Functional Impact of 10 Days of Bed Rest in Healthy Older Adults

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Background. Many older individuals decline functionally during hospitalization, and the deleterious consequences of bed rest may be one cause. This study reports on the effect of 10 days of bed rest on multiple functional parameters in healthy older adults.

Methods. Healthy older men and women (n = 11, 67 ± 5 years old) remained on bed rest for 10 days continuously, and consumed a eucaloric diet providing the Recommended Dietary Allowance for protein. Measures of lower extremity strength and power, aerobic capacity and physical performance, as well as physical activity were performed before and after bed rest.

Results. All measures of lower extremity strength were significantly lower after bed rest including isotonic knee extensor strength (−13.2 ± 4.1%, p = .004) and stair-climbing power (−14 ± 4.1%, p = .01). Maximal aerobic capacity was 12% lower after bed rest (p = .04), whereas measures of physical performance (Short Physical Performance Battery, and a five-item physical performance test) were not significantly different. Voluntary physical activity decreased after bed rest, and the percentage of time spent inactive increased (7.6 ± 1.8%, p = .004). There were no medical complications.

Conclusions. In healthy older adults, 10 days of bed rest results in a substantial loss of lower extremity strength, power, and aerobic capacity, and a reduction in physical activity, but has no effect on physical performance. Identification of interventions to maintain muscle function during hospitalization or periods of bed rest in older adults should be a high priority.

Key Words: Aging—Geriatric—Bed rest—Strength—Power—Aerobic capacity—Function.

Hospitalization results in a substantial decline in functional status in older adult patients; between 30% and 55% of older patients demonstrate a decline in activities of daily living and up to 65% in ambulatory function during hospitalization (1–6). Not infrequently, this decline in function results in nursing home placement (4,5). This is an important issue as older adults represent the majority of hospitalized patients (7) and the number of older adults is projected to double by 2030 (8).

Physical inactivity or bed rest during hospitalization has been proposed as a primary factor contributing to the functional decline of older hospitalized patients (9,10). Recently, we reported that healthy older adults lose almost 1 kg of lean tissue from the lower extremities after 10 days of bed rest, with an associated 16% decline in isokinetic knee extensor strength (11). This marked loss of muscle mass and strength is greater than that observed in young adults after 14 or 28 days of bed rest (12,13). These results are remarkable in that one could hypothesize that these older persons would lose less muscle with bed rest than would their young counterparts because older individuals, in general, have less muscle mass and are less physically active at baseline. In addition to a loss of muscle mass and strength, previous bed rest studies in younger persons have noted a significant decline in aerobic capacity (14,15). No previous studies have specifically examined the independent effect of bed rest on aerobic capacity and physical performance in older adults. This article expands on the results of our previous findings (11) and describes the functional impact of 10 days of bed rest in healthy older men and women, including lower extremity strength and power, maximal aerobic capacity, physical performance, and daily physical activity.

Methods

Participants

Healthy, older (60–85 years old) men and women (n = 6 each) were recruited from the communities of Little Rock, Arkansas, and Galveston, Texas. Their average age was 67 ± 5 years (range 62–75 years), with mean body mass index of 29 ± 3 kg/m². A medical history and physical examination were performed on each potential participant, as well as routine blood and urine analysis, and a maximal exercise stress test. Exclusion criteria included a positive exercise stress test, history of deep vein thrombosis (DVT)/
pulmonary embolism, and a Short Physical Performance Battery (SPBB) (16,17) score < 9. The study protocol was identical at both locations, and was approved by the institutional review board at each study site. Each participant signed a written informed consent prior to participation in the study. One male participant was not included in any ana-
tyses because of a dietary error (i.e., protocol deviation) and resultant insufficient protein intake (∼ 0.5 g/kg/d). Thus, analyses were performed on 11 participants, except as noted.

Study Protocol

Participants completed 10 continuous days of bed rest at the General Clinical Research Center (GCRC) of each institution. The study protocol is presented in Table 1. All participants performed all basic activities of daily living (e.g., eating, bathing) in bed, although they used a bedside commode or were transported by wheelchair for brief bathroom privileges (approximately 5 minutes). Bed rest procedures were reviewed with each participant and were reinforced by the investigators and the nursing staff. The study nurses monitored the participants for safety and protocol compliance via personal interaction and closed circuit cameras. All participants consumed a eucaloric (kcal protocol compliance via personal interaction and closed study nurses monitored the participants for safety and reinforced by the investigators and the nursing staff. The procedures were reviewed with each participant and were completed the study.

Maximal aerobic capacity (VO\textsubscript{2max}).—This was measured during a maximal exercise stress test on an electrically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands). Briefly, participants cycled at a warm-up intensity (30W for men, 10W for women) for 3 minutes, followed by two additional 3-minute periods at a slightly higher intensity (+20W each), with incremental increases (+20W) in intensity every subsequent minute until volitional fatigue or other termination criteria as per American College of Sports Medicine criteria (20). The pre-bed rest maximal stress test was completed within 2 months of initiating the bed rest. There was no significant change in habitual physical activity for any of the participants, thus this measurement is felt to be an accurate representation of baseline aerobic capacity. Data were available for nine participants, as two UTMB participants had already completed the bed rest before this measure was added to the protocol.

Physical performance.—This was determined with two validated measures: the SPBB (17), and a five-item physical performance test (5-minute walk, 50-foot walk, five-step test, functional reach, and floor transfer) (21). These two tests were performed as previously described (17,21).

Daily physical activity.—This was recorded with an activity monitor (Stepwatch 3; Cyma Corporation, Mountlake Terrace, WA). The participants wore the monitor on the ankle during the day, except for bathing. This monitor can record low-level activity (22), and provides information on the total number of steps per day as well as minute-by-minute data on activity intensity. The raw data were downloaded to a personal computer and analyzed by a single investigator (SC) using StepWatch 3.1 Analysis Software (Cyma Corporation). The average number of steps per minute was calculated, as well as the amount of time spent inactive (0 steps), or performing low (≤30 steps/min)-

### Table 1. Bed Rest Study Timeline

<table>
<thead>
<tr>
<th>Study Visit/Day</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening visit 1</td>
<td>Informed consent, blood tests, and OGTT</td>
</tr>
<tr>
<td>Screening visit 2</td>
<td>Medical health questionnaire, H&amp;P, and SPPB</td>
</tr>
<tr>
<td>Screening visit 3</td>
<td>VO\textsubscript{max} stress test (within 2 mo of start)</td>
</tr>
<tr>
<td>Prestudy visit</td>
<td>Activity monitor collection (M-F starting 2 wk prior to initiation of bed rest)</td>
</tr>
<tr>
<td>Study day 1</td>
<td>Admit GCRC, start diet, POMS, Strength/Functional testing</td>
</tr>
<tr>
<td>Study day 2</td>
<td>DEXA</td>
</tr>
<tr>
<td>Study day 3</td>
<td>Repeat strength testing</td>
</tr>
<tr>
<td>Study day 4</td>
<td>POMS, Arrive for study (evening)</td>
</tr>
<tr>
<td>Study day 5</td>
<td>1st metabolic study begins, orthostatic test</td>
</tr>
<tr>
<td>Study day 6</td>
<td>1st metabolic study ends, OGTT</td>
</tr>
<tr>
<td>Study day 7</td>
<td>D-dimer test, POMS</td>
</tr>
<tr>
<td>Study days 9–18</td>
<td>10 days’ bed rest, POMS (every 3 days)</td>
</tr>
<tr>
<td>Study day 17</td>
<td>D-dimer test &amp; lower extremity ultrasound examination</td>
</tr>
<tr>
<td>Study day 18</td>
<td>2nd metabolic study begins, orthostatic test</td>
</tr>
<tr>
<td>Study day 19</td>
<td>2nd metabolic study ends/bed rest complete, DEXA, OGTT, POMS, Strength/Functional testing</td>
</tr>
<tr>
<td>Study day 20</td>
<td>VO\textsubscript{max} activity monitor collection starts (matched for time period pre-bed rest), rehabilitation orientation, discharge home</td>
</tr>
<tr>
<td>Study day 22</td>
<td>Rehabilitation program starts</td>
</tr>
</tbody>
</table>

Notes: Metabolic Study: 24 hour muscle protein synthesis measurement. H&P = history and physical examination; OGTT = oral glucose tolerance test; SPPB = Short Physical Performance Battery; VO\textsubscript{2max} = exercise stress test/maximal oxygen uptake; M-F = Monday to Friday; GCRC = General Clinical Research Center; 1-RM = one repetition maximum; DEXA = dual x-ray absorptiometry; POMS = Profile of Moods State questionnaire.

Muscle strength.—Measurements included unilateral (right) maximal isometric and isokinetic (180°/s) knee extension and flexion torque using a Cybex dynamometer (Cybex Strength Systems, Ronkonkoma, NY), as well as maximal isotonic (one-repetition maximum; 1-RM) knee extension strength (University of Texas Medical Branch [UTMB]; Cybex Strength Systems, Ronkonkoma, NY; University of Arkansas for Medical Sciences [UAMS]: Keiser Sports Health Equipment, Fresno, CA). As different machines were used for the isotonic knee extension strength (1-RM) measure, this result is reported as a percent change only. Isokinetic knee extension torque at 60°/s was previously reported (11). Upper extremity strength measurements were not performed, as previous bed rest studies of longer duration in young adults have not detected any change (19).

Stair ascent power.—This was calculated with each participant’s weight (N) and the time in seconds to ascend 10 steps (Power = (Distance/Time) × Weight). Participants were instructed to climb the stairs as fast as comfortably possible with one hand near, but not on, the handrail. The results of eight participants are reported, as this test was not added to the protocol until three participants had already completed the study.

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medium (>30–80 steps/min), and high (>80 steps/min)-level activity. Participants kept a diary to record when the monitor was removed. As there was overlap with the post-bed rest exercise rehabilitation program, analysis of total daily activity was performed with and without the rehabilitation activity time included. In addition, we excluded any time period when the participants noted that they had removed the monitor. Participants wore the monitor for an average of 5 days before and after bed rest, and the monitoring times for each participant were matched for the specific days of the week and total number of days. Three to five days of monitoring time is recommended for a reliable estimate of physical activity (23). Data were available for eight participants; two participants had completed bed rest prior to the addition of this measure, and post-bed rest data were not available for one participant as the monitor was worn incorrectly.

Safety
The study physician examined the participants daily during bed rest, with particular attention to signs of DVT and skin erythema/breakdown. A screening evaluation for DVT was completed daily (24), and the following prophylactic measures were instituted during bed rest: compression stockings and sequential compression devices, active ankle plantar- and dorsiflexion intermittently each day, and passive range of motion of the lower extremities three times per day. A quantitative D-dimer test was also performed on two occasions (2 days prior to bed rest and on day 9 of bed rest) with a bilateral lower extremity ultrasound examination performed on day 9 of bed rest. If the pre-bed rest D-dimer was positive, a lower extremity ultrasound examination was performed at that time. No DVT was found in any participant. Participants were also monitored closely for symptoms of orthostatic hypotension whenever they were transferred, and were accompanied while ambulating immediately after bed rest. A formal orthostatic tolerance test was completed for all participants before and after bed rest, and the Profile of Mood State (POMS) questionnaire (25) was completed every 3rd day during the study to detect any depressive symptoms. These measures, as well as the results of the post-bed rest rehabilitation exercise program, will be reported separately.

Statistical Analysis
Data are presented as means ± standard error of the mean. Pre- and post-bed rest values for strength, power, maximal aerobic capacity, physical activity, and physical performance (SPPB, and cumulative five-item testing) were compared by paired t test, and a modified Bonferroni (Simes) correction (26) was performed to account for the multiple tests (R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing 2007, Vienna, Austria). The individual component measures of the SPPB and five-item physical performance test were analyzed using Wilcoxon rank-sum tests because of the skewed distribution of these data; the same statistical package (R: A Language and Environment for Statistical Computing) was used for these analyses. This study was powered to detect changes in muscle protein synthesis and

### Table 2. Lower Extremity Muscle Performance and Aerobic Capacity

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-Bed Rest</th>
<th>Post-Bed Rest</th>
<th>% Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee extension (N = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-RM</td>
<td>–</td>
<td>–</td>
<td>–13.2 ± 3.5</td>
<td>.004</td>
</tr>
<tr>
<td>Isometric (N)</td>
<td>133.7 ± 15.1</td>
<td>117.6 ± 13.6</td>
<td>–11.2 ± 3.9</td>
<td>.017</td>
</tr>
<tr>
<td>Concentric 180°</td>
<td>69.9 ± 8.1</td>
<td>60.1 ± 7.0</td>
<td>–13.5 ± 4.4</td>
<td>.011</td>
</tr>
<tr>
<td>(N·m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee flexion (N = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric (N)</td>
<td>76.8 ± 10.0</td>
<td>68.1 ± 10.5</td>
<td>–14.2 ± 3.6</td>
<td>.003</td>
</tr>
<tr>
<td>Concentric 60°</td>
<td>80.3 ± 8.8</td>
<td>71.6 ± 9.4</td>
<td>–11.8 ± 4.6</td>
<td>.03</td>
</tr>
<tr>
<td>(N·m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric 180°</td>
<td>51.8 ± 7.7</td>
<td>46.6 ± 8.2</td>
<td>–13.2 ± 4.3</td>
<td>.01</td>
</tr>
<tr>
<td>(N·m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stair ascent power</td>
<td>(N·m/s) (N = 8)</td>
<td>337 ± 48</td>
<td>–14.0 ± 4.1</td>
<td>.01</td>
</tr>
<tr>
<td>VO₂max (mL·kg/min)</td>
<td>22.7 ± 2.0</td>
<td>19.72 ± 1.7</td>
<td>–12.2 ± 4.5</td>
<td>.04</td>
</tr>
</tbody>
</table>

Notes: All values are mean ± standard error of the mean. 1-RM = one repetition maximum; VO₂max = maximal oxygen uptake.

knee extensor strength, and not the physical performance measures. Relevant covariates were not included in the statistical analyses, as adjusting for covariates may have produced unstable estimates due to the small sample size.

RESULTS

**Lower Extremity Strength and Power**

The relative and absolute changes in knee extension strength and torque are depicted in Table 2. There was a significant decrease in all measures of unilateral (right) knee extension strength including isometric (−11.2 ± 3.9%, p = .02) and isokinetic torque (180°/s) (−13.5 ± 4.4%, p = .01), as well as isotonic 1-RM (−13.2 ± 3.5%, p = .004). As noted, we recently reported a similar significant reduction in isokinetic knee extension torque at 60°/s (−15.6 ± 3.4%, p = .001) (11). All measures of unilateral knee flexion torque declined similarly (isometric: −14.2 ± 3.6%, isokinetic [60°/s]: −11.8 ± 4.6%, isokinetic [180°/s]: −13.2 ± 4.3%; p = .003, p = .03, p = .01, respectively). Also, a significant reduction in stair climbing power was found in these participants (−66.2 ± 22.2 Nm/s, −14.0 ± 4.1%; p = .02 and .01, respectively). All of these changes remained statistically significant with the Simes correction, except for isokinetic knee flexion at 180°/s.

**Maximal Aerobic Capacity**

Mean pre-bed rest VO₂max was 22.7 ± 2 mL/kg/min, and declined 12 ± 4% after the 10 days of bed rest (p = .04).

**Physical Performance and Physical Activity**

Neither of the two measures of physical performance changed significantly as a result of 10 days of bed rest; the mean summed score for the SPPB remained > 11 (pre-bed rest: 11.5 ± 0.2, post-bed rest: 11.3 ± 0.4 [range 10–12 before and after bed rest], p = .44), whereas the cumulative score for the five-item physical performance declined from
13.5 ± 0.5 to 12.7 ± 0.6 (range 11–15 pre-bed rest, and 9–15 post-bed rest) \( (p = .08) \). Evaluation of the individual components of the physical performance measures did not identify a statistically significant change either. The average number of steps walked per minute during each collection period was not significantly different when the rehabilitation time (average of 80 minutes per participant) was included (Table 3). The percentage of time spent inactive increased significantly (regardless of inclusion of the rehabilitation time), and this was almost exclusively due to a decline in low-level activity between the two time periods (Table 3). There was no significant change in medium- or high-level activity.

**Medical Issues**

There were no significant medical complications during this study. A few participants developed mild erythema of the extensor aspect of the elbow related to eating on their side; however, this resolved promptly after the bed rest. During the orthostatic tolerance testing at the completion of the bed rest, two participants were symptomatic with transient uncomplicated syncope.

**DISCUSSION**

The principal findings of this study are that in healthy older adults 10 days of bed rest results in a substantial loss of lower extremity strength and power, as well as aerobic capacity. These bed rest–induced changes are associated with a reduction in overall physical activity. The measures of physical performance examined did not demonstrate any significant change despite the substantial decline in strength and power. Although these results cannot be directly extrapolated to older hospitalized patients, these findings provide new information regarding the effect of bed rest alone in older persons, independent of the many other factors associated with hospitalization. Because our population was healthy, ill older adults hospitalized for a similar period of time are likely to experience a more pronounced loss of muscle strength, power, and aerobic capacity.

The detrimental effect of bed rest for hospitalized patients has been reported intermittently in the modern medical literature since at least 1944 (27–29). However, the specific effects of bed rest alone have not been previously evaluated in older adults. Rather, previous bed rest studies have primarily used this paradigm as a model for the effects of weightlessness related to space flight. These studies have almost exclusively examined young persons, although individuals up to approximately 50 years of age have participated as well (14,19). However, understanding the effects of bed rest in older individuals is important as older adults represent the majority of hospitalized patients (7), and patients may spend a substantial amount of time in bed during hospitalization (10,29,30).

Previous bed rest studies in young adults have reported a loss of muscle strength primarily of the lower extremity extensor muscle groups (19,31). Our findings were similar, although our participants experienced a >13% decline in 1-RM knee extensor strength, whereas Ferrando and colleagues (32) reported a 9% decline with 14 days of bed rest. Leblanc and colleagues (19) found a similar reduction in knee extensor torque (but no significant change in knee flexion torque) after 1 week of bed rest. Contrary to this latter finding, our older participants had at least a 12% decline in all measures of knee flexion. This result may indicate that older adults experience a more global loss of lower extremity strength as compared to younger individuals.

Lower extremity muscle power was also significantly reduced in these older adults after bed rest. These findings are consistent with results from bed rest studies that used younger participants, although direct comparisons are difficult as these other studies used different methods for measuring power, and the bed rest exposure was substantially longer than that for our participants (33,34). However, as lower extremity power has been recognized as a more influential component of lower extremity function than muscle strength in mobility-limited older adults, a similar decline in muscle power may be of substantial clinical relevance in older individuals exposed to bed rest (35,36).

Despite these substantial reductions in lower extremity strength and power, our participants did not experience any decrement in physical performance as measured by two validated geriatric instruments. This finding is likely related to the small number of participants, leading to inadequate power, and our exclusion of persons with functional limitations. The SPPB is acknowledged to be relatively insensitive to change in high-functioning older individuals (37). In contrast to our healthy participants, older hospitalized patients with a more limited physiological reserve are likely to decline functionally as a result of a similar impairment of lower extremity strength and power. For example, a study of frail community-dwelling older adults found that bed rest, even without hospitalization, is sufficient to detrimentally impact function (38).

To the best of our knowledge, no previous study has examined the effect of bed rest on maximal aerobic capacity in older adults. However, our results are similar to those reported by Convertino and colleagues (14) in middle-aged men (mean 50 years) also undergoing 10 days bed rest; we found a 12% decline in maximal aerobic capacity with our

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**Table 3. Bed Rest-Related Physical Activity**

<table>
<thead>
<tr>
<th></th>
<th>N = 8</th>
<th>Steps/min</th>
<th>No Activity</th>
<th>Low Activity</th>
<th>Medium Activity</th>
<th>High Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-bed rest</td>
<td></td>
<td>11.9 ± 1.4</td>
<td>54 ± 4%</td>
<td>32 ± 2%</td>
<td>12 ± 2%</td>
<td>2 ± 1%</td>
</tr>
<tr>
<td>Post-bed rest without exercise</td>
<td>9.7 ± 1.3 (0.02)</td>
<td>62 ± 3% (0.004)</td>
<td>26 ± 2% (0.02)</td>
<td>11 ± 2% (0.08)</td>
<td>1 ± 0.4% (0.11)</td>
<td></td>
</tr>
<tr>
<td>Post-bed rest with exercise</td>
<td>10.5 ± 1.3 (0.12)</td>
<td>61 ± 3% (0.005)</td>
<td>26 ± 2% (0.02)</td>
<td>11 ± 2% (0.08)</td>
<td>2 ± 1% (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Notes: Pre-bed rest activity monitoring occurred 2 weeks prior to bed rest, and the post-monitoring was initiated on the day after bed rest was completed. Physical activity: no activity (0 steps), low activity (<30 steps/min), medium activity (>30–80 steps/min) and high activity (>80 steps/min). An average of 80 minutes of rehabilitation exercise activity per participant was included in the “Post-Bed Rest with Exercise” analysis. All values are mean ± standard error of the mean (p value).*
mixed gender group, whereas they reported a nearly 16% change. Although all of our participants were fully independent, and most were active recreationally, their average VO$_{2\text{max}}$ performance is less than the 10th percentile for adults older than 60 years (20). As aerobic capacity, on average, drops about 1.5% per year in adults 50–70 years old (39), this loss of aerobic capacity after 10 days of bed rest was equivalent to almost a decade of decline. However, as maximal aerobic capacity declines even more precipitously in individuals older than 70 years (40), a similar decrement in older more frail individuals exposed to bed rest is likely to have an even more substantial impact on functional performance, particularly ambulatory endurance.

During the week after bed rest, our older participants were significantly less active. This decrease in physical activity was almost entirely due to a reduction in low-level physical activity, and remained unchanged, regardless of inclusion or exclusion of the rehabilitative exercise program from the analysis of total physical activity. The reduced physical activity in these participants may be attributable, directly or indirectly (e.g., fatigue), to their decline in aerobic capacity and lower extremity muscle function.

Our findings provide new information regarding the deleterious effect of bed rest in older men and women independent of the multiple other factors associated with hospitalization. It is likely that the loss of lower extremity muscle strength, power, and aerobic capacity in older hospitalized adults is even more pronounced than in our participants, particularly for patients requiring prolonged treatment in an intensive care setting. As with most geriatric problems, the functional decline of older hospitalized patients is a multifactorial process (9, 10). In addition to the bed rest and inactivity frequently attendant with hospitalization, other potentially detrimental processes may include baseline sarcopenia, a generalized inflammatory milieu with elevated cytokines (41), nutritional compromise (42), and the unique impact of the specific illness or injury precipitating hospitalization, as well as any iatrogenic complications (e.g., corticosteroids or neuromuscular blocking agents) (9). Although we did not measure cortisol levels, Ferrando and colleagues (12) found no change due to bed rest alone in cortisol, testosterone, insulin, or insulin-like growth factor 1 (IGF-1) in young adults. However, bed rest inactivity is known to sensitize skeletal muscle to the catabolic effects of corticosteroids (43). It is also important to note that, despite a eucaloric diet with the current RDA for protein, our healthy older participants still lost significant amounts of lean tissue (11) and strength. Thus, continued efforts are needed to identify methods of optimizing protein intake in patients during hospitalization.

The older adult population is projected to increase significantly over the next several decades, and the number of older adults requiring hospitalization will likely increase in a similar fashion. Our results indicate that bed rest alone has a substantial detrimental impact on lower extremity skeletal muscle function and aerobic capacity in healthy older adults. Given these findings, bed rest for older patients should be limited as much as possible during hospitalization. These patients should be actively encouraged to remain out of bed as early as medical treatment allows, and this should include assistance with ambulation from nursing staff or formal physical therapy. Additional means of maintaining muscle function during bed rest in older adults, including resistance exercise, and nutritional or pharmacological interventions, should be vigorously pursued.

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**REFERENCES**


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