm after exceeding threshold allowed for participants to continue increasing torque output after exceeding the threshold, thereby not triggering a stimulus until torque was no longer increasing even after the predicted MVIC (threshold) had been reached. If the participant was unable to reach the threshold during the trial, the stimulus was not delivered, and more rest was provided between trials. The MVIC values and superimposed-burst (SIB) torque values were used to calculate CAR, as seen by the equation. Two trials in which the stimulus was triggered successfully were performed on each limb, with at least 60 seconds of rest between trials. The trial with the greater MVIC was used for analysis.

respectively. For our exploratory analyses, we used a voluntary activation cutoff of 0.95, which was 95% of complete voluntary activation,[11,12] to separate the ACL-R group into low voluntary-activation (LVA) and high voluntary-activation (HVA) subgroups. Separate 1-way ANOVAs were conducted to analyze ACL-R subgroups and the control group's "injured" limb for all outcome measures. We calculated Tukey multiple comparisons to analyze groups if we found a difference with the 1-way ANOVA. Separate independent-samples t tests were performed to further analyze the effect of graft type on all outcome measures. The α level was set a priori at .05 for all analyses, which were performed using SPSS (version 19.0; IBM Corporation, Armonk, NY). Standardized effect sizes with corresponding 95% confidence intervals (CIs) were conducted to determine the magnitude of mean differences between graft types and LVA and HVA subgroups. Mean differences were standardized to pooled standard deviations from the compared means ([mean 1 − mean 2] / pooled standard deviations), with negative effects indicated by lower scores in the first mean than in the second. The strength of the effect was interpreted as published[47] (*small* = 0 to 0.29, *weak* = 0.3 to 0.49, *moderate* = 0.5 to 0.79, *strong* ≥ 0.8).

RESULTS

We observed no demographic differences between groups except for the IKDC score, which was lower in the ACL-R group than in the control group ($P < .001$; Table 1).

Spinal-Reflex Excitability

Spinal-reflex excitability was bilaterally higher in the ACL-R group than in the control group ($F_{1,55} = 5.17, P = .03$). We observed no effect for limb ($F_{1,55} = 0.52, P = .47$)

and no group-by-limb interaction ($F_{1,55} = 0.012, P = .91$; Table 1).

Corticomotor Excitability

We noted a group-by-limb interaction for quadriceps AMT ($F_{1,55} = 7.55, P = .008$). Quadriceps AMT was greater in the injured than in the uninjured limb of the ACL-R group ($t_{27} = 3.32, P = .003$; Table 1). The AMT in the injured limb was higher in the ACL-R than in the control group ($t_{55} = 2.05, P = .04$), whereas no difference existed in AMT between groups for the uninjured limb ($t_{55} = 0.4, P = .70$; Table 1). No difference was observed in AMT between limbs in the control group ($t_{28} = 0.44, P = .66$).

Voluntary Activation

Quadriceps CAR was bilaterally lower in the entire ACL-R group than in the control group ($F_{1,55} = 10.5, P = .002$; Table 1). We observed no effect for limb ($F_{1,55} = 0.004, P = .95$) and no limb-by-group interaction ($F_{1,55} = 0.787, P = .38$; Table 1).

Low and High Voluntary-Activation Analyses

No demographic differences were noted between voluntary-activation subgroups and the control group except for MVIC ($F_{2,54} = 3.04, P = .05$), such that MVICs were lower in the LVA subgroup than in the control group ($P = .05$; Table 2). Both LVA and HVA subgroups demonstrated lower IKDC scores than the control group ($P < .001$), yet no difference existed in the IKDC score between the HVA and LVA subgroups ($P = .84$; Table 2). The LVA subgroup had a lower level of voluntary activation than the HVA subgroup ($P < .001$) and the control group ($P < .001$), whereas no difference was observed in voluntary activation between the HVA subgroup and the control group ($P = .89$). The LVA subgroup displayed a higher AMT than the control group (P

Table 2. Anterior Cruciate Ligament Reconstruction and Quadriceps-Activation Failure, Injured Limb

Variable	Anterior Cruciate Ligament Reconstruction Subgroup		Control Group	Group Comparison, Effect Size (95% Confidence Interval)		
	Low Voluntary Activation	High Voluntary Activation		Low Voluntary Activation Versus High Voluntary Activation Subgroup	Low Voluntary Activation Subgroup Versus Control Group	High Voluntary Activation Subgroup Versus Control Group
Participants, n(%)	18 (64)	10 (34)	29 (69)	Not applicable	Not applicable	Not applicable
	Mean ± SD					
Age, y	21.47 ± 4.30	21.00 ± 2.80	21.55 ± 2.70	0.12 (−0.66, 0.89)	−0.02 (−0.61, 0.56)	−0.20 (−0.92, 0.52)
Height, cm	170.32 ± 11.05	173.29 ± 6.70	170.59 ± 8.92	−0.30 (−1.07, 0.48)	0.00 (−0.59, 0.59)	0.00 (−0.72, 0.72)
Mass, kg	72.00 ± 16.87	75.00 ± 20.39	71.89 ± 12.70	−0.17 (−0.93, 0.61)	0.01 (−0.58, 0.60)	0.21 (−0.52, 0.92)
Tegner Activity Scale score (range, 0–10)	6.17 ± 2.15	5.54 ± 1.86	6.00 ± 1.38	0.31 (−0.48, 1.07)	0.10 (−0.49, 0.69)	−0.30 (−1.02, 0.42)
International Knee Documentation Committee score (range, 0–100)	83.53 ± 9.70[b]	85.03 ± 10.14[b]	99.60 ± 1.06	−0.15 (−0.92, 0.63)	−2.67[d] (−3.42, −1.83)	−2.87[d] (−3.76, −1.86)
Maximal voluntary isometric contraction	2.45 ± 0.80[b]	3.03 ± 0.61	3.13 ± 1.07	−0.78 (−1.56, 0.04)	−0.70 (−1.29, −0.08)	−0.10 (−0.82, 0.62)
Central activation ratio	0.81 ± 0.12[a,c]	0.97 ± 0.02	0.96 ± 0.03	−1.64[d] (−2.47, −0.71)	−1.94[d] (−2.61, −1.20)	0.36 (−0.37, 1.07)
Active motor threshold, %	49.47 ± 16.99[b]	38.45 ± 9.10	37.50 ± 12.70	0.75 (−0.07, 1.52)	0.83[d] (0.20, 1.46)	0.08 (−0.64, 0.80)
Hoffmann reflex-to-muscle response ratio	0.25 ± 0.13	0.30 ± 0.18[b]	0.19 ± 0.10	−0.34 (−1.10, 0.45)	0.75 (0.13, 1.34)	1.23[d] (0.44, 1.98)

[a] Indicates different from the control group ($P < .001$).
[b] Indicates different from the control group ($P \leq .05$).
[c] Indicates different from the anterior cruciate ligament reconstruction high voluntary activation subgroup ($P < .001$).
[d] Indicates strong effect size.

$= .02$); no difference was seen between the LVA and HVA subgroups ($P = .10$) or between the HVA subgroup and the control group ($P = .98$). The HVA subgroup had a higher H : M ratio than the control group ($P = .05$), yet no difference in spinal-reflex excitability was evident between the LVA and HVA subgroups ($P = .53$) or the LVA subgroup and the control group ($P = .35$; Table 2). Strong effect sizes with conclusive 95% CIs that did not cross zero were found between (1) the LVA and HVA subgroups for CAR (Cohen d $= −1.64$); (2) the LVA subgroup and the control group for IKDC score (Cohen d $= −2.67$), CAR (Cohen d $= −1.94$), and AMT (Cohen d $= 0.83$); and (3) the HVA subgroup and the control group for IKDC (Cohen d $= −2.87$) and H : M ratio (Cohen d $= 1.23$; Table 2).

Graft-Type Analysis

Fourteen ACL-R participants received hamstrings-autograft reconstructions; 12, patellar-tendon–autograft reconstructions; and 2, allograft reconstructions with cadaveric tissue. Given the small cohort of participants with cadaveric allografts, we evaluated only the differences between participants who received hamstrings- and patellar-tendon autografts. We observed no differences in demographics or main outcome measures between the injured limbs of ACL-R patients with patellar-tendon or hamstrings-tendon autografts ($P > .05$; Table 3). No strong effect sizes were noted between graft types (Table 3).

DISCUSSION

We demonstrated both spinal-reflex– and corticomotor-excitability alterations in ACL-R patients compared with healthy control participants. The ACL-R group had lower IKDC scores than the healthy control group, indicating a reduced level of self-reported function. Conversely, Tegner Activity Scale scores were not different between the ACL-R and control groups (Table 1), suggesting that the level of physical activity for each participant did not influence differences in neuromuscular outcomes (spinal-reflex excitability, corticomotor excitability, and voluntary activation). The scores averaged between 5.92 and 6.0 at the time of testing, suggesting that individuals were participating in recreational or competitive sports with substantial self-reported functional (IKDC score), voluntary activation (CAR), and corticomotor-excitability (AMT) deficits. We do not know how ACL-R participants would have fared for self-reported activity level, IKDC score, voluntary-activity and corticomotor excitability at the time of ACL injury; therefore, we cannot determine whether the differences observed in measures of voluntary activation and corticomotor excitability restricted the ACL-R patients from returning to higher levels of activity. We also do not know whether participating in recreational or competitive sports with substantial deficits in voluntary activation and corticomotor excitability is detrimental to the long-term health of the knee with ACL-R.

The entire ACL-R group demonstrated bilateral voluntary quadriceps-activation deficits compared with the healthy matched control group. The bilateral voluntary-activation deficits that we noted corroborated the findings of Urbach et al,[29] who reported bilateral voluntary-activation deficits after unilateral ACL injury. These bilateral differences in voluntary activation have been hypothesized to be an effect

Table 3.   Graft Type and Outcome Measures for Injured Limb

Variable	Patellar-Tendon Graft	Hamstrings-Tendon Graft	Patellar Versus Hamstrings Tendon, Effect Size (95% Confidence Interval)
Participants, n (%)	12 (66)	14 (64)	Not applicable
	Mean ± SD		
Age, y	22.75 ± 4.84	20.28 ± 2.55	0.65 (−0.16, 1.42)
Height, cm	171.34 ± 10.71	172.17 ± 9.56	−0.08 (−0.85, 0.69)
Mass, kg	71.59 ± 18.96	76.78 ± 17.70	−0.28 (−1.05, 0.50)
Time after surgery, mo	61.66 ± 42.19	39.60 ± 28.90	0.62 (−0.19, 1.39)
Tegner Activity Scale score (range, 0–10)	5.50 ± 2.23	6.14 ± 1.83	−0.32 (−1.08, 0.47)
International Knee Documentation Committee score (range, 0–100)	83.91 ± 10.35	83.57 ± 9.92	0.03 (−0.74, 0.80)
Central activation ratio	0.89 ± 0.13	0.88 ± 0.10	0.09 (−0.69, 0.86)
Active motor threshold, %	43.58 ± 16.53	49.00 ± 13.57	−0.36 (−1.13, 0.43)
Hoffmann reflex-to-muscle response ratio	0.32 ± 0.17	0.23 ± 0.13	0.60 (−0.20, 1.37)

of complex neural adaptations from spinal-reflex– and corticomotor-excitability pathways.[29] In addition, graft type did not affect spinal-reflex excitability, corticomotor excitability, or voluntary activation of the quadriceps. Anterior cruciate ligament reconstruction uses various grafting procedures to surgically reestablish ligamentous stability of the knee. Grafts are often harvested from the reconstructed limb; the middle third of the patellar tendon, which attaches the quadriceps to the tibia, is commonly used. Patients who undergo ACL-R with patellar-tendon autografts are at higher risk of developing osteoarthritis later in life.[48] We hypothesize that harvesting a musculo-tendinous component of the quadriceps for ACL-R grafting may adversely affect spinal-reflex excitability, corticomotor excitability, and voluntary activation more than harvesting hamstrings tendon for the grafts. Our results do not seem to corroborate the hypothesis that harvesting the patellar tendon increases neuromuscular deficits in the quadriceps compared with hamstrings grafts. We noted no differences between ACL-R patellar-tendon–graft and hamstrings-tendon–graft subgroup means for CAR, AMT, or H-reflex and observed an inconclusive (95% CI crossed zero) moderate effect size, indicating higher quadriceps spinal-reflex excitability in the patellar-tendon–graft group. After reviewing 19 trials, Mohtadi et al[49] concluded that, whereas the quadriceps tended to be weaker in patients after ACL-R with a patellar-tendon graft than in patients with a hamstrings-tendon graft, no difference in knee-extensor strength was demonstrated between graft types. Future studies are needed, but the higher rates of knee osteoarthritis after reconstructions with patellar-tendon grafts[48] may be associated with biochemical alterations after the specific procedure rather than solely neuromuscular contributions from donor-site morbidity.

We found that spinal-reflex excitability of the quadriceps was higher in the entire ACL-R group than in the control group. Increased reflexive excitability in ACL-R patients was unexpected because researchers[21,23] have demonstrated reductions in spinal-reflex excitability after acute experimental joint effusions. Altered quadriceps spinal-reflex excitability can be modulated through both GABAergic presynaptic or Renshaw–cell-related postsynaptic inhibitory mechanisms.[21] Heroux and Tremblay[28] reported a trend for quadriceps H-reflexes to be lower in the involved limbs of ACL-D patients than in healthy participants. Conversely, Rosenthal et al[27] noted increased spinal-reflex excitability of the quadriceps at

1 and 3 months after ACL-R compared with preoperative measures. Spinal-reflex alterations may have differed in our participants but not in participants with acute artificial effusions for multiple reasons. Knee-effusion models are often criticized for neglecting the contributions that inflammation and tissue injury may have on spinal-reflex excitability. In addition, our ACL-R participants were, on average, 48.1 months postreconstruction, whereas researchers[21,23,50] using simulated effusion models evaluated spinal reflex-excitability immediately after simulated acute injury. Neural adaptations after disruption of joint homeostasis possibly are dynamic; therefore, acute adaptations to effusion may differ greatly compared with neuromuscular adaptions found around a joint that was injured years earlier. The higher spinal reflexes in the ACL-R patients than in the control participants may have been a neuromuscular strategy to maintain lower extremity muscle function and a desired level of physical activity. The HVA subgroup demonstrated greater spinal-reflex excitability than the control group did, suggesting that increasing spinal-reflex excitability above control levels may be a compensatory strategy for maintaining HVA after ACL-R. The LVA subgroup had greater but not different spinal-reflex excitability, which demonstrated conclusive moderate effect sizes compared with the control group (Table 2). Increasing spinal-reflex excitability to a currently unknown amount may be important for maintaining the ability to voluntarily activate the quadriceps musculature above 95%. Whereas the LVA subgroup demonstrated greater but not different spinal-reflex excitability than the control group, the increase in spinal-reflex excitability possibly did not reach a critical threshold that would allow voluntary activation to increase. In future research, investigators should determine the long-term consequences of increasing spinal-reflex excitability and whether modulating spinal reflexes will lead to increases in the voluntary activation of ACL-R patients with LVA. They should also determine the increase in voluntary activation that is both safe and necessary to maintain HVA after ACL-R.

Active motor threshold is a relatively gross measure of corticomotor excitability that provides an estimate of the excitability of individual intracortical synapses and descending spinal interneuronal relays.[22,51] The relative excitability of the neuronal membranes and the density of neurons (ie, the number of neurons in a specific area of the motor cortex, which project to the peripheral muscle of interest) are the 2 major contributors to AMT.[52] Higher AMTs, which require a

greater stimulus to the motor cortex to elicit a motor response in the muscle, are interpreted as an indicator of less corticomotor excitability.[22] We evaluated corticomotor excitability during muscular contraction (5% of MVIC), which differs from resting measures previously performed in ACL-D patients.[28] Heroux and Tremblay[28] demonstrated that resting motor thresholds were lower in the involved limb than in the injured limb of ACL-D patients. They suggested that the decrease in resting motor threshold may have been caused by deafferentation after ACL rupture, which had a tendency to excite the motor cortex after reductions in GABAergic inhibition.[28] Conversely, we found that ACL-R patients demonstrated increased AMTs in the injured limb compared with the uninjured limb and with healthy matched controls (Table 2). The ACL-R participants who had HVA and could maintain voluntary quadriceps activation greater than 0.95 exhibited AMTs that were very similar to the AMTs of control participants, whereas the LVA subgroup with voluntary-activation failure demonstrated higher AMTs than control participants. Maintaining lower AMTs may be important in maintaining higher voluntary activation after ACL-R (Table 3).

Treating quadriceps-activation failure has become a focus of joint-injury management for both acute and chronic pathologic knee conditions. Therapeutic exercise performed in conjunction with modalities aimed at altering voluntary quadriceps activation has demonstrated the ability to produce increases in muscle strength (average increase of 52% in 4 weeks) compared with therapeutic exercise alone (average increase of 13% in 4 weeks).[16] No current consensus exists about whether the magnitude of voluntary-activation deficits is associated with knee-extensor strength in ACL-R patients.[30,31] Improvements in CAR accounted for approximately 47% of muscle strength gains in a 4-week strengthening intervention in patients with knee osteoarthritis and quadriceps-activation failure.[53] These data may suggest that, regardless of the baseline voluntary activation and strength values of patients with knee injuries, the ability to clinically change voluntary activation will benefit strength gains. More data are needed to determine whether ACL-R patients respond as do patients with knee osteoarthritis to similar interventions that target the neuromuscular system.

Different modalities may alter neural excitability by strategically targeting spinal-reflex– and corticomotor-excitability pathways,[26] suggesting that knowledge of pathways affected by injury could be critical information for developing effective treatments. Transcutaneous electrical nerve stimulation and focal joint cooling have been hypothesized to target spinal-reflex–inhibitory pathways,[16,54] whereas TMS[18] and biofeedback[55] may manipulate corticomotor excitability.[26] Evidence from our study suggested that ACL-R patients without quadriceps-activation failure also had lower AMTs (Table 2). Developing a therapeutic method for lowering AMTs may allow for excitation of more cortical neurons within the primary motor cortex with less presynaptic excitement from motor-association areas in the brain responsible for planning movement. Lowering AMTs in specific regions of the primary motor cortex may give ACL-R patients the ability to depolarize cortical neurons, which previously had high AMTs and, therefore, were difficult to activate. We can hypothesize that activation of more cortical neurons and the corresponding descending corticomotor tracts will generate greater voluntary activation of motor neurons that excite the quadriceps and allow for greater voluntary activation. Whereas the HVA subgroup displayed higher reflexive excitability, we are uncertain whether interventions that may increase reflexive excitability will improve voluntary activation in ACL-R patients. Transcutaneous electrical nerve stimulation and focal knee-joint cooling have been reported to increase voluntary quadriceps activation in patients with osteoarthritis and quadriceps activation failure[16,54]; yet these same modalities did not alter voluntary quadriceps activation more than therapeutic exercise alone in ACL-D patients.[56] Although the dosing of transcutaneous electrical nerve stimulation varies among studies and optimal dosing has not been determined, manipulation of spinal-reflex– and corticomotor-excitability pathways may be unique to the specific pathologic condition and patient physiology. In addition, we do not know how to most effectively intervene in an interconnected neural system to improve motor output. Individually targeting either the spinal-reflex– or corticomotor-excitability pathways with a treatment may have an indirect effect on the other. Altering the excitability of these pathways may need to be conducted incrementally; systematically monitoring interactions between changes in spinal-reflex and corticomotor excitability after therapeutic interventions may be required to make small, incremental changes in both spinal-reflex and corticomotor excitability to produce desired neuromuscular outputs, such as HVA.

We evaluated spinal-reflex and corticomotor excitability in the vastus medialis. Whereas the vastus medialis has been used commonly to assess quadriceps excitability,[23,50] it may lack generalizability to the quadriceps musculature. In future studies, researchers may evaluate musculature at the hip[57] or in the leg[58,59] to provide a more comprehensive assessment of neuromuscular function of the lower extremity after ACL-R. In addition, we used AMT to assess corticomotor excitability because this area of inquiry is novel in these patients and AMT may provide a gross evaluation of descending corticomotor excitability. The inherent physiology involved with AMT may overlap with pathways that similarly could influence spinal reflexes. We found that alterations in spinal-reflex and corticomotor excitability did not manifest in the same direction,[28] suggesting that these outcomes were the result of different pathways within the central nervous system. In future studies, investigators may evaluate different paired-pulse paradigms involved in corticomotor excitability to understand whether corticomotor alterations are due to cortical-level facilitory or inhibitory mechanisms.[60] We found that graft type did not affect excitability, but future prospective studies using more specific time points for data collection may allow for the evaluation of additional covariates that may improve our understanding of factors that influence neuromuscular alterations after ACL-R. Researchers have indicated that the use of a knee brace may alter voluntary quadriceps activation[61,62]; given that we did not allow braces to be worn during testing, we do not know whether periodic brace use during activities outside of testing may have influenced lasting alterations in neuromuscular measurements.

Kim et al[63] suggested that participant position altered spinal-reflex excitability within individuals. For our study in which we evaluated differences between limbs and groups, we assumed that excitability differences between

limbs and groups would be similar, regardless of the position or contraction state used to measure the participants. The measurement of spinal-reflex– and corticomotor-excitability outcomes is inherently difficult because accessing the proper cortical neurons and peripheral nerves using magnetic and electrical stimulation can be challenging. To maximize our ability to elicit both quadriceps spinal-reflex– and corticomotor-excitability outcomes within each participant, we measured corticomotor excitability during an active contraction in a seated position and spinal-reflex excitability during a resting state in a supine position in all participants. We limited our primary analyses and discussions to spinal-reflex– and corticomotor-excitability alterations separately to focus the study on the case-control differences. Whereas no researchers have suggested the existence of an interaction among testing position, contraction status, involved limb, and ACL-R status, caution should be taken when interpreting interactions between volitional-activation and corticomotor-excitability outcomes measured during contraction and spinal-reflex– excitability measured during rest.

CONCLUSIONS

We demonstrated higher AMTs in the injured limbs of ACL-R patients than in the uninjured limb and the matched limb of control participants. Quadriceps spinal reflexes were bilaterally higher in the entire sample of ACL-R patients than in healthy control participants. The ACL-R patients with quadriceps-activation failure (CAR < 0.95) in the injured limb had higher AMTs than the control participants. The ACL-R patients who maintained voluntary activation greater than 0.95 demonstrated corticomotor excitability similar to that in control participants and greater spinal reflexes. In further studies, researchers should determine whether developing therapeutic strategies that increase spinal-reflex excitability and decrease AMT in ACL-R patients with voluntary-activation deficits will improve voluntary activation in these patients.

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