Respiratory Function and Fatigue in Pompe Disease

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Abstract

Pompe Disease is an inherited disorder caused by a mutation in the specific gene that is responsible for encoding the enzyme acid α-glucosidase, which is responsible for the breakdown of glycogen. The leading cause of death for patients with Pompe disease is respiratory failure. While current treatments have temporarily aided some of the symptoms attributed to the disease, progressive respiratory muscle weakness persists. The objective of this study was to determine the effect of fatiguing inspiratory resistive loading on breathing parameters. A Threshold Inspiratory Muscle Trainer was used to conduct this prospective cohort study on 7 subjects diagnosed with Pompe disease as well as 7 healthy comparison subjects all with ages ranging from 20 to 63. With p-values <0.05, a significant difference was found within the variables of end-tidal carbon dioxide and peak inspiratory flow as well as the time to fatigue when comparing the two groups. The significant elevation of ETCO2 in subjects with Pompe disease is due to their progressive respiratory muscle weakness, which makes it difficult to expel carbon dioxide. Next steps may include determining if respiratory muscle training could improve maximal inspiratory pressure and endurance time for patients with Pompe disease.

Introduction

Pompe disease is a chronic autosomal recessive disorder caused by a mutation in the gene that encodes acid α-glucosidase (GAA), a lysosomal enzyme involved in the breakdown of glycogen (Pellegrini et al., 2005). When the GAA levels drop below 30% of normal values, glycogen begins to accumulate in certain tissues, specifically the skeletal, cardiac, and smooth muscles, impairing their ability to function properly (Kishnani et al., 2006). Although it has been argued that the current incidence rates may not be a true representation of the population due to under diagnosis, ethnic distributions, and geographic divisions, the reported prevalence of Pompe disease is about 1 in 40,000 (Cavalcanti et al., 2017).

Typically, Pompe disease is categorized into infantile-onset and late-onset, but there is a clear range in disease severity (Chien & Hwu, 2007). While other hereditary neuromuscular diseases, such as Duchenne muscular dystrophy, typically present with loss of ambulation prior to respiratory difficulties, respiratory complications are often one of the first clinical manifestations of Pompe disease (Meilles & Lofaso, 2009). In adult-onset Pompe Disease, respiratory muscle weakness begins subtly with weakness of the diaphragm. This first occurs as nocturnal hypoventilation leading to sleep disruption, which results in excessive sleepiness during the day. Fatigue also contributes significantly to the muscular weakness and decreased motor function in patients with Pompe disease (Boentert et al., 2014). Respiratory muscle impairment is currently the most common cause of early death in Pompe disease (Meilles & Lofaso, 2009). In comparison to the infantile-onset form, adult-onset Pompe disease is typically slower, and ambulation can be maintained for years (Meilles & Lofaso, 2009). However, symptoms and outcomes tend to vary across individuals.

The most prominently affected respiratory muscle is the diaphragm, with less extensive involvement of the intercostal muscles (Fuller et al., 2013). While skeletal muscle weakness contributes significantly to respiratory dysfunction, neural defects can also affect respiratory control. As the glycogen accumulates in the respiratory motor units and neural networks, the

respiratory decline appears to progress (Fuller et al., 2014). Physiologically, the restrictive dysfunction is exhibited by a reduction in vital capacity (VC), maximal expiratory pressure (MEP), and maximal inspiratory pressure (MIP). As the dysfunction progresses, patients begin to develop alveolar hypoventilation and respiratory failure, which eventually lead to dependence on a mechanical ventilator (Berger et al., 2016). Although the rate of progression may vary, 75% of patients with Pompe disease eventually rely on a mechanical ventilator (Fuller et al., 2014).

While there is currently no cure for Pompe disease, the most common route of treatment is enzyme replacement therapy (ERT) to infuse the missing GAA enzyme (Lim, Li, & Raben, 2014). Studies have demonstrated that ERT temporarily improves mobility and muscle strength in adults with Pompe disease, but after two years of treatment, these symptoms begin to worsen once again (Anderson et al., 2014). Similarly, ERT initially improves pulmonary function during the first year and stabilizes function for months, but then lung function begins to diminish (Schneider et al., 2012).

While ERT helps to stabilize symptoms and delay the use of mechanical ventilation, progressive respiratory muscle weakness continues to be a critical concern for patients with Pompe disease. With declining respiratory muscle function, the mechanical load required to take a breath increases, leading to fatigue and ultimately respiratory failure (Matecki et al., 2000). The ability to test for susceptibility of respiratory muscle fatigue in Pompe might be important for identifying who could be at risk for respiratory failure. A standardized method for evaluating respiratory muscle endurance could be beneficial when analyzing the effects of a treatment and also for training of respiratory muscles (Matecki et al., 2000).

Aims and Hypotheses

The objectives of this study are (1) to analyze the effect of fatiguing inspiratory threshold loading on breathing parameters, and (2) to compare the responses of subjects with Pompe disease to healthy control groups. The goal is to examine the responses, so it can be predicted when subjects are about to reach maximum fatigue. This would explain which breathing

parameters are primarily affected prior to the fatigue. We expect variables, such as end-tidal carbon dioxide, to be elevated in patients with Pompe disease, but variables, such as maximal inspiratory pressure, to be reduced. We also hypothesize that patients will fatigue significantly faster than the healthy comparison group.

Methods

This study design was a prospective cohort trial of respiratory strength and endurance in adults with Pompe disease as well as age and gender-matched controls. Subjects were recruited by word of mouth, through clinicaltrials.gov, or locally using HealthStreet, a University of Florida research-matching program. The University of Florida Institutional Review Board approved the study design and procedures, and informed consent was obtained from each subject prior to participation. Eligibility requirements included a confirmed diagnosis of Pompe disease, unless they were healthy controls, no use of mechanical ventilation when awake and upright, and an age between 18 and 70 years old. Exclusions included a diagnosis of asthma or obstructive lung disease, pregnancy, inability to travel to the designated study site, or a forced vital capacity of less than 30% of the predicted values.

Respiratory muscle endurance can be measured through a variety of different methods. In this project, a Threshold Inspiratory Muscle Trainer (IMT) valve, was used to apply a consistent pressure load to breathing (Matecki et al, 2000). For the endurance test, patients breathed through a mouthpiece with a nose clip connected to the Threshold IMT device. A pneumotachograph and pressure transducer attached to the mouthpiece was used to measure breathing parameters. A data acquisition system (Powerlab S35/16) and computer were used to record the breathing parameters. While there was no resistance placed on exhalation, the IMT device applied a load of 40% of maximal inspiratory pressure (MIP) with each inspiratory effort.

Prior to the endurance test, each subject's individual resting breathing pattern was measured. The subject's natural, unloaded respiratory rate was the rate for the endurance test. A metronome was used in order to cue inhalation and exhalation, using a 50% duty cycle

(Ti/Ttot = 0.5) (Matecki, et al., 2000). The following breathing parameters were recorded during the endurance test: end-tidal carbon dioxide (ETCO2), blood oxygen saturation (SpO2), peak inspiratory flow (PIF), peak expiratory flow (PEF), inspiratory work of breathing (WOBi), inspiratory power of breathing (POBi), tidal volume (VT), inspiratory time (Ti), expiratory time (Te), Ti/Ttot, and occlusion pressure ($P_{0.1}$), which is a non-invasive estimate of respiratory drive. In addition, occlusion pressure ($P_{0.1}$) was calculated, to determine the inspiratory pressure generated in the first 0.1 second of a breath. $P_{0.1}$ is a reliable, indirect measure of the activity of the respiratory centers; therefore, the $P_{0.1}$ was used as an estimate of the subject's respiratory drive during the unloaded and loaded conditions (Conti, Antonelli, Arzano, & Gasparetto, 1997).

The study data were exported from the PowerLab into an excel spreadsheet and then into Prism statistical software (Graph Pad, Inc). Independent sample t-tests were used to compare patient and control $P_{0.1}$ values and endurance time in minutes. To determine how the breathing parameters changed as subjects fatigued, each subject's endurance test time was normalized to a 100% scale and clustered into 5 periods, accounting for 0-20%, 20-40%, 40-60%, 60-80%, and 80-100% of the time to fatigue. Then, each breathing parameter was evaluated with a 2-way ANOVA. Factors were subject group (patient vs control) and time (20% increments of the normalized endurance time). A level of $p<0.05$ was considered significant.

Results

In total, fourteen subjects participated in the study. Seven of whom had been diagnosed with Pompe disease and the other seven, who were used as the healthy comparison group. The average age for subjects with Pompe disease (n=7) was 43.6 (±12.79) years. The average age for the healthy comparison group (n=7) was 42.6 (±15.66). Specific demographic information is highlighted in Tables 1 and 2.

During the endurance test, the time to fatigue for subjects with Pompe disease was significantly shorter ($p<0.01$) shown in Figure 1. Subjects with Pompe disease fatigued in an average 2.93 (±2.83) minutes in comparison to control subjects, who fatigued after an average

of 7.7 (±3.15) minutes. In contrast, the $P_{0.1}$ did not differ significantly between the two groups. For resting breaths, $P_{0.1}$ was 0.52 (±0.30) in Pompe disease and 0.39 (±0.29) in controls (p= 0.43), while during the loaded breaths, $P_{0.1}$ was 2.086 (±0.90) in Pompe disease and 1.97 (±1.95) in controls (p= 0.89).

Of the breathing parameters, only ETCO2 and PIF variables differed significantly during the endurance test. Variation between groups with p-values of <0.0001 and 0.047, respectively. Throughout the duration of the endurance test, the mean ETCO2 for subjects with Pompe disease was 47.83 (±1.52) and the control group had a mean of 41.75 (±0.50). Values for subjects with Pompe disease remained relatively constant and higher than the control group, which can be seen in Figure 2. There was no significant interaction effect (p=0.86) as well as no significant time effect (p=0.83). While mean PIF for subjects with Pompe disease was 55.8 (±4.99), the mean PIF for the control group was 42.63 (±13.05). As depicted in Figure 3, PIF values for the control subjects showed much greater variability than subjects with Pompe disease, who remained fairly stable and consistent. Similar to ETCO2 results, there was no significant interaction (p=0.85) or time (p=0.21) effect with PIF.

Discussion

In terms of time of fatigue during the endurance test, there was a significant difference found showing that healthy controls lasted longer when performing these tests. There were two healthy individuals who did not reach the 10-minute mark due to high systolic and diastolic blood pressure as well as sustained inspiratory loading despite having no reported history of hypertension and having a normal resting blood pressure. These values lowered the mean for the healthy control group, but there was still a difference found between the two groups indicating that subjects with Pompe disease fatigue significantly faster than their healthy comparisons. One explanation for the fatigue in subjects with Pompe disease is their low MIP. The average MIP for subjects with Pompe disease was 58.6 (±19.76) in contrast to the average

MIP for the control group, which was 95.3 (±31.71). Low MIP scores indicate respiratory muscle weakness and, therefore, lead to less endurance.

As predicted, ETCO2 levels were significantly higher in subjects with Pompe disease in comparison to the control group. This is primarily due to the fact that the progressive weakness in their respiratory muscles makes it difficult for patients with Pompe disease to expel carbon dioxide. Increases in ETCO2 can be seen as a function of reduced minute ventilation or weakness. ETCO2 levels remained fairly stable in control subjects, but significantly lower than subjects with Pompe disease.

While PEF levels were not found to be significant, PIF levels were found to show significance. This indicates that there was little variation in expiration between subjects, but there was variation in inspiration, which is where the 40% load was applied. Control subjects showed greater variability in PIF, which may be because that they have more muscular ability to overcome the resistance load in various ways. Subjects with Pompe disease showed very little variability and remained at a relatively stable. Since patients with Pompe disease do not have much respiratory muscle strength, these subjects showed little variability in defeating the inspiratory load versus the control subjects that showed a variety of methods. PIF measurements can be used as an indication of strength with low PIF scores depicting an inadequate amount of respiratory muscle strength.

Not only is respiratory muscle weakness a symptom of Pompe disease, but neural problems can also result. Without proper GAA activity, glycogen accumulates not only in muscles, but also within neurons, where glycogen is typically not present (DeRuisseau et al., 2009). Increased glycogen accumulation within the spinal cord can cause respiratory deficits. In order to test for neural involvement, $P_{0.1}$ can be used as a measurement of the medullary respiratory drive. According to the p-values, there was no significant difference found for $P_{0.1}$ values between subjects with Pompe disease and healthy controls. This may be due to the fact that the subjects with Pompe disease's respiratory centers are signaling properly indicating that

there is not an extensive amount of glycogen accumulated in the neurons, so $P_{0.1}$ measurements are similar to healthy subjects.

While most of the subjects in the control group lasted 10 minutes or close to 10 minutes, one subject fatigued at 2.5 minutes and another at 4.1 minutes. Variations within this group may have been due to the amount of exercise regularly done by each individual subject. When recruited participants, subject's activity was permitted to be "recreationally active" or "sedentary". Younger subject's interpretation of recreationally active may have been more vigorous allowing for increased endurance and extreme values for some breathing parameters. Future research may include determining if respiratory muscle training, using the Threshold IMT device, could improve MIP and endurance time for patients with Pompe disease.

Tables and Figures

	Age (years)	BMI (kg/cm²)	FVC pred (%)	FEV1 pred (%)	MIP (cmH2O)	Resting $P_{0.1}$ (cmH20)	RR (bpm)	VT (mL)	Age at Diagnosis (years)	Use of ERT	Nighttime Support?
Pompe Subjects											
DRMF02	50	27.12	69.7	69	49	1.125	21	870.55	8	yes	NO
DRMF03	47	25.4	67	66.2	69	0.3075	16	869.57	-	yes	NO
DRMF04	52	26.4	36.7	35.9	36	0.532	17	554.66	12	no	NO
DRMF05	32	26.58	70.8	73.9	85	0.258	25	816.7	2	yes	BIPAP
DRMF07	32	25.08	95	86.6	79	0.483	18	913.76	-	no	NO
DRMF09	29	16.22	29.2	31.1	36	0.285	21	726.33	4	yes	NO
DRMF12	63	21.48	51.4	60.5	56	0.653	26	571.08	4	yes	CPAP
Average	**43.6(±12.79)**	**24(±3.92)**	**60(±22.55)**	**60.5(±20.15)**	**58.6(±19.76)**	**0.52(±0.30)**	**20.6(±3.87)**	**760.4(±147.23)**			

Table 1. Demographic Information on subjects with Pompe Disease. BMI, Body Mass Index; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume; MIP, Maximum Inspiratory Pressure; $P_{0.1}$, Occlusion Pressure; RR, 1/heart rate; VT, Tidal Volume; ERT, Enzyme Replacement Therapy.

	Age (years)	BMI (kg/cm²)	FVC pred (%)	FEV1 pred (%)	MIP (cmH2O)	Resting $P_{0.1}$ (cmH2O)	RR (bpm)	VT (mL)
Control Subjects								
DRMF10	55	35.47	99.7	109.6	83	0.2	21	619.3
DRMF14	49	24.86	133.2	119.6	118	0.429	9	1002.24
DRMF11	53	32.09	75	77.9	61	0.485	21	910.89
DRMF06	29	26.18	141.6	106.5	156	0.47	9	1451.41
DRMF08	31	22.72	112.5	121	78	0.945	16	672.25
DRMF01	20	23.32	117.7	121	88	0.12	15	816.72
DRMF13	61	23.16	95.3	102.9	83	0.078	9	1194.07
Average	**42.6(±15.66)**	**26.8(±4.99)**	**110.7(±22.9)**	**108.4(±15.32)**	**95.3(±31.71)**	**0.39(±0.29)**	**14.3(±5.44)**	**952.4(±294.24)**

Table 2. Demographic Information on Control subjects. BMI, Body Mass Index; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume; MIP, Maximum Inspiratory Pressure; $P_{0.1}$, Occlusion Pressure; RR, 1/heart rate; VT, Tidal Volume**.**

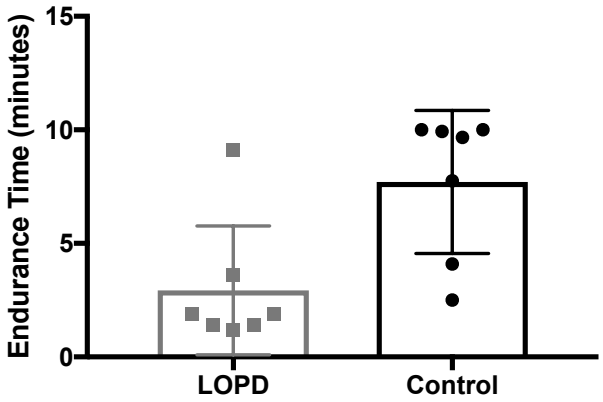

Figure 1. Relationship between the length of the endurance time test for subjects with Pompe disease and control subjects

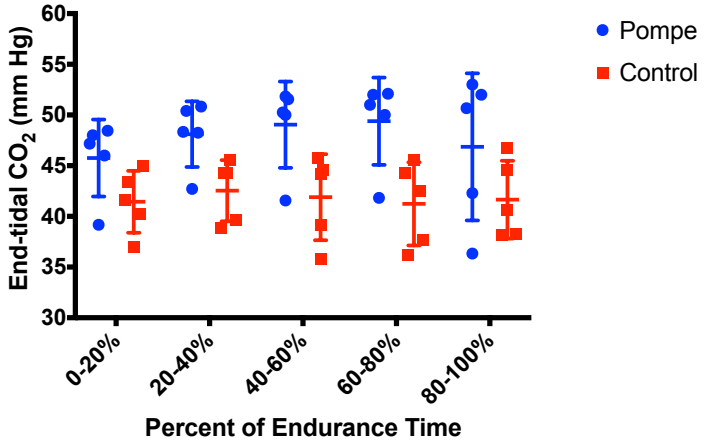

Figure 2. Relationship between ETCO2 and percent of endurance time test completed

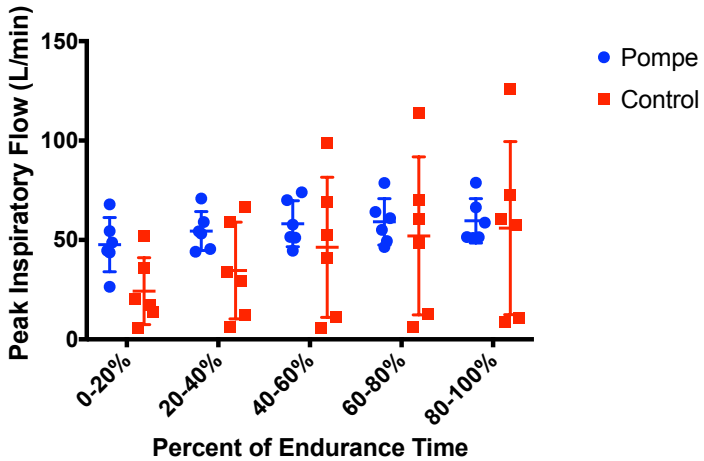

Figure 3. Relationship between PIF and the percent of endurance time test completed

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