



**HAL**  
open science

## Characterization of neuromuscular performances in adults with late-onset Pompe disease: A control case cross-sectional study

Théo Maulet, Céline Bonnyaud, Pascal Laforêt, Thomas Cattagni

### ► To cite this version:

Théo Maulet, Céline Bonnyaud, Pascal Laforêt, Thomas Cattagni. Characterization of neuromuscular performances in adults with late-onset Pompe disease: A control case cross-sectional study. *Neuromuscular Disorders*, 2023, 10.1016/j.nmd.2023.10.012 . hal-04321891

**HAL Id: hal-04321891**

**<https://hal.science/hal-04321891v1>**

Submitted on 5 Dec 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Characterization of neuromuscular performances in adults with late-onset Pompe disease: A control case cross-sectional study

Théo Maulet<sup>a,b,c</sup>, Céline Bonnyaud<sup>b,c</sup>, Pascal Laforêt<sup>a,d</sup>, Thomas Cattagni<sup>e,\*</sup>

<sup>a</sup>Laboratory End: icap, Inserm Unit 1179, UVSQ, 2 Av. de la Source de la Bièvre, 78180 Montigny-le-Bretonneux France

<sup>b</sup>Paris-Saclay University, Research Unit ERPHAN, UVSQ, 2 Av. de la Source de la Bièvre, 78180 Montigny-le-Bretonneux France

<sup>c</sup>Movement analysis laboratory, Functional exploration unit, APHP, Raymond Poincaré hospital, 104 Bd Raymond Poincaré, 92380 Garches, France

<sup>d</sup>Neurology unit, APHP, Raymond Poincaré hospital, 104 Bd Raymond Poincaré, 92380 Garches, France

<sup>e</sup>Nantes University, Mouvement - Interactions - Performance, MIP, UR 4334, F-44000, 25 bis, boulevard Guy Mollet, BP 72206 44322 Nantes Cedex 3, France

---

## A B S T R A C T

Adults with late-onset Pompe disease (aLOPD) are characterized by muscular contractile tissue deterioration. However, their neuromuscular performances are poorly known. We aimed to compare maximal muscle strength, activation, explosive strength and neuromuscular fatigue between aLOPD and controls. We studied 20 aLOPD and 20 matched controls. Isometric maximum voluntary contraction (MVC) torque was obtained for the hip, knee and ankle muscles. The voluntary activation level (VAL) during knee extensor MVC was assessed using interpolated twitch technique. Explosive strength was evaluated for knee and ankle muscles through the rate of torque development (RTD) during fast contractions. Neuromuscular fatigue was measured during a 30-second contraction of knee flexors and extensors. All muscle MVC torques were significantly lower in aLOPD than controls ( $p < 0.05$ ). The weakest muscles were the hip extensors followed by hip abductors and adductors. Raw value of RTD was lower in aLOPD for the majority of muscles ( $p < 0.05$ ). No intergroup differences were reported for normalized RTD, VAL and neuromuscular fatigue ( $p$ -values  $> 0.05$ ). Our study shows that maximal strength was the only neuromuscular characteristic affected in aLOPD with a proximal-distal intensity gradient. This suggests that the surviving muscle tissue of aLOPD is as functionally efficient as that of control individuals.

---

### Keywords:

Late-onset Pompe disease  
Maximal muscle strength  
Neuromuscular fatigue  
Muscular activation  
Explosive strength  
Instrumented assessments

---

## 1. Introduction

Pompe disease is a rare, progressive neuromuscular disorder caused by deficiency of lysosomal acid  $\alpha$ -glucosidase. It deteriorates muscle contractile tissue, leading to major deficits in muscle strength [1]. Symptoms may appear in the first few months of life (extremely severe infantile form), as well as in childhood or adulthood with a milder presentation known as late-onset Pompe disease. Adults with the late-onset form of the disease (aLOPD) account for over 90 % of all Pompe disease diagnoses [2,3]. Because of these deficits, motor impairments significantly and progressively impact mobility and quality of life of aLOPD [2]. There is an urgent need to deepen our knowledge on neuromuscular impairments of aLOPD to better describe their motor disability and improve their care and living conditions.

To date, only a few studies have specifically explored the pattern and amplitude of lower limb muscle weakness in aLOPD [4–7]. Authors showed that the hip muscles, in particular the extensors, abductors and flexors, are the most affected muscles in LOPD. However, these studies assessed maximal muscle strength with manual dynamometer [6] or manual muscle testing (MMT) [5,8]. The manual dynamometer has high inter-rater variability and MMT has low reliability and sensitivity, limiting the result interpretations [9,10]. More accurate and reliable information about the pattern and amplitude of maximal muscle strength (MMS) deficits in aLOPD could be obtained by using isokinetic dynamometers, as recommended and used for other neuromuscular diseases [9]. A better understanding of aLOPD-related MMS deficits is essential for effective management, especially with the emergence of new therapies.

Surprisingly, MMS is the only neuromuscular characteristic explored in aLOPD [7]. Other important neuromuscular characteristics, such as explosive muscle strength (EMS), muscle activation capacity, muscle contractile properties and neuromuscular fatigue explored in other populations [11–14], have

---

\* Corresponding author at: Nantes University, Mouvement - Interactions - Performance, MIP, UR 4334, F-44000, 25 bis boulevard Guy Mollet 44300, Nantes, France. Tel.: 0251837232.

E-mail address: [Thomas.Cattagni@univ-nantes.fr](mailto:Thomas.Cattagni@univ-nantes.fr) (T. Cattagni).

never been studied in aLOPD. Explosive muscle strength is the ability to voluntarily increase force or torque as quickly as possible from a resting level [15]. It is an important feature in some motor skills such as stair descent [16], or stabilization regulation after a sudden postural disturbance [17–19], where the ability to rapidly produce a contraction is an essential functional parameter [15,20,21]. Furthermore, explosive muscle strength may be more sensitive to changes in neuromuscular function than MMS [15].

Both MMS and EMS depend on the combination of muscle components (quality and quantity of contractile tissue) and central components (muscle activation) [22]. The exploration of contractile function through parameters such as peak contractions, contraction time or half-relaxation time after resting stimulation is relevant for probing muscle fiber qualities [13,14,23]. The central component exploration during neuromuscular testing provides information on the ability of motor units to be fully (MMS) and/or rapidly (EMS) recruited. Previous findings suggest that Pompe disease affects neural structures [24,25] and muscle activation [26]. Indeed, an altered activation pattern was found in the tibialis anterior in a small sample aLOPD [26]. However, it is not known if this contributes to the impaired neuromuscular performance in aLOPD. A possible alteration in the motor command addressed to muscles can be estimated during MMS testing with the use of the interpolated twitch technique [27–29], and during EMS testing by measuring the rate of force/torque development in the initial phase of an explosive contraction [15,22,30].

Finally, experienced fatigue is a frequent complaint reported by aLOPD [31]. It may have several physiological origins as in other neuromuscular diseases [32]. Neuromuscular fatigue (NMF), defined as the loss of voluntary strength during exercise [33,34], has never been studied in aLOPD.

NMF results from both central and peripheral mechanisms [35–37]. In aLOPD population, NMF may increase due to potential impairments in muscle activation and the degradation of the muscle contractile contingent. Thus, it is necessary to investigate this phenomenon in this population.

The main objective of this study was to compare MMS, EMS, muscle activation during maximal neuromuscular efforts, and NMF of lower limb muscles groups between aLOPD and healthy age-matched controls. In aLOPD, we expected to find lower i) MMS, especially in the hip muscles; ii) EMS; and iii) NMF, with alterations at the central and peripheral levels. As a secondary objective, we also investigated relationships between MMS obtained from MMT and MMS assessed with an isokinetic dynamometer. We hypothesized that there would be a poor agreement between these assessments.

## 2. Methods

### 2.1. Protocol and registration

This case control cross-sectional study is part of the “POMPE” project (ClinicalTrials.gov: NCT03564561), which aims to identify sensitive biomarkers for future therapeutic trials in aLOPD. All participants provided written consent before participation. The study was conducted according to STROBE 2007 guidelines, following the World Medical Association’s ethical codes (Declaration of Helsinki), and was approved by an ethics committee.

### 2.2. Participants

The study involved 20 aLOPD ( $58.0 \pm 12.8$  years) and 20 healthy controls ( $58.1 \pm 9.1$  years). The aLOPD were recruited from neurological consultations in our neuromuscular diseases reference hospital center. Control participants were recruited from

the general population after checking for confounding factors (age, sex, weight, height). To be included, all participants had to be 18 to 80 years of age. The aLOPD had to have Pompe disease (c.–32–13 T> G), not be dependent on invasive mechanical ventilation, and have no comorbidities. The control participants were not included if they had neurological or orthopedic disorders.

Participants took part in a 3.5-h experimental session that included the MMT assessment, then the instrumented assessments. At the start of each dynamometric muscular assessment, five minutes were allocated to familiarizing the participant with the isokinetic dynamometer. We explained the instructions and the overall principle of the device. The participants were then asked to try out the various efforts several times until they had a complete understanding of the task being assessed. After the hip MMS assessment, we assessed the MMS and EMS of the plantar and dorsi flexors. Then, we assessed the MMS, VAL, EMS and NMF of the knee extensors. Finally, we assessed the EMS and the NMF of knee flexors. All assessments were performed on the dominant leg, determined after asking participants “if you were to shoot a ball at a target, which leg would you use to shoot?” [38].

### 2.3. Clinical muscle strength assessment

Maximal muscular strength was firstly assessed using conventional MMT [39], which grades muscle strength from 0 (no contraction) to 5 (normal strength) for flexors, extensors, abductors and adductors of the hip, flexors and extensors of the knee, and plantar and dorsi flexors.

### 2.4. Instrumented neuromuscular testing

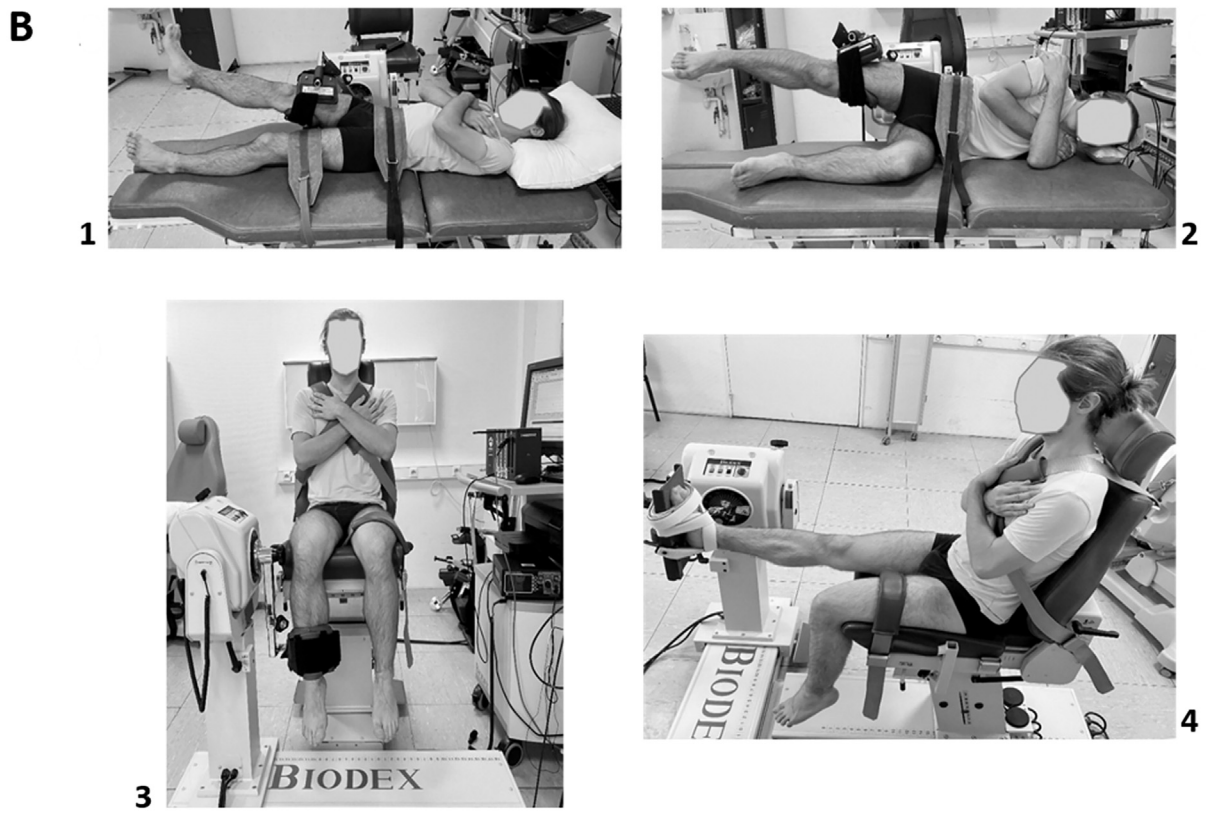
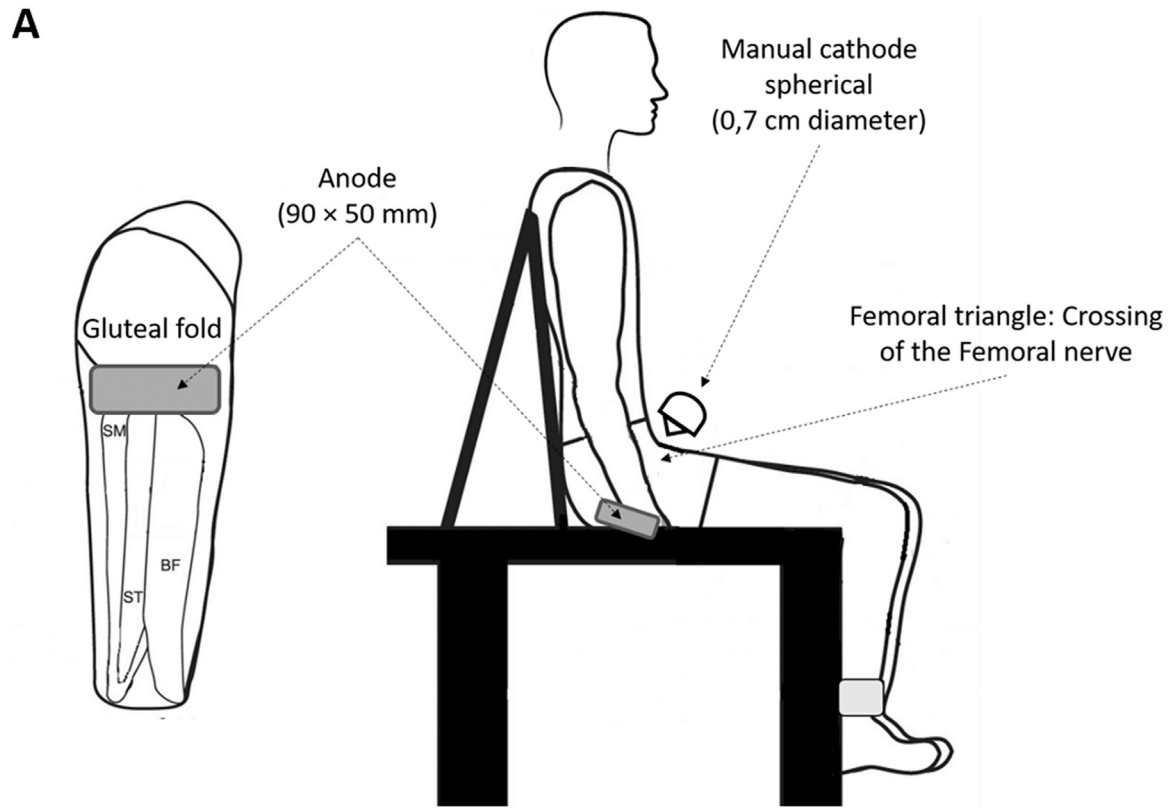
#### 2.4.1. Materials

2.4.1.1. *Torque recording.* An isokinetic dynamometer (Biodex Medical System 4, Shirley, NY) was used to record the torque signal. It was transmitted directly from the dynamometer to a 16-bit A/D converter (MP160, Biopac Systems, USA), then to Acknowledge 5.10 software.

2.4.1.2. *Electrical nerve stimulation of the femoral nerve.* A high-voltage (400 V) stimulator (model DS8RB, Digitimer Ltd., Hertfordshire, UK) was used to generate single and doublet twitches (100 Hz frequency) (rectangular pulses of 1 ms duration). To locate the optimal stimulation site and perform the stimulation, we used a hand-held ball cathode electrode (0.7 cm diameter) positioned over the inguinal space on the femoral nerve. Once the optimal position was determined, the cathode electrode was firmly held to maintain the position. The anodal electrode (89 × 50 mm, WX High Performance Inc.) was placed in the gluteal fold [40] (Fig. 1).

#### 2.4.2. Experimental procedure

2.4.2.1. *Position of participants during neuromuscular testing.* For hip extensors and flexors, participants were tested in the supine position. The hip and knee were in a neutral position in the frontal and transverse planes. The hip angle was set at 30° of flexion (0° the neutral joint position) and the knee was left free to improve participant comfort. The greater trochanter of the femur was aligned with the axis of rotation of the dynamometer. For the hip abductors and adductors, participants were tested in lateral decubitus with the tested limb in upper position. The hip angle was set at 15° of abduction and the knee was in neutral position. The axis of rotation of the dynamometer was aligned with the femur neck. The thigh was attached to the lever arm 5 cm above the base of the patella. The pelvis was securely fixed to the table by straps. For the knee extensors and flexors, participants were tested in a seated position, the hip angle was set at 85° of flexion



**Fig. 1.** A) Experimental set-up for manual cathode and anode electrode placement, ST: semitendinosus; SM: semimembranosus and BF: biceps femoris. Picture modified from Nuzzo et al. 2021. B) Positioning for dynamometric assessment, B1: Hip flexors and extensors; B2: Hip abductors and adductors; B3: Knee extensors and flexors and B4: Plantar and dorsalis flexors.

and the knee angle was set at 90° of flexion. For plantar and dorsi flexors, the hip angle was set at 85°, the knee angle was set at 0° and the ankle joint was in neutral position. The lateral epicondyle of the femur was aligned with the axis of rotation of the dynamometer. The lower leg was attached to the lever arm 5 cm above the ankle malleoli. The trunk and thigh were fixed securely to the dynamometer by belts. For all assessments, participants were instructed to keep their arms crossed over their chests during the contractions (Fig. 1).

**2.4.2.2. Assessment of muscle strength, voluntary activation, contractile properties and neuromuscular fatigue.** Maximal muscle strength was assessed during isometric MVC of hip flexors, extensors, abductors and adductors, knee flexors and extensors, and plantar and dorsi flexors. After familiarization with the dynamometer, a warm-up was performed with three 5 s contractions (at 25 %, 50 % and 90 % of maximum torque). Three MVC trials were then recorded for each muscle group. Standardized verbal encouragement was given during all contractions [41]. The three trials in each sequence were separated by 1 min of rest to minimize the effect of fatigue. All measurements and analysis were performed by the same operator to avoid inter-rater variability.

**2.4.2.3. Assessment of voluntary activation, contractile properties and neuromuscular fatigue.** Voluntary activation level (VAL) during MVC and doublet twitch contractile properties were investigated in the knee extensors and NMF during a 30-s MVC was investigated in the knee extensors and flexors. For VAL, doublet twitch contractile properties and NMF of knee extensors, percutaneous electrical stimulation was applied to the femoral nerve to evoke contraction. To determine the optimal stimulation intensity, a recruitment curve (single twitch) at rest was established before knee extensors MVC testing. The optimal stimulation intensity was reached when the resulting peak torque value stabilized between two intensities [42]. A supramaximal stimulation intensity (at 120 % of the optimal intensity) was selected to ensure maximal spatial recruitment of motor units in each trial [43].

For VAL, a superimposed doublet was delivered during the MVC plateau and a potentiated doublet delivered 3 s after the end of MVC [44,45] (Fig. 2).

The muscle contractile properties of the knee extensors were evaluated from the doublet twitch contraction evoked by the doublet stimulation prior to MVC. The following parameters were measured: peak doublet twitch torque (PT), which is the amplitude between the baseline signal and the peak torque value of the doublet twitch; doublet twitch contraction time (CT), which is the time elapsed between the onset of contraction and the peak doublet twitch torque; and doublet twitch half-relaxation time (HRT), which is the time elapsed between the peak doublet twitch torque and the 50 % decrease in peak doublet torque [14,23,46] (Fig. 2). For each resting contractile parameter, the two mechanical responses were averaged.

For NMF, peripheral fatigue was assessed with a resting doublet before the 30-second effort and a potentiated doublet sent 3 s after the end of the contraction [35]. To record central fatigue, a superimposed doublet was sent at 30 s and a potentiated doublet 3 s after the contraction end (Fig. 3).

**2.4.2.4. Explosive muscle strength.** Explosive muscle strength was assessed during explosive maximal isometric contractions of the knee flexor and extensor muscles, and plantar and dorsiflexor muscles (Fig. 3). After 5 trials to become familiar with the task, participants were asked to relax completely then perform the movement (knee and ankle extension and flexion) as fast and as

strongly as possible for 1 to 2 s [15]. Participants performed 6 trials, separated by 30-s rest periods. Participants were instructed to avoid any countermovement before the application of force. Any trial with a countermovement was considered unusable and required an additional trial. Standardized verbal encouragement was given during each trial [41].

#### 2.4.3. Data analysis

##### 2.4.3.1. Maximal voluntary contractions and voluntary activation level.

For each muscle group, the MVC torque recorded was the highest peak torque value measured over the three MVC trials.

To determine VAL, we used the formula originally described by Allen et al., [47] with the correction of Strojnik and Komi [48]:

$$VAL = \left[ 1 - \frac{\text{Superimposed doublet twitch torque} \times \frac{\text{Torque at stimulation}}{\text{MVC torque}}}{\text{Potentiated doublet twitch torque}} \right] \times 100$$

**2.4.3.2. Explosive muscle strength.** Analysis of EMS was based on the mean data of each RTD parameter for the three best trials, corresponding to the trials with the greatest values of peak RTD (Fig. 3). The onset of muscle contraction was determined visually using the torque signal filtered with a 30 Hz Butterworth IIR low-pass filter [15,49]. We calculated the RTD ( $\Delta\text{torque}/\Delta\text{time}$ ) for the time intervals 0–50, 100–200 and 0–200 milliseconds [10,22,50] and the peak RTD as the greatest slope of the force-time curve. All RTD values were normalized by the corresponding maximum MVC torque [50,51]

**2.4.3.3. Neuromuscular fatigue.** To assess the loss of muscle strength during the 30-second isometric MVC, we measured the average maximum torque of the first two seconds and the last two seconds of contraction. The percentage was calculated according to the formula

$$\% \text{ fatigue} = 100 - \left[ \frac{\text{Mean torque (at the last 2 seconds)} \times 100}{\text{Mean torque (at the first 2 seconds)}} \right]$$

For the knee extensors, NMF assessment was combined with electrical stimulation of the femoral nerve to dissociate the peripheral and central components of NMF.

To quantify the peripheral component of neuromuscular fatigue, we compared the contractile characteristics of knee extensors. At the end of the 30-second contraction, we calculated the peak doublet twitch torque (PT30s), contraction time (CT30s) and half-relaxation time (HRT30s). The following formulae were used:

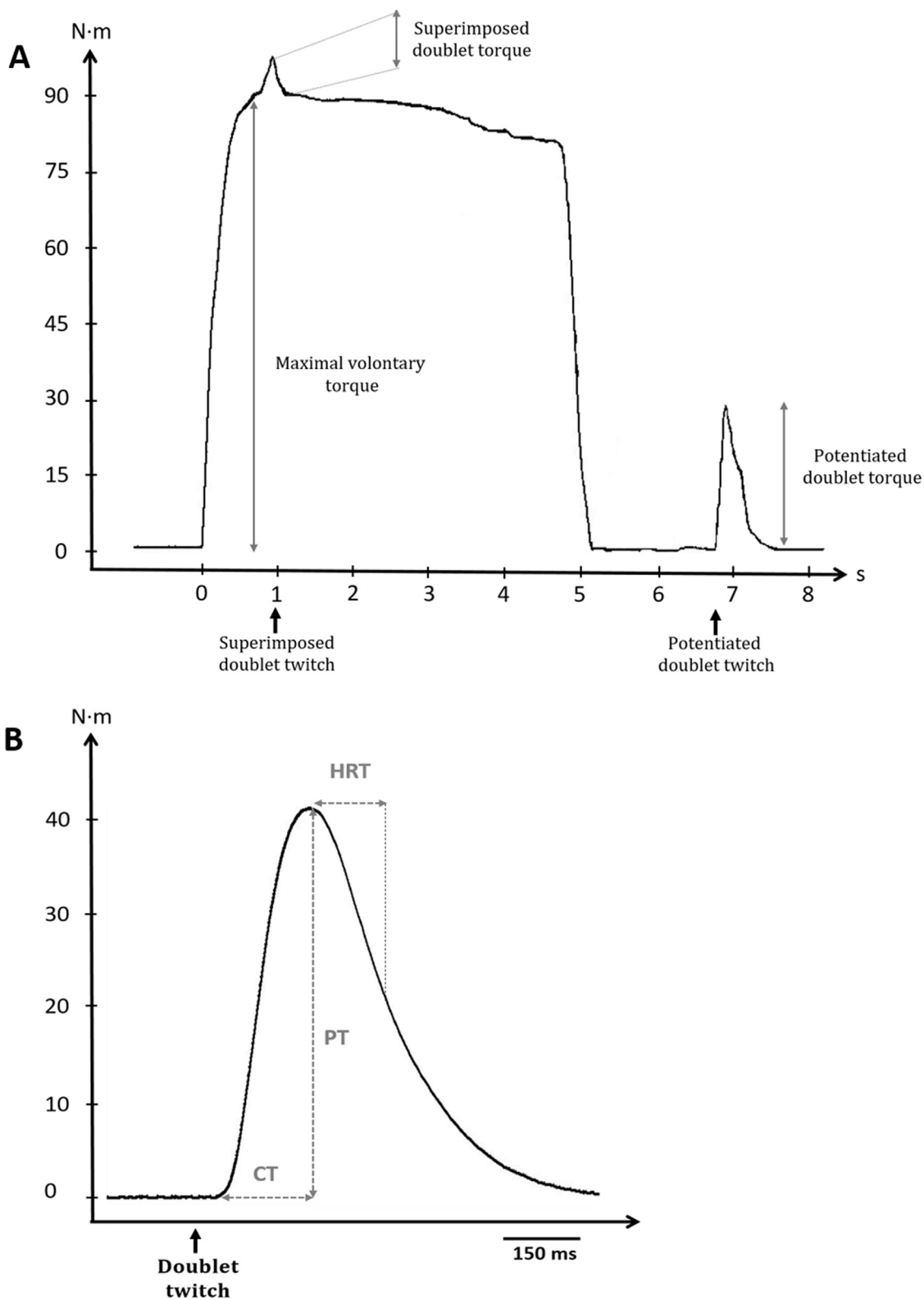
$$\Delta \text{ PT} = \left[ \frac{\text{PT30s} \times 100}{\text{PT}} \right] - 100$$

$$\Delta \text{ CT} = \left[ \frac{\text{CT30s} \times 100}{\text{CT}} \right] - 100$$

$$\Delta \text{ HRT} = \left[ \frac{\text{HRT30s} \times 100}{\text{HRT}} \right] - 100$$

For central fatigue, we calculated the VAL at the end of the 30-second contraction (VAL30s), based on the superimposed twitch doublet torque amplitude at 30 s [52,53]. Then, we calculated the central fatigue ratio by comparing VAL30s and VAL. The central fatigue ratio was calculated using the formula:

$$\text{Central fatigue Ratio} = \left[ \frac{\text{VAL30s} \times 100}{\text{VAL}} \right] - 100$$

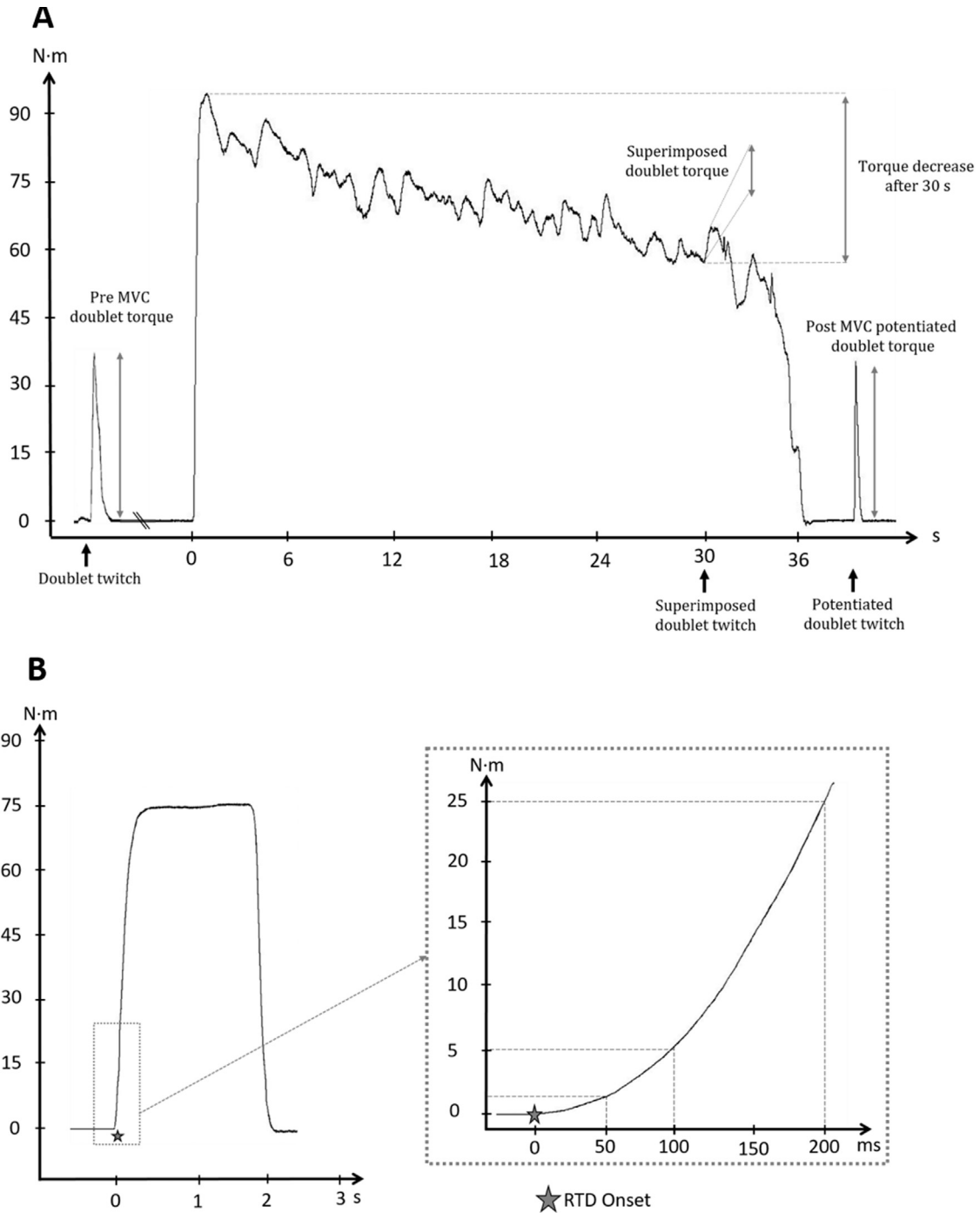


**Fig. 2.** Raw data traces of knee extensor torque A) during an isometric maximal voluntary contraction (MVC) associated with doublet twitch stimulations, B) during an evoked doublet twitch contraction at rest. PT: peak doublet twitch torque; CT: contraction time; HRT: half-relaxation time.

### 2.5. Statistical methods

Data were analyzed using JASP® version 0.16.4, the alpha risk was set at 5 %. Means, standard deviations and medians were calculated.

As some data did not have a normal distribution, we used nonparametric tests. Neuromuscular parameter comparisons between aLOPD and controls were analyzed using the Mann-Whitney U. test ( $p < 0.05$ ) and the effect size was given by the biserial correlation of rank  $\alpha$ . For MMS deficits, nonparametric



**Fig. 3.** Raw data traces of knee extensor torque A) during an isometric maximal voluntary contraction (MVC) of 30 s associated with doublet twitch stimulations, B) during an explosive contraction.

correlations (Spearman  $r$ ;  $p < 0.05$ ) were calculated between MVC torque and MMT data for each muscle group in aLOPD. Correlation coefficients were considered strong for  $r \geq 0.7$ , moderate for  $0.7 > r \geq 0.5$ , and weak for  $r < 0.5$  [54].

### 3. Results

In aLOPD group, the mean age of disease was  $15.0 \pm 9.2$  years. Eighty percent of aLOPD were treated with enzyme replacement therapy, with a mean duration of 7.3 years. All participant characteristics are detailed in Table 1.

#### 3.1. Maximal muscle strength and voluntary activation

##### 3.1.1. Clinical strength assessment (MMT)

Results of MMT are presented in Table 2. All muscle groups, except for plantar flexors, were significantly weaker in the aLOPD group than in the control group ( $p$ -value ranged from 0.001 to 0.047).

##### 3.1.2. Instrumented strength assessment (MVC torque)

Results of MVC torque are presented in Table 2. We found that all muscle groups were significantly weaker in the aLOPD group than in the control group (all  $p$ -values  $< 0.014$ ). Muscle groups

**Table 1**  
Participant characteristics.

Variable	LOPD group (n = 20)	Control group (n = 20)	p-value
Sex ratio, M/W, n	10/10	10/10	1
Age years, mean (SD)	58.8 (13.2)	53 (14.5)	0.96
Height, cm, mean (SD)	168.2 (8.1)	169.8 (9.6)	0.84
Weight, kg, mean (SD)	70.1 (15.0)	72.1 (12.5)	0.78
BMI	24.9 (4.3)	24.4 (3.3)	0.21
Time since diagnostic, years, means (SD)	15.0 (9.2)	-	-
Treatment by ERT, n	16/20	-	-
Time since ERT start, years, means (SD)	7.3 (5.2)	-	-

M/ W: Man / woman; SD: Standard deviation; ERT: enzyme replacement therapy; BMI: Body Mass Index;.

n: Number of participant.

\*significant difference between aLOPD group and control group:  $p < 0.05$  with Mann-Whitney U test.

-: Data not applicable to control group.

**Table 2**  
Strength assessments.

	LOPD Group (n = 20) Mean (SD)	Control Group (n = 20) Mean (SD)	p-value	Effect size $\alpha$
<b>Isokinetic dynamometer</b>				
Hip flexors (N-m)	61.5 (47.5)	122.2 (51.5)	<0.001*	0.64
Hip extensors (N-m)	47.6 (40.6)	119.7 (54.8)	<0.001*	0.79
Hip abductors (N-m)	45.3 (40.6)	99.6 (29.8)	<0.001*	0.78
Hip adductors (N-m)	37.3 (27.5)	77.5 (32.9)	<0.001*	0.66
Knee flexors (N-m)	36.3 (27.6)	64.2 (27.7)	0.002*	0.58
Knee extensors (N-m)	87.7 (62.7)	172.5 (78.3)	<0.001*	0.62
Plantar flexors (N-m)	104.6 (42.9)	146.3 (50.4)	0.007*	0.48
Dorsi flexors (N-m)	27.1(12.0)	37.9 (13.0)	0.014*	0.45
<b>Manual muscle testing</b>				
Hip flexors (0-5 scale)	4.0 (1.1)	5.0 (0.0)	<0.001*	0.65
Hip extensors (0-5 scale)	3.0 (1.1)	5.0 (0.0)	<0.001*	0.71
Hip adductors (0-5 scale)	3.0 (1.5)	5.0 (0.0)	<0.001*	0.65
Hip abductors (0-5 scale)	3.5 (1.3)	5.0 (0.0)	<0.001*	0.78
Knee flexors (0-5 scale)	4.0 (0.9)	5.0 (0.0)	<0.001*	0.65
Knee extensors (0-5 scale)	4.5 (0.7)	5.0 (0.0)	0.003*	0.41
Plantar flexors (0-5 scale)	5.0 (0.8)	5.0 (0.0)	0.22	0.13
Dorsi flexors (0-5 scale)	5.0 (0.6)	5.0 (0.0)	0.047*	0.24

For Mann-Whitney U test, effect size is given by rank biserial correlation.

SD: Standard deviation. N-m: Newton-meter.

\* Significant difference between aLOPD group and control group,  $p < 0.05$  with Mann-Whitney U test.

were classified according to their amplitude of deficits related to aLOPD, based on the effect sizes of intergroup differences. Fig. 4 illustrates the topography and amplitude of this MMS deficits. Ranking muscle groups from the highest to the lowest deficit in aLOPD, we found the following order: hip extensors ( $p < 0.001$ ,  $\alpha = 0.79$ ), hip abductors ( $p < 0.001$ ,  $\alpha = 0.78$ ), hip adductors ( $p < 0.001$ ,  $\alpha = 0.66$ ), hip flexors ( $p < 0.001$ ,  $\alpha = 0.64$ ), knee extensors ( $p < 0.001$ ,  $\alpha = 0.62$ ), knee flexors ( $p = 0.002$ ,  $\alpha = 0.58$ ), plantar flexors ( $p = 0.007$ ,  $\alpha = 0.48$ ) and dorsi flexors ( $p = 0.014$ ,  $\alpha = 0.45$ ).

### 3.1.3. Correlations between maximal voluntary torque and manual muscle test data

Correlations between the MMT score and MVC torque for each muscle group are presented in Fig. 5. Our results showed moderate significant correlations for hip flexors ( $p < 0.001$ ,  $r = 0.68$ ), hip abductors ( $p < 0.001$ ,  $r = 0.69$ ), hip adductors ( $p = 0.003$ ,  $r = 0.63$ ), knee flexors ( $p = 0.002$ ,  $r = 0.65$ ), knee extensors ( $p = 0.003$ ,  $r = 0.62$ ) and dorsi flexors ( $p = 0.004$ ,  $r = 0.62$ ). No significant correlation was found for hip extensors ( $p = 0.11$ ,  $r = 0.37$ ) or plantar flexors ( $p = 0.071$ ,  $r = 0.42$ ).

### 3.1.4. Voluntary activation level

We found no statistically significant difference between aLOPD and controls for knee extensors VAL (92.8% vs. 93.4 %, respectively,  $p = 0.650$ ,  $\alpha = 0.04$ ).

### 3.2. Explosive muscle strength

Results of the EMS parameters are presented in Table 3. We found that the RTD of the knee extensors and flexors for the three-time windows (0-50 ms, 100-200 ms and 0-200 ms) were significantly lower in the aLOPD compared to the controls (all p-values  $< 0.038$ ). For the plantar and dorsi flexors, we found that the RTD for 100-200 ms and 0-200 ms were significantly lower in the aLOPD (all p-values  $< 0.043$ ) but not different for 0-50 ms (p-values  $> 0.057$ ).

The peak RTD was also significantly lower in aLOPD than controls for knee extensors ( $p = 0.032$ ), knee flexors ( $p = 0.042$ ), dorsi flexors ( $p = 0.041$ ) and plantar flexors ( $p = 0.040$ ). After normalization by the respective MVC torque values of each participant, we found no intergroup differences for any of the muscle groups or for any parameters of the RTD (all p-values  $> 0.370$ ).

### 3.3. Muscle contractile properties of knee extensors

Table 4 shows results for muscle contractile properties of knee extensors. No differences were found between the two groups for peak torque (35.4 N-m vs. 41.2 N-m;  $p = 0.49$ ), contraction time (139.9 ms vs. 133.7 ms  $p = 0.31$ ) or half relaxation time (113.2 ms vs. 106.3 ms;  $p = 0.34$ ) of doublet twitch.



**Table 3**  
Rate of torque development.

	LOPD Group (n = 20) mean (SD)	Control Group (n = 20) mean (SD)	p-value	Effect size $\alpha$
<b>Knee Extensors</b>				
<i>RTD raw (N·m·s<sup>-1</sup>)</i>				
0–50 ms	117.5 (68.7)	292.1 (211.1)	<b>0.005*</b>	0.51
100–200 ms	293.5 (240.3)	496.4 (239.2)	<b>&lt;0.001*</b>	0.54
0–200 ms	291.7 (223.4)	572.7 (354.2)	<b>&lt;0.001*</b>	0.63
Peak RTD	249.2 (150.9)	599.1 (523.8)	<b>0.028*</b>	0.39
<i>RTD normalized (N·m·s<sup>-1</sup>/ N·m)</i>				
0–50 ms	1.5 (0.8)	1.7 (0.8)	0.55	0.11
100–200 ms	2.9 (0.8)	3.0 (0.9)	0.61	0.1
0–200 ms	3.0 (0.8)	3.1 (0.7)	0.49	0.2
Peak RTD	3.1 (1.3)	3.4 (2.5)	0.37	0.2
<b>Knee Flexors</b>				
<i>RTD raw (N·m·s<sup>-1</sup>)</i>				
0–50 ms	54.1 (30.7)	123.9 (115.8)	<b>0.038*</b>	0.39
100–200 ms	90.5 (40.4)	241.4 (176.7)	<b>&lt;0.001*</b>	0.70
0–200 ms	77.6 (31.9)	181.8 (142.6)	<b>0.018*</b>	0.44
Peak RTD	173.5 (81.1)	349.3 (267.6)	<b>0.046*</b>	0.37
<i>RTD normalized (N·m·s<sup>-1</sup>/ N·m)</i>				
0–50 ms	1.4 (0.9)	1.8 (1.0)	0.85	0.04
100–200 ms	3.4 (1.0)	3.6 (1.1)	0.89	0.03
0–200 ms	2.4 (1.4)	2.5 (1.2)	0.47	0.14
Peak RTD	4.6 (1.4)	4.9 (2.7)	0.78	0.05
<b>Plantar Flexors</b>				
<i>RTD raw (N·m·s<sup>-1</sup>)</i>				
0–50 ms	68.9 (38.2)	97.7 (46.2)	0.057	0.27
100–200 ms	262.1 (157.5)	380.8 (176.6)	<b>0.035*</b>	0.39
0–200 ms	202.6 (137.6)	291.9 (158.5)	<b>0.038*</b>	0.39
Peak RTD	269.2 (147.3)	402.2 (222.2)	<b>0.043*</b>	0.37
<i>RTD normalized (N·m·s<sup>-1</sup>/ N·m)</i>				
0–50 ms	0.64 (0.3)	0.68 (0.2)	0.47	0.13
100–200 ms	2.2 (0.7)	2.3 (0.9)	0.75	0.063
0–200 ms	1.7 (0.5)	1.7 (0.7)	0.47	0.14
Peak RTD	2.6 (0.3)	2.7 (0.2)	0.81	0.004
<b>Dorsi Flexors</b>				
<i>RTD raw (N·m·s<sup>-1</sup>)</i>				
0–50 ms	54.8 (31.3)	80.7 (47.5)	0.059	0.28
100–200 ms	87.0 (38.9)	127.9 (79.2)	<b>0.026*</b>	0.41
0–200 ms	73.8 (26.3)	108.2 (54.3)	<b>0.041*</b>	0.38
Peak RTD	163.1 (71.3)	263.7 (154.3)	<b>0.038*</b>	0.39
<i>RTD normalized (N·m·s<sup>-1</sup>/ N·m)</i>				
0–50 ms	1.7 (0.7)	1.8 (0.8)	0.84	0.04
100–200 ms	2.8 (0.8)	3.0 (0.9)	0.94	0.02
0–200 ms	2.5 (0.6)	2.4 (0.8)	0.62	0.1
Peak RTD	6.1 (3.1)	6.3 (3.8)	0.58	0.1

For Mann-Whitney U test, effect size is given by rank biserial correlation.

RTD: Rate of torque development; SD: Standard deviation; ms: millisecond.

\* Significant difference between aLOPD group and control group,  $p < 0.05$  with Mann-Whitney U test.

**Table 4**  
Muscle contractile properties and neuromuscular fatigue of knee extensors.

	LOPD Group (n = 20) Mean (SD)	Control Group (n = 20) Mean (SD)	p-value	Effect size $\alpha$
<b>Muscle contractile properties</b>				
PT (N·m)	35.4 (14.9)	41.2 (19.3)	0.07	0.42
CT (ms)	139.9 (22.1)	133.7 (17.8)	0.31	0.21
HRT (ms)	113.2 (18.3)	106.3 (12.8)	0.34	0.20
<b>Neuromuscular fatigue</b>				
% fatigue knee flexors	32.9 (11.5)	31.4 (7.9)	0.81	0.04
% fatigue knee extensors	33.5 (9.1)	32.2 (5.7)	0.39	0.11
<b>Central parameters</b>				
VAL knee extensors (%)	92.8 (12.5)	93.4 (7.1)	0.65	0.09
VAL30s knee extensors (%)	82.9 (19.6)	84.8 (12.8)	0.13	0.19
Central fatigue ratio (%)	- 9.2 (4.6)	- 8.8 (2.9)	0.77	0.06
<b>Peripheral parameters</b>				
$\Delta$ PT (%)	-17.5 (4.9)	-16.5 (5.2)	0.66	0.10
$\Delta$ CT (%)	2.3 (6.9)	1.2 (7.6)	0.74	0.08
$\Delta$ HRT (%)	10.1 (7.9)	7.2 (10.1)	0.35	0.20

PT peak torque of doublet twitch; CT contraction time of doublet twitch; HRT half-relaxation time of doublet twitch.

\*Significant difference between aLOPD group and control group,  $p < 0.05$  with Mann-Whitney U test. For Mann-Whitney U test, effect size is given by rank biserial correlation.

SD: Standard deviation. N·m: Newton-meter.

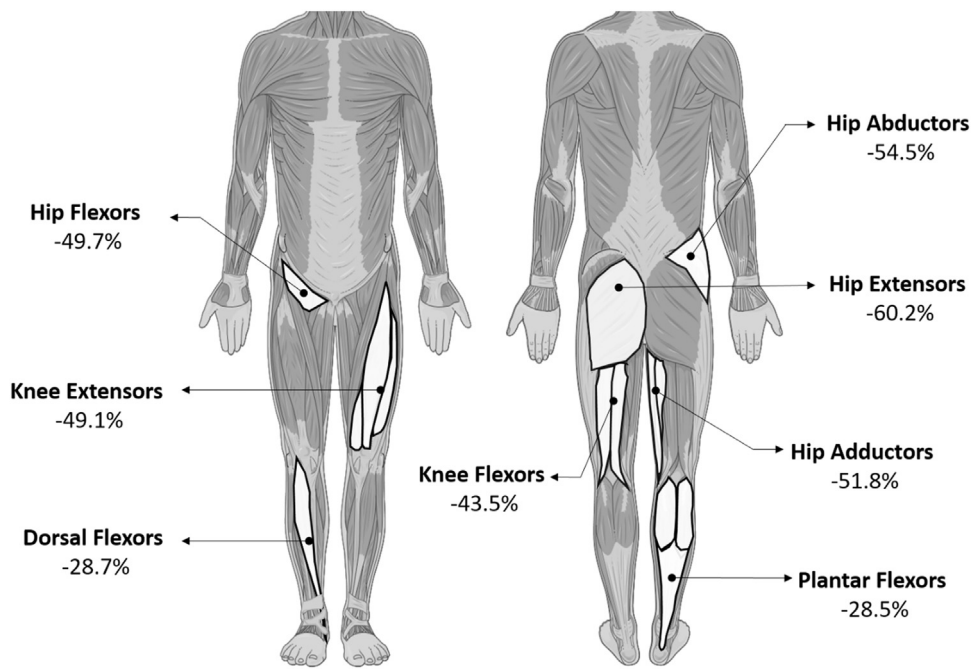


Fig. 4. Topography and intensity of muscular weakness measured by isokinetic dynamometer in aLOPD.

### 3.4. Neuromuscular fatigue of knee extensors and flexors

Table 4 shows results for neuromuscular fatigue of knee extensors and flexors. The percentage of strength loss during the 30-second MVC did not significantly differ between aLOPD and controls for knee extensors and flexors (33.5% vs. 32.2 %, respectively;  $p = 0.390$ ) and (32.5% vs. 32.6 %;  $p = 0.912$ ).

We found no significant differences between aLOPD and controls for central fatigue ration of knee extensors (9.2% vs. 8.8 %;  $p = 0.77$ ). No differences were found between the two groups for knee extensor peripheral fatigue. Indeed, delta peak torque (-17.5 % vs. -16.5 %;  $p = 0.66$ ), delta contraction time (2.3% vs. 1.2 %  $p = 0.74$ ) and delta half relaxation time (10.1% vs. 7.2 %;  $p = 0.35$ ) of doublet twitch were not different between aLOPD and controls.

## 4. Discussion

The main objective of this study was to characterize neuromuscular deficits in aLOPD compared with healthy controls. We found major MMS deficits in aLOPD, especially for hip muscles. We report significant deficits of EMS in aLOPD, but not after normalization by MVC torque, suggesting that the neural and muscular components of EMS of the surviving muscle tissue of aLOPD are preserved. We did not find significant differences between aLOPD and controls for knee extensor VAL and contractile properties, as well as for knee extensor and flexor NMF. Overall, our findings show that i) strength is the only neuromuscular characteristic affected in aLOPD, and ii) surviving contractile tissues of aLOPD are as functional as those of controls.

### 4.1. Specific muscular weakness pattern in aLOPD

Using recommended instruments and rigorous methodology, our study shows major MMS deficits in aLOPD associated with a specific topography. We identified a clear and precise picture of MMS deficit pattern by studying the effect sizes of intergroup

differences. Hip extensors, hip abductors, and hip adductors were the weakest muscle groups in aLOPD compared with controls. Hip flexors, knee extensors and knee flexors were strongly but less affected in aLOPD. Finally, plantar flexors and dorsi flexors were the least affected muscles.

Our results are consistent with present pathophysiological knowledge of Pompe disease [5,55]. These MMS deficits are mainly attributable to structural lesions of the myofibrils. Glycogen storage and autophagic flow disorders induce debris accumulation in muscle fiber. This non-contractile material may occupy almost the entire muscle fiber, interspersed between the myofibrils and impairing their contractile function [56]. As the disease progresses, the damaged muscle fibers are replaced by scarring/fibrosis and fatty inclusions, exacerbating the MMS deficits [5].

Our results confirm the proximal-to-distal gradient of impairment previously reported [2], but the order of deficits has never been previously presented. Interestingly, the most affected muscles in terms of strength are also those with the greatest tissue damage based on imaging [5,57]. The mechanism behind proximal-distal involvement in LOPD is still unknown from a pathophysiological perspective. Several theories have been proposed, in particular an increase in the proportion of 2x type fibers or specific damage to the most stressed muscles which undergo repeated and continuous contraction [1,58]. However, none of these hypotheses has been verified because of the inconsistency of muscle damage in aLOPD.

In this study, we assessed knee extensor VAL to identify a potential neural influence on muscle weakness in aLOPD. We did not find any intergroup difference in this respect, which suggests that muscle weakness in aLOPD does not result from a neural impairment. These results differ from those of Corti et al., who reported alterations in tibialis anterior activity during MVC (4 aLOPD vs. 4 controls) [26]. It can be explained by the fact that this previous study did not examine VAL, but M-wave peak characteristics and the EMG signal power spectrum. Moreover, authors evaluated a minimally affected muscle in a small sample of aLOPD [5].

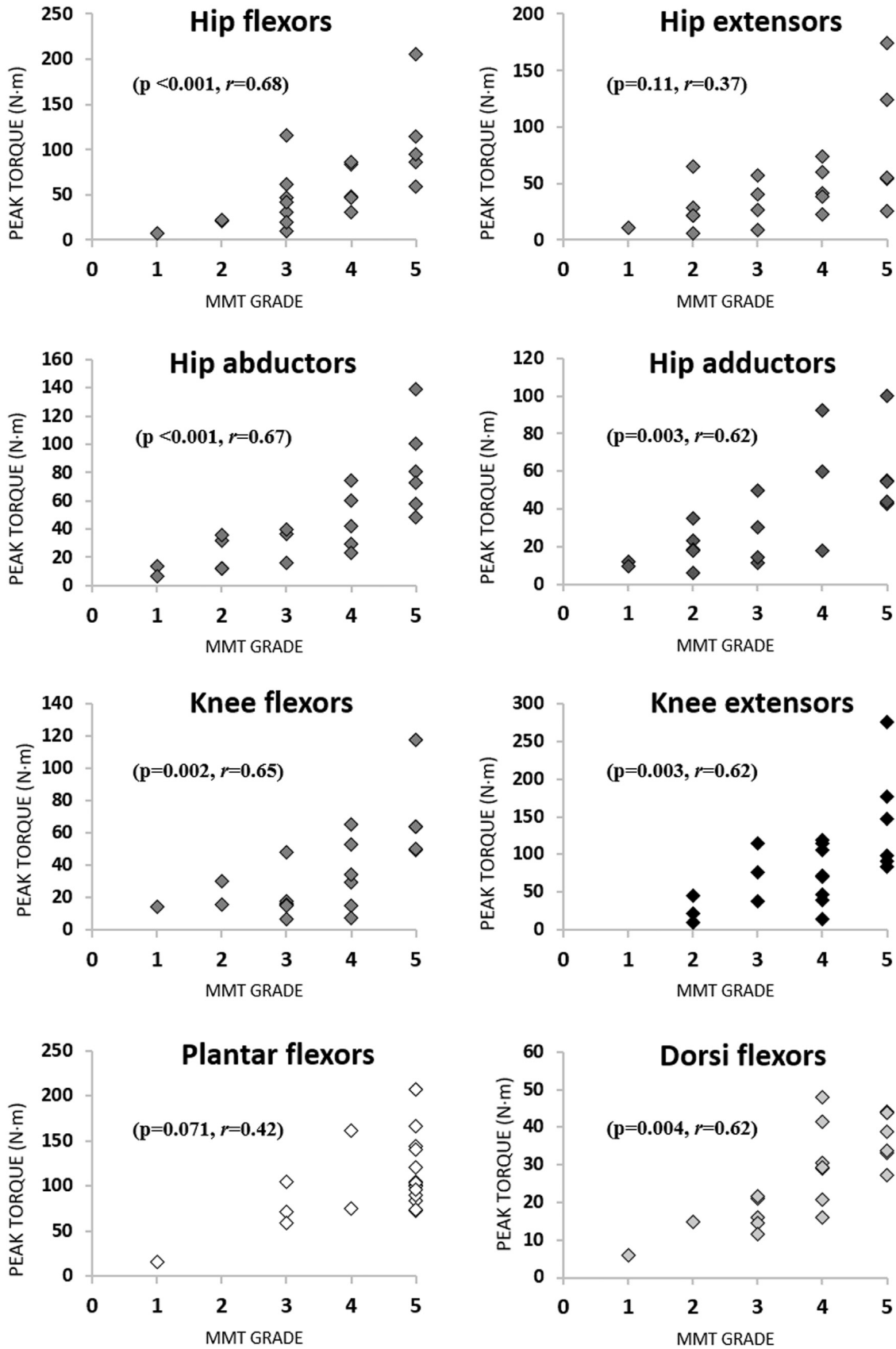


Fig. 5. Relationships between manual muscle testing (MMT) scores and isometric peak torque.

#### 4.2. Importance of instrumented MMS assessment

Our data also show that it is important to assess aLOPD with other tools than MMT since this technique does not provide an accurate value of MMS. We found moderate-to-strong correlations between MMT and MVT data for most muscle groups, except for hip extensors and plantar flexors for which no statistical correlations were found. While the hip extensors were identified as the weakest muscles in aLOPD, these correlations highlight the importance of using instrumented and accurate tools to assess MMS in aLOPD. Moreover, we found that a given MMT grade can correspond to a wide range of absolute strength values even though all the evaluations were done by the same expert evaluator (Fig. 5). Indeed, MMT is not specifically related to absolute strength, and its score depends on the segment weight [9]. Furthermore, the relationship between MVC data and MMT was not linear, with a greater difference between grades 4 and 5 than between grades 2 and 3.

Rarely used in aLOPD [7], isokinetic dynamometer assessments should be generalized in clinical and research practices for this and other neuromuscular diseases to better i) diagnose the strength deficit in each aLOPD and have an accurate follow-up and ii) determine the effects of innovative therapies on MMS.

#### 4.3. Explosive strength

Most raw RTD of the aLOPD were significantly lower than those of controls for knee and ankle muscle groups. However, after normalization by MVT, we found no intergroup difference for any of the muscle groups or time windows. The lack of between-group differences for normalized RTD, especially in the initial phase of explosive contraction (interval 0–50 ms), indicated that the rate of muscle activation during explosive contraction is likely not impaired in aLOPD. Indeed, the magnitude of RTD in the first 40–70 ms of an explosive contraction is highly related to the rate of increase in muscle activation [22,50,59]. Also, as there is no impairment of muscle contractile kinetics, it is consistent to observe that normalized RTD are not different between the aLOPD and controls. Our findings therefore suggest that i) EMS deficits in aLOPD only result from muscle weakness, ii) neural and contractile factors do not contribute to EMS deficits in aLOPD as these factors were not affected in surviving muscle contractile tissue.

#### 4.4. Neuromuscular fatigue

This is the first study of neuromuscular fatigue in aLOPD. We showed no intergroup differences in relative strength loss or in central or peripheral NMF after a 30-s MVC for knee extensors or flexors. This suggests that the high fatigue commonly reported by aLOPD during functional activities [31] would mainly result from muscle weakness or other fatigue components rather than a greater neuromuscular fatigue of the surviving muscle contractile fibers. Indeed, muscle weakness increases the relative involvement of affected muscles during functional tasks and may lead to early onset of neuromuscular fatigue [60,61]. Because aLOPD suffer from respiratory deficiencies [32], we chose a brief and isometric fatiguing task to involve more anaerobic metabolism than aerobic metabolism. Longer fatiguing tasks would have increased the contribution of aerobic metabolism and then, the NMF performance would have been more dependent on the respiratory function of participants. In this context, the contribution of specific muscle metabolism in NMF would have been less important.

#### 4.5. Limitations

In this study, we did not explore the VAL, RTD, or NMF of hip muscles, although these are the most affected muscle groups in aLOPD. The hip muscles NMF and VAL is difficult to explore because there is no available method to study it with percutaneous nerve stimulation. Recent findings in healthy individuals showed an intermuscular relationship in VAL [46]. Similar results were found for NMF [62]. Indeed, the central regulation and peripheral perturbations resulting from NMF seem to be similar between the different muscle groups of an individual [62]. Given these findings and the absence of neural deficits in aLOPD, we can assume that, as for knee extensors, NMF and VAL of hip muscles should not be impaired in aLOPD.

Performing hip RTD is extremely difficult in aLOPD with a major MMS deficit. Indeed, in our pre-tests, aLOPD were unable to perform hip-muscle explosive contractions without countermovement and the data was not usable. Only a few studies have performed explosive hip assessments and these were made on populations of healthy young adults and athletes [63,64]. As for the other muscle groups evaluated, we could expect a decrease in hip RTD due to MMS deficits.

Finally, in our study, 80 % of aLOPD participants were being treated with ERT. The impact of ERT on the improvement of MMS is controversial in the literature, without a clear consensus. For this reason, we performed complementary analyses to assess the role of treatment and its duration on our results and found that these parameters had no impact.

#### 4.6. Perspectives

Our study shows that MMS is the only neuromuscular characteristic impaired in aLOPD. These MMS deficits, which also caused EMS deficits, is explained by a lack of muscle contractile tissue integrity in aLOPD. Our results for VAL, EMS and NMF suggest that the neuromuscular characteristics of the contractile structures remaining intact in aLOPD are of comparable quality to those observed in healthy controls. Therefore, promotion of muscle tissue growth and enhancement of surviving muscle fiber capacity is crucial in aLOPD. Moreover, recent studies have highlighted the critical role of proximal muscle weakness on the performance [65] and walking capacities [66] of adults with LOPD. Hence, focusing on muscle strengthening is imperative in LOPD.

To date, only a few studies have explored the strengthening program effects on MMS in aLOPD [67–69]. The three existing studies report strength gains in aLOPD after this intervention, but the heterogeneity of programs, types of assessments, and characteristics of the participants included limit interpretation of the results. Moreover, evidence showed that muscular strengthening does not cause major muscle damage in aLOPD compared with controls [70]. There is an urgent need for more robust evidence on the effect of strengthening programs on aLOPD since they have the potential to offer a primary therapeutic avenue to improve muscle mass, MMS, EMS, and NMF in aLOPD.

### 5. Conclusion

Our results show that it is a priority to assess the hip extensors, abductors and adductors in aLOPD using a gold standard tool assessment, such as an isokinetic dynamometer. We have shown that MMS is the only neuromuscular characteristic affected in aLOPD, demonstrating that the surviving muscle tissue of aLOPD, including its neural and contractile factors, is functionally as efficient as in healthy controls.

These findings therefore support the investigation of specific muscular strengthening programs that could improve motor

function in aLOPD by improving quantity and/or quality of the surviving muscle.

## Abbreviations

aLOPD	adults with late-onset Pompe disease
BMI	body mass index
EMS	explosive muscle strength
ERT	enzyme replacement therapy
MMS	maximal muscle strength
MMT	manual muscle testing
MVC	maximal voluntary contraction
NMF	neuromuscular fatigue
RTD	rate of torque development
SD	standard deviation
VAL	voluntary activation level

## Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Declaration of Competing Interest

None of the authors has any conflict of interest to disclose

## Funding sources

This study was supported by 1) ARS Île-de-France: call for projects "support for the emergence of lecturer researchers" 2018, Regional Intervention Fund N °C 2018DOSRHS001 and 2) French National Research Agency (ANR) Grant N.° PRTS15009. These supports partly financed a PhD. We also thank Amicus Therapeutics SAS for their support in the analysis of the data.

## Acknowledgement

The authors would like to thank all the participants included in this study. The authors also thank the Bureau de Traduction de l'Université (BTU) of Université de Bretagne Occidentale (UBO) for proofreading the manuscript. We also thank the Garches Foundation for its collaboration in the project. We would also like to thank Thomas Gandois for his constructive criticism.

## References

- [1] Van Der Ploeg Reuser AJJ. Pompe's disease. *Lancet* 2008;372:1342–53.
- [2] Chan J, Desai AK, Kazi ZB, Corey K, Austin S, Hobson-Webb LD, et al. The emerging phenotype of late-onset Pompe disease: a systematic literature review. *Mol Genet Metab* 2017;120:163–72.
- [3] Lefeuvre C, Antonio MD, Bouhour F, Tard C, Salort-Campana E, Lagrange E, et al. Characteristics of patients with late onset pompe disease in france: insights from the french pompe registry in 2022. *Neurology* 2023. doi:10.1212/WNL.0000000000207547.
- [4] Illes Mike A, Trauninger A, Várdi K, Váci M. Motor function and respiratory capacity in patients with late-onset Pompe disease. *J Neuromusc Dis* 2015;2:S21.
- [5] Figueroa-Bonaparte Segovia S, Llauger J, Belmonte I, Pedrosa I, Alejaldre A, et al. Muscle MRI findings in childhood/adult onset pompe disease correlate with muscle function. *PLoS ONE* 2016;11:e0163493.
- [6] Van der Beek de Vries JM, Hagemans MLC, Hop WCJ, Kroos MA, Wokke JHJ, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis* 2012;7:88.
- [7] Maulet T, Bonnyaud C, Weill C, Laforêt P, Cattagni T. Motor function characteristics of adults with late-onset pompe disease: a systematic scoping review. *Neurology* 2023;100:e72–83.
- [8] Horvath JJ, Austin SL, Case LE, Greene KB, Jones HN, Soher BJ, et al. Correlation between quantitative whole-body muscle magnetic resonance imaging and clinical muscle weakness in Pompe disease. *Muscle Nerve* 2015;51:722–30.
- [9] Tiffreau V, Ledoux I, Eymard B, Thévenon A, Hogrel J-Y. Isokinetic muscle testing for weak patients suffering from neuromuscular disorders: a reliability study. *Neuromuscul Disord* 2007;17:524–31.
- [10] Van der Beek Hagemans MLC, Reuser AJJ, Hop WCJ, Van der Ploeg AT, Van Doorn PA, et al. Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. *Neuromuscul Disord* 2009;19:113–17.
- [11] Silva Cerqueira MS, Maciel DG, da Silva ST, de Figueiredo MCC, Cardoso DCR, et al. Rate of torque development of paretic lower limb is an excellent predictor of walking speed in chronic stroke individuals. *Clin Biomech (Bristol, Avon)* 2022;91:105527.
- [12] Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004;363:978–88.
- [13] Cattagni Harnie J, Jubeau M, Hucteau E, Couturier C, Mignardot J-B, et al. Neural and muscular factors both contribute to plantar-flexor muscle weakness in older fallers. *Exp. Gerontol.* 2018;112:127–34.
- [14] Peczkowski KK, Rastogi N, Lowe J, Floyd KT, Schultz EJ, Karaze T, et al. Muscle twitch kinetics are dependent on muscle group, disease state, and age in Duchenne muscular dystrophy mouse models. *Front Physiol* 2020;11:568909.
- [15] Maffiuletti NA, Aagaard P, Blazevich AJ, Folland J, Tillin N, Duchateau J. Rate of force development: physiological and methodological considerations. *Eur J Appl Physiol* 2016;116:1091–116.
- [16] Nyland J, Frost K, Quesada P, Angeli C, Swank A, Topp R, et al. Self-reported chair-rise ability relates to stair-climbing readiness of total knee arthroplasty patients: a pilot study. *J Rehabil Res Dev* 2007;44:751–9.
- [17] Pijnappels M, van der Burg PJCE, Reeves ND, van Dieën JH. Identification of elderly fallers by muscle strength measures. *Eur J Appl Physiol* 2008;102:585–92.
- [18] Horlings Küng UM, van Engelen BGM, Voermans NC, Hengstman GJD, van der Kooij AJ, et al. Balance control in patients with distal versus proximal muscle weakness. *Neuroscience* 2009;164:1876–86.
- [19] Horlings Engelen BG van, Allum JH, Bloem BR. A weak balance: the contribution of muscle weakness to postural instability and falls. *Nat Rev Neurol* 2008;4:504–15.
- [20] Maffiuletti NA, Bizzini M, Widler K, Munzinger U. Asymmetry in quadriceps rate of force development as a functional outcome measure in TKA. *Clin Orthop Relat Res* 2010;468:191–8.
- [21] Tillin NA, Folland JP. Maximal and explosive strength training elicit distinct neuromuscular adaptations, specific to the training stimulus. *Eur J Appl Physiol* 2014;114:365–74.
- [22] Folland JP, Buckthorpe MW, Hannah R. Human capacity for explosive force production: neural and contractile determinants. *Scand J Med Sci Sports* 2014;24:894–906.
- [23] Kisiel-Sajewicz K, Davis MP, Siemionow V, Seyidova-Khoshknabi D, Wyant A, Walsh D, et al. Lack of muscle contractile property changes at the time of perceived physical exhaustion suggests central mechanisms contributing to early motor task failure in patients with cancer-related fatigue. *J Pain Symptom Manage* 2012;44:351–61.
- [24] Musumeci O, Marino S, Granata F, Morabito R, Bonanno L, Brizzi T, et al. Central nervous system involvement in late-onset Pompe disease: clues from neuroimaging and neuropsychological analysis. *Eur J Neurol* 2019;26 442-e35.
- [25] Fidzińska A, Ługowska A, Tyłki-Szymańska A. Late form of Pompe disease with glycogen storage in peripheral nerves axons. *J Neurol Sci* 2011;301:59–62.
- [26] Corti M, Smith BK, Falk DJ, Lawson LA, Fuller DD, Subramony SH, et al. Altered activation of the tibialis anterior in individuals with Pompe disease: implications for motor unit dysfunction. *Muscle Nerve* 2015;51:877–83.
- [27] Allen GM, Gandevia SC, McKenzie DK. Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. *Muscle Nerve* 1995;18:593–600.
- [28] Kooistra RD, de Ruiter CJ, de Haan A. Conventionally assessed voluntary activation does not represent relative voluntary torque production. *Eur J Appl Physiol* 2007;100:309–20.
- [29] Shield A, Zhou S. Assessing voluntary muscle activation with the twitch interpolation technique. *Sports Med* 2004;34:253–67.
- [30] Aagaard Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Increased rate of force development and neural drive of human skeletal muscle following resistance training. *J Appl Physiol* 2002;93:1318–26.
- [31] Hagemans MLC, van Schie SPM, Janssens ACJW, van Doorn PA, Reuser AJJ, van der Ploeg AT. Fatigue: an important feature of late-onset Pompe disease. *J Neurol* 2007;254:941.
- [32] De Vries JM, Hagemans MLC, Bussmann JBJ, van der Ploeg AT, van Doorn PA. Fatigue in neuromuscular disorders: focus on Guillain-Barré syndrome and Pompe disease. *Cell Mol Life Sci* 2010;67:701–13.
- [33] Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol. Rev.* 2001;81:1725–89.
- [34] Place N, Yamada T, Bruton JD, Westerblad H. Muscle fatigue: from observations in humans to underlying mechanisms studied in intact single muscle fibres. *Eur J Appl Physiol* 2010;110:1–15.
- [35] Place N, Millet GY. Quantification of neuromuscular fatigue: what do we do wrong and why? *Sports Med* 2020;50:439–47.
- [36] Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. *Eur J Appl Physiol* 2003;90:562–8.
- [37] Hunter SK. Performance fatigability: mechanisms and task specificity. *Cold Spring Harb Perspect Med* 2018;8:a029728.
- [38] van Melick N, Meddeleer BM, Hoogeboom TJ, Nijhuis-van der Sanden MWG,

- van Cingel REH. How to determine leg dominance: the agreement between self-reported and observed performance in healthy adults. *PLoS ONE* 2017;12:e0189876.
- [39] Aitkens S, Lord J, Bernauer E, Fowler WM, Lieberman JS, Berck P. Relationship of manual muscle testing to objective strength measurements. *Muscle Nerve* 1989;12:173–7.
- [40] Neyroud D, Rüttimann J, Mannion AF, Millet GY, Maffiuletti NA, Kayser B, et al. Comparison of neuromuscular adjustments associated with sustained isometric contractions of four different muscle groups. *J Appl Physiol* 2013;114:1426–34.
- [41] Silva de, Abreu LC, Valenti VE, Nogueira DV, Moraes ER, Natividade V, et al. Verbal and visual stimulation effects on rectus femoris and biceps femoris muscles during isometric and concentric. *Int Arch Med* 2013;6:38.
- [42] Behm D g, Whittle J, Button D, Power K. Intermuscle differences in activation. *Muscle Nerve* 2002;25:236–43.
- [43] Neyroud D, Vallotton A, Millet GY, Kayser B, Place N. The effect of muscle fatigue on stimulus intensity requirements for central and peripheral fatigue quantification. *Eur J Appl Physiol* 2014;114:205–15.
- [44] Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. *J Neurol Neurosurg Psychiatry* 1986;49:1288–91.
- [45] Taylor JL, Olsen HB, Sjøgaard G, Sjøgaard K. Voluntary activation of trapezius measured with twitch interpolation. *J Electromyogr Kinesiol* 2009;19:584–90.
- [46] Hucteau E, Jubeau M, Cornu C, Cattagni T. Is there an intermuscular relationship in voluntary activation capacities and contractile kinetics? *Eur J Appl Physiol* 2020;120:513–26.
- [47] Allen GM, McKenzie DK, Gandevia SC. Twitch interpolation of the elbow flexor muscles at high forces. *Muscle Nerve* 1998;21:318–28.
- [48] Strojnik V, Komi PV. Neuromuscular fatigue after maximal stretch-shortening cycle exercise. *J Appl Physiol* (1985) 1998;84:344–50.
- [49] Rodríguez-Rosell D, Pareja-Blanco F, Aagaard P, González-Badillo JJ. Physiological and methodological aspects of rate of force development assessment in human skeletal muscle. *Clin Physiol Funct Imaging* 2018;38:743–62.
- [50] Cossich V, Maffiuletti NA. Early vs. late rate of torque development: relation with maximal strength and influencing factors. *J Electromyogr Kinesiol* 2020;55:102486.
- [51] Sahaly R, Vandewalle H, Driss T, Monod H. Maximal voluntary force and rate of force development in humans – importance of instruction. *Eur J Appl Physiol* 2001;85:345–50.
- [52] Place N, Maffiuletti NA, Martin A, Lepers R. Assessment of the reliability of central and peripheral fatigue after sustained maximal voluntary contraction of the quadriceps muscle. *Muscle Nerve* 2007;35:486–95.
- [53] Millet GY, Bachasson D, Temesi J, Wuyam B, Féasson L, Vergès S, et al. Potential interests and limits of magnetic and electrical stimulation techniques to assess neuromuscular fatigue. *Neuromuscular Disord* 2012;22:S181–6.
- [54] Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. *Malawi Med J* 2012;24:69–71.
- [55] Fukuda T, Ewan L, Bauer M, Mattaliano RJ, Zaal K, Ralston E, et al. Dysfunction of endocytic and autophagic pathways in a lysosomal storage disease. *Ann Neurol* 2006;59:700–8.
- [56] Hesselink RP, Schaart G, Wagenmakers AJM, Drost MR, van der Vusse GJ. Age-related morphological changes in skeletal muscle cells of acid alpha-glucosidase knockout mice. *Muscle Nerve* 2006;33:505–13.
- [57] Khan Boggs T, Bowling M, Austin S, Stefanescu M, Case L, et al. Whole-body MRI in late-onset Pompe disease: clinical utility and correlation with functional measures. *Mol Genet Metab* 2020;129:S88.
- [58] Van Der Ploeg Carlier PG, Carlier R-Y, Kissel JT, Schoser B, Wenninger S, et al. Prospective exploratory muscle biopsy, imaging, and functional assessment in patients with late-onset Pompe disease treated with alglucosidase alfa: the EMBASSY Study. *Mol Genet Metab* 2016;119:115–23.
- [59] Andersen Aagaard P. Influence of maximal muscle strength and intrinsic muscle contractile properties on contractile rate of force development. *Eur J Appl Physiol* 2006;96:46–52.
- [60] Van der Krogt MM, Delp SL, Schwartz MH. How robust is human gait to muscle weakness? *Gait Posture* 2012;36:113–19.
- [61] Cattagni Scaglioni G, Laroche D, Gremeaux V, Martin A. The involvement of ankle muscles in maintaining balance in the upright posture is higher in elderly fallers. *Exp. Gerontol.* 2016;77:38–45.
- [62] Chartogne M, Rahmani A, Nicolon L, Jubeau M, Morel B. Neuromuscular fatigability amplitude and aetiology are interrelated across muscles. *Exp Physiol* 2020;105:1758–66.
- [63] Casartelli NC, Lepers R, Maffiuletti NA. Assessment of the rate of force development scaling factor for the hip muscles. *Muscle Nerve* 2014;50:932–8.
- [64] Kollock R, Van Lunen BL, Ringleb SI, Oñate JA. Measures of functional performance and their association with Hip and thigh strength. *J Athl Train* 2015;50:14–22.
- [65] Maulet T, Cattagni T, Dubois F, Roche N, Laforet P, Bonnyaud C. Determinants and characterization of locomotion in adults with late-onset pompe disease: new clinical biomarkers. *J Neuromuscul Dis.* 2023 Epub ahead of print 4 August. doi:10.3233/JND-230060.
- [66] Favejee MM, van der Meijden JC, Kruijshaar ME, Rizopoulos D, van der Ploeg AT, Bussmann JB. Association of muscle strength and walking performance in adult patients with pompe disease. *Phys Ther* 2018;98:925–31.
- [67] Sechi A, Zuccarelli L, Grassi B, Frangiamore R, De Amicis R, Marzorati M, et al. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: results of a cross over study. *Orphanet J Rare Dis* 2020;15:143.
- [68] Van Den Berg Favejee MM, Wens SCA, Kruijshaar ME, Praet SFE, Reuser AJJ, et al. Safety and efficacy of exercise training in adults with Pompe disease: evaluation of endurance, muscle strength and core stability before and after a 12 week training program. *Orphanet J Rare Dis* 2015;10 Epub ahead of print. doi:10.1186/s13023-015-0303-0.
- [69] Terzis G, Dimopoulos F, Papadimas GK, Papadopoulos C, Spengos K, Fatouros I, et al. Effect of aerobic and resistance exercise training on late-onset Pompe disease patients receiving enzyme replacement therapy. *Mol. Genet. Metab.* 2011;104:279–83.
- [70] Váczi M, Nagy SA, Kőszegi T, Misovics B, Szabó E, Müller É, et al. Muscle damage in response to a single bout of high intensity concentric exercise in patients with Pompe disease. *Ann Transl Med* 2021;9:389.