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Altered Activation of the Tibialis Anterior in Individuals with Pompe Disease: Implications for Motor Unit Dysfunction

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Abstract

Introduction—Pompe disease is a progressive disease that affects skeletal muscles and leads to loss of ambulation. We investigated the activation of the tibialis anterior (TA) in late onset Pompe disease (LOPD) individuals during maximal voluntary contraction (MVC) and evoked involuntary responses.

Methods—Four LOPD patients and matched control subjects performed MVC of the TA using dorsiflexion and TA evoked responses. Activation of the TA was recorded with surface EMG.

Results—The Pompe patients exhibited greater power at frequencies below 60 Hz and reduced power above 100 Hz. They exhibited reduced increase in M-wave and prolonged M-wave latency and duration in response to stimulation.

Discussion—These results provide evidence that LOPD individuals have an altered activation pattern of the TA during maximal contractions. The observed activation pattern may reflect impairments in voluntary command, neuromuscular junction pathology, or compensatory drive due to a reduced number of functional motoneurons.

Keywords

Pompe disease; Glycogen Storage disease; Skeletal Muscle; Modulation; Motoneuron

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Introduction

Pompe disease is rare; it occurs in approximately 1 per 40,000 births. It is a progressive and often fatal neuromuscular disorder resulting from mutation in the gene for acid alpha-glucosidase (GAA), an enzyme necessary to degrade lysosomal glycogen. Weakness is the principal clinical feature in individuals with Pompe disease, due mainly to muscle pathology. In fact, there is evidence that Pompe patients exert approximately 38 % maximal force relative to controls in the lower extremity [1]. Nonetheless, little is known about their ability to activate the muscle maximally. In this study, we compared the activation of muscle during maximal contractions in individuals diagnosed with Pompe disease and control subjects.

The clinical spectrum of disease is extremely broad. Juvenile or adult-onset disease occurs after early childhood and manifests in skeletal muscles with a limb-girdle pattern of weakness and diaphragm paralysis. Skeletal muscle weakness in late-onset Pompe disease (LOPD) typically affects lower limbs and axial muscles and results in loss of ambulation and wheelchair dependence [2,3]. Additional insight has been gained from animal models. Plantar and dorsal muscle masses are approximately 20% less in the $AGLU^{-/-}$ mouse compared with controls [4-6]. In addition, absolute maximal plantarflexion and dorsiflexion torque during single tetanic (i.e. supramaximal) contraction is 53% and 49% lower in $AGLU^{-/-}$ mice than controls, respectively. When normalized to muscle mass, the decline in maximal torque of plantar and dorsiflexors of this Pompe mouse model amounts to 39% and 36%, respectively [4]. Hesselink, et.al. [4] proposed that loss of skeletal muscle mass cannot fully account for the decline in muscular force and that an additional factor exerting a negative effect on mechanical performance should be considered.

Our hypothesis is that the weakness observed in Pompe disease is the combined effect of muscular and neural pathology. This hypothesis is supported by the following 2 sets of evidence. First, there are several reports of abnormal spontaneous activity and muscle activation during voluntary or evoked responses in Pompe disease patients. For example, Hobson-Webb and colleagues [7] demonstrated spontaneous activity including fibrillation potentials, positive sharp waves, complex repetitive discharges, abnormal nerve conduction (23% of children), and early recruitment of motor unit potentials (53% of children). Although Hobson-Webb, et.al. [7] attribute these EMG abnormalities only to a primary muscle disorder, several authors have suggested a neurogenic origin, including central or peripheral structures [8-12]. Neurogenic involvement is also supported by muscle biopsies, which reveal neurogenic atrophy with fiber type grouping and target or targetoid fibers [8,9]. Second, glycogen accumulation in the central nervous system, in both human and animal models of Pompe disease [13-18], is associated with apoptosis in cell culture [19]. Spinal neurons seem to be particularly susceptible to excessive glycogen accumulation. The arguments that neural impairments contribute to respiratory and peripheral muscle dysfunction are summarized in our recent review paper [20].

Thus, although LOPD patients exert significantly less lower limb muscle force than control subjects [1], the exact mechanism of the deficits in maximal activation are not known. The purpose of this study was to determine whether tibialis anterior muscle activity, as assessed

with surface electromyography, differs between LOPD patients and control individuals during maximal voluntary contractions and evoked responses, thereby offering a further explanation of the cause of weakness in the disease. Our hypothesis is that LOPD patients would exhibit altered tibialis anterior muscle activity during maximal voluntary contractions and prolonged M-wave latency and duration in response to magnetic stimulation of the fibular nerve. To achieve this objective, we compared the activation of muscle during maximal contractions in individuals with LOPD and controls.

Methods

Participants—Four subjects with the diagnosis of LOPD (24.5 ± 10.08 years, 4 women) and four controls (31 ± 8.67 years, 2 women) volunteered to participate. All LOPD participants could complete the six-minute walk test (6MWT), except for 1 subject who was ambulatory only for short distances and wheelchair-dependent for long distances (Table 1). All Pompe subjects in this study were receiving standard of care enzyme replacement therapy (ERT) infusions at the time of study participation. The Institutional Review Board at the University of Florida approved the procedures, and subjects provided written informed consent before participating.

Experimental protocol—Each subject participated in 1 experimental session that lasted about an hour. Two tests were performed: 1) MVC of the tibialis anterior during dorsiflexion isometric contraction; 2) magnetic stimulation of the common fibular nerve. All tests were performed bilaterally. Activation of the tibialis anterior was recorded with surface EMG.

Maximal Voluntary Isometric Contraction (MVC): We investigated the maximal activation of the tibialis anterior muscle while subjects exerted a maximal voluntary isometric contraction during ankle dorsiflexion of the left and right limbs (MVC). Subjects were instructed to increase ankle dorsiflexion force from baseline to maximum over 3 seconds and then to maintain the maximum force for 7 seconds. This procedure allows for identification of a more conservative MVC that reflects the ability to maintain an isometric contraction. Three trials were performed with 1 minute of rest between trials.

Magnetic stimulation of the common fibular nerve: We investigated involuntary evoked responses by studying the M-wave generated by magnetic stimulation of the common fibular nerve. Stimulation was delivered using a single pulse, monophasic stimulator Magstim 200^2 (©2013 Magstim, Spring Gardens, Whitland, Carmarthenshire, SA34 0HR, UK) and a double 25mm coil (Peak Magnetic Field Strength − Tesla = 4). The M-wave was generated in response to stimulation of the common fibular nerve approximately 1cm posterior to the fibular head at progressively increasing intensities. We delivered 5 stimuli in 5% increments beginning at an intensity of 40% and increasing to 100% of stimulator output for both the right and left fibular nerves.

Muscle Activity: Tibialis anterior muscle activity was recorded with disposable bipolar surface EMG electrodes (Covidien/Kendall 31078135 Medi-Trace™ 200 Series Adult Electrodes). The location for the electrode was selected according to the European

Recommendations for Surface Electromyography [21]. The recording electrode was placed in line with the muscle fibers. The reference electrode was placed over the lateral malleolus of the fibula. The EMG signal was sampled at 2 kHz with PowerLab (ADInstruments), band-pass filtered at 10-500 Hz, and stored digitally on a personal computer.

Data analysis—Data were analyzed off-line using LabChart® (LabChart Pro V7) and custom-written programs in Matlab® (Math Works™ Inc., Natick, Massachusetts, USA).

Maximal Voluntary Isometric Contraction (MVC): The EMG signal during the MVC tests (Figure 1 top row) was analyzed from 3-7 s to exclude the initial adjustments by the subject (0-3 s). The EMG signal was bandpass filtered from 10-500 Hz and detrended. Fourier analysis (Figure 1 bottom row) was performed to quantify the power spectrum of the EMG signal [22]. For statistical comparison, the frequency data of the EMG signal was divided into the following frequency bands: 10-35, 35-60, 60-100, 100-150, and 150-200 Hz. Our interest was primarily the sub-100Hz bands, because power in these frequency bands reflects modulation of the motor neuron pool and is not associated with the shape of the action potential, which occurs primarily above 100 Hz [23-25]. Specifically, some bands (13-30 and 30-60Hz) have been associated recently with changes in voluntary effort [23]. The power in each frequency band was normalized to the total power from 10-200 Hz [(power in each band/total power from 10-200Hz) × 100].

Magnetic stimulation of the common fibular nerve: For each subject we analyzed the peak-to-peak amplitude of the M-wave at each stimulation intensity for each leg. M-wave peak amplitudes of 3 trials were averaged together and used to reconstruct the recruitment curve of the M-wave. We also calculated the M-wave increase, defined as the difference between the peak-to-peak amplitude at 100% and 40% stimulation output. Latency and duration of the MEP were also calculated.

Statistical analysis—We used an independent *t*-test to compare the M-wave amplitude at 100% stimulation, the M-wave increase, the M-wave latency, and M-wave duration in controls and Pompe patients. The values of the 2 legs were averaged together, because they did not differ significantly from each other. We used a mixed 4-factor repeated measures ANOVA (2 groups × 2 legs × 3 trials × 5 frequency bands) to compare the interference EMG power across the left and right leg, 3 trials, and 5 frequency bands (10-35, 35-60, 60-100, and 100-200 Hz) in controls and Pompe patients.

A stepwise multiple linear regression model was used to establish the association between M-wave amplitude and modulation of the interference EMG during the MVC trial. The goodness-of-fit of the model was given by the squared multiple correlation (R^2), Durbin Watson statistic and part correlation coefficients that demonstrate the unique contribution of each predictor to the criterion variable.

Analyses were performed with the IBM SPSS Statistics 21.0 statistical package (IBM Corp., Armonk, NY, USA). The alpha level for all statistical tests was 0.05. Data are reported as mean ± SD in the text and mean ± standard error of the mean (SEM) in the figures.

Results

Modulation of maximal muscle activity: We quantified the modulation of tibialis anterior muscle activity during MVC with the power spectrum of the EMG signal at different frequency bands from 10-200 Hz. There was a significant main effect for frequency band for the normalized power spectrum of the interference EMG ($F_{4,24}$=11.04, $P < 0.05$). This finding demonstrates that the normalized power in maximal EMG varied with frequency. Most importantly, there was a significant interaction between the group and frequency band for the normalized power spectrum of EMG ($F_{4,24}$=3.87, $P < 0.05$; Figure 2). *Post hoc* analysis reveals that the Pompe patients had greater power from 10-60 Hz and lower power from 100-200 Hz compared with controls.

Evoked responses: We compared the evoked responses of the tibialis anterior muscle activity for controls and Pompe disease subjects. The M-wave analysis demonstrated the following: 1) the absolute M-wave amplitude at 100% stimulation output was lower (2.48±1.22 mV) in Pompe disease subjects compared with controls (4.14 ± 1.98 mV; Figure 3A); 2) the M-wave increase was lower (t_6=-2.3, P=0.029) in Pompe disease subjects (1.72 ± 0.93 mV) compared with controls (3.8 ± 1.51 mV) (Figure 3B); 3) the latency of the M-wave was longer (t_6=2.1, P=0.04) in Pompe disease subjects (3.47 ± 0.72 mms) compared with controls (2.64 ± 0.33 mms) (Figure 3C); 4) the duration of the M-wave was longer (t_6=1.7, P=0.069) in Pompe disease subjects (26.49 ± 10.02 mms) than in controls (17.66 ± 2.56 mms) (Figure 3C).

Relation between M-wave amplitude and EMG power: The M-wave increase with increased stimulation of the peripheral nerve is associated with additional recruitment of motor unit potentials. To determine the frequency bands in the EMG signal during maximal contractions that were associated with the motor unit number we performed a multiple linear regression analysis for both groups. The increase in EMG power from 100-200 Hz was associated with greater rate of increase in M-wave (R^2 = 0.43) (Figure 4). As hypothesized, this result demonstrates that the EMG power from 100-200 Hz, is related to the size of the motor neuron pool.

Discussion/Conclusion

The findings in this study provide novel evidence that maximal activation of muscle in individuals with Pompe disease differs from control subjects. The Pompe disease subjects had prolonged M-wave latency and duration associated with reduced M-wave amplitude following stimulation. In addition, we found that EMG power is higher below 60 Hz and lesser above 100 Hz in Pompe disease individuals. Altered activation of muscle during maximal contractions may reflect an altered voluntary drive from higher centers, likely in response to loss of motor neurons in the spinal cord. Future studies should focus on determining whether altered muscle activation is in response to muscle pathology or to changes at higher centers.

Altered activation of the tibialis anterior muscle

The power spectrum of the EMG during maximal tibialis anterior contractions was different for Pompe disease subjects and controls. Specifically, we found that the Pompe subjects exhibited greater power at frequencies below 60 Hz and lesser power at frequencies above 100 Hz.

There is evidence that power below 60 Hz in the surface EMG during sub-maximal [23] and maximal contractions [26] may reflect changes in voluntary drive in healthy volunteers. Further, reduced power in surface EMG has been observed in a variety of neurological diseases, for example in stroke [27] and neuropathies [28]. The increased power below 60 Hz in Pompe subjects may reflect a stronger drive to the motorneuron pool of the tibialis anterior. The stronger drive may be an adaptation to the loss of motor units and an effort to increase force from the tibialis anterior. We provide indirect evidence for a decreased number of motor units in the tibialis anterior for the Pompe subjects. Specifically, they had decreased absolute M-wave amplitude following stimulation and a reduced magnitude of increase in the M-wave. The M-wave reflects summation of the stimulated motor units [29,30] and therefore the amplitude is believed to be proportional to the available number of motor units. The magnitude of increase in the M-wave with increasing stimulation intensity reflects the recruitment of motor units. Pompe subjects, therefore, appear to have fewer available motor units in the tibialis anterior and recruit them slower than controls. Furthermore, the M-wave increase was positively associated with power from 100-200 Hz, which is considered to be related to the shape of the motor unit action potential. Lower power within this band would reflect fewer numbers of motor unit action potentials recorded, which was our finding for the Pompe subjects relative to the controls (Figure 2). We recognized that magnetic stimulation might not elicit a maximal compound muscle action potential compared to electrical stimulation. However, our data suggest that all subjects reached a plateau at 100% magnetic stimulation output. Additionally, we found that electrical stimulation produced a higher level of discomfort compared to magnetic stimulation.

We used young adults as the control group and recognize that we did not exactly match for gender and age. However, we are unaware of any evidence that this will add any bias in the interpretation of the results.

These findings, therefore, support our hypothesis that decreased strength in Pompe disease is not associated with muscle pathology in isolation. Altered activation of the tibialis anterior muscle during maximal contractions provides evidence that there is neural involvement in Pompe disease. Nonetheless, the our findings cannot distinguish whether altered activation of muscle reflects impairments related to voluntary command, the neuromuscular junction, or a compensatory change in drive resulting from reduced size of the MN pool. Future studies are underway to distinguish these additional mechanisms.

Clinical relevance

These observations raise important considerations for the management of Pompe disease. The current approach to treatment is to replace GAA activity in muscle by ERT, which consists of bi-weekly infusion of human GAA (Myozyme®) and was approved by the FDA

in 2006. However, ERT does not effectively target GAA deficiency and glycogen accumulation in the nervous system, since it does not cross the brain-blood barrier. These findings underline the unmet need of alternative therapeutic approaches that efficiently target the neural component of Pompe disease.

In summary, our findings provide evidence that Pompe disease patients have altered activation of the tibialis anterior muscle during maximal contractions compared with controls. This finding is critical for understanding the complete pathophysiology in Pompe disease, since it provides evidence that muscle weakness is not related solely to muscle pathology but also to altered neural activation. Future studies will help to distinguish whether altered activation of muscle reflects impairments related to voluntary command, the neuromuscular junction, or a compensatory change in drive resulting from reduced size of the MN pool.

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Abbreviations

TA	tibialis anterior
LOPD	late-onset pompe disease
MVC	maximal voluntary contraction
GAA	acid alpha-glucosidase
AGLU	acid 1-4 a glucosidase
6MWT	six-minute walk test
ERT	enzyme replacement therapy
EMG	electromyography
FDA	food and drug administration

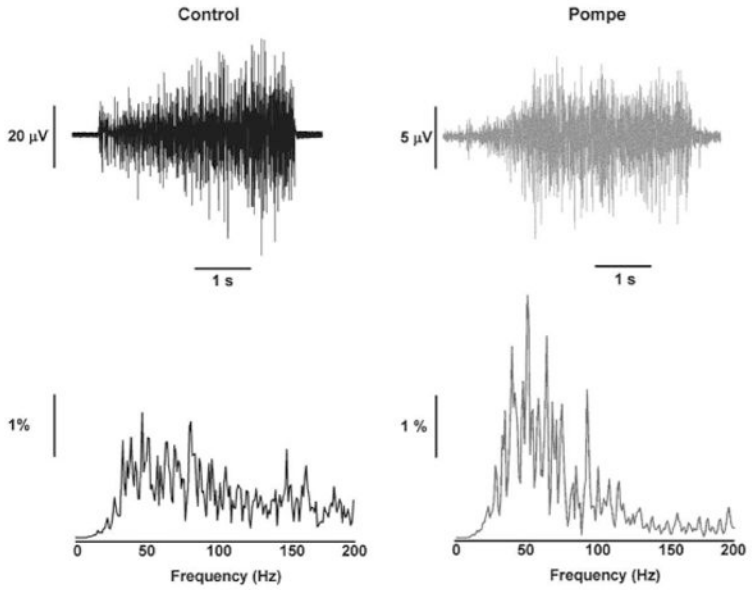

Figure 1. Raw EMG and power spectrum of EMG during MVC

A representative example of the raw EMG recorded during MVC (top row) and power spectrum of the EMG (bottom row) from a control (left column) and a Pompe individual (right column).

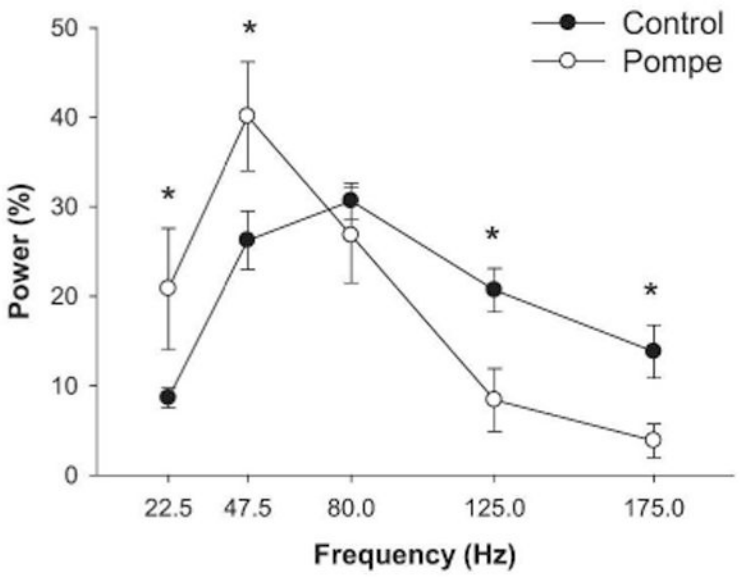

Figure 2. Power spectrum of the EMG during MVC in healthy and Pompe individuals

The overall results of the EMG power spectrum during MVC. Pompe individuals exhibited greater power from 10-60 Hz and lower power from 100-200 Hz compared with controls.

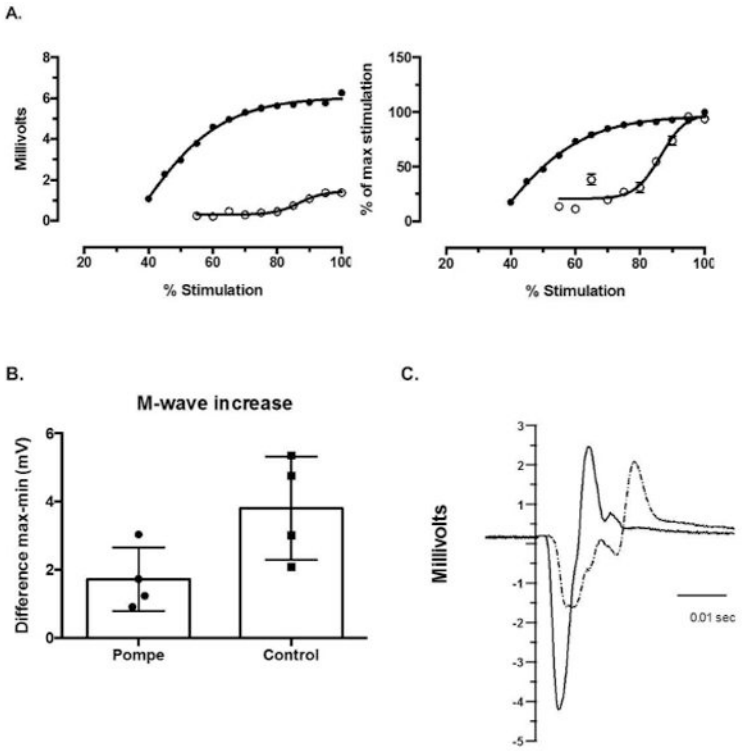

Figure 3. M-wave in controls and Pompe disease subjects

Panel A shows an example of the recruitment curve of the M-wave at each stimulation intensity for a healthy control (filled circles) and a Pompe disease subject (open circles). The left plot shows the absolute M-wave amplitude, and the right plot shows the normalized M-wave to the M-wave at maximum stimulation. The amplitude and the rate of increase of the M-wave is higher for the healthy individual relative to the Pompe individual. Panel B shows the M-wave increase (quantified as the maximum M-wave – minimum M-wave value) of the 4 Pompe disease and the 4 control subjects. The increase of the M-wave is higher for healthy individuals relative to the Pompe individuals. Panel C is an example of M-wave at 100% of Magstim output for a Pompe subject (dashed line) and a control subject (solid line). The Pompe subject has a more complex wave with prolonged duration and latency associated with a decreased peak-to-peak amplitude compared with the control subject.

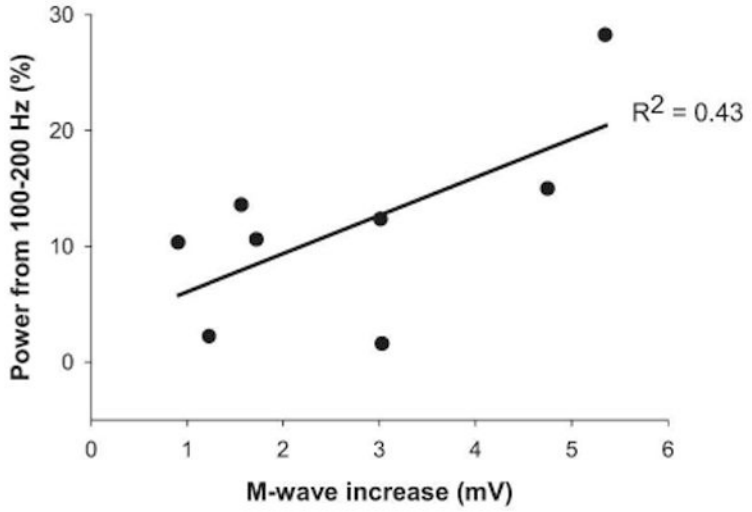

Figure 4. Relation between M-wave increase and EMG power

The M-wave increase was correlated positively with the power in the EMG signal from 100-200 Hz.

Table 1

Subject characteristics

Subjects	Sex	Age (years)	Age at diagnosis (years)	6MWT (meters)
Pompe disease patients				
P18	Woman	15	12	670
P19	Woman	19	16	665
P26	Woman	38	35	NA
P44	Woman	26	26	579.12
Average		**24.5(±10.08)**	**22.2(±10.34)**	**638.03(±51.09)**
Controls				
H01	Woman	32	NA	NA
H02	Woman	42	NA	NA
H03	Male	29	NA	NA
H04	Male	21	NA	NA
Average		**31 (±8.67)**		