

Inflammation Relates to Resistance Training–induced Hypertrophy in Elderly Patients

KRISTOFFER L. NORHEIM^{1,2,3}, CHRISTOPHER K. CULLUM^{1,2,3}, JESPER L. ANDERSEN^{2,3}, MICHAEL KJAER^{2,3}, and ANDERS KARLSEN^{1,2,3,4}

¹Department of Geriatrics, Bispebjerg Hospital, University of Copenhagen, København, DENMARK; ²Institute of Sports Medicine Copenhagen, Bispebjerg Hospital, University of Copenhagen, København, DENMARK; ³Faculty of Health and Medical Sciences, Center for Healthy Aging, University of Copenhagen, København, DENMARK; and ⁴Department of Biomedical Sciences, University of Copenhagen, København, DENMARK

ABSTRACT

NORHEIM, K. L., C. K. CULLUM, J. L. ANDERSEN, M. KJAER, and A. KARLSEN. Inflammation Relates to Resistance Training–induced Hypertrophy in Elderly Patients. *Med. Sci. Sports Exerc.*, Vol. 49, No. 6, pp. 1079–1085, 2017. **Purpose:** Aging is associated with a gradual loss of muscle mass, which some have suggested to be accelerated by short periods of muscle disuse due to medical illness. We investigated the effect of hospitalization on skeletal muscle mass in acutely ill geriatric patients with focus on the relationship between systemic inflammatory marker C-reactive protein (CRP) and changes in muscle mass, as well as the influence of resistance training upon muscle mass. **Method:** Unilateral leg press resistance exercise was conducted daily during the hospital period. Outcomes included changes in whole body and regional lean mass, maximal voluntary contraction of the knee extensors, leg extension power, and functional performance. Activity level was measured using ActivPAL accelerometers, and CRP levels were obtained from blood samples. **Results:** Sixteen subjects completed the study (eight men and eight women, age = 84.8 ± 1.9 yr, mean \pm SE). Lean mass at the midhigh region of the trained leg increased by $2.4\% \pm 1.1\%$ ($P < 0.05$) after the intervention period. There was a negative association between changes in midhigh lean mass of the trained leg and CRP ($r_s = -0.53$, $P < 0.05$). Leg extension power increased significantly in both legs ($P < 0.05$), with no difference observed between legs. There were no changes in maximal voluntary contraction or functional performance. **Conclusion:** Muscle mass is not significantly lost during short-term hospitalization of relatively high functioning and active geriatric patients although our findings are potentially affected by changes in hydration status. Resistance training during hospitalization increases skeletal muscle mass, and patients with high levels of systemic inflammation demonstrate less ability to increase or preserve muscle mass in response to resistance training during illness. **Key Words:** HOSPITALIZATION, GERIATRIC PATIENTS, EXERCISE, MUSCLE POWER, C-REACTIVE PROTEIN

Aging is associated with a gradual loss of skeletal muscle mass starting from the end of the fifth decade of life (21,22). This loss may be accelerated by short periods of inactivity and muscle disuse (11,26), as seen during hospitalization of elderly geriatric patients (17,34). Repeated hospitalizations followed by incomplete recovery may therefore accelerate the age-associated loss of muscle mass, which in turn could reduce the amount of years spent independently and without mobility limitations (16).

The effect of a hospital stay on muscle mass of geriatric patients is inconclusive. It has previously been observed that isometric knee extensor muscle strength remained unchanged, whereas functional performance increased slightly, despite very low levels of activity during hospitalization of geriatric patients (9). This could be due to the accompanying recovery from illness and gradual increase in activity during the hospitalization period itself. Yet, when elderly individuals are hospitalized for more than eight nonconsecutive days within a year, they appear to experience reductions in whole body lean mass and knee extensor strength (2). It is however not known whether this loss happens during hospitalization itself. Reduced activity after discharge (27) or an impaired ability to regenerate muscle mass and strength, as observed in elderly after short-term disuse (20,38), may contribute to such a loss.

Geriatric patients may be hospitalized for medical conditions, leading to elevated levels of proinflammatory markers (5). Systemic C-reactive protein (CRP) shows an inverse correlation with muscle mass in elderly (40), and high CRP levels are related to poor muscle function in hospitalized geriatric patients (5). This may indicate a negative correlation

Address for correspondence: Kristoffer Larsen Norheim, M.Sc., Bispebjerg Hospital, Building 3 (2nd floor), Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark; E-mail: kristofferlarsennorheim@gmail.com.

Submitted for publication September 2016.

Accepted for publication January 2017.

0195-9131/17/4906-1079/0

MEDICINE & SCIENCE IN SPORTS & EXERCISE®

Copyright © 2017 by the American College of Sports Medicine

DOI: 10.1249/MSS.0000000000001221

between CRP levels and muscle mass, but it is unknown whether hypertrophic responses to resistance training are correlated to levels of CRP in hospitalized patients.

Resistance training during bed rest has been used to attenuate the loss of muscle mass and strength in young healthy individuals (1,3) and during reduced activity in healthy elderly (15). However, the effects of resistance exercise on skeletal muscle mass during hospitalization in acutely ill geriatric patients have not yet been investigated.

The primary aim of the present study was to investigate the effect of resistance training upon skeletal muscle mass in acutely ill geriatric patients during hospitalization and to determine whether a relationship between systemic CRP and changes in muscle mass exists. This was done by performing unilateral heavy resistance training of one leg, whereas the contralateral leg served as control. It was hypothesized that there would be a loss of lean mass, strength, and power in the untrained leg, whereas the trained leg would show preservation of these. Further, it was expected that CRP would be negatively associated with changes in lean mass in the leg subjected to resistance training.

METHODS

Participants

Elderly hospitalized patients from the Geriatric ward at Bispebjerg Hospital, Denmark, were recruited between August 2015 and May 2016. Patients (≥ 65 yr) who were admitted because of acute illness were included. Patients were excluded based on three main criteria: (i) cognition—patients with dementia, deliria, and severe memory dysfunction and those who could not speak Danish; (ii) function—patients with a recent surgery (knee or hip replacement) in one or both of the lower extremities, with large unilateral strength differences in the lower extremities or patients with a functional level that made adequate testing impossible; and (iii) illness—patients with an acute medical condition that is known to accelerate loss of muscle mass (e.g., terminal cancer and HIV/AIDS), with an unstable chronic disease (e.g., dialysis, cardiac arrhythmias), those in isolation or patients who were terminal. Further, patients with expected short hospitalization periods (< 7 d) and those who were not approved for participation by the responsible doctor were excluded. The study was approved by the Research Ethics Committees of the Capital Region of Denmark (H-15005016) and conformed to the standards set by the Declaration of Helsinki. All volunteers gave written informed consent before inclusion.

Study Design

Patients were admitted to the department in the afternoon, where they were screened for eligibility in the study (day 1). Eligible subjects were then given verbal and written information about the project. On the following day (day 2), those who agreed to participate signed a letter of informed consent. Immediately after, the patients were pretested, followed by

completion of the first resistance exercise session in the afternoon. On the following days, the patients completed a daily resistance exercise session, until the day before the posttesting, which was performed 10 d after admission, or at the day of discharge in patients with a duration of stay < 10 d. Blinded examiners performed all tests.

Intervention

Resistance training was conducted daily $7 \text{ d}\cdot\text{wk}^{-1}$ in a standard leg press machine (Steens Physical, Steens Industrier AS, Norway), stationed in the dining room on the geriatric floor. The subjects, seated upright with their back supported, performed unilateral leg press. Adjustments were made so that the knee was flexed at $\sim 90^\circ$ at the starting position and extended to $\sim 10^\circ$ (0° being full extension). Two warm-up sets with incremental loads were completed before each training session. The subjects were instructed to perform 12 repetitions, with a 1- to 2-s concentric phase and a 2- to 3-s eccentric phase. The load was increased in 2.5-kg increments when more than 12 repetitions could be lifted so that the last repetition was close to voluntary failure, resulting in working sets of 10–12 repetitions. Patients were encouraged to complete as many sets as possible with a maximum of six sets per day. Some patients were not always able to complete six sets because of general tiredness or low motivation; however, three sets were noted as a successful training session. Rest intervals between sets were approximately 60–90 s. Training sessions lasted 10–20 min (including warm-up) and was supervised by the same investigator. Training loads and self-reported muscle soreness was recorded daily for each subject.

Measurements

Dual-energy x-ray absorptiometry. Body composition was assessed by dual-energy x-ray absorptiometry (DEXA) scans (Lunar DPX-IQ; GE Healthcare, Chalfont St. Giles, UK). The scanner was calibrated according to the manufacturer's guidelines. Skeletal muscle index was calculated as (bilateral arm + bilateral leg lean mass)/height², according to Baumgartner et al. (4). To estimate thigh lean mass, an artifact was drawn to cover everything below the lateral epicondyle of the femur, thereby removing the lower legs from the original scanning image. In addition, a 4.03-cm subregion of the lean mass of the thigh was measured at 50% femur length (midthigh region) (39). The same scanning images were analyzed two separate times to investigate the reliability of this method of analysis, showing a coefficient of variation of 0.15%. The subjects were transported to the DEXA scanner in a wheelchair and wore the same clothing each scan. All scans were analyzed in a blinded manner, using extended research analysis software (Lunar DPX, version 3.6z software).

Maximal voluntary contraction. Maximal voluntary contraction (MVC) strength of the knee extensor muscles was determined in a customized chair with the subjects seated with their knees at approximately 90° and their lower legs

hanging vertical without touching the floor. A dynamometer (Manual Muscle Tester, model 01165; Lafayette Instrument Company, Lafayette, IN) was placed 5 cm proximal to the malleoli. To optimize reliability of the measurement, the dynamometer was held by a rigid belt instead of by hand, as described by Bohannon et al. (10). In brief, an inextensible adjustable belt was wrapped over the back of the dynamometer and secured to the back of the chair. Chair adjustments were customized to the individual subjects so that the belt was in a horizontal position during the MVC. Two seat belt straps were also fastened over the thighs and hip of the subjects to avoid vertical displacement. The same chair settings were used for the posttest. With their arms folded across their chest, the subjects were given one test trial followed by three maximal trials, alternating between legs, separated by approximately 2 min. The dynamometer was set to a force threshold of 20 N, and the recording time was set at 6 s. Maximal force and moment arm (length from rotational axis to dynamometer) was recorded, and the maximal torque was calculated as force (N) \times moment arm (m).

Leg extension power. Maximal unilateral leg extension power (LEP) was determined using a Nottingham Leg Extensor Power Rig (Medical Engineering Unit, University of Nottingham Medical School, Nottingham, UK) according to Bassey et al. (36). Maximal power output was measured in watts with the standard software supplied by the manufacturer. Briefly, two test trials followed by five maximal trials were completed on the right and left leg, respectively. The subjects continued until there was no improvement in the last two trials.

Functional performance and activity levels. Mobility was assessed with the de Morton Mobility Index (DEMMI) (14). A 30-s chair stand test (30-s CST) (23) and a 4-m gait speed test (37) were used to assess physical function. Handgrip strength at admission, measured with a digital Jamar® handheld dynamometer (30), and New Mobility Score (33) served as descriptive variables. Activity levels were measured using ActivPAL accelerometers (PAL Technologies, Glasgow, Scotland) attached anterior on the midthigh of each subject. Recordings started after the pretests had been completed and stopped before the posttests began. Only full days of recording (24 h) were included in the analysis. Activity level was divided into the time spent sedentary (lying or sitting), standing, and walking.

Blood samples and analyses. For most patients, two blood samples were collected during the hospitalization period, both at 8 AM. The first blood sample was collected on days 2–5 ($n = 16$) and the second on days 5–7 ($n = 11$) with a range of 2–5 d between the two samplings. CRP levels from the patients with two blood samples were averaged for statistical analysis. Blood was drawn from the antecubital vein into 6-mL tubes, which were cooled in ice water for 10 min, followed by centrifugation (10 min at 3970g at 4°C). Plasma was stored at -80°C for analysis of CRP using enzyme-linked immunosorbent assay kits (CRP DuoSet DY1707) from R&D Systems (Minneapolis, MN).

Statistics

All continuous data were tested for normality and equal variance using the Shapiro–Wilk test and the Brown–Forsythe test, respectively. Functional test scores (30-s CST, DEMMI, 4-m gait speed) and CRP levels were nonnormally distributed. Differences in muscle mass and muscle power/MVC between the trained leg and the untrained leg were analyzed with a two-way repeated-measures ANOVA (time [pre vs post] \times treatment [trained vs untrained]). Significant interactions were analyzed using the Holm–Sidak *post hoc* test. Changes from pre to post were analyzed with a two-tailed *t*-test or with the Wilcoxon signed rank test for nonnormally distributed data. Spearman's rho (r_s) was used to determine the relationship between the CRP and the relative change in muscle mass in the trained leg. Normally distributed data are presented as arithmetic mean \pm SE, whereas nonnormally distributed data are presented as medians (interquartile ranges [IQR]). Differences were considered significant when $P < 0.05$. Statistical analysis was conducted using SigmaPlot version 13.0 for Windows (Systat Software Inc., San Jose, CA).

RESULTS

Recruitment and characteristics. A total of 566 patients were admitted to the department and screened during the study period, from where 151 patients were identified as eligible to participate in the study. One hundred and thirty-two patients declined to participate either after being given oral information about the study ($n = 110$) or after reading the study material ($n = 22$). Nineteen patients agreed to participate in the study; however, three of these patients were transferred to a different department before finishing the intervention. Hence, 16 patients completed the study. Characteristics of the 16 study patients who completed the entire intervention are presented in Table 1. The included subjects had multiple diagnoses at time of admission: pain or physical injury ($n = 7$), respiratory disease ($n = 7$), cardiovascular disease ($n = 6$), genitourinary disease ($n = 4$), endocrine disease ($n = 2$), gastrointestinal disease ($n = 1$), and other ($n = 7$).

Training. The number of possible training sessions and number of attended training sessions were 5.8 ± 0.3 and 4.9 ± 0.3 , respectively. This gave an average training compliance of $\sim 86\%$. The mean number of training sets after the warm-up was 4.5 ± 0.3 . None of the subjects experienced any form of injuries or self-reported incidences of muscle soreness during the intervention.

TABLE 1. Characteristics of the study patients.

| Characteristic | |
|------------------------------------|------------------|
| Age, yr | 84.8 \pm 1.9 |
| Sex, male/female | 8/8 |
| Weight, kg | 65.1 \pm 4.4 |
| Height, cm | 162.4 \pm 2.7 |
| BMI, $\text{kg}\cdot\text{m}^{-2}$ | 24.6 \pm 1.3 |
| Length of stay, d | 7.0 (6.3–12.3) |
| New Mobility Score | 9.0 (6.3–9.0) |
| Handgrip strength, kg | 20.2 (18.3–26.4) |

Data are presented as mean \pm SE or median (IQR). $n = 16$.

TABLE 2. Absolute changes in body composition from pre- to postintervention.

| | Preintervention | Postintervention |
|---------------------------|-----------------|------------------|
| Total LM (kg) | 42.6 ± 2.3 | 42.7 ± 2.3 |
| Total FM (kg) | 20.8 ± 2.7 | 20.7 ± 2.6 |
| Body fat (%) | 30.6 ± 2.1 | 30.6 ± 2.1 |
| SMI (kg·m ⁻²) | 6.8 ± 0.3 | 6.9 ± 0.3 |
| Leg LM (g) | | |
| Trained | 6970 ± 526 | 7040 ± 488 |
| Untrained | 6983 ± 538 | 6967 ± 487 |
| Thigh LM (g) | | |
| Trained | 4656 ± 358 | 4665 ± 332 |
| Untrained | 4725 ± 382 | 4675 ± 342 |
| Midhigh region LM (g) | | |
| Trained | 452 ± 30 | 460 ± 29 |
| Untrained | 460 ± 32 | 461 ± 28 |

LM, lean mass; FM, fat mass; SMI, skeletal muscle index = (bilateral arm + bilateral leg LM) × height (m)⁻². Data are presented as mean ± SE (n = 16).

Body composition. The mean number of full days between pre- and postassessment was 6.2 ± 0.5; hence, postassessments were on days 8.2 ± 0.5 of the hospitalization. Changes in whole and regional body composition are summarized in Table 2. Eight of 16 patients had a skeletal muscle index below the sex-specific cutoff points for sarcopenia (4). No effect was found when examining whether the presence of sarcopenia influenced any of the measured outcomes. There were no significant changes in absolute body composition during the intervention period. A significant interaction was found for the relative changes in lean mass of the midhigh region ($P < 0.05$), and *post hoc* testing revealed a significant increase (2.4% ± 1.1%) in the trained leg ($P < 0.05$), which was significantly different from the untrained leg at post ($P < 0.01$, Fig. 1), whereas no changes were observed in the control leg (0.9% ± 1.1%, $P = 0.42$).

CRP. There was no difference in CRP concentration between the first and the second sample (20.0 [14.3–41.0] vs 20.0 [13.0–31.5], median [IQR], respectively) for the patients with two blood samples. Levels of CRP during the intervention period were significantly associated ($r_s = -0.52$, $P <$

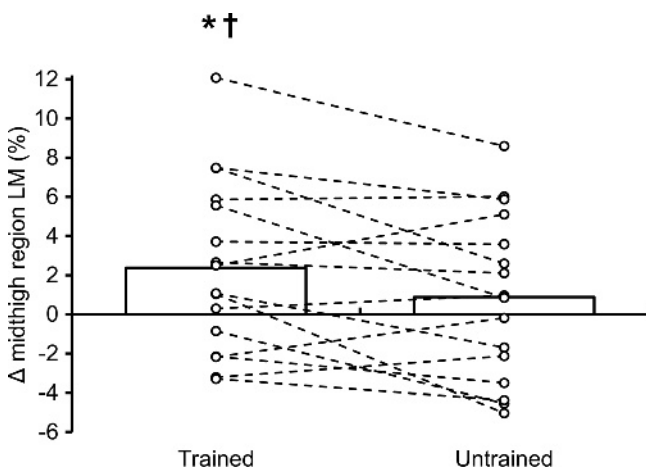


FIGURE 1—Relative change in midhigh region lean mass (LM) from pre- to postintervention in the trained leg and untrained leg. Histograms are mean values, whereas changes for each individual are displayed as open circles connected by a line (n = 16). *Significantly different from preintervention ($P < 0.05$). †Significantly different from untrained leg ($P < 0.01$).

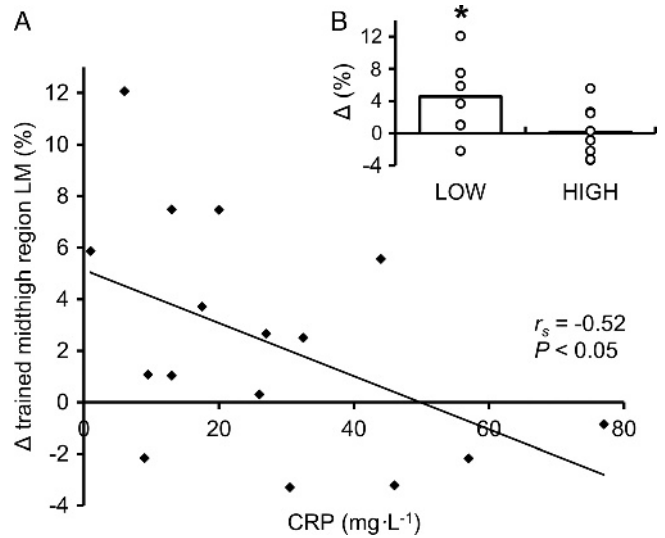


FIGURE 2—A, Correlation between CRP levels during the intervention period and the relative changes in midhigh region lean mass (LM) of the trained leg. B, Relative changes in midhigh region LM of the trained leg for the eight patients with the lowest levels of CRP (LOW) versus the eight patients with the highest levels (HIGH). Histograms are mean values with individual values displayed as open circles. *Significant difference between LOW and HIGH ($P < 0.05$).

0.05) with relative changes in midhigh region lean mass of the trained leg (Fig. 2A). Furthermore, by dividing the patients into two equally sized groups (eight in each) based on CRP levels, those with the lowest (LOW) CRP levels (CRP, 11.3 [8.3–14.1] mg·L⁻¹) significantly differed from those with the highest (HIGH) CRP levels (CRP, 38.3 [29.6–48.8] mg·L⁻¹) with regard to changes in midhigh region lean mass of the trained leg (+4.6% ± 1.6% vs +0.2% ± 1.1%, respectively, $P < 0.05$; Fig. 2B). Regarding the control leg, a weak, nonsignificant association ($r_s = -0.42$, $P = 0.10$) was observed between CRP and changes in midhigh region lean mass and a similarly nonsignificant difference in relative changes between the LOW and the HIGH group (+2.1% ± 1.7% vs -0.3% ± 1.2%, respectively, $P = 0.30$).

Muscle strength, power, and training load. Three subjects were unable to complete the MVC test because of local pain in the area where the dynamometer was positioned. Absolute changes in LEP, knee extension MVC torque, and training load are presented in Table 3. There was a significant main effect of time (+9.3% $P < 0.05$, Table 3) for LEP, but there were no significant changes in knee

TABLE 3. Changes in muscle power, strength, and training load.

| | n | Pre/First | Post/Last |
|--|----|------------|-------------------------|
| LEP (W·kg ⁻¹) ^a | 16 | | |
| Trained leg | | 0.9 ± 0.1 | 1.0 ± 0.1 |
| Untrained leg | | 0.9 ± 0.1 | 1.0 ± 0.1 |
| MVC torque (N·m) | 13 | | |
| Trained leg | | 64.9 ± 7.6 | 64.9 ± 7.3 |
| Untrained leg | | 62.5 ± 7.0 | 61.5 ± 7.0 |
| Training load (kg) | 16 | 40.9 ± 4.7 | 48.9 ± 5.8 ^b |

LEP, leg extension power. Data are presented as mean ± SE.

^aSignificant main effect of time ($P < 0.05$).

^bSignificant difference between first and last training session ($P < 0.05$).

extension MVC torque from pre- to postintervention (-0.8% , $P = 0.7$, Table 3). The average training load increased significantly ($+19.6\%$, $P < 0.05$, Table 3) from the first to the last training session.

Functional performance and activity levels. One subject did not complete the DEMMI test while another subject did not complete the 4-m gait speed test. No significant changes from pre- to postintervention could be detected in DEMMI score (67 [53–85] vs 74 [53–74], $P = 0.12$, $n = 15$), 30-s CST performance (5.5 [0.3–10.8] vs 7.5 [1.8–10.0] reps, $P = 0.47$, $n = 16$) or 4-m gait speed (5.7 [4.5–8.3] vs 5.7 [4.6–9.1] s, $P = 0.64$, $n = 15$). Activity level was measured in 15 of the subjects because one accelerometer was lost during the intervention period. The mean number of days measured was 4.9 ± 0.3 . The median (IQR) time spent lying or sitting was 21.9 (21.0–22.5) $\text{h}\cdot\text{d}^{-1}$, time spent standing was 1.9 (1.3–2.3) $\text{h}\cdot\text{d}^{-1}$, and time spent walking was 0.3 (0.2–0.6) $\text{h}\cdot\text{d}^{-1}$. There were no significant associations between activity levels and changes in muscle mass, strength, power, or functional performance (data not shown).

DISCUSSION

The main findings of the present study were that (i) muscle mass was not lost during short-term hospitalization in geriatric patients, (ii) muscle mass increased in the leg receiving resistance training during hospitalization, and (iii) CRP levels were negatively associated with resistance training-induced hypertrophy.

Contrary to our hypothesis, no loss of muscle mass during the relatively short period of hospitalization could be detected in the present study (Table 2). Although both bed rest (26) and reduced activity (11) are known to have a negative effect on muscle mass in elderly, no previous studies have directly investigated the effect of acute hospitalization on muscle mass in geriatric patients. It has been shown that even a very short period (4 d) of lower limb immobilization reduces muscle mass and strength markedly in elderly (38), and somewhat along this line, an observational cohort study found a significant loss of lean mass in elderly individuals (age = 70–79 yr) when hospitalized for more than eight nonconsecutive days within a year (2). Therefore, we hypothesized that 7–10 d of hospitalization would result in a loss of muscle mass in elderly geriatric patients. Normative data for community-living independent elderly have suggested that a DEMMI score <62 signify limited mobility, whereas a score ≥ 62 signifies high mobility (28). Hence, the patients in the present study had relatively high mobility, as 11 of 15 patients had a DEMMI score of 62 or higher. In line with this, the patients in the present study spent a median time of $2.1 \text{ h}\cdot\text{d}^{-1}$ either standing or walking, whereas previous studies found geriatric patients spending $0.8\text{--}1.1 \text{ h}\cdot\text{d}^{-1}$ either standing or walking (9,34), suggesting that the patients in the present study had a higher activity level than would be expected in geriatric patients. A higher level of mobility and activity during their hospital stay

could, in part, explain why no loss of muscle mass could be detected in the patients included here. It is furthermore possible that geriatric patients are mildly dehydrated at admission to the hospital, and that rehydration would mask a loss of muscle mass assessed with DEXA scan. Alternatively, several days before admission may have been spent inactive as illness progressed, and thus our initial determination of muscle mass and strength would underestimate the habitual level in these patients. In support of this, 65% of geriatric patients had a reduction in self-reported mobility at admission when compared with 2 wk before hospitalization (19). As the largest loss of muscle mass in elderly immobilized muscle occurs during the initial few (~ 4) days, without further decrease after 2 wk (38), it is possible that the most pronounced loss of muscle mass occurred before the intervention in these patients.

With respect to resistance training, there was a significant increase in the relative midhigh region lean mass (2.4%) in the trained leg after the intervention period (Fig. 1). This region corresponded to the area where others have found the thigh muscles to be the most adaptable to changes in size, either by resistance training (32) or bed rest (1). In a previous study, where elderly men were subjected to six total sessions of unilateral resistance exercise during 2 wk of reduced activity, leg lean mass was found to increase by 1.4% in the trained leg (15). Despite none of the subjects experiencing any form of muscle soreness, it could be argued that the relatively large increase ($+2.4\%$) found after only ~ 6 d in the present study was merely the effect of muscle edema because of unaccustomed exercise (12) and no recovery between exercise days. We did not in this study investigate this further and cannot completely rule this out. However, as the study was performed with patients being their own controls, at least the changes with training were only seen in the trained leg with no sign of any general increase in lean mass in other parts of the body. Despite this, the large increase in muscle mass in the trained leg could be explained by a combination of resistance training-induced muscle preservation and rehydration upon hospitalization.

Of clinical interest is the finding of a significant correlation between CRP and changes in midhigh region lean mass of the trained leg (Fig. 2A). Inflammation leads to the secretion of proinflammatory cytokines, which in turn induces the production of acute-phase proteins such as CRP (7). There are indications of an increased inflammatory susceptibility in age muscle, which may impair the regenerative capacity of muscle tissue (31). This is supported by a study reporting a negative correlation between serum CRP and muscle mass, in addition to indications of elevated CRP having negative effects on myoblast proliferation rate *in vitro* (40). Our findings suggest that patients with the highest levels of CRP during their hospital stay were less able to increase or regain muscle mass (Fig. 2B). These patients did not differ from the patients with LOW CRP with respect to training adherence and number of sets completed. There was however a numerical nonsignificant difference between the groups in terms of relative increases in training load ($+30.6$ vs $+13.2$, respectively, $P = 0.2$).

Supportive, geriatric patients admitted with elevated systemic inflammation have poorer muscle function compared with noninflammatory patients, which does not seem to improve during hospitalization, despite being medically treated (5).

In the present study, we found a significant main effect of time for LEP (+9.3%) with no difference between the trained and untrained leg (Table 3). In perspective, an 18% increase in LEP was found after 12 wk of resistance training in healthy elderly women (36). Surprisingly, no difference in LEP could be detected between the trained and the untrained leg although midhigh lean mass increased in the trained leg only. Although speculative, the reason for not finding any significant difference between the trained and the untrained leg could be due to cross education (35), and possibly also some degree of fatigue in the trained leg (18), as the posttest was performed the day after the last training session. Given our within-subjects design, no firm conclusions can be made regarding such adaptations. Alternatively, the increase seen in both the trained and the untrained leg may be explained by a learning effect because of the lack of a familiarization session; however, a previous reproducibility study in elderly patients found that two testing sessions, separated by 1 wk, led to a systematic decline in MVC while LEP was not affected by time (8). Nonetheless, poor LEP is associated with an increased risk of mobility limitations (6), and clinically meaningful improvements in LEP have been estimated to 9%–10% (25), which is comparable with the increase found in the present study.

Regarding isometric strength, no significant changes could be detected in the present study (Table 3), which is somewhat in line with previous observations in geriatric patients not subjected to any form of intervention (9). Interestingly, knee extension MVC decreased in both groups when young healthy individuals were subjected to either bed rest or bed rest in combination with leg press resistance training for 14 d (3). The trained group did however maintain their one-repetition maximum in leg press. Moreover, when reduced activity was combined with unilateral leg press and knee extension exercise, no significant change in knee extension MVC could be detected in either leg, whereas leg press one-repetition maximum was significantly increased in the trained leg only (15). These findings indicate training-specific adaptations to resistance training and might explain why no significant changes could be detected for isometric strength of the knee extensors in the present study, contrary to the ~20% increase in training load in the leg press machine (Table 3).

No significant changes in functional performance could be detected during hospitalization in the present study. Contrary, others have found improved function during hospitalization in geriatric patients (9). Although not statistically significant, the numerical improvements in function observed in the current study are comparable with previous observations in our department (24), and given that only one leg was trained with the current study design, we did not expect large functional improvements in tasks that involve both legs. In addition, it should be noted that these patients had a relatively high

functional level, and patients with higher function at admission are less likely to increase function during hospitalization (13).

The findings of the present study are limited by some factors that could not be controlled for. One factor that might have influenced the results is hydration level, as some patients might be dehydrated during the initial days of hospitalization, which would underestimate lean mass measurements at admission. If this was the case, then perhaps instead of an increase in midhigh leg lean mass, there might have been a decrease in the control leg, whereas the trained leg was maintained and not increased. This we cannot say for certain, but our within-subjects design should however account for this when comparing the training response between legs. Unfortunately, this design also confounds our results in terms of strength and power adaptations to resistance training through cross education, as well as the possibility of training-induced fatigue in the trained leg. Cross education may even have affected muscle mass (29), thereby attenuating a decline in muscle mass in the untrained limb. Also, the findings in the current study may not be generalizable to average geriatric patients given that the included patients were more active and had relatively high functional level compared with previous findings (9,34). In the current study, lean mass was assessed by a DEXA scan, and variability in this method might affect the results. Because of the intense test battery and physical status of the patients, we did not perform additional DEXA scans to assess the test-retest reliability of the method. However, the analysis of the midhigh region showed a good reliability ($CV = 0.15\%$), and the unilateral training design might have compensated for day-to-day variations in DEXA scans as well as for the hydration status. So although the direction of change in muscle mass may have been affected by hydration status, we are confident that the differences observed between the legs represent a physiological change as a result of the training.

In conclusion, patients with high levels of inflammation during hospitalization may be less able to increase or preserve muscle mass in response to resistance training during illness. Also, the findings of the present study suggest that muscle mass is not lost during short-term hospitalization of relatively high functioning and active geriatric patients; however, these findings are complicated by the fact that patients may have been dehydrated at admission, which would influence the muscle mass measurements. Future studies are needed where muscle mass is assessed at admission using a method not influenced by hydration status to determine the effects of short-term hospitalization on muscle mass in this population.

This work was supported by the Nordea Foundation (Healthy aging grant).

The authors declare no conflicts of interest, financial or otherwise. The authors also declare that the results of the present study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

- Akima H, Kubo K, Kanehisa H, Suzuki Y, Gunji A, Fukunaga T. Leg-press resistance training during 20 days of 6 degrees head-down-tilt bed rest prevents muscle deconditioning. *Eur J Appl Physiol*. 2000;82(1-2):30-8.
- Alley DE, Koster A, Mackey D, et al. Hospitalization and change in body composition and strength in a population-based cohort of older persons. *J Am Geriatr Soc*. 2010;58(11):2085-91.
- Bamman MM, Clarke MS, Feeback DL, et al. Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. *J Appl Physiol (1985)*. 1998;84(1):157-63.
- Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998;147(8):755-63.
- Bautmans I, Njemini R, Lambert M, Demanet C, Mets T. Circulating acute phase mediators and skeletal muscle performance in hospitalized geriatric patients. *J Gerontol A Biol Sci Med Sci*. 2005;60(3):361-7.
- Bean JF, Leveille SG, Kiely DK, Bandinelli S, Guralnik JM, Ferrucci L. A comparison of leg power and leg strength within the InCHIANTI study: which influences mobility more? *J Gerontol A Biol Sci Med Sci*. 2003;58(8):728-33.
- Bertsch T, Triebel J, Bollheimer C, et al. C-reactive protein and the acute phase reaction in geriatric patients. *Z Gerontol Geriatr*. 2015; 48(7):595-600.
- Bieler T, Magnusson SP, Kjaer M, Beyer N. Intra-rater reliability and agreement of muscle strength, power and functional performance measures in patients with hip osteoarthritis. *J Rehabil Med*. 2014;46(10):997-1005.
- Bodilsen AC, Pedersen MM, Petersen J, et al. Acute hospitalization of the older patient: changes in muscle strength and functional performance during hospitalization and 30 days after discharge. *Am J Phys Med Rehabil*. 2013;92(9):789-96.
- Bohannon RW, Kindig J, Sabo G, Duni AE, Cram P. Isometric knee extension force measured using a handheld dynamometer with and without belt-stabilization. *Physiother Theory Pract*. 2012;28(7):562-8.
- Breen L, Stokes KA, Churchward-Venne TA, et al. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. *J Clin Endocrinol Metab*. 2013;98(6):2604-12.
- Damas F, Phillips SM, Lixandrão ME, et al. Early resistance training-induced increases in muscle cross-sectional area are concomitant with edema-induced muscle swelling. *Eur J Appl Physiol*. 2015;116(1):49-56.
- De Buyser SL, Petrovic M, Taes YE, et al. Functional changes during hospital stay in older patients admitted to an acute care ward: a multicenter observational study. *PLoS One*. 2014;9(5):e96398.
- de Morton NA, Davidson M, Keating JL. The de Morton Mobility Index (DEMMI): an essential health index for an ageing world. *Health Qual Life Outcomes*. 2008;6:63.
- Devries MC, Breen L, Von Allmen M, et al. Low-load resistance training during step-reduction attenuates declines in muscle mass and strength and enhances anabolic sensitivity in older men. *Physiol Rep*. 2015;3(8):pii: e12493.
- English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care*. 2010;13(1):34-9.
- Fisher SR, Goodwin JS, Protas EJ, et al. Ambulatory activity of older adults hospitalized with acute medical illness. *J Am Geriatr Soc*. 2011;59(1):91-5.
- Häkkinen K. Neuromuscular fatigue and recovery in women at different ages during heavy resistance loading. *Electromyogr Clin Neurophysiol*. 1995;35(7):403-13.
- Hirsch CH, Sommers L, Olsen A, Mullen L, Winograd CH. The natural history of functional morbidity in hospitalized older patients. *J Am Geriatr Soc*. 1990;38(12):1296-303.
- Hvid LG, Suetta C, Nielsen JH, et al. Aging impairs the recovery in mechanical muscle function following 4 days of disuse. *Exp Gerontol*. 2014;52:1-8.
- Jackson AS, Janssen I, Sui X, Church TS, Blair SN. Longitudinal changes in body composition associated with healthy ageing: men, aged 20-96 years. *Br J Nutr*. 2012;107(7):1085-91.
- Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol (1985)*. 2000;89(1):81-8.
- Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport*. 1999;70(2):113-9.
- Karlsen A, Loeb MR, Andersen KB, et al. Improved functional performance in geriatric patients during hospital stay. *Am J Phys Med Rehabil*. 2017;96(5):e78-84.
- Kim DR, Reid KF, Hau C, Phillips EM, Fielding RA. What is a clinically meaningful improvement in leg-extensor power for mobility-limited older adults? *J Gerontol A Biol Sci Med Sci*. 2016;71(5): 632-6.
- Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA*. 2007;297(16):1772-4.
- Kortebein P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63(10):1076-81.
- Macri EM, Lewis JA, Khan KM, et al. The de Morton Mobility Index: normative data for a clinically useful mobility instrument. *J Aging Res*. 2012;2012:e353252.
- Magnus CR, Barss TS, Lanovaz JL, Farthing JP. Effects of cross-education on the muscle after a period of unilateral limb immobilization using a shoulder sling and swathe. *J Appl Physiol (1985)*. 2010;109(6):1887-94.
- Mathiowetz V, Rennells C, Donahoe L. Effect of elbow position on grip and key pinch strength. *J Hand Surg Am*. 1985;10(5):694-7.
- Merritt EK, Stec MJ, Thalacker-Mercer A, et al. Heightened muscle inflammation susceptibility may impair regenerative capacity in aging humans. *J Appl Physiol (1985)*. 2013;115(6):937-48.
- Narici MV, Roi GS, Landoni L, Minetti AE, Cerretelli P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. *Eur J Appl Physiol Occup Physiol*. 1989;59(4):310-9.
- Parker MJ, Palmer CR. A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br*. 1993;75(5):797-8.
- Pedersen MM, Bodilsen AC, Petersen J, et al. Twenty-four-hour mobility during acute hospitalization in older medical patients. *J Gerontol A Biol Sci Med Sci*. 2013;68(3):331-7.
- Scripture EW, Smith TL, Brown EM. On the education of muscular control and power. *Stud Yale Psychol Lab*. 1894;2:114-9.
- Skelton DA, Greig CA, Davies JM, Young A. Strength, power and related functional ability of healthy people aged 65-89 years. *Age Ageing*. 1994;23(5):371-7.
- Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-8.
- Suetta C, Frandsen U, Jensen L, et al. Aging affects the transcriptional regulation of human skeletal muscle disuse atrophy. *PLoS One*. 2012;7(12):e51238.
- Visser M, Fuerst T, Lang T, Salamone L, Harris TB. Validity of fan-beam dual-energy x-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, Aging, and Body Composition Study—Dual-Energy X-ray Absorptiometry and Body Composition Working Group. *J Appl Physiol (1985)*. 1999;87(4): 1513-20.
- Wählin-Larsson B, Carnac G, Kadi F. The influence of systemic inflammation on skeletal muscle in physically active elderly women. *Age (Dordr)*. 2014;36(5):9718.