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Circulating Acute Phase Mediators and Skeletal Muscle Performance in Hospitalized Geriatric Patients

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Background. There is growing evidence for the significant involvement of inflammatory processes in the development of muscle wasting in old age. Therefore, any disease accompanied by inflammation can be threatening to the muscle function in geriatric patients.

Methods. Sixty-three hospitalized geriatric patients (42 female, 21 male; mean age 84.2 ± 5.7 years) were monitored weekly for muscle function (grip strength, fatigue resistance, shoulder extension strength, and hip extension strength) and for concentration of circulating C-reactive protein (CRP), fibrinogen, interleukin 6 (IL-6), and tumor necrosis factor-α alpha (TNF-α).

Results. On the basis of circulating CRP and fibrinogen concentrations, 42 patients were categorized on admission as inflammatory and 21 as noninflammatory. Inflammatory patients presented significantly weaker grip strength, shoulder extension strength, and a worse fatigue resistance than did noninflammatory patients. These muscle functions were negatively correlated with the concentrations of circulating CRP and IL-6, but not with fibrinogen or TNF-α. In noninflammatory patients, the fatigue resistance improved significantly during the first week of hospitalization. In patients admitted with inflammation, no improvement of muscle function was observed. Patients who remained inflammatory for 2 weeks or more presented a significant worsening of fatigue resistance.

Conclusions. Geriatric hospitalized patients presenting with inflammation show significantly worse muscle functions, which do not improve during hospitalization despite adequate treatment of the primary disease. Reduced strength and fatigue resistance are significantly related to the concentration of circulating CRP and IL-6. Standard treatment of the underlying illness and classic physical therapy are not sufficient to normalize the skeletal muscle strength and fatigue resistance in these hospitalized patients.

SARCOPENIA, the age-related loss of skeletal muscle mass and strength, is one of the most prominent changes with advancing age (1–3). The underlying mechanisms of sarcopenia have not completely been identified, but there is growing evidence for the involvement of inflammatory processes (4,5). Inflammation is typically cytokine-mediated, implicating lymphocytes and monocytes (6). During pathologic conditions leading to inflammation, large amounts of cytokines are released. Inflammation in these situations is accompanied by a rapid and severe muscle wasting, which appears to be induced by the release of the proinflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α) (5–8).

Even in apparently healthy individuals, aging results in an increase of circulating IL-6. There is growing evidence that an increased concentration of circulating inflammatory cytokines, especially IL-6 and TNF-α, is related to a loss of skeletal muscle function and the development of disability in older persons (9–12).

It is obvious that, in elderly persons already presenting a certain degree of sarcopenia, a pathologically induced inflammation and its associated proteolysis can very rapidly lead to disability and morbidity. Such a situation is seen during infection and after trauma or surgical intervention (13–15). These events, therefore, are particularly dangerous and represent a high risk for loss of independence (16,17). Moreover, geriatric hospitalized patients presenting inflammatory conditions are most often confined to bed rest. It has been reported that 2 weeks of bed rest can reduce up to 15% of the maximal voluntary contraction of the lower limb muscles in healthy adult men (18). Therefore, it is to be expected that the immobility of geriatric hospitalized patients, even in a short stay, exacerbates the inflammation-induced muscle wasting. Determining the skeletal muscle function in frail geriatric patients is particularly difficult, especially when they are ill and unable to get out of bed and adapted techniques to measure muscle function are necessary.

The aim of this study was to evaluate the skeletal muscle function in hospitalized geriatric patients and to determine possible interactions with the degree of inflammation. We hypothesized that in hospitalized geriatric patients not only the decline in muscle force but also the degree of fatigability might be related to the level of circulating acute phase proteins.

Methods

Participants

All consecutively hospitalized patients at the Geriatric ward of the Academic Hospital of the Free University of Brussels were eligible for the study. At the time of admission, their health status was evaluated and the reason for

hospitalization was recorded. Patients who had undergone recent surgery, who used corticosteroids or nonsteroidal antiinflammatory drugs (NSAIDs), or who had a malignant tumor, dementia, or cognitive deterioration interfering with the test procedures were excluded from the study. From May through December 2000, 63 patients (42 female, 21 male) with a mean age of 84.2 ± 5.7 years were included. The study was approved by the local ethics committee (IRB OG016), and all patients provided written informed consent.

Measurements

On the day of admission and every 7th day thereafter during their stay in the hospital, patients provided blood samples in the morning after an overnight fast to determine levels of C-reactive protein (CRP; nephelometry, Behring, Marburg, Germany; normal value <10 mg/L) and fibrinogen (prothrombin time-derived automated method using ACL Futura Plus; Instrumentation Laboratory, Breda, The Netherlands; normal value <400 mg/dL) for screening and subsequent classification. Serum was frozen at −20°C for determination of cytokine levels at a later date. At the first evaluation, anthropometric measures were taken to estimate the total lean muscle mass and a cross-sectional ultrasonic measurement of the m. quadriceps and subcutaneous fat layer of the thigh.

Anthropometry.—The body mass index was calculated as weight (kg) / height $(m)^2$. Total body skeletal muscle mass was estimated with the formula (19):

$$\begin{aligned}\text{Muscle Mass (kg)} &= \text{Height (cm)} \times (0.0553\ \text{CTG}^2 + 0.0987\ \text{FG}^2 \\ &\quad + 0.0331\ \text{CCG}^2) - 2445\end{aligned}$$

where CTG = thigh circumference corrected for the front thigh skin fold thickness (cm), FG = uncorrected forearm circumference (cm), and CCG = calf circumference corrected for the medial calf skin fold thickness (cm).

Ultrasonic quadriceps muscle measurement.—At the middle of the line between the inguinal ligament (midpoint) and the cranial border of the patella, the ventral cross-sectional layer of the m. quadriceps (between femur and ventral fascia) and the subcutaneous adipose layer (between ventral fascia and skin) were measured using a real time ultrasonic device (Sonolayer L SAL-32B; Toshiba, Japan) equipped with a 3.5 MHz transducer for anthropometric classification of the patients.

Skeletal muscle performance.—Because most of the participants were severely ill and unable to get out of bed, conventional skeletal muscle function evaluation was not possible. Therefore, adapted techniques were used that allowed evaluation of bedridden patients. Grip strength and fatigue resistance were measured for the evaluation of distal muscle groups, and shoulder and hip extension for the evaluation of central muscle groups. All evaluations were performed with the subject lying supine, using a Martin vigorimeter device (Elmed, Addison, IL) consisting of an aneroid manometer connected to a compressible rubber bulb. During the compression of the rubber bulb, the air pressure in the system is recorded in KPa by a dynamic needle. This needle pushes on a supplementary passive needle, which remains in position until released by the observer.

Maximal grip strength was assessed as described by Desrosiers and colleagues (20); briefly, the shoulder was adducted and neutrally rotated, with the elbow flexed at 90°, the forearm in neutral position, and the wrist in light extension (0° to 30°). The patient was then instructed to squeeze the rubber bulb of the vigorimeter as hard as possible in three consecutive attempts. The highest score was recorded for each hand.

For the assessment of fatigue resistance, the patient was asked to squeeze the rubber bulb of the vigorimeter as hard as possible and to maintain this pressure as long as possible; the time (seconds) until the pressure diminished to half of the maximal grip strength was recorded for each hand. A standardized verbal encouragement (''keep squeezing, don't let go'') was given to the patient each time the pressure diminished. The same positioning of the patient's arm was adopted as for the grip strength test. The participants were instructed to maintain the elbow in 90° flexion and were not allowed to see the readings on the manometer during the entire procedure. Pilot data from a study by Bautmans and Mets (21) demonstrate good inter- and intrarater reliability for this fatigue resistance test with intraclass correlation coefficients [model (3,1)] (22) ranging from 0.88 to 0.94.

To evaluate the strength of larger muscle groups at the trunk and hip, maximal shoulder and hip extension strength were measured while the patient was in a supine position. For shoulder extension, the rubber bulb of the vigorimeter was positioned in the middle of a wooden plate (45 cm × 45 cm), which was placed next to the patient on the bed. The subject was asked to compress the rubber bulb as hard as possible on the wooden shelf with the ventral side of the hand while keeping the elbow and fingers extended. Hip extension was assessed similarly by instructing the patient to compress the rubber bulb with the heel of the foot as hard as possible against the wooden shelf while keeping the knee extended. The highest score of three attempts was recorded for each arm and leg.

Cytokine assay.—Sera were assayed for IL-6 and TNF-α by commercialized enzyme-linked immunosorbent assay (ELISA) kits (Biosource International, Nijvel, Belgium), according to the manufacturer's instructions. Cytokine concentrations were detected by comparing sample absorbance with the absorbance of a reference-purified recombinant cytokine. The lower limits of detection were <2 ng/L for IL-6 and 1.7 ng/L for TNF-α.

Categorization

On the basis of the levels of circulating CRP and fibrinogen, the participants were categorized into an inflammatory or noninflammatory group (neither marker elevated). Only patients presenting severe inflammation, due to, e.g., infectious processes, were considered to be inflammatory. Therefore, cutoff values for inflammation were 10 mg/L for CRP (23,24) and 400 mg/dL for fibrinogen.

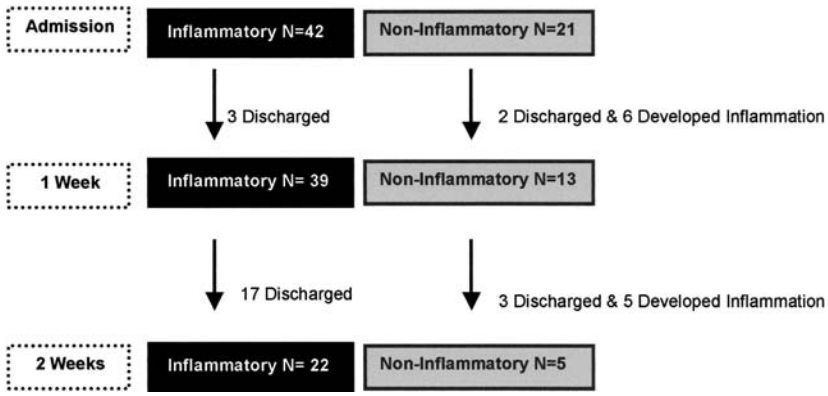

Figure 1. Evolution of the number of observed hospitalized geriatric patients and reasons for dropout.

Treatment

Patients received all treatment judged necessary by the resident in charge, independent from the evaluation procedures. When necessary, patients received acetaminophen to reduce fever or pain. Patients who needed treatment with NSAIDs or corticosteroids during their stay were excluded from the study. A standard physical therapy treatment was provided, according to the needs of the patient. Physical therapy interventions included mainly training of transfers and walking, respiratory exercises (i.e., for patients with pneumonia) and, when necessary, passive mobilizations of the limbs (i.e., for bedridden patients). No specific strength training exercises were administered to the observed patients. Physical therapists worked independently of the study and were unaware of the categorization of the patients and of the results of the measurements.

Statistical Analysis

All data subsets were assessed for normal distribution using the Kolmogorov–Smirnov goodness of fit test. For normally distributed data subsets, parametric statistics were performed (Pearson's correlation, Student's t test, analysis of variance). Those subsets not normally distributed were analyzed with nonparametric tests (Spearman's rho correlation, Mann–Whitney U test, Wilcoxon's signed rank test). Significance was set a priori at $p < .05$.

Results

Admission

On admission 42 patients (28 female, 14 male) were categorized as inflammatory and 21 (14 female, 7 male) as noninflammatory (see Figure 1). The most frequent diagnoses for inflammatory patients were respiratory and urinary tract infections and for noninflammatory patients cardiovascular or psychic disorders.

Male participants were significantly taller and stronger (grip, shoulder and hip extension strength) and had less subcutaneous mid-thigh fat than the female participants (all p values $< .01$). No significant differences concerning age, weight, body mass index, mid-thigh quadriceps muscle thickness, or fatigue resistance were observed between male and female participants. Two-way analysis of variance revealed no significant interactions between sex and inflammatory status for all observed parameters ($F = 1.2$; $p = .33$). Therefore, sexes were combined for further analysis of the inflammatory and noninflammatory groups.

As shown in Figure 2, significant differences in grip, arm and leg strength, and fatigue resistance were observed according to the inflammatory status on admission. As can be seen in Table 1, the serum level of IL-6 was significantly elevated in patients with inflammation, but the TNF-α serum concentration was only slightly and not significantly elevated. No significant differences were found between the inflammatory and noninflammatory participants concerning anthropometric measures and ultrasonic mid-thigh measurements.

Because the group of inflammatory patients was slightly but significantly older than the noninflammatory group (85.8 ± 5.6 years vs 81.0 ± 5.6 years, $p < .01$, see Table 1), this age difference could potentially influence the association between inflammation and muscular performance. Therefore, partial correlations, corrected for age, were calculated (see Table 2): grip strength, fatigue resistance, and shoulder and hip extension performance were negatively correlated with the serum concentrations of CRP and IL-6, but not with fibrinogen or TNF-α.

Evolution During Hospitalization

The median hospitalization length was 18 (5–51) days. Patients with inflammation on admission stayed on average 3 days longer than those without. Eleven patients developed inflammation during their stay (six and five patients, respectively, during the 1st and 2nd week) and were then excluded for further analysis (Figure 1).

First week.—As shown in Figure 2, no significant changes were found concerning grip strength or shoulder or hip extension strength in the inflammatory patients or in the noninflammatory patients. The fatigue resistance of the noninflammatory patients improved significantly (within-subjects contrasts: nondominant hand $F = 5.9$, $p < .05$) and the evolution of these patients was significantly different from the evolution of the inflammatory patients who remained at the same level (between-subjects contrasts: fatigue resistance

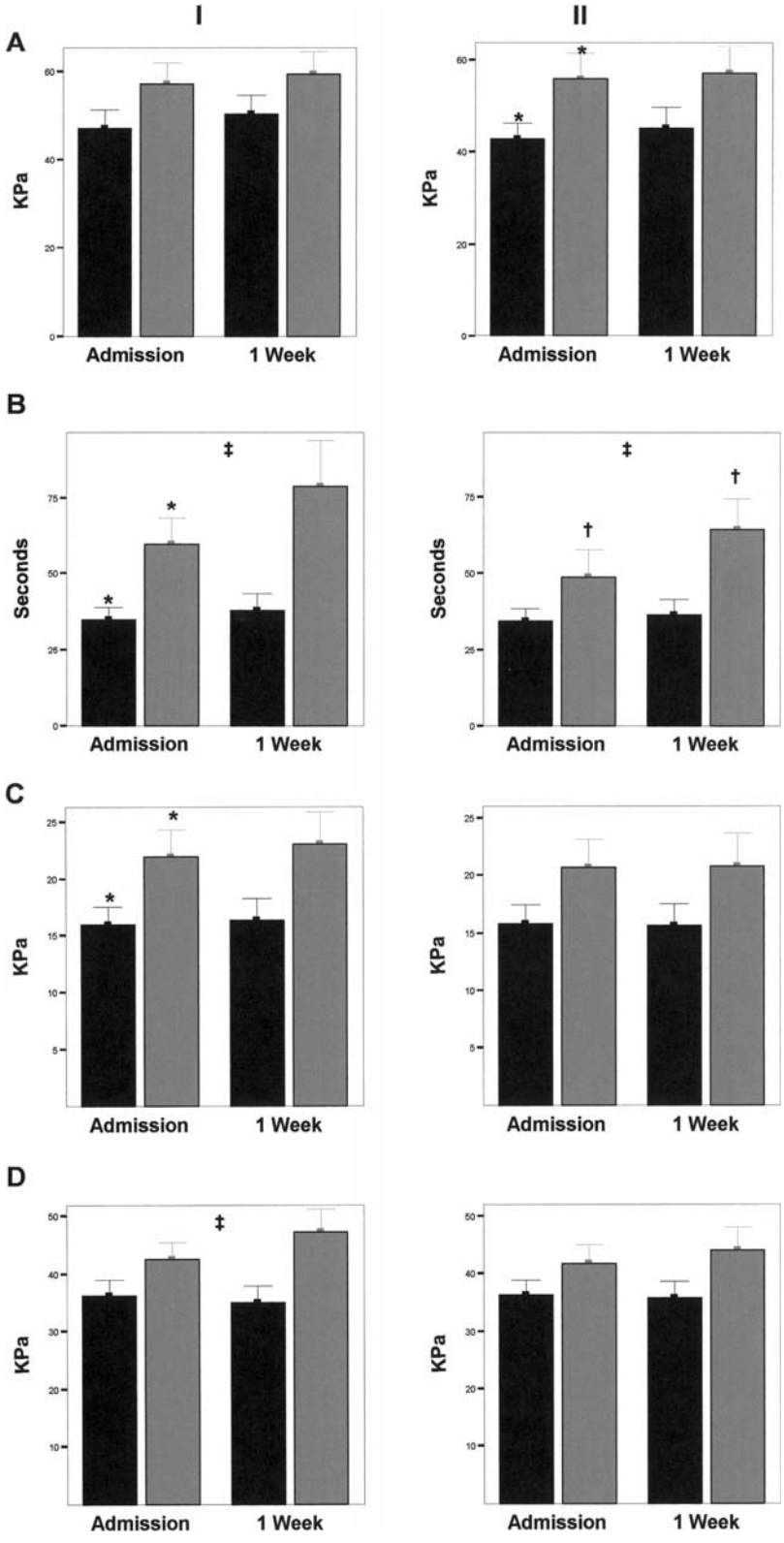

Figure 2. Difference in skeletal muscle performance between geriatric hospitalized patients with and without inflammation on admission; and evolution to 1-week hospitalization. **A**) Grip strength; **B**) fatigue resistance; **C**) shoulder extension strength; **D**) hip extension strength. I = Dominant hand, arm, or right leg; II = nondominant hand, arm, or left leg. *Significant difference between inflammatory and noninflammatory patients on admission (unpaired comparisons). †Significant increase ($p < .05$), ‡significant difference in evolution between inflammatory and noninflammatory patients ($p < .05$) (repeated measures analysis of variance).

Table 1. Profile of Geriatric Hospitalized Patients According to Inflammatory Status on Admission

Characteristic	Inflammatory ($N = 42$)	Noninflammatory ($N = 21$)
Sex, female/male (N)	28/14	14/7
Age, y*	85.8 ± 5.6	81.0 ± 5.6
Height, cm	159.3 ± 10.0	157.4 ± 7.1
Weight, kg	62.4 ± 14.4	62.5 ± 6.7
Body mass index, kg/m^2	24.5 ± 5.4	25.4 ± 3.6
Muscle mass estimation, kg	22.8 ± 6.2	23.9 ± 3.9
Muscle layer quadriceps (left), cm	1.7 ± 0.6	2.0 ± 0.6
Mid-thigh fat layer (left), cm	1.1 ± 0.7	1.0 ± 0.5
Muscle layer quadriceps (right), cm	1.7 ± 0.6	1.8 ± 0.5
Mid-thigh fat (right), cm	1.1 ± 0.6	1.0 ± 0.3
Serum concentration		
CRP, mg/L*	31.8 ± 34.6	6.8 ± 1.2
Fibrinogen, mg/dL*	473.4 ± 80.6	314.7 ± 43.1
IL-6, ng/L*	24.0 ± 59.2	1.2 ± 1.9
TNF-α, ng/L	52.0 ± 20.2	45.0 ± 21.0

Notes: Mean ± *SD*, except for sex.

*Difference between inflammatory and noninflammatory patients: $p < .01$.

CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α.

dominant hand $F = 11.3$, $p < .01$, fatigue resistance nondominant hand $F = 5.8$, $p < .05$). Also, the evolution of the hip extension strength (dominant leg) in the noninflammatory patients was significantly different than that in the inflammatory patients ($F = 4.5$, $p < .05$). As can be seen in Table 3, the inflammatory patients showed a significant decrease in circulating CRP ($p < .01$) and IL-6 ($p < .05$) concentrations during the 1st week of observation. In contrast, the levels of fibrinogen and TNF-α remained elevated in these patients.

Second week.—Paired comparisons were made using the Wilcoxon's signed rank test between day 8 and day 15. As shown in Table 4, the fatigue resistance worsened significantly within the 2nd week of hospitalization in those patients who remained inflammatory. No further changes in circulating inflammatory proteins were detected. Fatigue resistance in the noninflammatory patients appeared to remain stable (mean, both hands: 71.9 ± 62.0 s and 75.6 ± 57.9 s on day 8 and day 15, respectively) but, because this group was too small ($N = 5$), no statistical analysis was performed.

Table 2. Interrelationships Between Acute Phase Markers and Muscle Performance in Geriatric Hospitalized Patients ($N = 63$)

First Parameter	IL-6	TNF-α	CRP	Fibrinogen
Grip strength, dominant hand	−0.32*	−0.30	−0.21	−0.08
Fatigue resistance, dominant hand	−0.26*	0.09	−0.20	−0.10
Shoulder extension, dominant arm	−0.31*	−0.03	−0.27*	−0.13
Hip extension, right leg	−0.40†	<−0.01	−0.34†	−0.16
Fibrinogen	0.32*	0.30*	0.51†	
CRP	0.67†	0.08		
TNF-α	<0.01			

Notes: All values represent partial correlation coefficients, corrected for age.

*$p < .05$; †$p < .01$.

IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α; CRP = C-reactive protein.

Table 3. Evolution of the Concentration of Circulating Acute Phase Proteins During the First Week of Hospitalization in Geriatric Patients With Inflammation ($N = 39$) and Without Inflammation ($N = 13$)

Parameter	On Admission	Day 8
CRP, mg/L		
Inflammatory†	33.4 ± 35.9	17.8 ± 18.6
Noninflammatory	6.8 ± 1.6	6.2 ± 2.2
Fibrinogen, mg/dL		
Inflammatory	470.7 ± 77.2	470.4 ± 102.2
Noninflammatory	312.7 ± 38.0	289.6 ± 33.0
IL-6, ng/L		
Inflammatory*	23.4 ± 60.9	9.8 ± 18.5
Noninflammatory	0.7 ± 0.9	1.6 ± 2.3
TNF-α, ng/L		
Inflammatory	51.5 ± 20.5	50.5 ± 20.0
Noninflammatory	43.9 ± 15.5	42.2 ± 17.8

Notes: Data are presented as means ± *SD*.

Significant decrease: *$p < .05$; †$p < .01$.

CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α.

Discussion

Although widely accepted, decreased skeletal muscle function during inflammation has not been well documented in geriatric hospitalized patients. Determining the skeletal muscle function in these patients is particularly difficult, especially when they are ill and unable to get out of bed. In the present study, the Martin vigorimeter was used to measure muscle function. The validity (25) and reliability of this instrument for the evaluation of grip strength (26) and fatigue resistance (21) has been established. The shoulder and hip extension strength measurements were derived from the method described by Helewa and colleagues (27), who used a modified sphygmomanometer.

Table 4. Evolution of Muscle Function Capacities and Concentration of Circulating Acute Phase Mediators Over the 2nd Week of Hospitalization in Geriatric Patients Who Remained Inflammatory ($N = 22$)

Parameter	Day 8	Day 15
Grip strength, dominant hand (KPa)	52.0 ± 26.8	50.9 ± 26.9
Grip strength, nondominant hand (KPa)	43.7 ± 27.5	45.8 ± 26.3
Fatigue resistance, dominant hand (s)*	42.7 ± 40.0	31.8 ± 27.9
Fatigue resistance, nondominant hand (s)*	41.8 ± 32.1	32.6 ± 26.4
Shoulder extension, dominant arm (KPa)	16.5 ± 9.8	16.9 ± 11.5
Shoulder extension, nondominant arm (KPa)	16.3 ± 10.8	16.5 ± 10.8
Hip extension, right leg (KPa)	36.4 ± 14.9	37.7 ± 17.2
Hip extension, left leg (KPa)	38.0 ± 15.5	36.8 ± 18.1
CRP, mg/L	16.8 ± 15.5	15.3 ± 14.0
Fibrinogen, mg/dL	475.3 ± 97.4	461.7 ± 92.7
IL-6, mg/L	8.8 ± 20.2	8.1 ± 10.0
TNF-α, mg/L	53.6 ± 22.6	50.7 ± 21.6

Notes: Data are presented as means ± *SD*.

Significant difference between day 8 and day 15: *$p < .05$.

CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α.

In this study, the inflammatory profile of the patients was based on circulating CRP and fibrinogen concentrations, which are reliable markers of inflammatory processes (24,28). Only significant elevations in circulating acute phase proteins (>10 mg/L for CRP and/or >400 mg/dL for fibrinogen) were considered to be indicators for acute inflammation related to active disease. The Centers for Disease Control and Prevention (29) recommends considering circulating high sensitivity CRP concentrations >3 mg/L to be a risk factor for the development of cardiovascular disease in asymptomatic individuals. CRP levels >3 mg/L indicate an ''inflammatory load.'' In our study, the aim was to distinguish geriatric patients suffering from severe inflammatory conditions from those without major inflammation. It has been demonstrated that in situations like infection, trauma, surgery, burns, tissue infarction, and advanced cancer, circulating CRP levels can rise up to 1000-fold (23). These acute phase reactions are typically cytokine-mediated and can lead to muscle wasting (7,8). We chose the cutoff value of 10 mg/L for circulating CRP concentration to identify hospitalized geriatric patients with inflammatory conditions. The geriatric patients who presented a generalized inflammation on admission were significantly weaker and less fatigue resistant than noninflammatory patients. No significant differences could be found concerning the whole-body muscle mass estimations or cross-sectional ultrasonic m. quadriceps measurements between both groups, indicating that no anatomical explanation existed for the functional differences. These results also point out that, during severe inflammation, muscle function is impaired before muscle atrophy becomes measurable.

The inflammatory patients in the study were slightly but significantly older than the noninflammatory ones (85.8 $\pm$ 5.6 years vs 81.0 $\pm$ 5.6 years, $p < .01$). This might indicate that older patients are more likely to be hospitalized because of inflammatory diseases, but cautious interpretations should be made regarding this age difference, because the study sample is rather small.

The skeletal muscle function was found to correlate negatively (after correction for age) with the circulating IL-6 and with CRP but not with fibrinogen or TNF-α. This seems to indicate that the degree of strength deficit and fatigue resistance might be related to the extent of the acute phase reaction. These findings correspond with those of Drent and colleagues (30) who describe a significantly higher CRP concentration in sarcoidosis patients suffering from fatigue and exercise intolerance compared to those without fatigue. It is not clear by which mechanism IL-6 and CRP could influence the reductions in strength and fatigue resistance during inflammation. On the one hand, it has been demonstrated that IL-6 can increase protein breakdown in skeletal muscle during pathological situations (31), leading to muscle weakness. On the other hand, the increase in circulating cytokines can provoke—through stimulation of the paraganglia surrounding terminations of the n. vagus—a sickness behavior that is characterized by fatigue and reduced activity (32).

After the 1st week of hospitalization, a significant decrease in circulating CRP and IL-6 levels was observed in the inflammatory patients, indicating an improvement in their underlying disease state. This improvement in inflammatory status did not result in improved muscle strength or fatigue resistance. However, in the noninflammatory patients, the fatigue resistance improved significantly after 1 week of hospitalization. Because a large number of the patients needed hospitalization for less than 2 weeks and five noninflammatory patients developed inflammation after the 1st week at the hospital, only 22 inflammatory and 5 noninflammatory patients remained in the study at the end of week 2. During the 2nd week of hospitalization, fatigue resistance worsened significantly in the inflammatory patients. After 2 weeks, the group of noninflammatory patients had become too small to allow further analysis.

It is noteworthy that the grip strength performance of the inflammatory patients was below the sex- and age-matched quantile .05 values for apparently healthy persons as proposed by Merkies and colleagues (33). Standard treatment of the disease and classic physical therapy during hospitalization, therefore, seem insufficient to maintain or improve skeletal muscle strength and fatigue resistance in these patients. Clinicians must place more importance on the reduced skeletal muscle function in their hospitalized geriatric patients presenting severe inflammatory processes.

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