Aerobic exercise capacity in post-polio syndrome
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The aim of this thesis was to expand the body of knowledge on the diminished aerobic capacity of individuals with post-polio syndrome (PPS). The studies described in this thesis were based on the assumption that, besides a reduced muscle mass, deconditioning contributes to the severely diminished aerobic capacity found in many of these individuals. Deconditioning may result from two factors, the disease process itself and a sedentary lifestyle. While the disease process itself is irreversible, deconditioning as the consequence of a sedentary lifestyle may be reversed by increasing physical activity in daily life or by following exercise programs.

In chapters 2 and 3 of this thesis it was investigated whether altered intrinsic properties of the muscle fibers and peripheral circulation underlie early muscle fatigue, thereby limiting the aerobic capacity in PPS. Chapters 4, 5, and 6 focused on aerobic exercise in PPS: in particular on determining the appropriate individual training intensity and evaluating the effectiveness of an intervention aimed at improving the aerobic capacity through lower extremity exercise in a randomized controlled trial, FACTS-2-PPS. In this final chapter, the main findings of these studies are discussed along with their implications for clinical practice. Furthermore, methodological considerations of the studies performed are addressed as well as recommendations for future research.

MAIN FINDINGS

Muscle adaptations and aerobic muscle capacity in post-polio syndrome

The results from the study described in chapter 3 did not support the assumption of deconditioning of the remaining muscle mass in individuals with PPS. The objective of this study was to investigate fatigue resistance of the knee extensor muscles in individuals with PPS during electrically evoked contractions in comparison with healthy subjects in the same age range. The rate of fatigue appeared to be comparable in both groups both in the situation with intact circulation and when the blood flow was occluded. Moreover, there were no differences in favor of the healthy subjects with respect to the recovery of fatigue, which depends to a great extent on the aerobic capacity of the muscle fibers. Contrary to muscle biopsies from individuals with PPS showing a reduced capillary supply and aerobic enzyme activity, these results argue against an impaired blood flow or reduced aerobic capacity of the fibers in PPS muscles.

Despite the findings suggesting that aerobic muscle capacity in PPS does not differ from healthy individuals, a marked variability was observed, underscoring the heterogeneity in muscle function between individuals. Hence, aerobic metabolism may be reduced in part of the individuals with PPS as well as in part of the healthy adults. The results of the study described in chapter 2 showed that the assessment of contractile properties, as obtained from electrically evoked contractions, is sufficiently reliable to distinguish individuals with PPS with different fatigue resistance of the knee extensor muscles from each other, and, to evaluate changes over time following interventions. Furthermore, considering the high reliability, it is unlikely that differences between individuals with PPS and healthy subjects could not be detected.
Aerobic exercise training in post-polio syndrome

The anaerobic threshold (AT) is widely used for setting target intensity for aerobic training. Usually, the AT is assessed through graded maximal exercise testing. In PPS, and other neuromuscular diseases (NMDs), maximal exercise testing is not feasible in all individuals because performance is often symptom-limited. Furthermore, because of the potential risk of muscular overload and excessive fatigue, with a prolonged recovery, maximal exercise testing should be avoided.

In chapter 4 it was shown that submaximal incremental exercise testing can be used for assessment of the AT in most individuals with PPS who can cycle on a bicycle ergometer, enabling physical therapists to better individualize exercise intensity for aerobic training. Furthermore, current guidelines for training intensity prescription based on ratings of perceived exertion (RPEs) corresponded better to the AT than prescription based on estimated heart rate reserve (HRR). Considering these findings, it was recommended that, if the AT cannot be identified (e.g. because gas analysis equipment is not available), training prescription should preferably be based on RPEs, rather than on a fixed percentage of the estimated HRR for the entire study group, offering a more individualized target for aerobic training in PPS.

Because these new insights regarding the AT were not yet available prior to the start of the FACTS-2-PPS trial, intensity prescription of the aerobic exercise program was still based on the estimated HRR, an easy applicable method. The results of the FACTS-2-PPS trial were described in chapter 5 and failed to show improvements in fatigue through an exercise therapy intervention with a home-based high intensity aerobic exercise program. This was consistent with the absence of an increased cardiorespiratory fitness following the training program.

The process evaluation in which possible causes for the lack of efficacy were explored (chapter 6) revealed that participants attended most training sessions, and that the actually achieved duration of the training sessions increased in accordance with the protocol. Actually sustained exercise intensities, on the other hand, increased throughout the entire training program, but remained clearly below designated intensities (60%–70%HRR) in nearly all participants. Other studies investigating high intensity aerobic exercise programs in PPS also showed that, in some participants, duration and intensity had to be adjusted downward. Based on these findings, it was concluded that, for most individuals with PPS, high exercise intensities are too exhausting to sustain during training on a bicycle ergometer.

While high intensities were difficult to sustain, it was shown that participants in the exercise program of the FACTS-2-PPS trial exercised at or above their AT during most of the training period. In addition, participants rated most training sessions as 12 or higher on the Borg Scale, which is in line with findings from a recent study showing that in PPS, the heart rate attained at the AT corresponds well to a score of 12 on the Borg Scale. Nonetheless, there were no indications of improved cardiorespiratory fitness levels following the exercise program. This is surprising given the extensive use of the AT for setting target intensity for aerobic training, which has shown to be effective in healthy subjects, as well as in individuals with chronic disease.
Subsequently, it was investigated whether the exercise program resulted in positive muscular adaptations, which, due to the limited muscle mass of the lower extremities, did not lead to an increased cardiorespiratory fitness. However, as for the cardiorespiratory fitness, there were no indications of an improved muscle function—neither muscle strength, nor muscle endurance improved following the training program (chapter 6). It must be realized though that the findings regarding muscle function, especially those for endurance, should be interpreted with caution because they are based on a limited number of observations. Possibly, the presence of muscular adaptations could not be detected due to the small sample size.

When assuming that muscle function was indeed not improved as a consequence of the training program, this indicates that, apparently, the training dose was insufficient to induce positive training effects. The absence of muscular adaptations following the FACTS-2-PPS exercise program is consistent with findings from Willén and colleagues who also found no changes in knee extensor muscle function following a 5-month dynamic water exercise program. Contrary, Ernstoff and colleagues found an increased muscle strength in some—mainly upper extremity—muscle groups, as well as an increased fatigue resistance of the weaker leg, though without any change in aerobic enzyme activity or cross-sectional areas of the muscle fibers. Together with the results from chapter 3 this raises the question whether the muscles of the lower extremities in PPS were, apart from the reduced muscle mass, deconditioned. Hence, as it was shown in older adults that individuals with the lowest aerobic capacity show the greatest response to training it may be possible that the potential for aerobic muscle adaptations induced by the exercise program in the FACTS-2-PPS study group was limited.

Physical activity, training and aerobic capacity in post-polio syndrome

Several studies have shown that polio survivors are less active than healthy controls using both reported activity and objectively measured activity. Using activity monitors, Klein, Winberg, and colleagues reported mean values of 6450 and 6212 steps per day, respectively, which is comparable to the values found in the FACTS-2-PPS trial. The mean number of steps recorded in the FACTS-2-PPS trial varied between 6200 and 7050 per day. Based on the proposed recommendations of 8000 to 10000 steps per day, most individuals with PPS are therefore considered to be “low active” according to Tudor-Locke and colleagues. These authors suggested that 3000 to 4000 steps are needed for daily activities and consider less than 5000 steps per day indicative of a sedentary lifestyle in healthy adults.

In addition, based on reported activity measures, Winberg and colleagues found that the amount of physical activity varied considerably among individuals with PPS, but on average participants in their study were active almost 3 hours per day. This suggests that individuals with PPS meet the WHO recommendations of 150 minutes of physical activity per week. However, much of the activities in PPS are performed as part of their household activities, which are generally considered as low level physical activities. The recommendations by the WHO may include household chores, but they have to be at least moderate in intensity and performed in bouts of at least 10 minutes in order to be beneficial in
Considering that most of the activities performed by individuals with PPS are low level physical activities, whereas the WHO recommends activities that are at least moderate in intensity, it was concluded that most of them do not reach the recommended amount of physical activity. The question is, however, whether such extrapolation from healthy persons to individuals with PPS is allowed.

It is in this light important to realize that if a person’s capacity is reduced as a consequence of muscle paresis from polio, performing activities in daily life will require more of the available capacity. Brehm, Nollet and colleagues found that the energy cost and heart rate were higher in polio survivors compared to healthy subjects for walking and during cycling on an ergometer, mainly in association with the reduced muscle mass. Activities being characterized as low intensity in healthy adults (such as household activities) may therefore well be of moderate intensity in people with residuals of polio. This may explain why there were, apart from the reduced muscle mass, no signs of deconditioning of the knee extensor muscles found in the FACTS-2-PPS study group. Possibly, this muscle group, that is of major importance during locomotion-related activities, has already adapted considerably in response to the relatively higher loading during daily life activities. A recent study showing that the muscle strength declines at a slower rate in PPS compared to healthy age-matched persons supports this hypothesis. The extra loading of the reduced muscle mass during daily tasks could act as a stimulus to help maintain strength. That the remaining muscles of polio subjects are adapted as a consequence of the extensive use in daily life is further corroborated by findings of type I fiber predominance and muscle fiber hypertrophy in lower extremity muscles. Whether these muscular adaptations were also present in participants of the FACTS-2-PPS trial is however not entirely certain because there were no muscle biopsies taken.

The finding that, in most individuals with PPS, the muscles of the lower extremities appear not be deconditioned, does not necessarily imply that exercise is to be considered an ineffective method to improve the aerobic capacity in PPS. There are in fact studies that demonstrated an improved aerobic capacity following aerobic training. Other studies found an improved peak workload, however, without demonstrating effects on cardiopulmonary fitness or aerobic muscle capacity. Because it cannot be ruled out that the improved peak workload is the result of habituation rather than an improved aerobic capacity, these studies provide no conclusive evidence on the efficacy of training to improve the aerobic capacity in PPS. Contrary to the FACTS-2-PPS exercise program, the training programs of Willén, Ernstoff, and colleagues aimed at whole body exercise, including the use of muscle groups of the upper extremities. It is well conceivable that the additional use of other large muscle groups explains why cardiorespiratory fitness levels increased in their study group, while fitness levels remained unchanged following the FACTS-2-PPS exercise program. Despite an increased cardiorespiratory fitness, the studies by Willén, Ernstoff and colleagues found however little or no improvement in lower extremity muscle function. This is in line with findings from the FACTS-2-PPS trial and corroborates the other findings arguing against deconditioning of the lower extremity muscles.
STRENGTHS AND LIMITATIONS OF THE THESIS

Study population

One could criticize the selection of the population studied in this thesis. Participants had to be able to cycle on an ergometer, and walk, with or without walking aids. Furthermore, the FACTS-2-PPS trial was a relatively demanding study with extensive assessments for which participants sometimes had to travel far. Possibly this resulted in a selection of participants with a rather good exercise capacity. Nevertheless, the distance covered during the 2 minute walk test, was somewhat lower in participants of the FACTS-2-PPS trial (mean (SD), 118 (23) meters at baseline in the exercise therapy group), compared to participants from a previous cohort of polio survivors, the CARPA cohort (136 (28) meters)).

The CARPA cohort included participants with co-morbidities and is therewith considered a good representation of the general population of polio survivors. Therefore, even though walking capacity is not the sole determinant of exercise capacity, there are no clear indications that our inclusion criteria resulted in a selection bias toward participants with a better physical capacity, thereby restricting generalizability of results to the population of individuals with PPS in general.

Measurements

The measurements for muscle function were performed solely on the knee extensor muscles and not on other muscle groups. Although from literature it is known that the effects are widespread and not necessarily restricted to one muscle group this muscle group was investigated, because muscle weakness in PPS often affects the lower limbs, and also measurements can easily be performed on this muscle group that is of major importance for locomotion-related activities. Nonetheless, even though it is considered legitimate to perform measurements on the knee extensor muscles, it must be realized that results cannot simply be generalized to other muscles, because muscle function characteristics may differ between muscle groups depending on their use in daily life.

A limitation of using electrically evoked contractions to evaluate muscle function is that not all participants tolerate the electrical stimulation. Both, in the cross-sectional study and in the FACTS-2-PPS trial a number of participants did not complete the measurements due to discomfort of the electrical stimulation. In addition, some participants had difficulty in relaxing the muscles during the stimulated contractions. This resulted in fewer observations that could be included in the analyses. Involuntary muscle activation has been reported in earlier studies, but the factors responsible for this are unknown. Especially in the FACTS-2-PPS trial, a substantial number of participants discontinued the muscle endurance measurements. Of the 31 participants performing these measurements at baseline, only 16 participants were willing to perform the measurements after the intervention period. The explanation for this high dropout rate is not fully known to us because the reasons for withdrawal were not explored in detail. Some participants experienced the stimulated muscle contractions as uncomfortable. Others found the FACTS-2-PPS trial highly demanding. The muscle function measurements were performed on a separate occasion, which may explain why part of the participants decided not to participate in the follow up measure-
ments. Therefore, the findings regarding muscle function, especially those for endurance, should be interpreted with caution because they are based on a limited number of observations. This is less the case for the cross-sectional study results. Because of the relatively large sample size included in this study, the withdrawal of some participants probably did not influence the results concerned. For both studies, however, the possibility cannot be excluded that there was a selection bias, possibly toward less severely affected patients, which may have influenced results.

The intervention

A principal strength is that the heart rate of all participants was monitored during the training sessions of the FACTS-2-PPS exercise program. This enabled us to quantify actual training dose in terms of intensity and duration. Even though previous training studies reported their designated program, most of these studies provide incomplete or no insight in the training intensity and duration actually achieved. The process evaluation of the FACTS-2-PPS exercise program showed that training duration increased in accordance with the protocol. More importantly, even though there was a pattern of increasing intensity throughout the training program, it remained clearly below designated intensities (60%–70%HRR). Contrary to earlier reports, these findings indicate that high exercise intensities are too exhausting to sustain during training in PPS. Moreover, they emphasize the need to monitor the actually achieved training dose and to reconsider the application of such programs in clinical practice.

CLINICAL IMPLICATIONS

Increasing the aerobic capacity through exercise may be possible in PPS, provided that training programs are highly individualized with respect to the aerobic (muscle) capacity. In part of the individuals, the muscles that are required for activities in daily life have probably already been largely adapted as a consequence of extensive use. During recovery from the acute polio, denervated muscle fibers from permanently lost motor neurons were reinnervated by means of collateral sprouting from intact axons, leading to the formation of giant motor units. Furthermore, the remaining muscle fibers hypertrophied in response to exercise and performing daily life activities. Although the reduced muscle mass is most likely the primary factor responsible for the diminished aerobic capacity in those individuals, it seems, in the light of these muscular adaptations, undesirable to increase the muscle mass in order to improve the aerobic capacity. Therefore, for those individuals, increasing the aerobic capacity may be possible by using exercise modes that require the use of other large muscle groups instead. One must realize, however, that if the involved muscles are not used during daily life activities, the obtained training effects will probably not sustain and therefore not result in improved physical functioning and perceived health in the long term.

In other individuals with PPS, the muscles required for daily tasks may be deconditioned due to physical inactivity. Obviously, in this case, exercise modes should be selected that require the use of those deconditioned muscle groups, in order to improve the aerobic
(muscle) capacity. Therefore, when prescribing aerobic exercise, one should determine whether functionally important muscle groups are underloaded during daily life activities. If this is the case, those muscle groups should be involved in the training regime. If not, other exercise modes should be considered. The fatigue resistance measurements that were presented in this thesis can be used to determine the extent to which the knee extensor muscles, a muscle group that is of major importance during locomotion-related activities, are deconditioned. Future research is however required to develop new, preferably less demanding, methods to accurately determine the degree of deconditioning of independent muscle groups.

In addition, training intensity prescription should also be tailored to the individual patient. The AT enables physical therapists to better individualize intensity prescription for aerobic exercise in PPS and can be assessed from submaximal exercise testing on a bicycle ergometer. If the AT cannot be identified, for example because the gas analysis equipment is not available, intensity prescription should preferably be based on RPEs, rather than on a fixed percentage of the HRR. This offers a more individualized target for aerobic training in PPS. Whether this can also be applied to other exercise modes such as arm ergometry or four limb ergometry is uncertain and requires further investigation.

Besides the positive effects on cardiorespiratory and muscle function, physical activity is known to be essential for good health. Polio survivors have a high prevalence of co-morbidities, which negatively impact on health and quality of life. Many of the conditions commonly reported in polio survivors, such as type 2 diabetes, stroke and other cardiovascular diseases, have significantly lifestyle related risk factors. For example, physical activity will reduce the risk of developing type 2 diabetes by improving insulin sensitivity and assist in diminishing elevated blood glucose levels. Therefore, irrespective of the effects of exercise on the aerobic capacity, staying physically active is essential for individuals with PPS.

FUTURE RESEARCH

More research is required to optimize and further individualize training programs for individuals with PPS. Even though it remains uncertain whether there exists a training intensity below which no improvement of the aerobic exercise capacity occurs with training, it is now known that, for most individuals with PPS intensities of >60%HRR seem too exhausting to sustain during cycle ergometry training. However, the participants in the FACTS-2-PPS were capable of exercising around the AT for prolonged periods of time. The fact that no positive effects of training were found, indicates that the selected exercise mode was not appropriate for this study group. Therefore, the next step should be to study the efficacy of training programs based on exercise modes tailored to the individual’s aerobic (muscle) capacity.

Although it may eventually be possible to increase the individual’s aerobic capacity through individualized exercise programs, the potential benefits in terms of physical functioning and perceived health should be assessed. In line with the FACTS-2-PPS trial, some other studies reported the effects of training on such outcome measures. The number of studies is however limited, and, moreover, results are inconsistent. Further research in
this area is therefore necessary. In addition, a study in individuals with PPS and other neuromuscular diseases revealed that this population experiences difficulties with integrating training programs into their lives.\textsuperscript{40} One of the research priorities for this population is therefore to find the best ways to tailor training to the individual patient, by finding a balance between staying sufficiently physically active the one hand, and preventing overburdening on the other hand. For, in the end, it is not the effectiveness of aerobic training programs per se, but the potential benefits in terms of physical functioning and perceived health that is the primary concern for individuals with PPS.
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