CHAPTER 1

General introduction and outline of the thesis

INTRODUCTION

Human (manned) spaceflight became a reality on April 12, 1961 when cosmonaut Yuri Gagarin from the former Soviet Union became the first human to orbit Earth. By doing so, Russia embarked the beginning of a new era, that of the "Space Race". With only two competitors involved, the race was ultimately won by the United States when the Lunar Module "The Eagle" (Apollo 11) landed on the Moon on July 20, 1969. Hours later, American astronaut Neil Armstrong was the first human to set foot on another celestial body. With the Moon conquered and NASA at its glory days, it seemed only a matter of time before the next (and only accessible) alien body would be visited by human explorers: the planet Mars. Now, somewhat 40 years later, Mars has only been visited by several unmanned robots, but renewed interest in the planet has also reawakened the planning for a human mission to Mars. There are, however, medical concerns related to such missions that must be addressed first before humans can start such an endeavor.

Physiological consequences of spaceflight

Although many factors affect human health during spaceflight, the dominant and single most important one is the vastly different environment encountered by human space travelers: the persisting condition of microgravity, where the weight of an object (such as the human body) is reduced to negligible values. It is this lack of weight that initiates a cascade of interrelated physiological responses that ultimately affects the whole human body, from brain to bones. This thesis outlines one biological system that is influenced by spaceflight: the neuromuscular system, which comprises skeletal muscle and the central nervous system controlling these muscles. On Earth, muscles evolved to support our upright posture and to move body parts against the pull of gravity. But in space, such antigravity functions are no longer needed for that purpose [4;7]. The dramatic interruption in load-bearing activity leads to muscular atrophy through changes in protein content with associated weakening, whereas changes in myosin phenotype result in altered contractile and biochemical characteristics and reduced endurance capacity [11;18;19;27;29]. In addition, there is compelling evidence that the central nervous system is also subjected to deconditioning by spaceflight [17]. None of these changes presents an acute problem to space travelers as long as they perform only light work, but they may very well endanger survival capabilities in emergency situations, such as fire on board a space vehicle during, or immediately post-landing on Earth (or Mars) after a long duration space mission. Unassisted emergency egress from such a craft would require immediate full strength and endurance capabilities of the anti-gravity muscles, as well as adequate neural control. As humans plan to stay in space for increasing periods of time, it will be essential to have a thorough understanding what effects, both reversible and irreversible, prolonged microgravity will have on the various constituents of the neuromuscular system, and equally important, how such adaptations can be prevented .

Bed rest as an Earth-bound simulation model

Because of the complexity and limited opportunity to study humans in space, we used a spaceflight analogue, i.e. an Earth-bound model that simulates the condition of reduced muscle usage during spaceflight, to address questions related to the alterations in the neuromuscular system and the development and testing of potential preventative measures. Several simulation models exist, but the bed rest model has been generally accepted as the most applicable one, because confinement to bed rest not only results in physiological alterations in the neuromuscular system similar to spaceflight, it also reproduces physiological alterations related to human spaceflight in many other biological systems [1]. Although quite a substantial number of bed rest campaigns have been performed over the past years, ranging from 3 up to 120 days in duration [16;25], and a substantial body of knowledge about the effects of physical inactivity on neuromuscular function has been gathered from these studies, part of the information that could be obtained is consistently lacking. In order to obtain uncompromised results, the assessment of changes in neuromuscular function as a consequence of bed rest has generally been limited to pre – post comparisons, i.e. in most bed rest campaigns functional measurements are not conducted *during* the bed rest period. The main disadvantage of such an approach is the inability to accurately assess the time course of changes as a function of bed rest duration. As such, it remains largely unresolved to what extent and in what timely manner the various subsystems within the neuromuscular system contribute to the overall deconditioning of neuromuscular integrity. This information is imperative because (1) it may identify dominant processes underlying the various manifestations of muscle weakness, which may improve the development of effective therapeutic interventions, and (2) it allows the extrapolation of gathered data to longer periods of disuse, such as during actual long-term spaceflight. Of course, cross-sectional comparisons of different studies with various study durations provide some insight in the time course of changes, but interpretations have been largely restricted by a lack of methodological standardization between different studies. The experiments described in this thesis were aimed to bridge this gap in knowledge by longitudinally studying various components of the neuromuscular system under bed rest conditions.

Another major goal of experimental bed rest studies is to develop efficient countermeasures that prevent the adaptive physiological responses in the human body as a consequence of spaceflight, i.e. nutritional, pharmaceutical and/or exercise-based procedures are first tested an refined on Earth before being applied during space missions. [13;14;21;24;26]. With respect to the neuromuscular system, it appears that conventional resistance training is effective to maintain or at least to minimize structural and functional changes in muscle mass and to preserve muscle strength during bed rest [2;12;15]. Although promising, the majority of studies that have incorporated resistance training as a countermeasure have yet only shown the potential of this training modality. Because most of the adopted training paradigms make use of the presence of gravity (for instance when lifting weights), they cannot be directly implemented during actual spaceflight, where gravity is virtually absent. To be effective in such an environment, the loading of skeletal muscles should thus arise from another source than gravitational pull. Recent developments involve devices that make use of elastomer or mass-inertia to load the skeleton and muscles [5;23]. Unfortunately these methodologies proved only partly successful to preserve mass and strength of bone and muscle [3;21]. Although the main rationale for organizing the Berlin Bed Rest study as a whole was to test resistive vibration exercise as a novel, and potentially more efficient training paradigm for both bone and muscle preservation, the focus of this thesis is on the efficacy resistive vibration exercise to preserve neuromuscular integrity of the quadriceps femoris muscle during bed rest. Resistive vibration exercise combines classical resistive exercise with vibration exercise. It is assumed that the applied vibrations to the feet evoke muscle contractions via stretch reflexes, initiated by the activation of muscle spindle (Ia) fibers [22]. This feedback loop would increase the alpha-motoneuron activity and may thus result into a greater facilitation of the muscle drive during training.

Methodological outline of the Berlin Bed Rest study

Healthy men between 20 and 45 years with a modest to active lifestyle and a high motivation for this study were recruited via various German media. Out of the 694 individuals who applied, 20 subjects were included in the study. These subjects were subsequently randomly assigned to either an inactive control group (Ctrl), or to an resistive vibration exercise (RVE) training group. The Berlin Bed Rest Study was conducted between February 2003 and June 2004 in the Charité Benjamin Franklin Hospital [20]. The study was organized in five campaigns, each comprising four subjects. In all campaigns, subjects from the training group were living in one room and the subjects from the control group in a different room. All subjects were confined to 56 days of strict horizontal bed rest, during which the subjects were by no means allowed to sit or stand up. Subjects were further instructed to limit lower leg muscular activity during the BR to an absolute minimum. As far as possible, adherence to this protocol was controlled by continuous video recordings and by force transducers in the frames of the bed. Subjects of the RVE group participated in a resistance-type strength training program that consisted of twice-daily, five days per week resistance vibration exercises in the supine position (Fig. 1), using a dedicated vibration device (Galileo Space, Novotec, Pforzheim, Germany).

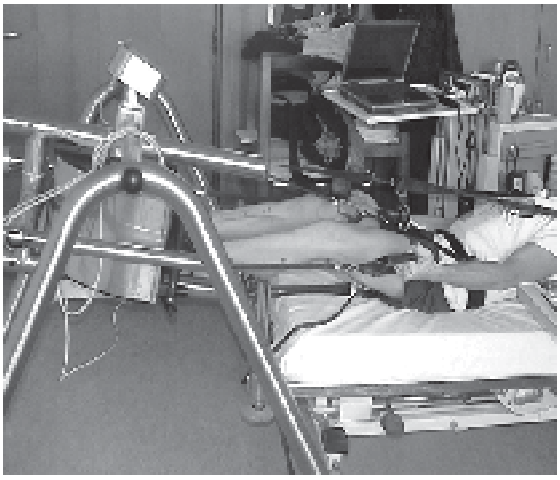

Fig. 1. The Galileo Space Device used for resistive vibration exercise at supine position during 56 days of strict bed rest.

Each training session comprised of four exercises (squats, heel and toe raises and 'kicks') that specifically targeted weight-bearing structures (muscles, tendons, bones). During morning sessions, exercises were performed for > 60 seconds (approximately ten repetitions). If 100 seconds were exceeded, vibration frequency was increased. During afternoon sessions, subjects exercised at a reduced workload (60-80% of the morning session), but performed the exercise as many times as possible for 60 seconds each without rest between successive repetitions. On Wednesday mornings, subjects were asked to exert themselves maximally by exercising each unit as long as possible. No training sessions were scheduled at Sundays.

Aim and outline of this thesis

The general aim of the present thesis was to longitudinally study the changes in the structural, contractile and electrophysiological properties of the human quadriceps muscle during prolonged bed rest. In addition, the effect of bed rest on the fatigability and associated metabolic and circulatory properties of the quadriceps femoris muscle was studied before and shortly following reambulation. Finally, this thesis further aims to evaluate the efficacy of resistive vibration exercise training to preserve neuromuscular integrity and endurance capacity under bed rest conditions. To investigate the time course of changes in neuromuscular function, a supine dynamometer was developed that allowed for the quantification of mechanical properties of the quadriceps muscle during the course of the bed rest. A pre-existing high density surface electromyography (HD-sEMG) system [6] was used to measure electrophysiological muscle characteristics during voluntary activation. The number and frequency of tests were carefully chosen to allow the assessment of an accurate time frame of changes in the neuromuscular system, whereby we anticipated that the testing regime itself would not significantly interfere with the quality or quantity of deconditioning of the neuromuscular system.

All studies reported in this thesis were conducted on the quadriceps femoris muscle group, which, because of its role as an antigravity muscle, would be significantly subjected to bed rest-induced neuromuscular deconditioning. In addition, part of the countermeasure was designed to particularly target the knee extensor group. The functional measurements during bed rest were conducted on the right leg, using the abovementioned two groups of subjects.

Chapter 2 describes a study which aimed to determine the time course of changes in muscle size, strength and voluntary activation of the quadriceps femoris muscle during bed rest in the presence and absence of a countermeasure. To assess the time course of changes in knee extensor size, measurements were conducted five times during bed rest period (in two-week intervals) by means of magnetic resonance imaging. Maximal voluntary isometric knee extensor strength was recorded prior to, and seven times during the bed rest at the optimal knee flexion angle. Associated maximal voluntary activation levels were measured by means of a superimposed stimulation technique. In addition, pre-post bed rest experiments were conducted to determine (a) whether changes in maximal muscle strength were dependent on knee flexion angle, and (b) to elucidate whether the physical testing procedure performed during bed rest had influenced the changes in neuromuscular function.

Chapter 3 deals with an elaborate analysis of high-density surface electromyography (HD-sEMG) signals that were recorded from the vastus lateralis muscle during isometric knee extensions at a range of sub-maximal contraction intensities, as well as during maximal effort. Measurements were conducted prior to and repeatedly during bed rest. Surface EMG signals were analyzed for amplitude, median frequency and muscle fiber conduction velocity and were subsequently related to isometric muscle strength to assess whether alterations in neuromuscular control strategies existed that were not, or could not have been detected by the methodology described in Chapter 2. For instance, mean muscle fiber conduction velocity is mainly related to the (changing) size of the muscle fibers, whereas the sEMG amplitude and median frequency are related both to this velocity and to alterations in neuromuscular drive to the muscle. The absolute and relative relation between sEMG variables and muscle force were used to discover potential changing muscle activation strategies.

The requisites of successful spaceflight missions aboard the International Space Station, to the Moon and to Mars with respect to muscle integrity encompass more than the preservation of muscle mass, muscle strength and adequate neural control. Importantly, there is also the need to maintain functional capacity for tasks that may require prolonged work output. In Chapter 4 we describe a study aimed to elucidate whether the fatigability of the quadriceps femoris muscle increased as a consequence of the 56-day bed rest intervention. Before and after bed rest, subjects performed a 5-min sub-maximal intermittent fatigue task in the supine position. To increase our understanding of the mechanisms that relate to changes in quadriceps femoris fatigability following bed rest, we simultaneously recorded voluntary isometric knee extensor torque and HD-sEMG signals of the vastus lateralis muscle. In addition, because of the potential effect of bed rest-induced vascular deconditioning on muscle fatigability, local blood flow and oxygenation indices were obtained at rest and during the second minute of fatiguing exercise by means of near-infrared spectroscopy (NIRS).

Apart from the capacities to produce short ‘steady-state’ (sub-)maximal muscle force (Chapters 2 and 3), and prolonged muscle force (Chapter 4), another equally important muscle functionality to be maintained during spaceflight, is the rate at which muscle force develops at the start of a forceful voluntary contraction. Because much higher activation levels are needed to reach maximal rates of force development than required for maximal isometric strength [8;9] we hypothesized that explosive muscle strength would be more affected by bed rest-induced neural deconditioning than maximal isometric ‘steady-state’ muscle strength. The study described in Chapter 5 was conducted to test this hypothesis. Although it is acknowledged that the rate of fore rise during fast voluntary contractions is predominantly determined by neural activation characteristics [10], the intrinsic contractile properties are also important. In fact, it was shown that in previously unloaded muscles the *in-vivo* muscle function is influenced by alterations in contractile properties of single fibers [28]. Therefore, to more clearly understand the processes involved in bed rest induced deconditioning, we also investigated the contractile properties of electrically evoked isometric contractions. The combination of these results with the recordings of voluntary contractions and associated HD-sEMG would allow disentangling alterations in intrinsic (peripheral) muscle properties from changes in (central) activation strategies.

Finally, main and auxiliary results of our experiments conducted during the Berlin Bed Rest study are given in Chapter 6. These findings are discussed, not only with respect to their implications for human spaceflight, but also how they, in more clinical terms, could also improve the healthcare for the elderly, or for individuals afflicted with muscle and bone-wasting diseases on Earth. Likewise, also the treatment and recovery of those that are only transiently hospitalized, bedridden or otherwise physically inactive, may be improved by studies as presented in this thesis.

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