Aerobic exercise capacity in post-polio syndrome
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Chapter 3

FATIGUE RESISTANCE OF THE KNEE EXTENSOR MUSCLES IS NOT REDUCED IN POST-POLIO SYNDROME

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ABSTRACT

The present study investigated whether intrinsic fatigability of the muscle fibers is reduced in patients with post-polio syndrome (PPS). This may contribute to the muscle fatigue complaints reported by patients with PPS. For this purpose, we assessed contractile properties and fatigue resistance of the knee extensor muscles using repeated isometric electrically evoked contractions in 38 patients with PPS and 19 age-matched healthy subjects. To determine whether any difference in fatigue resistance between both groups could be attributed to differences in aerobic capacity of the muscle fibers, 9 patients with PPS and 11 healthy subjects performed the same protocol under arterial occlusion. Results showed that fatigue resistance of patients with PPS was comparable to that in controls, both in the situation with intact circulation and with occluded blood flow. Together, our findings suggest that there are no differences in contractile properties and aerobic muscle capacity that may account for the increased muscle fatigue perceived in PPS.
INTRODUCTION

Post-polio syndrome (PPS) is a complex of late onset neuromuscular symptoms with new or increased muscle weakness and abnormal muscle fatigability as key symptoms.\(^1^,^2\) Knowledge about the origin of the muscle fatigue perceived by patients with PPS is presently limited. The muscle fatigue may result from the motor unit reorganization and the altered pattern of activity and function of the remaining muscle fibers that occurred during recovery from the acute polio and the secondary decline.\(^3\)

Several adaptations have been described that may change the fatigue resistance of the muscle fibers in PPS.\(^4^\)\(^-^6\) Mean muscle fiber cross-sectional area was found to be about twice as large in patients with PPS compared to healthy subjects, probably due to excessive use of remaining fibers.\(^6\) Secondary to this hypertrophy, a reduced capillary supply in relation to fiber area was observed, that might impair diffusion capacity, leading to shortage of substrate during muscle work. This assumption is supported by the low aerobic enzyme activity of the muscle fibers.\(^5\) A low capillary density in combination with decreased aerobic enzyme capacity would reduce fatigue resistance of the muscle fibers. Furthermore, a muscle fiber transformation from type II fibers to type I fibers was reported, most likely also resulting from overuse of the reduced muscle mass. Contrary to the other adaptations, this would enhance fatigue resistance.\(^4^,^6\) Therefore, it remains unclear whether the combination of these opposite adaptations will enhance or reduce the fatigue resistance of the muscle fibers in patients with PPS compared to healthy subjects.\(^3\)

The few studies on fatigability of muscles in PPS reported contradictory results. Some have shown that muscles of patients with PPS are more fatigable than muscles of healthy subjects, irrespective of strength,\(^7^\)\(^-^9\) while other studies reported no differences.\(^10^\)\(^-^13\) All these studies have in common that voluntary contractions were used to induce fatigue. Because fatigue is influenced by both central neural and peripheral muscle factors, the use of voluntary contractions complicates the search for the relative contribution of each of these factors. The use of electrically evoked contractions, an experimental situation that completely removes the volitional element, allows studying the intrinsic fatigability of the muscle fibers.\(^14^,^15\)

Our primary objective was to investigate fatigue resistance of the knee extensor muscles in patients with PPS during electrically evoked muscle contractions in comparison with healthy subjects. The knee extensor muscles were chosen, because muscle weakness in PPS often affects the lower limbs, and measurements can accurately be performed on this muscle group that is of major importance during locomotion-related activities.\(^16\) The second objective was to determine whether differences in fatigability between both groups could be attributed to differences in blood flow or aerobic capacity of the muscle. Therefore, we compared fatigue with an intact circulation with fatigue under ischaemic conditions, during which the ability for aerobic energy regeneration was largely eliminated.\(^17\) If differences in fatigue resistance between PPS and healthy subjects during the protocol with an intact circulation are attributed to differences in aerobic muscle capacity or blood flow then no differences will be evident when the blood supply is occluded.
MATERIALS AND METHODS

Subjects

A sample of 38 former polio patients who were diagnosed with PPS according to the criteria published by the March of Dimes participated in this study. The criteria for PPS are as following: (1) prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG), (2) a period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic function, (3) gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain, (4) symptoms persist for at least 1 year, and (5) exclusion of other neurologic, medical, and orthopedic problems as causes of symptoms. Patients were recruited from the Dutch expert center for polio survivors of the Academic Medical Center in Amsterdam. Twenty-eight of these patients performed the measurements as part of an ongoing clinical trial of the efficacy of exercise therapy and cognitive behavioral therapy to improve fatigue, daily activity performance, and quality of life in PPS. The remaining 10 patients responded to an invitation after chart review for eligibility. All patients were capable of walking with or without walking aids and had minimum knee extensor strength of 30 Nm in at least one leg, assumed as minimal muscle strength for functional use. In addition, healthy individuals, matched for age and gender, who never had polio or any other neurological disease served as controls. The control subjects were recruited from employees of the university and others who had responded to a recruitment advertisement for the study. The study was approved by the medical ethics committee of the Academic Medical Center (University of Amsterdam, The Netherlands), and written informed consent was obtained from all participants.

Instrumentation

Isometric torque recordings were made of maximal voluntary and electrically evoked contractions of the knee extensor muscles. Subjects were seated in a specially designed dynamometer with a knee angle of 60° and a hip angle of 100°. The upper body and pelvis were restrained with adjustable belts to prevent the hip from extending when the knee extensor muscles contracted. The lower leg was tightly strapped to a lever arm, immediately proximal to the malleoli. The torque applied by the knee extensor muscles was displayed on a screen, digitized (1,000 HZ), and stored on disk for off-line analysis.

Electrical stimulation of the knee extensor muscles was delivered through two self-adhesive surface electrodes (8×13 cm, Schwa-medico, Leusden, The Netherlands) placed over the proximal and distal part of the anterior thigh. A personal computer running custom-made software controlled the frequency and number of square-wave pulses (200 µs) delivered by a constant-current high voltage stimulator (model DS7H, Digitimer Ltd., Welwyn Garden City, UK).
Fatigue resistance in PPS

Procedure

In patients with PPS measurements were performed on the leg which they felt was most limiting performance during activities in daily life. However, if maximum knee extensor strength in this leg was <30 Nm, measurements were performed on the other leg. In healthy subjects, the leg on which measurements were performed was selected randomly. Subjects performed 3 maximal voluntary isometric knee extensions. They received visual feedback of the torque and were verbally encouraged to exert maximal isometric torque for approximately 3 s, with 1 min of rest between contractions. The highest torque was taken as the maximal voluntary torque (MVT). Subsequently, electrical bursts (150 Hz, to ensure maximal activation) of 1 s duration were delivered to the muscle with increasing current until ~30% of MVT was reached, sufficient to activate a representative part of the muscle mass.19 After a 5-min resting period, the resistance to fatigue was determined by a series of electrically evoked isometric contractions (50 Hz) of 1 s duration and 1 s of rest in between for a period of 5 min (150 contractions). At this 50 Hz frequency, torque is approximately 80–85% of the torque attained at 150 Hz, and high frequency fatigue is prevented.20 Subjects were instructed to relax the muscles as much as possible during the protocol. Recovery of fatigue, which depends to a great extent on the aerobic capacity of the muscle fibers,21 was also monitored. This was done by applying similar 1 s contractions (50Hz) at different times (15, 30, 45, 90 and 180 s) after the end of the fatigue protocol.

On an additional occasion, a subgroup of subjects, who were willing to participate, performed the same fatigue test under arterial occlusion. Three seconds prior to the protocol, the blood flow was occluded by rapid (<3 s) inflation of a cuff (Hokanson SC 10D, Bellevue, WA) to a pressure of ~250 mmHg. The occlusion was applied to prevent the return of blood in the intervals between the stimulated contractions and hence to prevent aerobic energy regeneration.17 To ensure that the cuff did not unwrap, an extra strap was secured around the cuff before inflation. When torque did no longer decline the protocol was stopped and the cuff was deflated.

Data analysis

Off-line analysis of torque records was performed using Matlab (Matlab, the Mathwork Inc., S. Natik, MA, USA). Each torque signal was filtered with a low-pass fourth order Butterworth filter with a 50 Hz cut-off frequency. The 50/150 Hz ratio and half-relaxation time (RT50) were assessed in the pre-fatigue state as indices of contractile speed of the muscle. Those muscles with faster relaxation rates and lower 50/150 Hz ratios are assumed to contain a higher proportion of fast twitch fibers and consequently will be less fatigue resistant.14,15 RT50 was determined from the first contraction (50 Hz) of the fatigue protocol and was defined as the time taken for torque to decline from the value at the end of stimulation to 50% of that value.

In the present study we focused on two important properties that change during muscle fatigue: the decline in torque-generating capacity and the slowing of relaxation.20 Peak torque and RT50 during the fatigue protocol were expressed as a percentage of the values obtained in the first contraction of the protocol (= 100%) to correct for torque differences among subjects. The subsequent recovery of parameters was expressed as a percentage of
the difference between the first and the average of the last 15 contractions of the fatigue protocol.

**Statistics**

Statistical analysis was performed with the SPSS statistical software package (version 19.0.0.1). Descriptive data were expressed as mean and standard deviation (demographic data) or as median and range (polio characteristics). Differences with respect to demographic data and pre-fatigue contractile characteristics (MVT, RT50 and 50/150 Hz ratio) between patients with PPS and healthy subjects were analyzed with the Student’s t test. Dichotomized variables were analyzed with Fisher’s exact test. A two-factor (“PPS” and “gender”) analysis of variance, with repeated measures (“time”) was used to test for significant differences in the course of fatigue and recovery. Gender was added as a factor since there are sex differences in muscle fatigue resistance. For the standard fatigue protocol and the fatigue protocol under arterial occlusion, total duration of the protocol was divided into five equal intervals. Peak torque and RT50 values of the contractions corresponding to the resulting six time points were accordingly used for analysis. An alpha level of 0.05 was used for all tests of significance.

**RESULTS**

**Study group**

Characteristics of patients with PPS and healthy control subjects, both for the total study group (38 PPS, 19 control), and the subgroup performing the fatigue protocol under occlusion (9 PPS, 11 control), are presented in Table 1. Regular exercise (a minimum of 150 min per week with at least moderate intensity) was reported by 11 healthy subjects and 6 patients with PPS. All patients reported that they suffered from generalized fatigue. Clinical signs of polio residuals in the lower extremities, based on manual muscle testing, were present in all, except 3 patients. No significant differences were found between patients with PPS performing the occlusion measurements and those who did not, with respect to demographic data and polio characteristics.

Some subjects had difficulty in relaxing the leg during the stimulated fatigue protocol. This involuntary activity, judged on basis of visual inspection of the data by experienced investigators, sometimes caused unsteady baseline torque resulting in unreliable measurements. These results were therefore not included in the statistical analysis, leading to different numbers of observations for different parameters (the exact numbers used for analysis are given in the legends with the figures).

**Pre-fatigue contractile characteristics**

The MVT of the knee extensor muscles of patients with PPS was significantly lower compared to healthy subjects (mean difference -74 Nm, 95% CI -96 to -51, \( p \leq 0.001 \)). In 20 of the 26 female patients MVT was below the lowest value found in the healthy women (128 Nm), and 11 of the 12 male patients had an MVT below the lowest value found in healthy men.
Fatigue resistance in PPS

(150 Nm). No significant differences in pre-fatigue state with respect to contractile speed (RT50 and 50/150 Hz ratio) were found between both groups (Table 1).

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>All subjects</th>
<th>Subgroup (occlusion)</th>
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<tbody>
<tr>
<td></td>
<td>PPS (n=38)</td>
<td>Control (n=19)</td>
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<tr>
<td>Gender (male/female)</td>
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<td>7/12</td>
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<td>Age (yrs)</td>
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<tr>
<td></td>
<td>PPS (n=9)</td>
<td>Control (n=11)</td>
</tr>
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<td>4/5</td>
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<tr>
<td></td>
<td>26.2±1.9</td>
<td>24.8±3.3</td>
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</tbody>
</table>

| Polio characteristics                  |               |                      |
|                                       | PPS (n=9)    | Control (n=11)       |
| Age at acute polio (yrs)              | 2.0 (0–9)    | 2.0 (0–9)            |
| Present walking distance               | 3 (2–4)      | 4 (3–4)              |
| Measured leg clinically affected (yes/no) | 27/11     | 5/4                  |
| Reported abnormal fatigue in measured leg (yes/no) | 23/15 | 6/3                  |
| MMT knee extension measured leg (0–5)  | 5 (4–5)      | 5 (4–5)              |
| MMT sum score legs (0–80)              | 69.4±8.6     | 71.3±5.1             |

| Pre-fatigue contractile characteristics |               |                      |
|                                       |               |                      |
| MVT (Nm)                              | 106±42       | 179±34               |
| RT50 (ms)                             | 127±10       | 122±8                |
| 50/150 Hz ratio (%)                   | 79±12        | 84±10                |

Values for age, body weight, BMI, MMT sum score, and pre-fatigue characteristics are mean ± SD; values for age at acute polio, present walking distance and MMT knee extension are median (range). Abbreviations: BMI, body mass index; MMT, manual muscle testing; MVT, maximal voluntary torque; RT50, half-relaxation time.

Walking distance was classified in 4 categories: 1 = indoors only; 2 = around the house; 3 = seldom >1km; 4 = regularly >1km.

Sum score for the muscle strength of the legs was calculated by adding 16 muscle groups. Each muscle group had a score between 0 and 5, sum score ranged from 0 to 80. \( p \leq 0.001 \) (PPS versus control subjects, in the total study group).

Fatigue resistance

The relative torque level during the initial contraction of the fatigue protocol was comparable in PPS and healthy subjects (33.4 ± 9.3 %MVT versus 30.8 ± 5.6 %MVT, \( p=0.300 \)). No difference was found between both groups with respect to the course of fatigue (\( p=0.780 \)). During the protocol torque declined to 50.6 ± 10.5% in the last contraction in patients with PPS and to 52.2 ± 11.9% in healthy subjects (Fig. 1A).
No difference in slowing of relaxation during the fatigue protocol was found between PPS and healthy subjects. After an initial increase in RT50 during the first 40 contractions, muscles of both groups showed a gradual decrease towards the end of the protocol (Fig. 1B). In the last contraction of the protocol, RT50 was increased by 32.5 ± 17.5% in the PPS group compared to 34.2 ± 16.0% in the control group ($p=0.366$).

Figure 1. Changes in parameters during the standard fatigue protocol with an intact circulation. Peak torque (A) and half-relaxation time (B) are expressed as percentages of pre-fatigue values (=100%). Mean data ± SD are shown for every fifth contraction for PPS (open squares; $n=36$) and control subjects (black circles; $n=17$).

Figure 2. Change in peak torque during the fatigue protocol under arterial occlusion. Values are expressed as percentages of pre-fatigue value (=100%). Mean data ± SD are shown for every fifth contraction for PPS (open squares; $n=9$) and control subjects (black circles; $n=11$).
All subjects (n=20) continued the protocol under occlusion for at least 70 contractions. Therefore the 70th contraction was used as the last contraction in the analysis (Fig. 2). During the protocol, torque declined to 24.9 ± 14.5% in patients with PPS and to 28.8 ± 7.2% in healthy subjects (p=0.173). When compared to the torque decrease with intact blood circulation, the additional decrease in peak torque as a consequence of the occluded blood flow was similar in the PPS (25.0 ± 11.8% during the last contraction) and control group (31.1 ± 12.0%) (p=0.802).

Recovery

Recovery from the reduction in peak torque during the fatigue protocol was better in patients with PPS compared to healthy subjects (p=0.043). The recovery was however incomplete in both groups. In muscles from healthy subjects, only 54.9 ± 20.4% of the reduction in torque during the fatigue protocol recovered within 3 min, while patients with PPS recovered to 68.9 ± 20.5% of the reduction (Fig. 3A).

Although still incomplete, RT50 recovered to a higher extent compared to torque (Fig. 3B) and no difference was found between PPS and healthy subjects (p=0.138). In patients with PPS 85.9 ± 21.0% of the increase in RT50 during the fatigue protocol recovered within 3 min, compared to 86.7 ± 19.0% in the healthy subjects.

Figure 3. Recovery of parameters following the standard fatigue protocol with an intact circulation. Peak torque (A) and half-relaxation time (B) are expressed as percentages of the change during the fatigue protocol (=100%). Mean data ± SD are shown for every contraction for PPS (open squares; n=34) and control subjects (black circles; n=16).
Chapter 3

Additional analyses

Comparing results of patients reporting abnormal increased muscle fatigability (n=23) in the measured leg to those without this complaint (n=15) revealed no significant differences with respect to any of the studied variables, except for the slowing of relaxation, showing less change in the group with fatigue complaints (p=0.031).

DISCUSSION

Contrary to our expectations no differences in fatigue resistance of the knee extensor muscles between patients with PPS and healthy control subjects were found, indicating that the abnormal muscle fatigue reported by many patients with PPS is most likely explained by factors other than impaired intrinsic fatigability of the muscle fibers.

Fatigue resistance is determined by the interplay of energy utilization and energy production. During prolonged series of stimulated contractions, the production of energy depends largely on aerobic metabolism. Several observations from the present study showed that for the knee extensor muscles in PPS, neither the rate of energy utilization is higher, nor the aerobic energy regeneration capacity is lower compared to normal. The first important observation to support this conclusion is that the rate of fatigue was comparable in patients with PPS and healthy subjects both in the situation with intact circulation and when the blood flow was occluded (Figs. 1A and 2). Contrary to findings in muscle biopsies from patients with PPS that showed a reduced capillary supply and oxidative enzyme activity,5,23 this indicates that impaired blood flow or reduced aerobic capacity of the muscle fibers does not contribute to the abnormal muscle fatigue perceived by these patients. This is further supported by the recovery measurements, where no differences were found between PPS and healthy subjects with respect to recovery of half-relaxation time, and an even faster and more complete recovery of peak torque in patients with PPS (Figs. 3A and B). Although the explanation for the latter finding remains unclear, these results argue against a compromised aerobic metabolism in PPS muscles, since recovery depends to a large extent on the aerobic capacity of the muscle fibers.21

In addition, we found no indications that the rate at which energy was utilized was higher in knee extensor muscles of patients with PPS compared to healthy subjects. One way to investigate this is by comparing the extent of fatigue under occlusion between both groups. In this situation blood flow to the muscles is restricted and consequently fatigue will be determined primarily by anaerobic energy utilization since aerobic energy regeneration is no longer possible.27 Our results showed that fatigability under occlusion was comparable in PPS and healthy subjects (Fig. 2) and therefore suggest that the speed of energy utilization is similar in both groups. This is consistent with the findings regarding the half-relaxation time and the 50/150 Hz ratio which were measured in the pre-fatigue state as indices of contractile speed. Compared to type II fibers, type I fibers have a slower speed of contraction and consequently a slower rate of energy consumption. Therefore, the absence of significant differences in these parameters suggests that large dissimilarities in muscle fiber type composition of the tested knee extensor muscles, between PPS and healthy subjects are not likely.
Our findings of no differences in contractile properties and aerobic capacity of the muscle fibers between both groups were unexpected given the muscular adaptations and fatigability complaints that have been described in patients with PPS.\(^4\)\(^-\)\(^6\) This may indicate that our study group was not representative for the PPS population. However, based on the considerably lower muscle strength, low physical activity level, and complaints of generalized fatigue and local muscle fatigue in the majority of patients, which is consistent with characteristics that are known in the literature,\(^24\)\(^,\)\(^25\) this seems unlikely. The clinical relevance of these opposite adaptations has been debated before\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^26\) and it may well be that the combination of adaptations, such as the predominance of type I fibers with a decreased oxidative enzyme activity, ultimately has no effect on the fatigability of the muscle fibers in patients with PPS.

A methodological limitation is the small subgroup that performed the occlusion measurements. Nevertheless, despite the limited sample size, characteristics of these patients did not differ from the characteristics of the other patients, indicating that they formed a representative subgroup. Furthermore, all patients suffered from generalized fatigue, and MVT of the knee extensor muscles was below the lowest values found in healthy subjects in 82% of the patients, indicating that the majority of measured legs were clinically affected. Part of the patients, however, reported no complaints of abnormal muscle fatigability in the measured leg. Nevertheless, further analyses revealed that, except for the slowing of relaxation, there were no differences between patients with abnormal muscle fatigability complaints in the measured leg compared to those without this complaint. In addition, it should be realized that neuromuscular adaptations have also been found in clinically unaffected muscles and therefore this probably did not negatively influence generalizability of results.\(^27\)\(^-\)\(^29\)

With the present study we have shown that the muscle fatigue complaints reported by many patients with PPS are most likely explained by factors other than intrinsic fatigability of the muscle fibers. Previous studies that investigated the contribution of central fatigue indicate that an impaired voluntary activation does not seem to be a major factor as well,\(^8\)\(^,\)\(^13\) but evidence is limited, and therefore this factor should be considered.\(^3\)\(^,\)\(^30\) Another possible explanation, which has been proposed before,\(^3\)\(^,\)\(^13\)\(^,\)\(^31\) is that perceived fatigue is mainly related to a reduced muscle mass. Given the substantially lower maximal isometric knee extensor muscle strength (41%) that we found in PPS compared to healthy subjects, it is reasonable to assume that the relatively higher loading of active muscles contributes to the increase in muscle fatigue in executing daily life activities.\(^32\)

In conclusion, the present study did not find differences in fatigue resistance of electrically activated knee extensor muscles between patients with PPS and a healthy control group. Our findings suggest that there are no differences with respect to contractile properties and aerobic muscle capacity that contribute to the increased muscle fatigue reported by many patients with PPS during daily life activities. Probably, this symptom is most likely the result of muscle weakness that requires individuals to perform at higher relative muscle load, inducing early fatigue.
REFERENCES


