CHAPTER 6

General discussion

INTRODUCTION

The first aim of this thesis was to obtain insight into the changes in neuromuscular integrity of an antigravity muscle as a consequence of 56 days of bed rest immobilization. We were particularly interested in the time course of changes in knee extensor muscle size, strength, contractile characteristics and neural activation processes during bed rest, because such information might increase the understanding of dominant processes underlying the various manifestations of muscle weakness following muscle unloading. In addition, another equally important aim of this thesis was to assess whether such changes could be effectively prevented by resistive vibration exercise training during bed rest. In this chapter, the main results of, and conclusions drawn from the studies performed will be revisited and supplemented by noteworthy findings that have not been addressed in the main chapters in this thesis. The findings are placed into perspective with respect to their implications for human spaceflight, as well as their clinical relevance.

NEUROMUSCULAR ADAPTATIONS TO BED REST

Exposure to microgravity conditions initiates a cascade of interrelated events that result in the adaptation of virtually the entire human body. Because of the complexity and limited opportunity to study humans in space, we used the bed rest model to simulate conditions of microgravity. For the neuromuscular system, the most important aspect of bed rest immobilization is the interruption of the weight-bearing activity of skeletal muscles whose primary task it is to stabilize body posture and to move body parts against gravity. Such reduced muscle usage has been demonstrated to cause unambiguous adaptations in muscle function, but not much is known about the time course in which these adaptations occur.

The lack of longitudinal information on time course of changes in neuromuscular function, despite a wealth of bed rest campaigns, is not without reason. The assessment of the time course of changing muscle function presents a scientific challenge, because repeated functional testing, which is needed to allow an accurate time course evaluation, may oppose the very effects of the bed rest intervention [33]. Mindful of this consideration, we tried to prevent such an effect by two means. First, we limited the number of high-force contractions for each test session, especially during bed rest, because these were expected to elicit the most potent training response. Secondly, we substantially reduced the frequency of testing during the course of the bed rest. Based on cross-sectional comparison of previous reports, the most rapid changes were foreseen for the first 10 days of bed rest, such that we expected an accurate estimate of changes with longer testing intervals after this time period.

Despite the abovementioned two precautions, a consistent observation over subjects was an absence of deconditioning of neural control in the frequently tested right leg, whether assessed by means of the twitch interpolation technique (Chapter 2), or assessed by the analysis of vastus lateralis high density surface electromyography (sEMG) amplitude during steady-state and ballistic voluntary contractions (Chapters 3 and 5). The most likely explanation for these findings was that indeed the repeated functional testing during bed rest caused a habituation to the performed tasks. For steady-state contractions, this notion was supported by the findings for the left leg, which was only tested pre- and post bed rest. For this leg, the loss in muscle strength exceeded the loss in muscle size by almost a factor two (Chapter 2). From a scientific point of view these findings illustrate that longitudinal study designs may not be appropriate to address questions related to the time course of changes in neural capacity, and that such information should be obtained by cross-sectional comparison of studies with varying study durations, instead. However, at present there is no international agreement on a common procedure to measure and evaluate the effects of bed rest. Strict standardization of methods in future bed rest campaigns is therefore an absolute necessity. In practical terms, the abovementioned findings for the tested leg, although not intended, are significant and encouraging because they seem to demonstrate that relatively little effort is needed to preserve neural integrity. Such conclusions may direct future space medicine research to address the minimal requirements of preventative interventions to combat the effects of prolonged spaceflight.

Eight weeks of bed rest resulted in a significant reduction in the anatomical cross-sectional area (CSA) of the knee extensor group of about 14% as measured with magnetic resonance imaging (MRI). Interestingly, for the muscular system the repeated functional testing presented no significant stimulus, as the change in CSA following bed rest was similar between the frequently tested right leg and the non-tested left leg (Chapter 2). Apparently, more muscular activity is needed to preserve muscle size than to maintain voluntary activation processes. The observation that changes in muscle size were well described by a linear model (Chapter 2) indicated that the rate of downsizing of the quadriceps femoris muscle as a whole had not reached its nadir during the 56 days of bed rest. However, the susceptibility to atrophy was not equally shared among the four heads of the quadriceps femoris muscle. It was interesting to find that the size of the rectus femoris muscle was not influenced by bed rest confinement at all. Because both left and right leg showed this absence of change in size, the finding was apparently not related to the functional testing during bed rest. Instead, this finding may be explained by the continued use of this muscle to raise the leg under bed rest conditions. Such interpretation would be consistent with the absence of changes in size of this muscle during unilateral lower limb suspension [18]. In this model, the rectus femoris of the suspended leg is also likely to be activated to some degree, particularly during the forward swing in crutch-assisted walking. By continuously recording sEMG signals of the rectus femoris muscle, future studies might be able to determine how often and at what intensity this muscle is activated under unloading conditions. Interestingly, we did also not find a change in the angle-dependency of maximal voluntary torque production. This suggests that the length characteristics of the quadriceps femoris muscle did most likely not change as a consequence of the bed rest intervention, whereas previously significant changes in muscle fiber length following bed rest were reported for the plantar flexor [22]. Video surveillance of the subjects evidenced that the knee was frequently held in flexed positions, i.e. at a stretched quadriceps femoris muscle length. Such passive stretching may haven been sufficient to oppose changes in muscle fiber length.

In addition to the downsizing in muscle mass as a result of the reduced physiological demands during bed rest, modulation of the muscle phenotype appears to be another important adaptive capacity of skeletal muscle [32]. However, the conversion of fiber properties to faster (Chapter 5) and potentially less oxidative characteristics in response to unloading can also be referred to as deconditioning because it may substantially impair the capacity for prolonged exercise following unloading [30]. The increase in *relative* quadriceps femoris muscle fatigability as a consequence of bed rest was, based on changes in sEMG variables, most likely of a peripheral origin (Chapter 4). The assessment of vastus lateralis oxygenation and hemodynamics during exercise by near-infrared spectroscopy (NIRS) further suggested that the increased fatigability resulted predominantly from the consequences of a significant reduction in muscle blood flow during exercise and not, or at least to a lesser degree, to a reduced oxidative capacity of the quadriceps femoris muscle. In fact, with respect to the pre-bed rest condition, the relative extraction of oxygen from the blood was increased during exercise, following bed rest. This is interesting, because bed rest resulted in an impaired oxygen-carrying capacity, as red blood cell mass decreased by approximately 11% (D. Böning, personal communication). The increased oxygen extraction could only partly diminish the dramatic reduction in its delivery. Hence, it can be expected that there was an increased need for energy supply by anaerobic pathways in order to fulfill the energy demand of the required task. Although not mentioned in Chapter 4, the reduction in blood flow was further consistent with the slower rate of recovery from fatigue following bed rest. Indeed, it seems likely that the wash-out of produced metabolic waste products would also have been significantly reduced by an impaired muscle blood flow. Bleeker et al. [5] reported a ~17% reduction in the diameter of the quadriceps femoris muscle feed arteries, yet the reduction in blood flow in our study was dramatically more reduced, implying that other factors contributed to the reduction in blood flow. One such a factor might be a significant reduction in total plasma volume as a consequence of bed rest [17]. It should be mentioned that in the study presented in Chapter 5, total blood volume was not measured. In addition, blood flow was assessed during the second minute of exercise only. For future studies it would not only be desirable to measure blood flow throughout the entire fatigue protocol, but also blood flow in all superficial heads of the quadriceps femoris muscle to obtain a more comprehensive picture. Hardware limitations prevented such quantifications during the Berlin Bed Rest study, as the NIRS apparatus had a maximal storing capacity of approximately 2 minutes worth of data.

EFFICACY OF RESISTIVE VIBRATION EXERCISE

A major objective of space medicine research is to provide astronauts with time-efficient and effective countermeasures to combat the adaptive changes in the human physiological system as a consequence of spaceflight. Over the last decades, the generally accepted countermeasure during actual spaceflight has been physical exercise with a high aerobic component, such as pedaling a cycle-ergometer or exercising on a rowing machine. Although such efforts have been partly effective to maintain muscle function, these interventions are particularly ineffective to preserve the integrity of the weight-bearing skeleton [8]. In contrast, 'conventional' resistance training, which involves isometric and dynamic (concentric and eccentric) contractions against gravity, should be more promising, because under ambulant conditions such exercise paradigms provide the most potent stimulus for simultaneously increasing mass en strength of muscle and bone. Recent bed rest campaigns have indeed confirmed the potential of resistance training to maintain neuromuscular function as well as bone mass and strength under simulated spaceflight conditions [1;14;19;28]. However, minimal requirements with respect to training modality, types of exercises, the volume and frequency of training sessions have yet to be determined. Moreover, to be effective during actual spaceflight, the loading of weight-bearing structures cannot arise from gravity, but has to originate from other sources. Recent developments in exercise hardware that was designed according to such criteria were found insufficiently effective to preserve bone and muscle simultaneously [2;25].

This thesis addresses one of the latest developments in countermeasure design: resistive vibration exercise (RVE). In short, RVE is a neuromuscular training technique where subjects perform loaded weight-bearing exercises on a platform which applies vibrations to the two feet. It is assumed that these imposed vibrations evoke reflexive muscle contractions [24], probably via stretch reflexes, i.e. through the activation of muscle spindle (Ia) fibers [26]. This feedback loop increases the alpha-motoneuron activity and may thus result into a greater facilitation of the muscle drive during training. Under ambulant conditions, vibration training has been successfully tested for prevention and treatment of osteoporosis in postmenopausal women as well as in physically disabled children [34;35]. In contrast, the effect of vibration training to induce muscular changes in healthy adults has been discussed with much more controversy [11;12;26;31]. De Ruiter et al. [11] suggested that that young, physically fit, individuals may not necessarily benefit from such a training paradigm, unless additional loads are applied. Hence in the Berlin Bed Rest study the allocated training regime consisted of strength training exercises performed during whole body vibration. Because of this, the magnitude of stimulus due to vibration alone has yet to be quantified. From a biomechanical perspective it can be speculated, however, that the added vibration increased the efficacy of the countermeasure for two main reasons. First, without added vibration, the loading of the subject would have been generated only by means of the springs that restrained the subject to the footplate of the Galileo device. Springs have the disadvantage that they absorb energy; energy that is otherwise transferred into an impulse-type loading on the skeletal muscles and skeleton. This impulse is suggested crucial for maintenance of bone under disuse conditions [27]. In addition, the efficacy of standard weight-lifting programs is partly ascribed to the performance of eccentric contractions [13]. In the case of resistance created by means of springs or by other materials with elastic properties, this eccentric component may be greatly reduced, which means that part of the efficacy of the training program will be lost. To test these hypotheses, the most direct approach for future research would to be to incorporate two training groups; one group would perform resistive exercise in the presence of added vibrations, whereas the other group would execute an identical protocol, but without the added vibrations. It should be recognized, however, that such an approach is feasible only, when a limited number of different countermeasures are compared for their individual and combined effect(s). Since different types of countermeasures offer different degrees and even different kinds of protection, future bed rest studies will most likely integrate nutritional, pharmacological as well as exercise prescriptions in search for the most effective 'cocktail of stimuli' that simultaneously provides the best overall protection against spaceflight-induced deconditioning. For such studies, it will be practically impossible to determine single contributing effects of the various components.

When compared to the present exercise prescriptions for astronauts aboard the International Space Station, total RVE training time was very short; less than 10 minutes per day. Nonetheless, this proved effective to substantially diminish loss of muscle mass (Chapter 2), and to prevent changes in intrinsic contractile characteristics related to muscle speed (Chapter 5). Such preservations are not necessarily sufficient to maintain voluntary muscle strength. Indeed, the concept of training specificity indicates that adequate maintenance of neural control may still be compromised even when muscle mass is maintained, particularly when tasks performed during training substantially differ from those performed during testing [3;4]. In this thesis it could not be ascertained whether RVE training truly contributed to the preservation of neural capacity under bed rest conditions. The efficacy of RVE training as presented in Chapter 2 is confounded by the preservation of maximal voluntary activation for Ctrl. In Chapter 3 it is demonstrated that the amplitude of the high density sEMG substantially increased during the bed rest period for the trained individuals, suggesting that maximal neural drive was in fact rapidly intensified for RVE subjects during the course of the bed rest. Because such changes were not seen for Ctrl, it seems reasonable to expect that the difference between groups relates to the presence or absence of the countermeasure. Because the increased neural drive was not accompanied by strength gains, and could also not be attributed to motor unit synchronization, we speculated that sEMG amplitude increased during bed rest as a result of an increase in the mean firing rate of motor units.

In Chapter 4, we demonstrated that the relative resistance to fatigue increased following bed rest with RVE training. Bleeker et al. [5] showed that RVE training also significantly diminished vascular deterioration during bed rest. Nonetheless, because blood flow during the fatigue task was reduced following bed rest, and red blood cell mass was also decreased for most RVE subjects (D. Böning, personal communication), it can be expected that oxygen supply was also impaired. It remains difficult to explain why this did not present a functional limitation for the RVE subjects. Although no clear changes in fiber type in the quadriceps femoris muscle were seen following bed rest [7], it is possible that some metabolic properties of the quadriceps muscle changed as a result from adaptations to intense training [16]. For instance, Rittweger et al. [23] noted that, concomitant with increased training duration for the squat exercise, progressively higher lactate values were recorded for RVE subjects during the course of the bed rest. Such changes may indicate an increased tolerance to anaerobic conditions of training, which could have resulted in a lower relative fatigability following bed rest.

METHODOLOGICAL CONSIDERATIONS

We realize that some methodological issues must be regarded in the interpretations of our results. Some are inextricably connected to this study; others could be taken care of in future studies. One factor that potentially may have influenced some of our findings was the relatively large heterogeneity in properties related to neuromuscular function in the subjects at the start of the study. Apart from genetic factors, the observed initial heterogeneity may have been related to differences in active life style of the subjects. For bed rest studies, this notion may be critically important, because the difference between the level and mode of normal physical activity and that during bed rest is one, if not the most important factor that dictates the severity of the deconditioning [9;29]. In other words, physically fit individuals are likely to decondition more than those that are less fit. For bed rest studies it may be difficult to reduce subject heterogeneity on the basis of narrowing already stringent inclusion criteria, because such effort will further limit the number of suitable volunteers. However, because initial subject differences will confound statistical interpretations of the study, it would be desirable to increase group homogeneity prior to the start of the bed rest phase as much as possible. One option would be to match groups according to subject activation history over the last months preceding the study, instead of randomly assigning subjects to one of the experimental groups upon inclusion.

Part of the initial heterogeneity might also be attributable to the short baseline data collection period of the Berlin Bed Rest study, which covered only three days immediately preceding the start of the bed rest phase. For an accurate determination of baseline muscle functionality it is imperative that the subjects are properly familiarized with the required tasks. Although a learning response was apparent for most subjects, some subjects clearly profited more from the repeated testing than did others. Indeed, some subjects reached their highest maximal voluntary strength after several days of bed rest. Needless to say, for these individuals, pre- to post bed rest comparisons would not have been very accurate to represent the effect of the bed rest intervention. The main advantage of repeated testing showed here. The measurement of variables also during the bed rest allowed us to use a statistical tool that not only reduced the effect of day-to-day variations, it also allowed the assessment of more accurate baseline values at the start of the bed rest.

In the field of kinesiology, the electrical activity of superficial muscles is commonly recorded at the skin surface by a single bipolar electrode montage. In the Berlin Bed Rest study, we used a high density sEMG recording montage instead [6], in which a large number of electrodes is distributed over the vastus lateralis muscle. This system provided multiple advantages, such as proper reproducibility, a larger field of view, and the assessment of muscle fiber conduction velocity. The main disadvantage of any sEMG recording at higher force levels is the inability to disentangle the interference pattern into its constituents: the contribution of single motor units and their firings characteristics. A complete disentanglement of high density sEMG is only feasible at force levels too low for practical relevance in our study. This is the reason that we could not ascertain the exact origin of changes in sEMG recordings in RVE subjects (Chapter 3). For future bed rest studies, it may be desirable to include the use of wire electrodes to record EMG in combination with agonist and antagonist sEMG during voluntary contractions to determine the mechanism(s) underlying neural deconditioning typically seen following bed rest. However, the invasive character combined with the time consuming process of this technique most likely limits extensive practical application.

CLINICAL IMPLICATIONS

The Berlin Bed Rest study was in part funded by the European Space Agency's Microgravity Application Program, which looks to involve universities and industry in the development of space-related research. In the case of the Berlin Bed Rest study, the main objective was to assess the changes in muscles and bones typically arising during long-duration spaceflight and to evaluate an exercise countermeasure to counteract such changes. Because spaceflight and bed rest immobilization affects virtually all biological systems, a great number of additional experiments were conducted during the study. For instance, the assessment of cardiovascular function pre and post bed rest may not only improve our understanding of the effect of strict bed rest on cardiovascular deconditioning, the experiments also help to determine how an exercise countermeasure for bone and muscle may affect other physiological systems.

Part of the commitment of space agencies to fund bed rest studies is related to the awareness that space medicine may also greatly benefit the healthcare for individuals afflicted with muscle and bone-wasting diseases, or improve the treatment and recovery of hospitalized, bedridden or otherwise immobilized individuals on Earth. Indeed, most biological disorders are quickly complicated by their subsequent effect on neuromuscular activity levels and mobility. For instance, arthritis-induced pain leads to a reduced motivation to move, which results in reduced muscle use, disrupted metabolic priorities, which can lead to diabetic and cardiovascular dysfunction. Spaceflight and experimental bed rest studies provide such excellent research opportunities because they study how all physiological systems accommodate reduced muscular demands in healthy subjects.

From a clinical viewpoint, what are then the important functional neuromuscular parameters of this thesis? Of course, maintenance of muscle size and strength of anti-gravity musculature is important because muscle strength is needed for carrying body weight and activities such as walking up and down stairs. Nonetheless, it is likely that the muscle strength requirements to perform such activities are well below the maximal isometric knee extension strength in normal healthy individuals, meaning that most individuals can cope with some reduction in maximal muscle size and strength before any significant impairment is evident during normal daily life activities. In contrast, adequate neural control of such activities is a necessity, especially in the light of the reduction in bone mineral density that accompanies inactivity. Any deterioration in the capacity to quickly and adequately avoid obstacles during gait after resumption of daily life activities may increase the incidences of fall-related bone fractures. Interestingly, one of the main observations presented in this thesis was the finding that neural deconditioning could be comparatively easily prevented. With respect to the reduction in bone mineral density, resistive vibration exercise, or at least whole body vibration training - vibration training with only body weight - might be a particularly promising training modality in geriatric and therapeutic sectors. Whole body vibration appears a safe and valid substitute for conventional strength training for those who are not attracted or able to perform this type of exercise [26]. Finally, many tasks in daily life comprise repetitive muscle contractions at low muscle forces. Based on the findings of Chapter 4, it is imperative to minimize changes in endurance capacity, because this would significantly impair a patient's ability to perform such tasks independently. In Chapter 4, the workload after bed rest was corrected for changes in absolute muscle strength, as we were interested in changes in intrinsic muscle fatigability. Of course, in daily life such normalization has no practical relevance. In fact, a similar absolute load (e.g. body mass) presents an even increased relative workload for disused muscles because of the reduction in maximal force generating capacity. Because it is the relative load that dictates the severity of muscle fatigue, it can be expected that for daily life, the changes in muscle fatigability exceed the findings in Chapter 4. Additionally, because our subjects were tested in the supine position (Fig. 2 in Chapter 2), orthostatic factors such as an increased venous compliance of the legs [10] did not contribute to the reduction in muscle blood flow in our experiments. In the upright posture, however, such factors will undoubtedly further impair blood flow and hence exercise tolerance following bed rest.

By the continued monitoring of the subjects after the cessation of the bed rest period, we aimed to determine the time course of recovery of the neuromuscular system. Such information can be helpful in improving medical rehabilitation programs for various patient populations for whom exercise prescriptions are not applicable during a period of restricted mobility. From the Berlin Bed Rest study, but also from preceding studies it is evident that previously disused skeletal muscle are highly susceptible for muscle damage due to eccentric muscle actions [15;20;21;23]. Hence, at the initiation of the rehabilitation process, such muscle activity should be limited, for instance by applying alternative training regimes such as swimming. Because the Berlin Bed Rest study did not incorporate a standardized rehabilitation program, we chose not to address the time course of recovery of the neuromuscular system in the main chapters of this thesis. However, it can be mentioned here that maximal isometric muscle strength recovered to baseline values between 45 and 90 days after reambulation, which roughly equals the time of the inactive period. Since we did not observe any reductions in neural activation during the bed rest period, the recovery of maximal muscle strength may reflect the recuperation of muscle mass. It has long been questioned whether weight-bearing bones have a similar capacity to fully recover, i.e. there has been concern that some changes in muscle structure might be irreversible damaged by periods of simulated or actual spaceflight. Preliminary data (J. Rittweger, personal communication) indicate that during reambulation, bone mineral is deposited at sites where it was previously lost, implying that also changes in weight-bearing bones are completely reversible by resumed weight-bearing activity. These are reassuring observations indeed, for patients, future bed rest volunteers, as well as for those of us who dare to venture into the cosmos.

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