ORIGINAL ARTICLE

Hip, thigh and calf muscle atrophy and bone loss after 5-week bedrest inactivity

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Abstract Unloaded inactivity induces atrophy and functional deconditioning of skeletal muscle, especially in the lower extremities. Information is scarce, however, regarding the effect of unloaded inactivity on muscle size and function about the hip. Regional bone loss has been demonstrated in hips and knees of elderly orthopaedic patients, as quantified by computerized tomography (CT). This method remains to be validated in healthy individuals rendered inactive, including real or simulated weightlessness. In this study, ten healthy males were subjected to 5 weeks of experimental bedrest and five matched individuals served as ambulatory controls. Maximum voluntary isometric hip and knee extension force were measured using the strain gauge technique. Cross-sectional area (CSA) of hip, thigh and calf muscles, and radiological density (RD) of the proximal tibial bone were measured using CT. Bedrest decreased ($P < 0.05$) average (SD) muscle strength by 20 (8)% in knee extension, and by 22 (12)% in hip extension. Bedrest induced atrophy ($P < 0.05$) of extensor muscles in the gluteal region, thigh and calf, ranging from 2 to 12%. Atrophy was more pronounced in the knee extensors [9 (4)%] and ankle plantar flexors [12 (3)%] than in the gluteal extensor muscles [2 (2)%]. Bone density of the proximal tibia decreased ($P < 0.05$) by 3 (2)% during bedrest. Control subjects did not show any temporal changes in muscle or bone indices ($P > 0.05$), when examined at similar time intervals. The present findings of a substantial loss in hip extensor strength and a smaller, yet significant atrophy of these muscles, demonstrate that hip muscle deconditioning accompanies losses in thigh and calf muscle mass after bedrest. This suggests that comprehensive quantitative studies on impaired locomotor function after inactivity should include all joints of the lower extremity. Our results also demonstrate that a decreased RD, indicating bone mineral loss, can be shown already after 5 weeks of unloaded bedrest, using a standard CT technique.

Keywords Computerised tomography · Humans · Maximum voluntary strength · Microgravity · Muscle mass · Unloading · Unweighting

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Introduction

Reduced daily physical weight-bearing activity is normally a consequence of injury, disease or advanced age, but is also present during prolonged sojourn in weightlessness during spaceflight. The lower limbs of astronauts and bedridden or cast-immobilized patients show profound functional as well as structural adaptations, which have been attributed mainly to the muscular unloading caused by reduced weight-bearing

activity (cf. Adams et al. 2003; Berg 1996; Booth and Golnick 1983).

Human data from spaceflight will remain limited and difficult to interpret, because of the small sample sizes and the variations in flight duration and physical activity in-flight. The applicability of most patient studies is limited by their design, as typically only retrospective comparisons between one injured and the contralateral limb are available. Therefore, experimental prospective studies of healthy human volunteers, subjected to either strict bedrest or unilateral limb unloading using crutches, is currently the main source of information on the time course and extent of skeletal muscle deconditioning in response to inactivity and unloading (cf. Adams et al. 2003). After introducing the unilateral lower limb unloading model (Berg et al. 1991; Hather et al. 1992), we and others have shown that such ambulatory unweighting (Adams et al. 1994; Berg et al. 1991, 1993b, 1997; Berg and Tesch 1996; Dudley et al. 1992; Tesch et al. 2004; Trappe et al. 2002; Schulze et al. 2002) evokes muscular adaptations similar to those induced by horizontal bedrest (Akima et al. 1997; Berg et al. 1997; Berry et al. 1993; Dudley et al. 1989; Ferrando et al. 1995; Gogia et al. 1988; Hikida et al. 1989; LeBlanc et al. 1988).

Muscle atrophy of the thigh and calf has been described in detail using either strict bedrest or unilateral lower limb unloading. In brief, the cross-sectional area (CSA) of weight-bearing muscles decreases at a rate of approximately 2–3% per week during the first months, whereas their antagonists show less, or no atrophy. Interestingly, the decrease in maximal voluntary strength of weight-bearing muscles is far greater: 4–5% weekly (cf. Adams et al. 2003; Alkner and Tesch 2004; Berg 1996). Although the importance of the force-generating capacity about the hip joint is established for a variety of activities (Jacobs et al. 1996; Wretenberg and Arborelius 1994), functional and structural data on inactivated hip muscles are largely lacking. The first and major aim of this study was therefore to assess and compare the adaptations of important weight-bearing muscles along the lower limb, by relating hip, thigh and calf muscle atrophy to the muscular strength loss.

Bone loss and muscle atrophy are considered to be closely linked (LeBlanc et al. 1988). There are, however, no comparisons reported between the losses in muscle and bone mass in the same individuals. Therefore, the second aim of this study was to assess bone loss in the proximal tibia, and to establish whether potential changes in bone mass would accompany the anticipated muscle atrophy during 5 weeks of experimental bedrest. By using computerized tomography (CT), both muscle

and bone mass could be recorded simultaneously in one session. The development of a clinically applicable protocol for such simultaneous assessment of muscle and bone mass was the third aim of the study.

The rate of recovery in bone mass, muscle size and function after restored ambulatory physical activity is important, both from a practical and mechanistic perspective. This process could be influenced not only by the magnitude of disuse, but also by factors specific to bone or muscle tissue. We have previously shown that after a short period (10 days) of unloading, the first 4 days of weight-bearing fully restored strength loss (Berg and Tesch 1996), and after a 6-week bedrest, almost half of the strength loss was recaptured within that time frame (Berg et al. 1997). This rapid recovery in strength during the first days of re-ambulation is a consistent and intriguing finding. The time required to regain full muscle strength, however, seems to increase with the duration of unloading, and after 6 weeks of bedrest a strength deficit was still present after 7 weeks of free ambulation (Berg et al. 1997). There are still little data that describe how exercise programs during recovery might speed the restoration of muscle mass and function. A fourth aim of this study was therefore to assess the recovery of bone and muscle mass, as well as in function, following supervised training.

Methods

Ten healthy males [25 (5) years, 1.80 (0.09) m, 70.5 (8.2) kg], who had given their written consent, completed 35 days of horizontal bedrest. Five healthy males [25 (5) years, 1.78 (0.09) m, 71.5 (22.3) kg] volunteered to serve as control subjects. The experimental protocol was approved by the Human Ethics Committee of the Republic of Slovenia. Experiments were conducted in accordance with the Declaration of Helsinki.

Protocol

Bedrest group. Bedrest was conducted in a hospital ward (Valdoltra Orthopaedic Hospital, Ankaran, Slovenia). Subjects remained in the horizontal position at all times. They were allowed to use one pillow under their head, and to occasionally lean on one elbow during meals or for transfer to a stretcher, which was used for all transportation (showers, toilet visits, etc.). Subjects were provided with hospital meals; alcohol consumption was prohibited. Muscular exercise (e.g. static contractions using the foot board of the bed as support) was prohibited. To minimize problems with bedrest induced neck or back pain and stiffness of joints

subjects received physiotherapy twice a week, and on request. The therapy was performed with the subject in horizontal position and consisted of massage as well as assisted (passive) stretching and assisted joint flexions. To ensure that subjects complied with the bedrest restrictions they were under 24 h video surveillance.

During the recovery period, bedrest subjects were assigned to two groups. Both conducted supervised exercise thrice weekly, each time for a minimum of 1 h. One group exercised on a cycle ergometer, and another conducted resistance exercise.

Control group. The control subjects were instructed to maintain their normal life style throughout the bedrest period. They were not supervised or monitored in any way during this period.

Tomographic imaging

CT imaging was conducted before and after bedrest, and after 4 weeks of active recovery. Strength tests were conducted before bedrest, on day 2 immediately after completion of the bedrest, and after 4 weeks of active recovery.

Multiple limb segments and muscle groups of the lower limbs were imaged in order to quantify and compare their relative rate of atrophy. Transaxial bilateral CT scans (Picker 4000 SD Spiral Scan, Philips Medical Systems, Best, The Netherlands; 130 kV, 200 mA, 1.5 s scan time) were obtained. Radiation dose was minimized by shielding the gonads (testicles), while executing narrowed scout images, and restricting trans-axial scanning outside that segment.

The pre- and post-bedrest scans were obtained after a minimum of 2 h of horizontal bedrest to avoid the influence of postural fluid shifts on muscle CSA (Berg et al. 1993a). Subjects were carefully positioned for equal leg length, and a foot restraint minimized limb rotation. Scout images over the knee and hip joint-lines were used for reference, and multiple trans-axial images (slice thickness 1.5–3.0 mm) were obtained across 15–30 mm limb segments at four different levels (gluteal, mid-thigh, tibial plateau and upper calf). Muscle CSA and radiological density (RD; Hounsfield units) was analysed at three of these levels (gluteal, mid-thigh and upper calf), and bone RD at the tibial plateau.

Dedicated software (Osiris 3.0, University Hospital of Geneva, Switzerland) for computerized planimetry was used. Proper axial location was identified in the right limb, and areas of interest (individual muscles or bone) manually circumscribed and automatically computed. The knee-extensor group comprises mm. vastus lateralis, vastus medialis, vastus intermedius and rectus femoris. The hip-extensor group comprises mm. glu-

teus maximus, medius and minimus. The ankle plantar-flexor group comprises mm. soleus, gastrocnemius, tibialis posterior, flexor digitorum longus, and flexor hallucis longus. RD of the tibial plateu was averaged for cortical and cancellous bone.

Muscle function

Maximal voluntary isometric contraction (MVC) was assessed unilaterally (right) for the knee and hip extensor and handgrip muscles. During knee extension, the subject sat in a chair with a slightly reclined back support: 15° from vertical, with hip and knee angles maintained at 90°. Chest and pelvis were secured with Velcro straps, and a force transducer (Nobel Elektronik Force Transducer Type KRG-4, Karlskoga, Sweden) was attached around the distal leg just above the ankle. Hip extension was assessed lying in the prone position, similarly with hip and knee angles maintained at 90° and the pelvis and chest secured with Velcro straps. The force transducer was here attached around the distal portion of the thigh adjacent to the knee joint, and the experimenter supported the lower legs of the subject thus maintaining his knee angles at 90° throughout each contraction. Both during the knee and hip extensions, the subject was instructed to contract maximally without kicking and to sustain maximal force for two seconds. The procedure was repeated five times with a 30-s rest period between contractions, and MVC was defined as the average of the three best trials. Force output was measured on a computer (Apple, Cupertino, USA) using a BioPac data acquisition system in combination with AcqKnowledge software (BioPac Systems, Santa Barbara, USA). Handgrip strength was measured with a Baseline Hydraulic hand dynamometer (FEI, Irvington, NY, USA). The subject was standing upright keeping his right arm by his side. He was instructed to contract maximally and to sustain force for 2 s. Measurements were repeated three times and MVC was defined as the best of the three trials.

Statistics

Repeated measures ANOVA with single contrast means comparisons for selected factors (muscle morphology), or the paired t test (muscle function, bone density) was used. Statistical significance was set at $P < 0.05$, or for repeated comparisons $P < 0.01$.

Results

The observed changes in subjects' physical characteristics, aerobic work capacity, muscle strength and function

have been reported previously (Mekjavic et al. 2005), and are in agreement with observations of other bedrest studies of similar duration. More importantly, the results confirm that the subjects adhered to the bedrest regimen during the study. There were significant differences neither in muscle strength nor in CSA and RD at the end of the recovery period between the two groups having different supervised exercise, and the data for all bedrest subjects were therefore pooled in the final analysis.

Muscle morphology

Bedrest reduced ($P < 0.05$) CSA of the ankle plantar-flexor muscles by 11.9 (3.2)% from pre-bedrest values of 4,518 (693) to 3,976 (605) mm^2 at the completion of the bedrest. Following the recovery period, plantar-flexor CSA had reassumed baseline values [4,435 (640) mm^2]. Bedrest reduced ($P < 0.05$) the CSA of the knee-extensor muscles by 9.4 (3.6)% from 7,347 (740) mm^2 pre-bedrest to 6,650 (673) mm^2 post-bedrest. Following the recovery period, knee-extensor CSA had reassumed baseline values [7,309 (643) mm^2]. Bedrest reduced ($P < 0.05$) the CSA of the hip-extensor muscles by 2.2 (2.3)% from 8,931 (771) mm^2 in the pre-trial to 8,728 (661) mm^2 post-bedrest. This slight, but significant reduction prevailed after the recovery period [8,707 (749) mm^2].

Muscle function

Bedrest decreased ($P < 0.01$) knee-extensor MVC by 20% from a pre-bedrest value of 604 (64) to 502 (41) N post-bedrest; after the active recovery period, subjects regained their knee-extensor strength [624 (89) N]. Bedrest decreased ($P < 0.01$) hip-extensor MVC by 22% from a pre-bedrest value of 1,303 (280) to 1,012 (184) N post-bedrest; after the recovery period the subjects had regained their hip-extensor strength [1,241 (271) N]. There was no significant difference ($P > 0.05$) in handgrip strength observed before [470 (86) N], and after bedrest [464 (92) N], and after the recovery period [493 (94) N].

Bone density

Bedrest reduced ($P < 0.05$) the RD of the tibial bone by 3.5 (1.6)% from 209 (34) to 201 (33) Hounsfield units, a reduction that prevailed [3.7 (2.8)%; 200 (30) units] after the recovery period.

Average pre-bedrest values of the measured variables for the control group were similar to those observed in the bedrest group, with the exception that

values remained unchanged during a 5-week period ($P > 0.05$). Over a 5-week period, handgrip strength in the Control group of subjects ranged from 526 (70) to 581 (71) N. Hip and knee extension force ranged from 1,460 (374) and 638 (109) N to 1,354 (324) and 630 (106) N, respectively. Ankle plantar-flexor CSA ranged from 5,132 (1,386) to 5,241 (1,354) mm^2. Knee-extensor CSA ranged from 7,242 (1,465) to 7,246 (1,395) mm^2. Hip-extensor CSA ranged from 9,384 (2,171) to 9,324 (2,098) mm^2. Tibial bone density ranged from 220 (70) to 227 (76) Hounsfield units.

Discussion

The present findings of a substantial loss in hip-extension strength and a smaller, yet significant atrophy of the gluteal muscle group, demonstrate that deconditioning of hip muscles accompanies changes in thigh and calf muscles during prolonged bedrest. Therefore, it might be argued that any comprehensive quantitative study on the effect of inactivity or unloading on locomotor function, should investigate muscles acting about all joints of the lower extremity.

Bone loss of the proximal tibia accompanied muscle atrophy and strength loss after only 5 weeks of experimental bedrest in healthy young individuals, and it was not yet reversed after 4 weeks of active weight-bearing recovery. These findings were demonstrated using a standard CT scanning protocol and measured within the same session as the assessment of muscle CSA. This procedure might therefore become of value for future patient studies.

The atrophy of thigh and calf muscles demonstrated in the current study closely corresponds with previous bedrest or unloading data (cf. Adams et al. 2003; Berg et al. 1997; Tesch et al. 2004). Thus, reductions in CSA of knee extensors (9%) and ankle plantar flexors (12%) were about 2% per week if averaged across the 5-week period. These findings confirm that the experimental design and performance of this study, including subject compliance, was satisfactory.

The strength loss of knee extensors (20%) also corresponds to previously reported data (cf. Adams et al. 2003; Berg et al. 1997; Tesch et al. 2004), confirming the well-documented fact, that inactivity induces strength decrements that are substantially larger than can be accounted for by muscle atrophy. It has been suggested that the share of the strength reduction not attributable to atrophy, results from reduced neuromuscular drive in combination with decreased force-generating capacity of the muscle fibers (Berg 1996;

Berg et al. 1997). Although the present deterioration in muscle function, in terms of isometric strength, was similar in knee and hip extensors, muscle atrophy was less pronounced in the hip than in the knee extensors. We have no explanation for this discrepancy between the relative decrements in strength and mass, and there are no previous studies that have compared the relation between muscle mass and force in the hip or along the extremity. In a small sample of astronauts, we found similar atrophy in knee and hip muscles (Tesch et al. 2005).

In a previous 6-week bedrest study, we have shown that muscle atrophy varies within the thigh, such that knee extensors atrophied more than flexors, while hip adductors, which are also accessory hip extensors, showed intermediate response (Berg 1996; Berg et al. 1997). We concluded that the adaptation to unweighting of each muscle group shows a hierarchy in relation to their importance for weightbearing. Those and other studies, however, did not include the gluteal hip muscles. The load induced by body weight, is probably not only related to the biomechanical function of individual muscles, but should also consider the number of carried body segments. It is well known that upper extremity muscles, which carry a marginal gravitational load, show less adaptation than lower limb muscles after unloaded inactivity (Leblanc et al. 1992). Consequently, it might be speculated that postural muscle adaptation of the lower extremity would increase gradually towards the feet, where the ankle-plantar flexors balance the full body weight, and hip extensors the trunk, head and upper extremities only. A direct comparison of our data along the whole limb, including the hip, seems to support this notion (see Fig. 1). When compiling data from several studies (cf. Adams et al. 2003; Akima et al. 1997; Alkner and Tesch 2004), there actually seems to be a slightly greater atrophy of calf compared to thigh muscles after bedrest, although no previous reports on hip muscles are available.

The measured gluteal hip muscle group however comprises one primary hip extensor (m. gluteus maximus) and two smaller primary hip abductors, which are also accessory hip extensors (m. gluteus medius et minimus). It is equivocal how these hip muscle CSA changes should be valued versus thigh and calf CSA and their more affected weight-bearing muscle groups (see Fig. 1). Even though subjects were prohibited to perform muscle exercise in bed, it is possible that the transitions from bed to stretcher for showering and passive physiotherapy during bedrest may have counteracted hip abductor atrophy.

The small decrease in hip muscle area is still compelling. Reference literature for methodological errors of
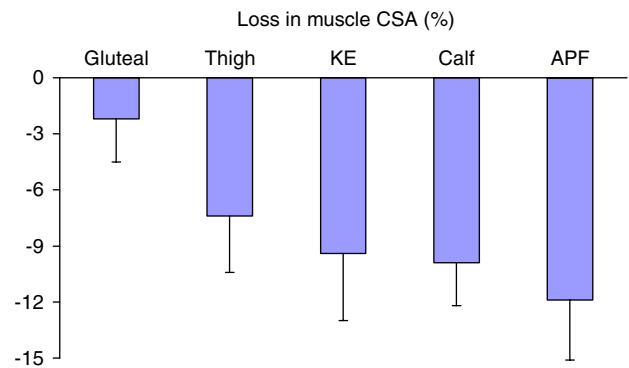
Fig. 1 Mean values of relative (%) change in cross-section area (*CSA*) of the thigh and calf muscle groups, and of the gluteal hip muscles, the knee extensors (*KE*) and the ankle-plantar flexors (*APF*). Values are means (SD); $n = 10$

tomographic hip muscle CSA assessment is lacking, but we have found no obvious pitfalls when applying the highly accurate CT method (CV < 2%; cf. Berg 1996) to the hip. The gluteal muscles (hip extensors and abductors) are in fact large, exceeding both calf or knee extensor CSA, and there were no major difficulties to circumscribe the selected muscles in the image slice. Moreover, the bony landmarks of the pelvis are easily identified and we therefore feel convinced that the anatomical slice level for each limb and test session was maintained, and also we found no tendency for a pelvic tilt that could potentially alter muscle length and projected muscle CSA. Since variation of CSA measurement was similar for all sites along the limb, moreover, we feel confident with our measured values.

Fluid shifts after transition from standing to supine prior to tomographic muscle size assessment might indeed alter the measured CSA by several per cent (Berg et al. 1993a), and it might be speculated that such methodological errors have contributed to the remarkable changes in muscle CSA occasionally reported within the first weeks of bedrest or spaceflight. We used 2 h of supine rest prior to all CSA measurements. Because the proximal thigh muscles show less and more rapidly leveled fluid shift compared to the more distal calf (Berg et al. 1993a), it seems unlikely that gluteal hip muscle size was substantially altered by postural fluid shifts.

A reduction in bone density (RD) of the proximal tibia was observed after bedrest, and this change prevailed even after the recovery period. Our results thus demonstrate that a decreased RD, indicating bone mineral loss, can be shown already after 5 weeks of unloaded bedrest using the CT technique. In contrast to changes observed in muscle mass and strength, the bone loss did not recover after 5 weeks of regained weight-bearing including exercise training. These

results concord with data from elderly orthopaedic patients where thigh muscle atrophy but not tibial bone loss showed recovery 6 months after reconstructive hip surgery (Neander et al. 1999). Appreciating the extreme stimulus of complete unloading during 5 weeks of bedrest and the slower process of bone remodeling, it is reasonable to expect that the impact on bone metabolism might remain for a longer time. From these data, it is not possible to predict when or if the bone loss will be regained in full. The risk for adverse effects, including osteoporotic fractures in advanced age, after bone loss in response to spaceflight has been discussed, and this might be relevant also for patients subjected to unloaded rehabilitation programs. Future studies should try to evaluate how the extreme unloading during short-term spaceflight, bedrest or other non-weightbearing situations compares to a sedentary but ambulatory life style, in terms of skeletal bone metabolism.

The protocol for simultaneous study of muscle and bone during a standard 30 min CT examination seems promising for future research on both healthy humans and patients, and could be implemented in any modern Spiral-CT unit.

The recovery in muscle mass and strength already after 4 weeks of active recovery seems to confirm that the exercise program was effective to accelerate rehabilitation. Even though corresponding time points in other studies are lacking, existing bedrest data (Berg et al. 1997) suggest that a remaining deficit should be expected at this time after free re-ambulation. The assignment of subjects to two different exercise protocols for the recovery phase was part of a pilot study that aimed to refine exercise recovery protocols. Possibly due to the small group size and the limited observation time, no group differences were observed and thus no conclusions can be drawn regarding specificity of rehab exercise. It should be appreciated, however, that recent studies have proven resistance exercise, during long-duration bedrest (Alkner and Tesch 2004) and lower limb unloading (Tesch et al. 2004), to be effective in preventing muscle atrophy and strength loss. Future studies to optimize rehab programs after atrophy and muscle deconditioning is established, should consider that there are still no data to challenge the traditional exercise paradigms applicable to healthy humans (cf. Tesch et al. 2004).

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