Atrophy and Impaired Muscle Protein Synthesis during Prolonged Inactivity and Stress

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Context: We recently demonstrated that 28-d bed rest in healthy volunteers results in a moderate loss of lean leg mass and strength.

Objective: The objective of this study was to quantify changes in muscle protein kinetics, body composition, and strength during a clinical bed rest model reflecting both physical inactivity and the hormonal stress response to injury or illness.

Design: Muscle protein kinetics were calculated during a primed, continuous infusion (0.08 μmol/kg/min) of 15N2-phenylalanine on d 1 and 28 of bed rest.

Setting: The setting for this study was the General Clinical Research Center at the University of Texas Medical Branch.

Participants: Participants were healthy male volunteers (n = 6, 28 ± 2 yr, 64 ± 4 kg, 178 ± 3 cm).

Intervention: During bed rest, hydrocortisone sodium succinate was administered iv (d 1 and 28) and orally (d 2–27) to reproduce plasma cortisol concentrations consistent with trauma or illness (~22 μg/dl).

Main Outcome Measures: We hypothesized that inactivity and hypercortisolemia would reduce lean muscle mass, leg extension strength, and muscle protein synthesis.

Results: Volunteers experienced a 28.4 ± 4.4% loss of leg extension strength (P = 0.012) and a 3-fold greater loss of lean leg mass (1.4 ± 0.1 kg) (P = 0.004) compared with our previous bed rest-only model. Net protein catabolism was primarily due to a reduction in muscle protein synthesis [fractional synthesis rate, 0.081 ± 0.004 (d 1) vs. 0.054 ± 0.007%/h (d 28); P = 0.023]. There was no change in muscle protein breakdown.

Conclusion: Prolonged inactivity and hypercortisolemia represents a persistent catabolic stimulus that exacerbates strength and lean muscle loss via a chronic reduction in muscle protein synthesis. J Clin Endocrinol Metab 91: 4836–4841, 2006

INJURY OR ILLNESS often necessitates a period of prolonged inactivity or bed rest. In the absence of the stimulation afforded by physical activity, metabolic homeostasis is compromised, and a rapid deterioration in functional capacity can occur. Mechanistically, many of the negative consequences of prolonged inactivity result from an imbalance between skeletal muscle protein synthesis and breakdown. Acute changes in both of these parameters can be accurately measured in vivo using stable isotope methodology (1, 2).

As a research tool, bed rest is widely regarded as the most applicable model to mimic the morphological and functional changes associated with exposure to microgravity (1, 3, 4). In one recent study, we demonstrated that 28-d bed rest in otherwise healthy young volunteers resulted in a 0.4 ± 0.1 kg loss of lean leg mass and a 22.9 ± 3.5% reduction in leg extension strength (1). If allowed to progress, such decrements would ultimately compromise metabolic and functional capacity in previously healthy individuals.

Although bed rest studies provide important mechanistic insight into the deleterious consequences of inactivity, an individual is most likely to experience a period of prolonged inactivity after severe injury or illness. Furthermore, bed rest alone cannot fully address the concomitant stress response and hormonal deregulation observed in clinical environments.

It has been suggested that cortisol is one of the primary mediators of muscle protein catabolism (5–8). After trauma or stress, plasma cortisol concentrations can increase severalfold with a loss of the normal diurnal variation (9). Although many of the acute (4, 5, 10, 11) and chronic systemic effects of elevated plasma cortisol concentrations (7, 12) have been studied extensively, there is a lack of mechanistic research focusing specifically on skeletal muscle. Nevertheless, it is abundantly clear that in clinical situations, prolonged inactivity coupled with injury and cortisol-mediated catabolism can result in a massive loss of lean body mass (LBM) (13, 14). This in turn increases morbidity and is directly related to increased length of recovery after discharge (15, 16). However, the complex interplay of clinical events contributing to overt changes in muscle mass and functional capacity in patient populations makes it difficult to provide more than a basic mechanistic framework. Thus, there is a need to identify the primary deficit in muscle protein kinetics responsible for muscle loss. This in turn may have direct relevance to the choice of interventional strategy (e.g. anti-catabolic vs. anabolic).

We have demonstrated previously that an acute increase in plasma cortisol concentration (via exogenous infusion)
results in a nonsignificant reduction in muscle protein synthesis (17). We also demonstrated that an acute hypercortisolemic challenge administered after 14- or 28- d bed rest temporarily amplifies protein catabolism beyond that associated with prolonged inactivity alone (4, 17, 18). It remains unclear, however, whether there is adaptation to prolonged inactivity and hypercortisolemia or whether chronic exposure results in a progressive, substantial loss of lean muscle mass and function.

The primary purpose of the current study was to quantify changes in body composition and muscle protein kinetics during 28-d inactivity and chronically elevated cortisol, a paradigm that more closely reflects the catabolic environment associated with clinical populations. We hypothesized that the combination of inactivity and exogenous cortisol administration would exacerbate muscle protein catabolism resulting in a greater loss of lean muscle mass compared with a previous study of bed rest alone (1).

Subjects and Methods

Subjects

Six healthy male volunteers participated in this project (Table 1). All volunteers provided informed, written consent according to the guidelines established by the Institutional Review Board at the University of Texas Medical Branch. Subject eligibility was assessed using a battery of medical screening tests as previously described (18). Although differences in the objectives and design of the stable isotope infusion protocols prevented direct comparison of muscle protein kinetics, body composition and strength outcome measurements may be compared with a previous 28-d bed rest-only study that used the same bed rest and dietary protocol (1).

Admission and pre- and posttesting

The experimental protocol is depicted in Fig. 1. Subjects were admitted and housed in the General Clinical Research Center (GCRC) at the University of Texas Medical Branch for pretesting and 5-d dietary adaptation and housed in the General Clinical Research Center (GCRC) at the University of Texas Medical Branch for pretesting and 5-d dietary adaptation. Pretest measures were performed 2–3 d before the start of bed rest. During this period, subjects were sedentary but remained ambulatory. The Harris-Benedict equation was used to estimate daily energy requirements as previously described (1, 18). Subjects were placed on a 3-d rotating diet with daily nutrient intake evenly distributed between three meals (0830, 1300, 1830 h). Carbohydrate, fat, and protein intake represented 55, 27, and 14% of the daily energy intake, respectively (1, 18, 19). Water was provided ad libitum.

Volunteers were familiarized with the leg extension equipment and procedure during their initial screening visit approximately 2 wk before admission. Pretest measures were performed 2–3 d before the start of bed rest and included body composition assessment using dual-energy x-ray absorptiometry (Hologic, Inc., Natick, MA), anthropometric determination of leg volume (20), and single-leg one-repetition maximum (1RM) leg extension strength (Quantum, Seated Leg Extension, Stafford, TX). In preparation for 1RM leg extension strength assessment, volunteers performed light range of motion exercises and four warm-up sets of six to eight repetitions at intensities ranging from approximately 30–80% 1RM. To minimize the potential acute confounding effect of exercise on the measurement of muscle protein metabolism, only the right leg underwent 1RM testing.

Experimental paradigm

We quantified changes in in vivo muscle protein metabolism in a physiological environment consistent with a number of the key physiological perturbations observed in hospitalized patients. Specifically, we combined prolonged inactivity (bed rest) with an elevated stress response (chronic hypercortisolemia) and quantified the resultant muscle metabolic changes using established stable isotope methodology. To abolish the normal diurnal variation and achieve a stable plasma cortisol concentration of approximately 20–25 µg/dl, subjects received five daily doses of 10–15 mg of oral hydrocortisone sodium succinate throughout bed rest (2–27, 0800, 1200, 1600, 2000, and 2400 h). During the stable isotope infusions studies on d 1 and 28 of bed rest, a continuous infusion of hydrocortisone sodium succinate was administered iv to induce/maintain hypercortisolemia and reduce potential minor fluctuations in plasma cortisol concentrations during measurement of muscle protein kinetics.

Stable isotope protocol

Stable isotope infusion studies were performed in the postabsorptive state on d 1 and 28 of bed rest (Fig. 1). At 2400 h on each study day, a constant peripheral venous infusion (18-gauge polyethylene catheter, Insite-W, Becton Dickinson, Sandy, UT) of hydrocortisone sodium succinate (Pharmacia Diagnostics, Kalamazoo, MI) (60 µg/kg) was initiated after an intravenous primed, continuous infusion (0.08 µmol/kg/min) of 13C-phenylalanine (Cambridge Isotope Laboratories, Inc., Andover, MA) was started at 0600 h and maintained for the duration of the study. Peripheral blood samples for determination of plasma concentrations of cortisol, glucose, and insulin were drawn through a contralateral 18-gauge polyethylene peripheral venous catheter.

At 0700 h, 8-cm polyurethane catheters were inserted into the femoral vein and artery of one leg under local anesthesia and maintained patent by normal saline (Cook Catheters, Bloomington, IN). Femoral arterial and venous blood samples were obtained between 0800 and 1100 h. Leg plasma flow was calculated from steady-state indocyanogreen concentrations and converted to leg blood flow using hematocrit as previously described (21, 22).

At 0800 and 1100 h, muscle biopsy samples (approximately 50 mg) were taken from the lateral portion of the vastus lateralis using a 5-mm Bergstrom biopsy needle and local anesthesia (1% lidocaine) as previously described (17, 23).

Bed rest

Subjects maintained strict bed rest throughout the study and were continually monitored by scientific and GCRC nursing staff. Subjects were encouraged to change position periodically to alleviate positional discomfort and to eat. Bathing and hygiene activities and urine collection were performed during bed rest. Subjects were permitted to use a bedside commode for bowel movements, but the time out of bed was nonweight bearing and limited to approximately 5 min.

Analytical methods

Plasma concentrations of cortisol and insulin were determined by chemiluminescent enzyme immunoassay using the Immunolite Automated Analyzer (Diagnostic Products Corporation, Los Angeles, CA). In preparation for the measurement of phenylalanine enrichment and concentration, femoral artery and vein blood samples were mixed and precipitated in a 15% sulfosalicylic acid solution. Blood amino acids were extracted from 500 µl of supernatant by cation exchange chromatography (Dowex AG 50W-8X, 100–200 mesh H+ form, Bio-Rad Laboratories, Richmond, CA) and dried under vacuum (Savant Instruments,
Farmingdale, NY). Phenylalanine enrichments and concentrations in the blood were measured using gas chromatography mass spectroscopy (Hewlett-Packard Co., Palo Alto, CA) as previously described (1, 18, 24, 25).

Muscle biopsy samples were immediately rinsed, blotted, and frozen in liquid nitrogen until analysis. Upon thawing, muscle protein was precipitated with 800 μl 14% perchloroacetic acid. Approximately 1.5 ml supernatant was collected after tissue homogenization and centrifugation and processed in the same manner as the supernatant from blood samples. Intracellular phenylalanine enrichment and concentrations were determined using the tert-butyl(dimethyl)silyl derivative (23, 26). The remaining muscle pellet was washed and dried, and the proteins were hydrolyzed in 6 N HCl at 50°C for 24 h. The protein bound phenylalanine enrichment was determined using gas chromatography mass spectroscopy (HP model 5989, Hewlett-Packard Co.) with electron impact ionization (27).

Calculations

This experimental protocol used established stable isotope methodologies to measure phenylalanine kinetics in human skeletal muscle: direct amino acid incorporation via measurement of the mixed muscle fractional synthesis rate (FSR), the three-pool compartment model, and the two-pool arteriovenous model.

The three-pool compartment model of the leg enables the calculation of several kinetic parameters as previously described (4, 22, 28–30). Assumptions and derivations of the model have been discussed by Biolo et al. (22, 28). Phenylalanine transport into and out from the vastus lateralis muscle is calculated as follows:

\[
F_{M,A} = \left[\frac{[E_M - E_V]}{(E_A - E_M)}\right] \times C_V + C_A \times BF
\]

\[
F_{V,M} = \left[\frac{[E_M - E_V]}{(E_A - E_M)}\right] \times C_V + C_V \times BF
\]

where \(F_{M,A}\) refers to the net amino acid movement from the artery to the muscle, whereas \(F_{V,M}\) refers to the movement from the muscle to the vein. \(C_A\) and \(C_V\) are amino acid concentrations in the femoral artery and vein, respectively, and BF is leg blood flow. \(E_A\) and \(E_M\) are the tracer amino acid enrichments in the femoral artery, femoral vein, and muscle, respectively.

Intracellular amino acids can be derived from endogenous sources. However, because phenylalanine cannot be synthesized in the muscle, \(F_{M,O}\) describes the phenylalanine derived from protein breakdown, such that:

\[
F_{M,O} = F_{M,A} \times \left(\frac{E_A}{E_M} - 1\right)
\]

\(F_{O,M}\) represents the rate of disappearance of intracellular amino acids. Because phenylalanine cannot be oxidized in the muscle, this term represents protein synthesis where:

\[
F_{O,M} = \left(\frac{C_A \times E_A - C_V \times E_V}{E_M}\right) \times BF
\]

Two-pool arteriovenous model parameters for phenylalanine were calculated as follows:

- **Net phenylalanine balance**:
  \[
  NB = (C_A - C_V) \times BF
  \]

- **Rate of appearance**:
  \[
  R_A = R_D - NB
  \]

- **Rate of disappearance**:
  \[
  R_D = (E_A \times C_A - E_V \times C_V) / E_A \times BF
  \]

\(R_A\) is an estimation of the amount of phenylalanine released from breakdown that appears in the plasma, and \(R_D\) is an estimation of the rate of phenylalanine incorporation into muscle protein (26). These calculations do not include phenylalanine that is recycled and does not appear in the blood after breakdown. BF represents leg blood flow, as determined by the indocyanogreen dye dilution method (21).

Mixed muscle FSR was calculated by measuring the direct incorporation of \(^{13}\)C\(_6\)-phenylalanine into protein, using the precursor-product model:

\[
FSR = \left(\frac{[E_{P2} - E_{P1}]}{(E_M \times t)}\right) \times 60 \times 100
\]

where \(E_{P1}\) and \(E_{P2}\) are the enrichments of bound \(^{13}\)C\(_6\)-phenylalanine in the first and second muscle biopsies, \(t\) is the time interval between biopsies, and \(E_M\) is the mean \(^{13}\)C\(_6\)-phenylalanine enrichment in the muscle intracellular pool (31).

**Statistical analysis**

Data were subjected to a one-way repeated measures ANOVA with Tukey post hoc testing. Student’s t tests were used to compare outcome variables (muscle loss, strength) between the current and previous study (1). Data are presented as means ± sem. Differences were considered significant if \(P < 0.05\).

**Results**

**Subject demographics and physical outcomes**

Volunteer demographics are presented in Table 1. No major compliance issues relating to bed rest, diet, or medications were noted during the study. Bed rest with hypercortisol-
emia resulted in a 1.4 ± 0.1 kg or 6% loss of lean leg mass (P = 0.004). This loss of lean muscle mass was accompanied by a 28.4 ± 4.4% loss of 1RM leg extension strength (P = 0.012). Whole-body fat mass did not change (P = 0.64). There was no change in leg blood flow (d 1, 3.7 ± 0.3 vs. d 28, 3.4 ± 0.3 ml/min/100 ml leg volume) (P = 0.31).

**Plasma hormone concentrations**

Administration of exogenous cortisol throughout bed rest abolished the normal diurnal variation in endogenous plasma cortisol concentration. Mean plasma cortisol concentrations during bed rest (obtained twice weekly at 1800 h) are presented in Fig. 2. During stable isotope infusion studies, plasma cortisol concentrations were 19.9 ± 2.2 (d 1) and 22.0 ± 1.3 µg/dl (d 28), respectively. This represents an approximate 2-fold increase in plasma cortisol concentrations observed in the absence of exogenous cortisol administration (1).

Postabsorptive plasma insulin concentrations did not change significantly over the course of the study. Values were 11.4 ± 2.1 (d 1) and 14.2 ± 2.9 µU/ml (d 28) (P = 0.175). Similarly, plasma glucose concentrations were 95.3 ± 3.1 (d 1) and 94.0 ± 3.1 (d 28), respectively (P = 0.752).

**Phenylalanine concentrations and kinetics**

Phenylalanine concentration and kinetic data are presented in Table 2. There were no significant changes in plasma phenylalanine concentration or enrichment after bed rest. Muscle intracellular (C_M) phenylalanine concentrations increased significantly after bed rest.

Bed rest with exogenous cortisol administration resulted in a reduction in amino acid transport into the muscle (F_MA) and a corresponding reduction in both direct (FSR) (Fig. 3) and model-derived (R_x) indices of muscle protein synthesis. F_MAn, the three-pool model-derived indices of muscle protein synthesis, trended lower after bed rest, but was not significant. This was most likely a power issue because analysis indicated that an additional three volunteers (at a power level of 0.8) would be needed to detect a significant difference. There were no changes in indices of muscle protein breakdown (R_x, F_MB). These data were consistent with a reduction in phenylalanine net balance, an index of the balance between synthesis and breakdown.

**Discussion**

This study describes key alterations in muscle protein kinetics and body composition associated with chronic inactivity and stress. Compared with bed rest alone (1), the combination of hypercortisolemia and prolonged inactivity substantially increased muscle protein catabolism via a reduction in muscle protein synthesis. This defect in protein synthesis after bed rest occurred despite elevated precursor availability (C_M, muscle intracellular phenylalanine concentrations) and is consistent with the reduced need for amino acid transport into the muscle (F_MA). Understanding these key physiological perturbations is crucial in the development of interventional strategies to target the mechanism responsible for muscle loss specifically and promote recovery after clinically mandated inactivity associated with illness or injury.

The bed rest model is widely employed to mimic the lower body hypokinesia experienced during exposure to microgravity (4, 32). However, prolonged bed rest is also encountered in a variety of clinical populations. When individuals are confined to bed due to illness or injury, hypercortisolemia ensues, muscle protein catabolism is accelerated (7, 33), and if the condition is severe or prolonged, the preservation of LBM can become critical for survival (34). Thus, it is clear that although the bed rest model can mimic the physical inactivity associated with trauma or pathology, it cannot duplicate the complex hormonal and metabolic disruption (8, 35). The chronic administration of exogenous cortisol in this study was designed to elevate plasma cortisol concentrations to the upper physiological range, consistent with values observed after moderate trauma or pathological insult (8, 36).

Maintenance of skeletal muscle mass and functional capacity is a fundamental determinant of patient morbidity and speed of recovery after injury or illness. After severe burn injury or in response to radiation therapy for lung cancer, survival is further compromised when LBM is reduced (34). Furthermore, the loss of muscle mass and function during hospitalization directly impacts recovery, with less than 50% of intensive care patients returning to work within a year of discharge (37) and less than 50% of women over 65 walking again after hip fracture (38).

In a recent study employing the same dietary and bed rest regimen without exogenous cortisol administration, we demonstrated that 28-d inactivity in otherwise healthy young males with similar physical characteristics to the present study results in a 0.4-kg loss of leg muscle mass and a 23% reduction in leg extension strength (1). Although significant, it is clear that these data do not approach the mag-
nitude or severity of changes observed after trauma or illness (33, 35, 36).

The most phenotypically obvious consequence of the present study was the 6% loss of lean muscle mass from the legs. This represents a 3-fold greater loss of muscle compared with a previous 28-d bed rest protocol without exogenous cortisol administration (1); based on body proportions, it is theoretically consistent with an approximately 4-kg loss of whole-body lean muscle mass. Catabolism of this magnitude or severity of changes observed after trauma or illness is consistent with clinical paradigms. For example, in a study of critically injured blunt trauma patients, Monk et al. (36) reported a 6.4-kg (~23%) loss of whole-body lean muscle mass over a 25-d period after injury. It must be noted, however, that the bed rest model does not typically result in a uniform loss of muscle mass (1, 18). Although bed rest restricts movement of the lower body (lower limbs, trunk), the shoulders and arms, which have less absolute muscle mass, are also engaged in various activities during the bed rest period. Consequently, the absolute and relative loss of muscle mass in the upper extremities is less pronounced than the more heavily muscled lower limbs (Table 1).

In the current study, there was no change in plasma insulin or glucose concentrations. However, compared with bed rest alone (1), insulin concentrations were approximately 50–100% higher and could reflect progression toward the development of insulin resistance. Changes in lean muscle mass and strength were facilitated by a reduction in muscle protein synthesis and associated with a reduction in amino acid transport into the muscle. This is consistent with previous bed rest studies (1, 19, 39) but does not reflect the large increase in protein turnover (increased synthesis and breakdown) observed after a severe injury such as a burn (40).

Thus, despite the expansion of the free muscle intracellular phenylalanine pool (i.e. increased precursor availability) on d 28, a reduction in protein turnover in this model may be due in part to both an induced defect in skeletal muscle protein synthesis and/or the lack of a downstream destination/requirement for plasma amino acids (e.g. wound site, splanchnic bed). In other words, protein turnover in this bed rest model may not have increased because there was no increased demand for the synthesis and use of acute phase proteins and proteins involved in tasks such as immune function and wound healing (7, 35).

In conclusion, chronic inactivity and stress exacerbates muscle protein catabolism via a chronic reduction in muscle protein synthesis despite an increase in precursor availability and with no concomitant change in muscle protein breakdown. Understanding these key physiological perturbations is crucial in the development of targeted interventional strategies to promote anabolism and facilitate recovery after inactivity associated with illness or injury.

Acknowledgments

We gratefully acknowledge the assistance of Melissa Bailey, Stephaine Blase´, David Chinkes, Christopher Danesi, and Guy Jones for invaluable assistance with sample and data processing.

Received March 24, 2006. Accepted September 8, 2006.

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This work was supported by National Space Biological Research Institute Grant NPPR00285, by National Aeronautics and Space Administration Grant NAG9-1155, by National Institutes of Health Grant 5 RO1 GM 57295, and by Shriners Hospital Grant 8490. Studies were conducted on the GCRC at The University of Texas Medical Branch at Galveston and funded by Grant M01 RR 00073 from the National Center for Research Resources.

The authors have nothing to disclose.

References

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**TABLE 2. Phenylalanine concentration, enrichment, and kinetics on d 1 and 28 of bed rest**

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<th>d 1</th>
<th>d 28</th>
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<tr>
<td>Femoral artery (C_A)</td>
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<td>Transport in (F_M)</td>
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<td>Synthesis (R_A)</td>
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<td>0.016a</td>
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</table>

Values are means ± SEM.

6 Significant pre- to postbed rest change (P < 0.05).

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