Muscle Adaptations with Immobilization and Rehabilitation after Ankle Fracture

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ABSTRACT

STEVENS, J. E., G. A. WALTER, E. OKEREKE, M. T. SCARBOROUGH, J. L. ESTERHAI, S. Z. GEORGE, M. J. KELLEY, S. M. TILLMAN, J. D. GIBBS, M. A. ELLIOTT, T. N. FRIMEL, C. P. GIBBS, and K. VANDENBORNE. Muscle Adaptations with Immobilization and Rehabilitation after Ankle Fracture. *Med. Sci. Sports Exerc.*, Vol. 36, No. 10, pp. 1695–1701, 2004. **Introduction/Purpose**: The widespread occurrence of muscular atrophy during immobilization and its reversal presents an important challenge to rehabilitation medicine. We used 3D-magnetic resonance imaging (MRI) in patients with surgically-stabilized ankle mortise fractures to quantify changes in plantarflexor and dorsiflexor muscle size during immobilization and rehabilitation, as well as to evaluate changes in force generating capacity (specific torque). **Methods**: Twenty-individuals participated in a 10 wk rehabilitation program after 7 wk of immobilization. MRIs were acquired at baseline, 2, and 7 wk of immobilization, and at 5 and 10 wk of rehabilitation. Isometric plantarflexor muscle strength testing was performed at 0, 5, and 10 wk of rehabilitation. **Results:** Dorsiflexors and plantarflexors atrophied 18.9% and 24.4% respectively, the majority of which occurred during the first 2 wk of immobilization (dorsiflexors: 9.6%; plantarflexors: 14.1%). Likewise, more than 50% of hypertrophy during rehabilitation occurred within the first 5 wk of rehabilitation for both the dorsiflexors (12.9%) and plantarflexors (13.2%), when compared to the total amount of hypertrophy over 10 wk of rehabilitation (dorsiflexors: 17.6%, plantarflexors: 22.5%). There were no significant differences in hypertrophy or atrophy of the dorsiflexor or plantarflexor muscles, despite a rehabilitation emphasis on the plantarflexors. Patients had significantly lower plantarflexor specific torque (torque/CSA) than healthy, control subjects immediately after cast immobilization, which did not return to normal after 10 wk of rehabilitation ($P < 0.05$). **Conclusion**: Our investigation of the consequences of limb immobilization on rehabilitation outcomes in patients can be applied directly to optimizing rehabilitation programs. Although muscle hypertrophy occurred early during rehabilitation, plantarflexor muscle function (specific torque) should remain the focus of rehabilitation programs because although CSA recovered quickly, specific torque still lagged behind that of control subjects. **Key Words:** MUSCLE ATROPHY, MUSCLE HYPERTROPHY, MRI, SPECIFIC TORQUE

Fractures of the ankle mortise remain a very common, yet disabling injury of the lower extremity (1). Surgical stabilization of an ankle mortise fracture requires weeks to months of immobilization and results in substantial muscle atrophy and corresponding functional limitations (22,25). The appropriate length of immobilization following surgical stabilization varies because of differences in surgical protocols and the lack of studies investigating the impact of immobilization or recovery during rehabilitation, although the lower limit for immobilization time is dictated by healing time for bone tissue. Making informed decisions for the required duration of immobilization to minimize the degree of muscle atrophy and the appropriate length of rehabilitation to maximize recovery are difficult without longitudinal studies that document the reversibility of the muscular changes induced by disuse.

Longitudinal studies of muscle dysfunction with disuse in healthy subjects indicate the extent of the muscle atrophy is muscle specific, such that some muscles demonstrate greater rates of atrophy than others, correlated with the duration of immobilization (3,4,13,16,18), and atrophy is most pronounced during the early phases of immobilization (3,16). In a case study, we recently demonstrated that the maximal cross-sectional area (CSA) of the triceps surae muscles decrease 20–32% in patients after 8 wk of cast immobilization and the highest degree of atrophy was measured during the first 2 wk of immobilization (8.3% per week) (29). Also, Hather (13) found a greater amount of initial quadriceps muscle atrophy after 4 wk of lower extremity unloading (12%), compared to 6 wk of unloading (16%). In fact, LeBlanc (18) measured the CSA of various muscle

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groups in subjects who underwent up to 17 wk of bed rest and found that the extent and rate of muscle atrophy can be characterized by an exponential function for the hamstrings, quadriceps, dorsiflexors and plantarflexors, such that greater atrophy occurs during early periods of immobilization.

It is well established that disuse or inactivity causes significant muscle remodeling, including loss of myofibrillar proteins, changes in metabolic enzyme activities, and vascular and neural alterations (6,9). The rapid loss in myofibrillar proteins during disuse is mediated by a transient decrease in protein synthesis, followed by an increase in protein degradation, resulting in net protein loss (6,28). Interestingly, the degree of atrophy may be muscle specific, such that bed rest results in greater atrophy in lower extremity muscles compared to back muscles or upper extremity muscles (18). Less clear is whether there is a disparity in the degrees of muscle atrophy within the lower extremities. Some studies provide evidence for preferential atrophy of certain lower extremity muscles, such as the quadriceps compared to the hamstrings (13). A smaller body of evidence suggests that the plantarflexors may be more susceptible to atrophy than the dorsiflexors (17), but no such comparative evidence has been provided for a patient population following an ankle fracture. Yet, muscle-specific atrophy of lower extremity muscles may dictate an appropriate targeting of muscles during lower extremity strength training to improve the speed and extent of recovery.

Although considerable attention has focused on muscle atrophy with disuse, less attention has centered on the rate of muscle hypertrophy during rehabilitation. Increases in neuromuscular activity (e.g., during resistance training) induce an intricate repair response involving the inflammatory system, capillary morphogenesis, and myogenic progenitor cells (satellite cells) (9,14). Only a small number of longitudinal studies have actually documented the recovery of muscle function resulting from this coordinated process of muscle regeneration after either immobilization or unloading (nonweight bearing) (4,12). Data presented by Berg et al. (4), using an unloading model in healthy subjects, indicate that the recovery time in healthy subjects is approximately equal to the duration of disuse. Less consensus exists on the rate of recovery in patient populations. In an early study, Halkjaer-Kristensen and Ingemann-Hansen (12) demonstrated that patients immobilized for 4–6 wk following surgical and conservative treatment of knee ligament injuries regain between 69 and 92% of isometric and isokinetic knee extension strength with one month of rehabilitation. Tegner et al. (26) followed patients with chronic conservatively managed anterior cruciate ligament injuries and found a 10% quadriceps deficit immediately after three months of resistance training, as well as at a 2 yr follow-up. Few studies actually quantified the rate of hypertrophy following cast immobilization or measured the changes in the force generating capacity per contractile area (specific force) during recovery.

The objective of this investigation was to quantify plantarflexor muscle atrophy during cast immobilization and hypertrophy during rehabilitation and to evaluate changes in force generating capacity (torque and specific torque) in patients with surgically-stabilized ankle mortise fractures. Additionally, we compared adaptations in ankle plantarflexor muscle size to that of the dorsiflexors during immobilization and rehabilitation.

MATERIALS AND METHODS

Subjects

Twenty-individuals (9 males, 11 females) who sustained a unilateral fracture of the ankle malleolus and were treated by open reduction-internal fixation participated (16 bimalleolar; 1 lateral malleolar; 2 medial malleolar; 1 trimalleolar). All subjects were studied during 10 wk of rehabilitation and a subset of these subjects ($N = 8$) were studied during the immobilization phase of this study. Fourteen *healthy* subjects (5 male, 9 female) also participated in this study. Ages ranged from 19 to 62 yr (average = 39 ± 3) for patients and 25 to 56 yr (average = 40 ± 2) for control subjects. Following surgery, patients were immobilized with the ankle in a neutral position using a short leg cast for 6–8 weeks (depending on healing time of the fracture site), hereafter referred to as 7 wk of immobilization. Following immobilization, patients received 10 wk of physical therapy as described below. All subjects were informed of the purpose of the investigation and all provided written informed consent for study participation.

Experimental Protocol

Magnetic Resonance Imaging (MRI) and isometric muscle strength testing was performed at multiple timepoints during cast immobilization and rehabilitation. The first MRI (baseline) was acquired at the earliest opportunity following surgery, on average 3 d into immobilization (range: 1–5 d). Subsequent MRIs were acquired after 2 wk immobilization (2w-IM) and 7 wk immobilization (7w-IM), and at 5, and 10 wk of rehabilitation (5w-R and 10w-R). Isometric plantarflexor muscle strength testing was performed at 0, 5, and 10 wk of rehabilitation (0w-R, 5w-R, and 10w-R). For comparison purposes, strength testing was also performed in the uninvolved lower extremity at 10 wk of rehabilitation.

Healthy, control subjects were used to assess the reliability of the MRI and isometric strength testing measures. These subjects were not immobilized and did not undergo rehabilitation, but were tested at matching timeframes to those of the patients.

Magnetic Resonance Imaging

Three dimensional proton MRIs were obtained with a fast three-dimensional fast gradient echo imaging sequence using a 1.5-T magnet (General Electric) and standard quadriture extremity coil. The data were acquired in three series to cover the total region from the mid thigh to the calcaneus. Each series employed an encoding matrix of 256×256×28, a field of view of 16×16×19.6 cm, resulting in a slice thickness of about 7 mm. Data were acquired with 2 NEX, no phase wrap, a pulse repetition time (TR) of 51 ms, and an echo time (TE) of 10 ms. Chemically selective fat suppression optimization was used to

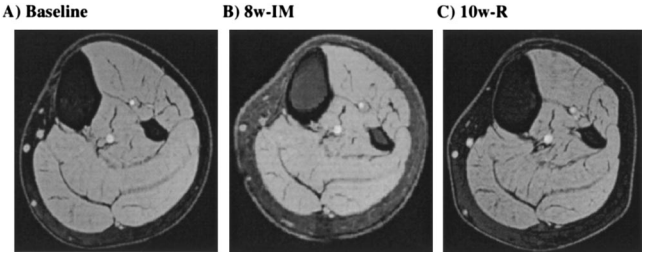

FIGURE 1—Representative ^{1}H-MRI transaxial images of the lower leg at A) baseline, B) 7 wk immobilization (7w-IM), and C) 10 wk rehabilitation (10w-R). Images were acquired using a 3D fast gradient echo imaging sequence in a 1.5-T magnet with an encoding matrix of 256×256×28, a field of view of 16×16×19.6 cm, 2 NEX, a pulse repetition time (TR) of 51 ms, and an echo time (TE) of 10 ms.

enhance the definition between muscle groups. The fat-free maximal muscle cross-sectional area (max-CSA) of the posterior and anterior compartment muscles were determined using a custom-designed interactive computer program that allows for correction of partial volume filling effects, as described previously (10). Posterior compartment muscles included in the analysis were the medial gastrocnemius, lateral gastrocnemius, and soleus muscles, which serve as important plantarflexors of the ankle. The sum of the max CSA of each individual muscle was defined as the total posterior compartment CSA, instead of choosing one slice in which the combination of posterior compartment muscle CSA was the largest. Analysis of anterior compartment muscles included the tibialis anterior, extensor digitorum longus, and the extensor hallucis longus. Because the definition between each of these muscles is less obvious than between the muscles of the posterior compartment, the max-CSA of these muscles was determined collectively, rather than as the sum of the individual max-CSA of each muscle (Fig. 1).

Isometric muscle testing

Plantarflexion peak torque was measured using a Biodex isokinetic Dynamometer. Ankle plantarflexor strength testing was performed for the involved and uninvolved legs of patients and unilaterally in the healthy subjects (right leg). Subjects were tested while seated and stabilized in the exercise chair as per the manufacturer's recommendation. The subject's hips were flexed to 90–100° and the knee was flexed 10°. The anatomical axis of the ankle was aligned with the axis of the dynamometer while the foot was secured to the foot plate with a strap placed at the forefoot and ankle. Proximal stabilization was achieved with the straps at the chest, hips, and knee. Isometric plantarflexion strength was assessed at 0° plantarflexion as measured with a standard goniometer from a neutral position (90° angle between the fibula and calcaneus). After warm-up, subjects performed three isometric contractions (5-s contractions separated by 2 min of rest). The largest plantarflexion peak torque of the three attempts was determined after calculating the gravity-corrected peak torque values.

Rehabilitation Protocol

Following 7 wk of cast immobilization, patients participated in a 10-wk rehabilitation program (3×1 h training sessions/week) that focused on both strength and endurance of the plantarflexors, as described previously (25). Although patients began physical therapy immediately after cast removal, strength and endurance training were delayed until 1 wk after reambulation (0w-R) for fear of iatrogenic injury. During this first week, patients received moist heat, joint mobilization and passive stretching.

Endurance training consisted of uphill treadmill walking using the handrail for assistance, as necessary. The intensity of the endurance program was progressively adjusted by increasing the inclination of the treadmill (0–10%), the duration of the walk (10–20 min) and the walking speed (1.5–3 mph). Strength training was based on a progressive resistance training principle with the knee extended to emphasize the use of the gastrocnemius and with the knee flexed 30° to emphasize the soleus muscle (24). Resistance was provided by a custom-built hydraulic plantarflexion machine that provided a constant resistance for plantarflexion over the entire ROM (25). Patients were seated with their hips flexed to 85°, their back supported against a fixed upright support, and their involved foot secured to a foot pedal. Resistance was provided by a hydraulic machine attached to the foot pedal (25). The subjects performed two warm-up exercise sets — 10 repetitions at 40% of 1 repetition maximum (1RM) — and three work-out sets — 8 repetitions at 80% of 1 RM — at both angles during each rehabilitation session. During the first week of strength training (0w-R), however, the work-out sets were performed at 50% of 1RM. The 1 RM was assessed on a weekly basis. Each repetition was performed slowly throughout the available ROM. Daily treatments also included joint mobilizations, passive stretching, moist hot packs, and ankle proprioceptive exercises, as considered necessary.

Reliability Assessment

In order to determine the intrasubject reliability, as well as possible training effects related to the multiple testing sessions, repeated measurements were performed in six healthy, control subjects. The measurements were performed over the same timeframes as those performed in the patients. Interclass correlation coefficients (ICC (2,1)) and coefficients of variation ($CV_{test\text{-}retest}$ = SD/mean) were calculated (23) for each CSA measurement during three MRIs over 18 wk (ICC = 0.978–0.999; $CV_{test\text{-}retest}$ = 4.5–6.4%) and three torque measurements over 10 wk (ICC = 0.933–0.964; $CV_{test\text{-}retest}$ = 3.6%).

DATA ANALYSIS

All statistical analyses were performed with SPSS for Windows, Version 11.0.1. Initially, descriptive statistics were generated for the entire sample for demographic, maximum CSA, and specific torque information. The presence of outliers or skewed distributions was assessed through scatter plots and histograms. All research hypotheses were tested at an alpha level of 0.05.

The hypotheses involving changes in CSA over time during immobilization and rehabilitation were tested using

normalized values. CSA for each compartment (anterior vs posterior) or muscle (soleus, medial and lateral gastrocnemius) was normalized to the initial CSA at the beginning of the immobilization and rehabilitation periods, respectively. Then, the hypotheses were tested with separate, repeated measures ANOVA models. For immobilization, the within-subject factor was time (baseline and 7wk-IM) and the between-group factor was compartment (anterior or posterior) or posterior compartment musculature (soleus, medial, and lateral gastrocnemius). For rehabilitation, the within-subject factor was time (7w-IM, 5w-R and 10w-R) and the between-group factor was compartment (anterior or posterior) or posterior compartment musculature (soleus, medial and lateral gastrocnemius).

Independent *t*-tests were used to compare the specific torque (torque per muscle cross sectional area) between patients at 0w-R and 10w-R with healthy controls. Improvements in specific torque of the plantarflexors over time were investigated by using a repeated measures ANOVA as an omnibus test, followed by planned comparisons between 0w-R to 5w-R, and 5w-R to 10w-R.

RESULTS

Magnetic Resonance Imaging

The majority of muscle atrophy occurred during the first 2 wk of immobilization (anterior: 9.6%; posterior: 14.1%) compared to the total anterior (18.9%) and posterior (24.4%) compartment atrophy (Fig. 2a; Table 1). A comparison between the individual plantarflexor muscles of all subjects indicated that there were no significant differences in the rates of atrophy between the soleus, medial and lateral gastrocnemius muscles during immobilization (Fig. 2a). There also was no significant difference between anterior and posterior compartment musculature atrophy during immobilization based on the lack of a significant interaction between type of compartment and amount of CSA decrease.

Muscle hypertrophy during rehabilitation followed a pattern that was similar to that seen with muscle atrophy. The majority of muscle hypertrophy occurred within the first 5 wk of rehabilitation for both the anterior (12.9%) and posterior (13.2%) compartments, when compared to the total amount of hypertrophy over 10 wk of rehabilitation (anterior: 17.6%, posterior: 22.5%) (Fig. 3a; Table 1). When comparing individual plantarflexor muscles, there were no significant differences in the rate of hypertrophy between the soleus, medial and lateral gastrocnemius (Fig. 3b), although the medial gastrocnemius appeared to hypertrophy slightly more (28.0%) than the soleus (21.3%) and lateral gastrocnemius (20.4%). There were no significant differences in hypertrophy between anterior and posterior compartments.

Specific Torque

Patients had significantly lower specific torque (torque/CSA) of the plantarflexors than healthy, control subjects immediately after cast immobilization (0w-R) (Fig. 4) ($P <$ 0.05) (95% CI of difference = 1.19–2.15, $P < 0.05$). There was a significant improvement in plantarflexion specific torque over the 10 wk of rehabilitation ($P < 0.05$). A significant improvement ($P < 0.05$) in plantarflexion specific torque was observed from 0w-R to 5w-R ($P < 0.05$), but not from 5w-R to 10w-R ($P > 0.05$). At 10w-R, significant differences in specific torque remained between control subjects and patients (95% CI of difference = 0.15–1.12, $P < 0.05$).

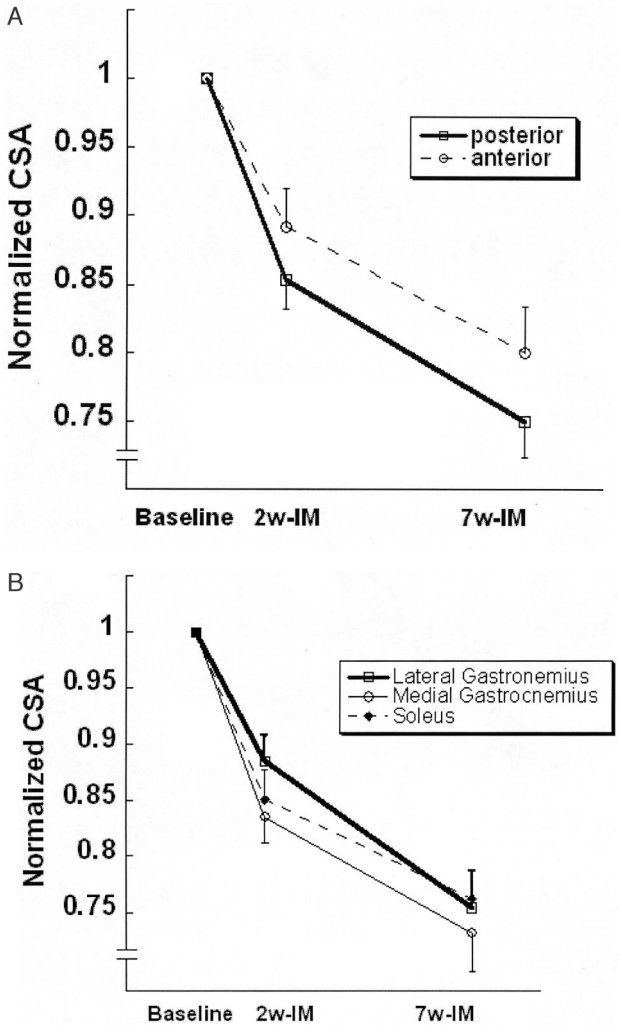

FIGURE 2— A) Normalized CSA during immobilization (CSA ± SE) ($N = 8$) anterior vs posterior compartment atrophy; B) soleus, medial, and lateral gastrocnemius muscle atrophy

DISCUSSION

Patients recovering from immobilization after surgically-stabilized malleolar fractures exhibited the greatest degree of muscle plasticity during the *initial* phases of immobilization and rehabilitation. In fact, more than 50% of muscle atrophy occurred during the first 2 wk of immobilization, and more than 50% of muscle hypertrophy occurred during the first 5 wk of rehabilitation. By the end of 10 wk of rehabilitation, anterior and posterior compartment muscle CSAs were almost completely restored to initial, baseline

TABLE 1. Cross-sectional area (cm^2) ± SE.

	(A) Immobilization (N = 8)			(B) Rehabilitation (N = 20)		
	Baseline	2w-IM	7w-IM	7w-IM	5w-R	10w-R
Lateral Gastroc	8.65 ± 0.95	7.70 ± 0.95	6.52 ± 0.77	6.07 ± 0.44	6.81 ± 0.42	7.31 ± 0.48
Medial Gastroc	12.79 ± 0.97	10.75 ± 0.99	9.42 ± 0.96	10.24 ± 0.65	11.73 ± 0.77	13.11 ± 0.91
Soleus	22.71 ± 1.48	19.47 ± 1.70	17.41 ± 1.52	17.45 ± 0.82	19.69 ± 0.90	21.16 ± 0.98
Total Posterior Compartment	44.15 ± 2.87	37.93 ± 3.14	33.35 ± 2.88	33.76 ± 1.75	38.22 ± 1.91	41.35 ± 2.23
Anterior Compartment	11.59 ± 1.0	10.47 ± 01.16	9.39 ± 1.05	9.14 ± 0.49	10.32 ± 0.49	10.74 ± 0.50

values (92.7% and 93.7%, respectively) and no differences in rates of hypertrophy were found between ankle plantarflexors and dorsiflexors, despite the greater rehabilitation emphasis on the plantarflexors (Table 1B). Interestingly, no significant differences in the rates of muscle atrophy during immobilization or hypertrophy during rehabilitation were found between the anterior and posterior compartments, although ankle plantarflexors exhibited a slightly larger drop in CSA (24.5%) than the dorsiflexors (18.9%) during immobilization, consistent with the results of other studies of disuse in healthy subjects (15,17). Within the posterior compartment, the soleus, medial and lateral gastrocnemius muscles also showed similar rates of atrophy and recovery. Specific torque measurements showed a significant reduction (59.0%) in the force generating capacity with immobilization, which improved considerably during the first 5 wk of rehabilitation, yet surprisingly, was still not restored completely by 10w-R (20% deficit).

Few studies have examined the amount of muscle hypertrophy resulting from resistance training at timepoints less than after 8 wk of strength training (27), so little quantitative evidence exits to support the assumptions of Moritani and deVries (21) that whole muscle hypertrophy after 3–5 wk of resistance training accounts for the majority of strength gains. Most assessments of cross sectional area changes with resistance training have focused on interventions lasting at least 8 wk (19), with some lasting longer than 20 wk (2). Evidence for muscle hypertrophy at earlier timepoints, such as those found in the present study, supports the hypothesis that contributions from muscle hypertrophy begin to dominate over neural factors in accounting for increases in muscle strength with resistance training lasting longer than a few weeks. Of the handful of studies that examine muscle hypertrophy within the first weeks of resistance training, the results of a study by Tesch et al. (27) also provides evidence for early muscle hypertrophy. After 5 wk of resistance training, they found that quadriceps volume increased by 6.1% in healthy men and women (ages 30–53

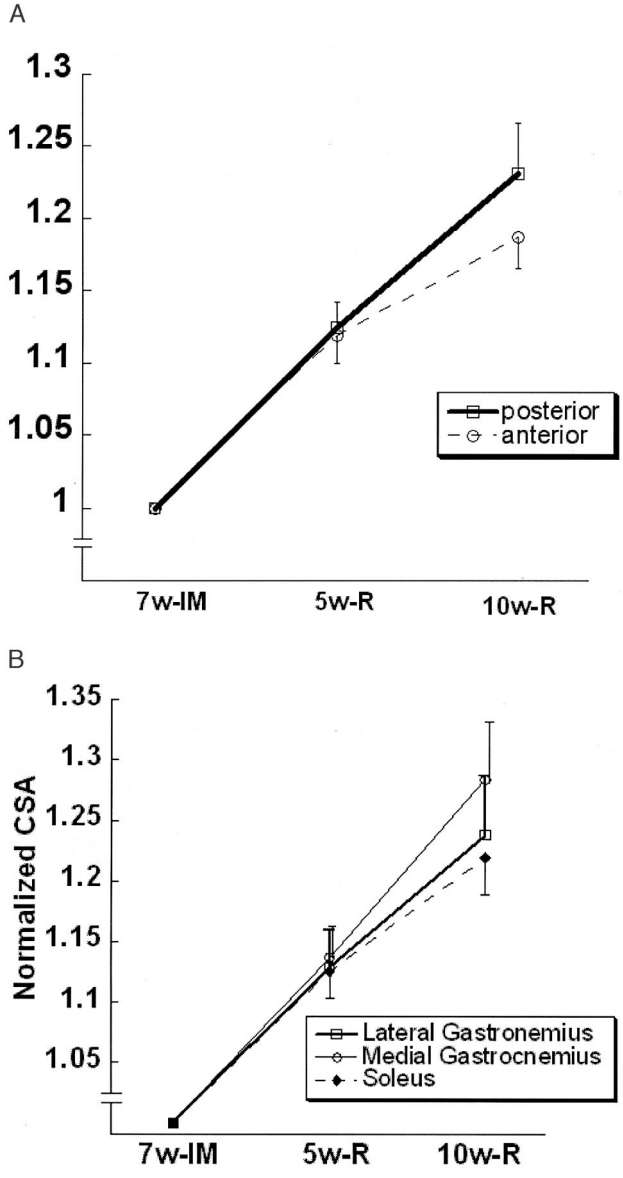

FIGURE 3—A) Normalized CSA during rehabilitation (CSA ± SE) (N = 20) anterior vs posterior compartment hypertrophy; B) soleus, medial, and lateral gastrocnemius muscle hypertrophy

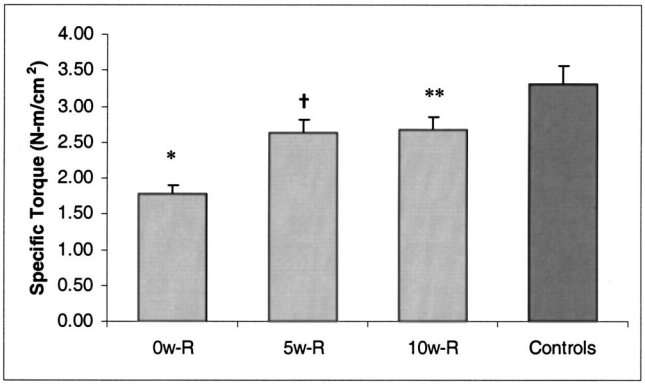

FIGURE 4—Plantarflexor specific torque ($N \cdot m \cdot cm^{-2}$ ± SE) for patients during rehabilitation (N = 20) and control subjects (N = 12). * Statistically significant difference between healthy control subjects and patients at 0w-R ($P < 0.05$).† Statistically significant improvement in specific torque between 0w-R and 5w-R ($P < 0.05$). Statistically significant difference between healthy control subjects and patients at 10w-R ($P < 0.05$).**

yr). Even greater gains were seen in the present study (12.9% to 13.2%) after 5 wk of rehabilitation most likely because this patient population had greater room for improvement than a healthy population.

Few studies have compared changes in dorsiflexor and plantarflexor muscle size with disuse or immobilization, and even fewer have compared changes across individual plantarflexor muscles. Animal studies consistently report greater atrophy of the *soleus* than the *gastrocnemius* with disuse, not only because of fiber type differences, but also because of the conjecture that mono-articular muscles atrophy to a greater degree than bi-articular muscles (5). Only a handful of human studies have investigated this issue. Berry et al. (5) found that six subjects who underwent one month of bed rest had greater soleus muscle atrophy (12.8%) than the gastrocnemius atrophy (8.5%). In contrast, Hather et al. (13) found a greater degree of atrophy of the bi-articular gastrocnemius muscle than the mono-articular soleus muscle in eight subjects who underwent 6 wk of lower limb suspension. The results of the present study also throw into question the expectation that mono-articular muscles are more susceptible to atrophy than bi-articular muscles, since there were no differences in atrophy in any of the plantarflexor muscles studied.

The relationship of muscle atrophy to the duration of immobilization is an important matter. The loss of muscle mass during cast immobilization has been shown to follow an exponential function (16). In agreement with this observation, we found that for all muscles, atrophy was greatest during the initial 2 wk of immobilization. We may have even underestimated the rate of atrophy early on, because our baseline data were acquired, an average of 3 d after initial immobilization. Although longer periods of immobilization may still compromise recovery of joint range of motion, it appears that most of the damage in terms of muscle atrophy occurs within the first weeks of immobilization.

Despite the current, muscle-specific focus on restoring plantarflexor muscle function in most rehabilitation programs, no previous studies have provided justification for a rehabilitation emphasis on the plantarflexors. Often, the current rehabilitation focus on the plantarflexors is based on the observation that patients are more functionally limited during ambulation by deficits in push-off (plantarflexor weakness), rather than deficits in toe clearance or foot slap (dorsiflexor weakness). Surprisingly, a rehabilitation program focusing on the recovery of plantarflexor muscle function resulted in comparable hypertrophy of the plantarflexors and dorsiflexors. Quite possibly, *without* the targeted strength training program for the plantarflexor muscles, patients would not have exhibited comparable anterior and posterior muscle hypertrophy. 1RM-based, high-intensity strengthening protocols have consistently resulted in significant strength gains (19). Our results support the clinical observation that an emphasis on the strength training of the posterior compartment muscles is appropriate for comparable anterior and posterior compartment muscle recovery.

As part of this study, we also set out to compare the speed and extent of recovery after 7 wk of immobilization. Our data indicate that muscle size of the anterior and posterior compartment muscles recovered almost completely to initial values after 10 wk of rehabilitation (Table 1). With respect to speed of recovery, the increase in max-CSA in the anterior and posterior compartments was approximately equal to 2.5% and 2.6% per week respectively during the first 5 wk of rehabilitation and 0.8% and 1.6% per week respectively during the final 5 wk. The rates of atrophy in the anterior and posterior compartment muscles during the first 2 wk of cast-immobilization was two- to threefold faster than the rates of hypertrophy, with values of 4.8% (anterior) and 7.1% (posterior) per week.

TABLE 2. Torque ± SE.

1w-R	5w-R	10w-R	Uninvolved Leg (10w-R)	Control Subjects
52.36 ± 5.33	89.32 ± 6.07	109.24 ± 7.62	114.97 ± 6.73	126.91 ± 10.37

Changes in plantarflexor muscle torque after immobilization were disproportionate to the change in muscle CSA, a finding that is common to many studies of muscle strength after disuse (3,15). In addition, improvements in muscle torque during rehabilitation were larger than can be explained by increases in muscle cross-sectional area alone, reinforcing the concept that the muscle's capacity to generate force per unit area changes. Based on specific torque measurements (torque/max CSA) in the plantarflexor muscles, we found that 7 wk of cast immobilization results in more than a 50% decrease in specific force. The deficits in specific torque that patients experienced improved considerably by 5w-R, although a comparison between control subjects and patients still showed a remaining 20% deficit at 10w-R. In order to affirm that the differences in specific torque between patients at 10w-R and control subjects were attributable to differences in the patients' recovery of muscle size and function, and not to patient selection, we performed an additional analysis. We did not have CSA data for the uninvolved leg of patients because of the expense associated with MRI, so we compared torque measurements for the uninvolved leg at 10w-R (114.97 ± 6.73) with that of control subjects (126.91 + 10.37), using independent *t*-tests (Table 2). We found no significant differences between the uninvolved leg at 10w-R and control subjects (95% CI of difference = −1.3 to 35.26, $P > 0.05$). Therefore, these patients appear to have initial, rapid improvements in muscle contractile capabilities during the first 5 wk of rehabilitation, but still have deficits that persist after 10 wk of rehabilitation.

Altered central nervous system drive may account for some of the strength loss not explained entirely by decreased CSA, especially, early during recovery from immobilization (7,8,29). Deschenes et al. (7) recently demonstrated that neural factors almost entirely accounted for quadriceps strength deficits after only two weeks of lower extremity unloading. They found that changes in activation of the vastus lateralis and vastus medialis, as measured by EMG, were closely related to decreased knee extensor torque. There were no significant changes in muscle fiber size or fiber type distribution to account for decreased torque pro-

duction after only 2 wk of unloading. Others have shown that at least part of the change in muscle contractile function is the result of alterations in processes of muscle contraction that are distal to sarcoplasmic reticulum Ca^{2+} release (11,30). A potential inhibitor of force production that may play a role during disuse is inorganic phosphate, which has been found to inhibit actomyosin cross-bridge cycling and suppress muscle force in studies using skinned muscle fibers (20).

Unlike the majority of studies that have investigated the plasticity of muscle resulting from limb disuse in *healthy* subjects, this study focused on a *patient* population, which allows results to be applied directly to optimizing rehabilitation programs. Although the variability in the responses of individual patients to immobilization and rehabilitation can make interpretation of some results more challenging, ultimately, this collective, longitudinal information provides a valuable stepping stone for designing targeted clinical interventions.

In summary, the greatest changes in muscle hypertrophy and atrophy occurred during the initial weeks of rehabilitation and immobilization, respectively. No muscle specific differences were detected, despite the rehabilitation emphasis on the ankle plantarflexors. Although plantarflexor specific torque improved during the course of 10 wk of rehabilitation, deficits still remained. Future work may include measurements of dorsiflexor torque for comparison of specific torque values between anterior and posterior compartment muscles, in addition to measurements of muscle activation and muscle metabolites that may help account for specific torque deficits after disuse.

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