SUMMARY

NEUROMUSCULAR ADAPTATIONS DURING LONG-TERM BED REST

The weightless environment encountered during human spaceflight virtually eliminates the mechanical loading of the human body. The accompanying physical inactivity sets in motion a cascade of changes that affects practically every physiological system in the human body. Of particular medical and operational concern are the decrements in skeletal muscle strength (force, power and endurance capacity) of the legs and the demineralization of weight-bearing bones. By now, it is acknowledged that these functional impairments may be prevented by adequate muscle exercise.

This thesis addresses the study into the neuromuscular adaptations in the quadriceps femoris muscle as a consequence of bed rest-induced physical inactivity. Bed rest is hereby used as a simulation model of human spaceflight. The nature and progression of the adaptations, but also the preventative effect of physical excersise were studied. In the Berlin Bed Rest study, the used training paradigm comprised combined resistance and vibration exercise. Strength training exercises were performed against a mechanically vibrated platform.

We were interested in the changes that occur during – particularly in the early stage of – bed rest. Hence, besides conducting experiments pre- and post bed rest, we also performed seven experiments – with an increasing time interval between experiments - during the eight weeks of bed rest. The assessment of the time course of changes in the neuromuscular system required an experimental setup that was suited for conducting functional measurements under bed rest conditions. Most notably was the development of a supine dynamometer that allowed the assessment of specific neuromuscular properties of the knee extensor muscle during contractions under isometric conditions during bed rest. To disentangle the neural activation of the muscle from more intrinsic muscle characteristics both voluntary and electrically stimulated contractions were assessed. Voluntary motor control was assessed using two procedures. In Chapter 2 we utilized electrical stimulation and a modified twitch interpolation technique to study the extra capacity of a muscle over maximal voluntary drive. In Chapters 3, 4 and 5, voluntary motor control was determined by recording the electrophysiological properties of the quadriceps muscle by means of a sophisticated high-density surface electromyography methodology (HD-sEMG).

In Chapter 2, a study is described which aimed to determine the time course of changes in muscle size, voluntary activation and maximal voluntary isometric knee extension strength during bed rest. In the inactive control subjects, the decrease in anatomical cross-sectional area (CSA) of the quadriceps femoris muscle and the decrease in maximal voluntary isometric knee extension torque both evolved linearly in time to approximately 15%. In contrast to previous research, which indicated that decrements in voluntary muscle force often exceed those in mass or CSA after unloading, for the control subjects the reduction in maximal voluntary isometric strength was comparable to that in muscle size. By means of the twitch-interpolation technique, this finding could be explained by the absence of a decrease in maximal voluntary activation of the quadriceps femoris muscle during bed rest. In contrast, for the contra lateral leg, which was only tested pre- and post bed rest, the loss in muscle strength exceeded the reduction in muscle size by almost a factor two. Based on these observations, it was concluded that the functional testing conducted during the bed rest had preserved the integrity of motor control of the repeatedly re-tested quadriceps femoris muscle. Although unintended, these findings provide valuable information, because it was shown that neural deconditioning can be prevented without vigorous exercise regimes, even during long-term bed rest. However, the preservation of neural integrity for the repeatedly re-tested right leg of the control subjects complicated the interpretations for the subjects that underwent training. Even though the allocated countermeasure contributed substantially to diminish quadriceps femoris atrophy, the possibility that the absence of a significant change in neural activation also in this group could have resulted from the repeated functional testing during bed rest could not be entirely excluded.

In Chapter 3 we used a different approach to assess alterations in voluntary motor control. HD-sEMG signals were repetitively recorded from the vastus lateralis muscle during bed rest for a series of isometric knee extensions, which varied in intensity from low to maximal. Surface EMG signals were analyzed for amplitude, median frequency and muscle fiber conduction velocity, and were subsequently related to isometric muscle strength to obtain HD-sEMG-force relationships. The normalized relationships were used to obtain a global indication of muscle activation with increasing voluntary force. Motor control of isometric force production was robust to the effects of bed rest, as none of the normalized relations between surface EMG characteristics and muscle force changed as a consequence of bed rest. This implies that the neural strategy to increase muscle force did not change by bed rest. In addition, the amplitude of the sEMG at maximal effort remained unaltered in the control group. The latter implies also the maintenance of maximal neural capacity, which is in agreement with the findings presented in Chapter 2. The observed changes sEMG median frequency and muscle fiber conduction velocity were interpreted as a reflection of atrophy of the quadriceps femoris muscle (vastus lateralis) for these subjects (Chapter 2). The group that underwent resistive vibration exercise training displayed a substantial (around 30%) and rapid (after 10 days bed rest) increase in sEMG amplitude, with no change in maximal muscle strength. These observations not only differed from the findings of the control group, they also contrasted the findings presented in Chapter 2. We speculated that the intensified muscle activation might have resulted from an increase in the mean firing rate of motor units, as a consequence of the training regime. The discrepancy between the findings of Chapters 2 and 3 might be explained if the sEMG methodology were more sensitive than the twitch-interpolation technique to detect specific neural modulations. From the unchanged knee extension strength for this group, it appeared that the proposed altered neural strategies were functionally ineffective to influence isometric knee extension strength.

The purpose of the study presented in Chapter 4 was to test the effect of the 56 days of bed rest on the fatigability of the quadriceps femoris muscle. The experiments were conducted only prior to and immediately following bed rest. The results show that the relative fatigability increased for the control subjects, as maximal voluntary strength decreased faster during 5 minutes of voluntary repetitive sub-maximal isometric knee extensions following bed rest as compared to before. In accordance with this increased fatigability was the observation of an accelerated decline in HD-sEMG median frequency and mean muscle fiber conduction velocity following bed rest. These findings suggested that the increased fatigability was most likely of peripheral origin. Near-infrared spectroscopy measurements indicated that this was most likely the consequence of a strong reduction in local muscle blood flow and hence oxygen delivery during exercise, following bed rest. For the trained group muscle fatigability decreased. The changes in sEMG variables as seen in the inactive control subjects were effectively prevented. The reduction in muscle blood flow was also mitigated for this group. The latter findings might be related to the - also in this bed rest campaign shown - attenuation of structural and functional changes in the vascular system by the adopted training paradigm.

Apart from the capacities to produce short steady-state (sub-)maximal muscle force (Chapters 2 and 3), and prolonged repeated sub-maximal muscle force (Chapter 4), another important muscle functionality that was studied, is the rate at which muscle force develops at the start of a forceful voluntary contraction. As described in Chapter 5, also the contractile properties of the quadriceps femoris muscle were repetitively tested during bed rest for fast voluntary and electrically evoked contractions. It was clearly shown that the quadriceps femoris muscle of the control subjects acquired the intrinsic contractile properties of a faster muscle. Daily resistive vibration exercise proved effective to prevent such changes. Unexpectedly, the ability to produce a high rate of torque development during voluntary contractions was preserved and the addition of resistive vibration exercise did not influence this capacity. This maintained functionality was, simular to that described in Chapters 2 and 3, associated with an absent neural deterioration, as measured by means of HD-sEMG. It was concluded that the alterations in mechanical properties during electrically evoked contractions were of insufficient magnitude to (detectably) affect voluntary muscle functionality. This was most likely a consequence of the large inter-, but also intra-individual variability in the performance of the fast voluntary contractions. However, we could not rule out the possibility that also here the repeated functional testing conducted during bed rest sufficed to maintain adequate motor control. This could even apply to a more skilful task that requires considerably more neural activation than needed for steady-state contractions.

Finally, Chapter 6 contains a general discussion of the results presented in this thesis, their relation to auxiliary and previous findings, as well as their practical implications for both human spaceflight and physically inactive individuals on Earth. The results of the studies described in this thesis have contributed to a better understanding of the underlying mechanisms and the time course in which they contribute to the various manifestations of muscle weakness as a result of physical inactivity imposed by strict bed rest. Most notably were the findings of a linear reduction in voluntary isometric knee extension strength, and an increase in relative muscle fatigability. These adaptations were predominantly the result of a linear decay in the cross-sectional area of the quadriceps femoris muscle and a reduced blood flow as a consequence of bed rest. The changes in intrinsic contractile characteristics of the quadriceps femoris towards a faster muscle also progressed linearly in time. An unexpected finding across experiments was that the adopted longitudinal study, which included repeated functional re-testing of the quadriceps femoris muscle during 56 days of bed rest, fully prevented neural deconditioning. Vigorous resistive vibration exercise training during bed rest appeared a suitable gravity-independent countermeasure that offset or substantially mitigated most of the adaptive changes in quadriceps femoris muscle that evolved during bed rest in the absence of this countermeasure.