Aerobic exercise capacity in post-polio syndrome
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Chapter 1

GENERAL INTRODUCTION
At its peak in the 1940s and 1950s, polio paralyzed or killed over half a million people worldwide every year. Due to the introduction of routine vaccination in the late 1950s, and in 1988, the Global Polio Eradication Initiative spearheaded by the World Health Organization (WHO), Rotary International, UNICEF and the Center for Disease Control (CDC), the number of polio cases per year declined dramatically, from over 350,000 new cases in 1988 to 406 in 2013.

Polio has become a rare and almost forgotten disease in the Western world. The virus is however still endemic in some developing countries (Pakistan, Afghanistan and Nigeria). Virus spread from these countries remains a significant risk for polio reintroduction and periodically causes outbreaks in other countries, including Syria most recently.

Despite the low number of new polio cases, there are still many individuals suffering from the late effects of polio. The WHO estimates the number of polio survivors worldwide at 20 million. In the Netherlands the last large epidemic, with 2,206 cases notified to the health authorities, dates from 1956. Since then, some sporadic cases and small outbreaks have occurred in 1978 (110 cases) and 1992/1993 (71 cases), mainly in communities that refuse vaccination on religious grounds. Most polio survivors of the epidemics in the Netherlands are now in their late fifties or aged above. However, due to immigration, our country is today home to younger polio survivors as well.

**ACUTE POLIO AND THE RECOVERY**

Poliomyelitis is a highly contagious viral disease that spreads by faeco-oral route with humans as the only host. In most cases, the infection passes by unnoticed without symptoms. Due to an immune response the infected person develops immunity for the polio virus. In 4–8% of all infections, polio results in mild, flue-like symptoms, such as fever, sore throat, nausea or diarrhoea. However in approximately 0.1 to 2% of the infected persons, the virus invades the central nervous system leading to destruction of the motor neurons in the anterior horns of the spinal cord. This results in an acute, usually asymmetrically distributed, flaccid paresis of a varying number of muscle groups.

The acute paralytic phase, which may last for several weeks, is followed by a recovery period. Restoration of motor function mainly occurs within the first 3 months, but may continue for several years. There are several mechanisms that contribute to this recovery. Some motor neurons survive and regain their function, usually within 1 month. Denervated muscle fibers from permanently lost motor neurons are reinnervated by means of collateral sprouting from intact axons leading to the formation of giant motor units that can increase up to 10 times in size. Furthermore, strength increases as a result of muscle fiber hypertrophy, in response to exercise and performing activities of daily life.

Full restoration of function may be achieved with apparently normal strength, but with a reduced number of enlarged motor units. In many cases, however, the recovery is incomplete, leaving patients with greatly varying clinical presentations, from local residual paresis in one extremity to severe residual paresis of all four extremities, trunk and bulbar muscles. Usually, this is accompanied by bony deformities and limb length deficiencies which develop during growth. From then on, muscle function and functioning remain stable for many years.
Introduction

THE POST-POLIO SYNDROME

For a long time it was believed that the residual neurological deficits resulting from polio would remain stable throughout life. However in the late 1970s and early 1980s polio survivors were found to develop new symptoms related to the polio they had contracted many years before. The combination of these late symptoms are referred to as the post-polio syndrome (PPS) and include new or increased muscle weakness, abnormal muscle fatigability, generalized fatigue, muscle atrophy, muscle and joint pain, muscle cramps and cold intolerance. The prevalence of PPS has been reported from 15% to 80% of all individuals with previous paralytic polio depending on the criteria applied and population studied. Nearly 60% of a sample of Dutch survivors of the 1956 outbreak experienced late onset polio sequelae about forty years after the acute stage of polio.

FATIGUE AND FUNCTIONAL DECLINE IN POST-POLIO SYNDROME

Individuals with PPS report fatigue and a decline in their functional abilities, especially walking outdoors, standing, and climbing stairs, as their major problems. An important factor that contributes to the symptoms of fatigue and increased difficulties in performing (sustained) activities is a reduced muscle strength, primarily caused by a reduced muscle mass. Another factor that is assumed to contribute is the severely diminished aerobic capacity found in these patients. Aerobic capacity is defined as the (maximum) amount of oxygen the body can use during a specified period. It is a function both of cardiorespiratory performance and the maximum ability to extract and utilize oxygen from circulating blood in the muscles.

Previous studies have shown that individuals with PPS have a lower aerobic capacity than healthy persons, mainly due to the reduced muscle mass. The gradual loss of muscle strength in PPS leads to a decline in functional abilities and may induce a relatively sedentary lifestyle. This decrease in physical activity leads to deconditioning, which causes even more difficulties in performing sustained activities. Consequently, two factors may contribute to the diminished aerobic capacity in PPS: (1) alteration of muscle function due to the disease process itself, and (2) deconditioning due to a sedentary lifestyle.

MUSCLE ADAPTATIONS AND FATIGUE IN POST-POLIO SYNDROME

In addition to the reduced muscle mass, alterations of the intrinsic properties of the remaining muscle fibers and peripheral circulation may lead to early muscle fatigue, thereby limiting the aerobic capacity in these patients.

Several muscular alterations have been described in polio survivors. Muscle biopsy studies of polio subjects have found mean muscle fiber cross-sectional area to be about twice as large in PPS compared to healthy subjects, probably due to excessive use of remaining fibers. Secondary to hypertrophy, a reduced capillary supply in relation to fiber area was observed, that might impair diffusion capacity, leading to shortage of substrate during work. This is accompanied by a low aerobic enzyme activity of the muscle fibers. A low capillary density in combination with decreased aerobic enzyme capacity would lim-
it muscle endurance. Furthermore, a muscle fiber transformation from type II fibers to type I fibers was reported in polio survivors, most likely also resulting from overuse of the reduced muscle mass. Given that type I fibers better resist fatigue than type II fibers, this would, contrary to the other adaptations, favor muscle endurance, unless type I fiber characteristics in PPS differ from those in healthy subjects. Therefore, it remains uncertain whether the combination of these opposite adaptations leads to early muscle fatigue, thereby limiting the aerobic capacity in individuals with PPS. Although there have been a few studies investigating fatigability of muscles in PPS, results were contradictory, emphasizing the need for further research in this area.

Muscle fatigue depends on several factors that may reside in the brain or spinal cord (here defined as central fatigue), and/or in the muscles themselves (here defined as peripheral fatigue) and can be quantified using different techniques and devices. Previous studies indicate that the contribution of central fatigue in PPS is only limited. In combination with the adaptations that have been described above, it seems therefore likely that mainly peripheral mechanisms, such as the muscle’s aerobic capacity, fiber type composition and capillary supply, are involved in muscle fatigue. These can be investigated by electrically evoked muscle contractions; an experimental condition that completely removes central mechanisms. In this thesis we used this technique to study whether differences in contractile properties between individuals with PPS and healthy subjects may account for the increased muscle fatigue perceived by many individuals with PPS, thereby contributing to the diminished aerobic capacity.

AEROBIC EXERCISE TRAINING IN POST-POLIO SYNDROME

Secondary to the muscular adaptations due to the disease process itself, a diminished aerobic capacity may as well arise from deconditioning due to the low physical activity levels of many individuals with PPS. Although there is strong scientific evidence confirming the health benefits of regular physical activity, there is a lack of high quality evidence of similar benefits for people with PPS and other neuromuscular diseases. It is therefore important that interventions aimed at maximizing health among polio survivors are developed, to improve physical functioning and perceived health and reduce lifestyle related risk factors.

Although the evidence base is limited, physical therapy recommendations for individuals with PPS include aerobic exercise. The studies that have been conducted so far show inconsistent results with respect to the efficacy of aerobic exercise in PPS, which may, at least in part, be explained by the limited methodological quality of most studies. Further research is therefore required to draw definite conclusions on the effectiveness of this intervention. Another important factor explaining the inconsistent results may relate to the problems therapists experience when designing training schedules for individuals with PPS; exercise levels should be sufficiently intense to stimulate a training effect, yet avoid muscular overload.
INDIVIDUALIZING AEROBIC TRAINING INTENSITY IN POST-POLIO SYNDROME

Guidelines for aerobic exercise training in healthy subjects recommend training intensities relative to the individual’s maximal capacity. In PPS, however, a true maximum oxygen consumption or maximal heart rate is often not reached because the leg muscles frequently fatigue before the cardiorespiratory system reaches its maximum. Therefore, in this patient group, maximal heart rate is often estimated based on age. Another method to prescribe training intensity uses ratings of perceived exertion (RPEs), and is preferred in individuals using beta-blocking agents. Our experience is that, when applying these guidelines, physical therapists often have to adjust the training intensity. This is probably due to the fact that none of these guidelines makes use of measures of someone’s aerobic capacity, resulting in exercise prescription to be insufficiently tailored to the individual.

The anaerobic threshold (AT), a direct indicator of aerobic capacity, may be useful to overcome this problem. The AT is widely used for setting target intensity for aerobic training in healthy subjects, as well as individuals with chronic diseases such as multiple sclerosis, coronary heart disease, hypertension, and obesity. Usually, the AT is assessed through graded maximal exercise testing. In PPS and other neuromuscular diseases, maximal exercise testing is not feasible in all individuals because performance is often symptom-limited. Furthermore, maximal exercise may provoke muscle complaints and excessive fatigue, with a prolonged recovery, and should thus be avoided. Therefore, the AT should preferably be obtained from submaximal exercise testing. Whether this is possible in individuals with PPS is still uncertain and was investigated in this thesis. Furthermore, realizing that the expensive gas analysis equipment that is necessary for determining the AT, is often not available in physical therapy practices, we also compared commonly used markers for training intensity prescription with the AT.

THE FITNESS AND COGNITIVE BEHAVIORAL THERAPIES FOR FATIGUE AND ACTIVITIES IN POST-POLIO SYNDROME TRIAL–FACTS-2-PPS

Based on the knowledge that current evidence regarding exercise therapy in PPS is restricted to studies of limited methodological quality, we designed the FACTS-2-PPS trial. The FACTS-2-PPS trial (Dutch trial register NTR1371) is a multicenter randomized controlled trial (RCT), in which the effectiveness of exercise therapy and cognitive behavioral therapy on fatigue, daily activities and health-related quality of life in patients with PPS was studied. In this study, the Academic Medical Center in Amsterdam collaborated with other university hospitals and rehabilitation centers throughout the country. The exercise therapy had a duration of 4 months and was designed specifically to enhance aerobic capacity. The cognitive behavioral therapy, also lasting 4 months, is outside the scope of this thesis.

The primary purpose of the FACTS-2-PPS trial was to investigate the effect of both interventions on reducing fatigue and improving activities and quality of life. Next to this, we investigated in more detail the working mechanisms underlying the exercise intervention. It is known from literature that there is a large variability in the way individuals respond to exercise training. This may be the result of several factors such as the initial training status,
exercise capacity and psychological factors. An important factor for the effectiveness of exercise in PPS may be the training dose (i.e. intensity and duration) and most of the previous studies on aerobic exercise in PPS report the designated training dose for their program quite well. Precise quantification of the actually realized training dose, its relationship with the subsequent training response and the working mechanisms of improvement are however unknown. This information will provide better insight in the potential role of aerobic exercise and will help to provide more effective training methods to alleviate fatigue symptoms in PPS.

AIMS OF THIS THESIS

This thesis aims to improve our understanding of the diminished aerobic capacity of individuals with PPS. The first objective of this thesis was to investigate whether, besides the reduced muscle mass, altered intrinsic properties of the muscle fibers and peripheral circulation result in early muscle fatigue, thereby contributing to the limited aerobic capacity in these individuals. The second objective was to obtain more knowledge about aerobic exercise in PPS: in particular on determining the appropriate individual training intensity and evaluating the effectiveness of an aerobic exercise intervention in the FACTS-2-PPS trial.

OUTLINE OF THIS THESIS

Chapter 2 describes a study in which we established test-retest reliability of some fundamental contractile properties derived from electrically evoked contractions of the knee extensor muscles. Accordingly, in chapter 3, these measures were used to investigate whether differences in contractile properties between individuals with PPS and age-matched healthy subjects may account for the increased muscle fatigue perceived by many individuals with PPS, thereby contributing to the diminished aerobic capacity.

In chapter 4 we determined whether the AT could be identified through submaximal exercise testing in PPS. In addition, we compared commonly used markers for training intensity based on estimated heart rate reserve (HRR) and RPEs according to current guidelines, with the AT.

Chapter 5 describes the results of the FACTS-2-PPS trial we performed to study the efficacy of exercise therapy and cognitive behavioral therapy for reducing fatigue and improving activities and quality of life in individuals with PPS. Additionally, in chapter 6, we investigated whether the exercise program as conducted in the FACTS-2-PPS trial had favorable effects on cardiorespiratory fitness and muscle function. We also quantified the actually achieved training dose and its relationship with the subsequent training response.

The general discussion, in chapter 7 reflects on the main findings and discusses the clinical implications. Finally, some methodological considerations of the study and recommendations for future research together with an overall conclusion are described.
REFERENCES


