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Cardiopulmonary Exercise Testing in Two Patients with Late-Onset Pompe Disease Receiving Enzyme Replacement Therapy: A Case Report and Mini-Review

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In this case report, we present a pair of siblings, a 16-year-old boy and a 19-year-old woman, who were both diagnosed as having late-onset Pompe disease. Each underwent cardiopulmonary exercise testing (CPET) in 2013 and 2015, respectively. The major finding in these two cases was that enzyme replacement therapy (ERT) over a 24-month period improved or stabilized pulmonary function despite late-onset Pompe disease. CPET revealed improved aerobic capacity in the brother, who was physically active, but deterioration in the sister, who lived a sedentary lifestyle. The findings of our cases are compatible with the current consensus that ERT can stabilize or even improve preexisting restrictive lung conditions in patients with late-onset Pompe disease. In addition to the traditional pulmonary function test, CPET is valuable for detecting a subtle decline in aerobic capacity over a short period and can guide clinicians to promptly initiate a cardiopulmonary rehabilitation program. (Tw J Phys Med Rehabil 2016; 44(4): 211 - 217)

Key Words: glycogen storage disorder; Pompe disease; enzyme replacement therapy; cardiopulmonary exercise testing; pulmonary function test; aerobic capacity

INTRODUCTION

Pompe disease, also known as acid maltase deficiency, is a rare autosomal recessive glycogen storage disorder in which the lack of endogenous acid alpha-glucosidase leads to excessive glycogen accumulation in the lysosome. The build-up of glycogen causes progressive muscle weakness throughout the body and affects various tissues.1 Pompe disease includes classic infantile and late-onset forms. The former is characterized by early manifestations of cardiac and pulmonary dysfunction within a few months after birth. The latter, on the other hand, is insidious and variable in disease progression. Glycogen deposition is confined to the skeletal muscles, causing progressive limb-girdle myopathy and respiratory insufficiency. Forced vital capacity (FVC) deteriorates at the rate of 2–3% per year...
in affected patients.[2]

No treatment was available for late-onset Pompe disease until 2006, when enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme, Genzyme) was first introduced and approved for all patients with Pompe disease in the United States and European Union. Prior studies confirmed the efficacy of ERT for stabilizing pulmonary function and improving exercise tolerance.[2-5] In these studies, measurement was performed using functional testing such as the 6-minute walk test (6-MWT). Nevertheless, the improvement of functional capacity cannot be interpreted as the amelioration of cardiopulmonary dysfunction alone but of all systems involved in exercise performance.

In this report, we present a pair of siblings, a 16-year-old boy and a 19-year-old woman, who were both diagnosed as having late-onset Pompe disease at the ages of 11 and 14 years, respectively. To our knowledge, there is a dearth of published studies in the English literature on cardiopulmonary exercise testing (CPET) as a diagnostic tool in patients with Pompe disease. Our study, with patient follow-up of up to 2 years, might be the investigation with the longest follow-up period.

**CASE REPORT**

**Case 1**

Ms. Wang is a 19-year-old woman with a normal birth history. She started experiencing intolerance to physical activity at the age of 9 years. She was diagnosed as having late-onset Pompe disease at the age of 14. Thereafter, she received ERT on a biweekly basis. At the age of 14 years, her condition was complicated by tracheomalacia that required bronchial stenting. She underwent CPET at the ages of 17 and 19 at Taipei Veterans General Hospital. Echocardiography revealed a normal left ventricular size and normal systolic function. Her left ventricular ejection fractions were 77%, 71%, 61%, 76%, and 64% on subsequent examinations.

**Case 2**

Mr. Wang is a 16-year-old boy with an uneventful birth history who presented with lower-extremity weakness, exertional dyspnea, and sleep disturbance as initial symptoms at the age of 9. Owing to significant family history, he underwent muscle biopsy. Late-onset Pompe disease was diagnosed at the age of 11 years. Since then, he has received ERT on a biweekly basis. No adverse effects or further deterioration of clinical function was observed after the initiation of ERT. He underwent CPET at the ages of 13 and 16 at Taipei Veterans General Hospital. He currently plays on the school’s basketball team and leads a physically active life. A follow-up echocardiogram disclosed a normal left ventricular size and normal ventricular systolic function. His left ventricular ejection fractions were 73%, 69%, and 70% on subsequent examinations.

We used a $V_{max}$ Encore Pulmonary and Cardiopulmonary Stress Testing System (Sensor Medics, Yorba Linda, CA, USA), a treadmill-based method for maximal programmed exercise testing. We employed a modified Bruce protocol. Exhaled gases were saved in a collecting tube and analyzed breath by breath to obtain the peak $\dot{V}O_2$ value.[6] Each patient completed an entry procedure by exercising on a treadmill until subjective exhaustion was reached, oxygen intake plateaued, or clinical contraindications appeared.[6] Percent functional aerobic impairment (FAI) assesses the difference between a person’s predicted and actual aerobic capacity according to age, sex, and usual activity level. Percent FAI was calculated using the equation.[6] The $\dot{V}O_2_{max}$ was defined as a respiratory exchange ratio (RER) >1.1 or heart rate (HR)>85% of the maximal age-predicted HR. When either of the criteria is met, the peak $\dot{V}O_2$ value is equivalent to the “maximal” value.

$$\text{%FAI} = \frac{\text{Predicted } \dot{V}O_2_{peak} - \text{measured } \dot{V}O_2_{peak}}{\text{Predicted } \dot{V}O_2_{peak}} \times 100\%$$

The predicted $\dot{V}O_2$ peak (mL/[kg-min]) was calculated using the following equations[6]:

- Male: $57.8 - 0.445 \times \text{age}$
- Female: $42.3 - 0.356 \times \text{age}$
Table 1. Case 1: CPET results after 24-month follow-up with ongoing biweekly ERT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>In 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>0.76L (23%)</td>
<td>1L (28%)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.66L (22%)</td>
<td>0.85L (27%)</td>
</tr>
<tr>
<td>Pimax</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td>Pemax</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>50 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td><strong>CPET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \dot{V}O_2) peak (mL/[kg·min])</td>
<td>23.5 (56%)</td>
<td>21.4 (52%)</td>
</tr>
<tr>
<td>( \dot{V}O_2) at AT (mL/[kg·min])</td>
<td>5.1</td>
<td>5.9</td>
</tr>
<tr>
<td>FAI</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>HR&lt;sub&gt;peak&lt;/sub&gt; (bpm)</td>
<td>136 (66%)</td>
<td>169 (88%)</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; pulse (mL/beat)</td>
<td>5.7 (62%)</td>
<td>4.8 (55%)</td>
</tr>
<tr>
<td>DI</td>
<td>0.92</td>
<td>0.78</td>
</tr>
<tr>
<td>RER</td>
<td>1.04</td>
<td>0.92</td>
</tr>
</tbody>
</table>

PFT: Pulmonary function test, ERT: Enzyme replacement therapy, FVC: Forced vital capacity, FEV<sub>1</sub>: Forced expiratory volume in 1s, Pimax: Maximal inspiratory pressure, Pemax: Maximal expiratory pressure, %: Percentage of predicted value

CPET: Cardiopulmonary exercise testing, ERT: Enzyme replacement therapy, \( \dot{V}O_2\): Oxygen consumption, FAI: Functional aerobic impairment, DI: Dyspnea index, HR: Heart rate, max: Maximum, RER: Respiratory exchange ration

Table 2. Case 2: CPET results after 24-month follow-up with ongoing biweekly ERT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>In 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>2.48L (62%)</td>
<td>2.67L (58%)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>2.27L (66%)</td>
<td>2.24L (56%)</td>
</tr>
<tr>
<td>Pimax</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td>Pemax</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>&gt;60 mmH&lt;sub&gt;2&lt;/sub&gt;O</td>
</tr>
<tr>
<td><strong>CPET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \dot{V}O_2) peak (mL/[kg·min])</td>
<td>49.2 (94%)</td>
<td>35.5 (69%)</td>
</tr>
<tr>
<td>( \dot{V}O_2) at AT (mL/[kg·min])</td>
<td>24.0</td>
<td>26.0</td>
</tr>
<tr>
<td>FAI</td>
<td>6%</td>
<td>31%</td>
</tr>
<tr>
<td>HR&lt;sub&gt;peak&lt;/sub&gt; (bpm)</td>
<td>166 (80%)</td>
<td>166 (86%)</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; pulse (mL/beat)</td>
<td>12.9 (94%)</td>
<td>10.6 (85%)</td>
</tr>
<tr>
<td>DI</td>
<td>0.87</td>
<td>0.64</td>
</tr>
<tr>
<td>RER</td>
<td>1.16</td>
<td>1.05</td>
</tr>
</tbody>
</table>

PFT: Pulmonary function test, ERT: Enzyme replacement therapy, FVC: Forced vital capacity, FEV<sub>1</sub>: Forced expiratory volume in 1s, Pimax: Maximal inspiratory pressure, Pemax: Maximal expiratory pressure, %: Percentage of predicted value

CPET: Cardiopulmonary exercise testing, ERT: Enzyme replacement therapy, \( \dot{V}O_2\): Oxygen consumption, FAI: Functional aerobic impairment, HR: Heart rate, DI: Dyspnea index, max: Maximum, RER: Respiratory exchange ration
RESULTS

In case 1, the baseline FVC and FEV₁ were 23% and 22% of the predicted normal values, respectively. After 24 months of ERT, slight improvement was observed in both variables, with an FVC of 28% and a FEV₁ of 27%. The peak values of oxygen consumption (VO₂), FAI, HR, O₂ saturation, and dyspnea index (DI; defined as minute ventilation divided by maximal voluntary ventilation) are shown in Table 1. The pulmonary function variables showed improvement after 24 months of ERT. The patient reached her anaerobic threshold (AT) at 5.1 mL/[kg.min] and 5.9 mL/[kg.min], respectively.

In case 2, the baseline FVC and FEV₁ were 62% and 66% of the predicted normal value, respectively. However, after 24 months of ERT, the FVC volume improved, but a slight decline in percentile was found compared with that in individuals in this age group. CPET was discontinued before the RER exceeded 1.1, yet the HR reached 86% of the predicted value; thus, the result was considered maximal.

DISCUSSION

The major finding in these two cases is that ERT over a 24-month period improved or stabilized pulmonary function in two patients with late-onset Pompe disease. Although different variables were used, CPET revealed improved aerobic capacity in the brother, who was physically active, but deterioration in the sister, who lived a sedentary lifestyle.

Strong evidence suggests the benefits of exercise in modifying the natural course among patients with late-onset Pompe disease by halting and even reversing the deterioration of muscle strength, endurance, core stability, and functional capacity. However, exercise alone does not appear to effectively slow the deterioration of pulmonary function in cases of late-onset Pompe disease.

Previous studies consistently showed that both short- and long-term ERT improved functional capacity measured on the 6-MWT and halted the deterioration of pulmonary function. ERT combined with exercise training does not seem to promote enzyme uptake in skeletal muscles, which reduces glycogen content and normalizes autophagy, compared with ERT alone. This combination has no additional functional benefits based on current limited evidence, regardless of whether aerobic and resistance training are concurrently or simultaneously added to the ERT. In ERT combined with exercise training, Myozyme uptake was not increased and reduction of glycogen content and normalization of macroautophagy were not achieved beyond that seen with traditional ERT. In our cases, although functional capacity was measured, differences in the trend of aerobic capacity with and without physical activity were observed, indicating the potential benefit with exercise training.

According to the consensus treatment recommendations for late-onset Pompe disease published in 2011, the ideal training for Pompe disease patients is submaximal aerobic exercise because it might assist with the elimination of excessive glycogen storage from muscle cells, thus improving muscle strength and function. On the other hand, high-intensity resistance and eccentric muscle training should be avoided in patients with Pompe disease, as the lysosomes could be damaged during vigorous muscle contraction with further muscle function impairment. As a result, aerobic exercise using large muscle groups, such as treadmill, cycling, and swimming, and low-intensity resistance training are preferred. However, the optimal dose, frequency, and intensity of the exercise prescription in patients with late-onset Pompe disease have not yet been established.

Currently, no consensus or recommendation has been indicated in guidelines on cardiac system follow-up in patients with late-onset Pompe disease. Although most clinicians will acquire at least a baseline echocardiogram, considering that ventricular hypertrophy is a possible complication of late-onset Pompe disease, the identification of abnormalities on an echocardiogram is rare. In 2011, Marzorati et al. used CPET to evaluate pulmonary function and aerobic capacity in patients with late-onset Pompe disease undergoing ERT in a 12-month follow-up period and showed positive effects. CPET seems feasible, has clinical value, and should be integrated into the routine follow-up protocol of patients with late-onset Pompe disease. Based on the findings of our study, cardiac function may still decline despite ERT, which potentiates the importance of early detection by
CPET. In our case series, two patients underwent echocardiogram on a regular basis, but functional decline was not promptly identified. CPET subjected the participants under real-world physical challenge and will more consistently reveal their existing deficits.

**CONCLUSION**

Our cases are compatible with the current consensus that ERT can stabilize or even improve preexisting restrictive lung conditions in patients with late-onset Pompe disease. Meanwhile, we theorize that aerobic capacity might deteriorate if adequate physical activity cannot be maintained; in addition to the traditional pulmonary function test, CPET is valuable for clinicians in detecting a decline in aerobic capacity over a short period and guiding clinicians to promptly initiate intervention with cardiopulmonary rehabilitation.

**CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest relevant to this article.

**FUNDING/SUPPORT STATEMENT**

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**REFERENCES**


晚發型龐貝氏症接受酵素治療後的心肺運動測試：案例報告與文獻回顧

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臺北榮民總醫院復健醫學部 1  國立陽明大學醫學系 2

龐貝氏症又稱作第二型肝醣儲積症，是一種罕見的體隱性遺傳疾病，有缺陷的基因造成體內負責分解肝醣的酸性α-葡萄糖苷酶缺乏，使得肝醣分子堆積在細胞內的溶小體中，而堆積的肝醣會使得許多器官逐漸衰竭。最常影響的器官為骨骼肌，因此患者常會出現肌肉無力，呼吸肌衰竭甚至有些患者會有心臟的侵犯。龐貝氏症根據病發的時點可分為早發與晚發型，早發型龐貝氏症往往在嬰兒出生後幾個月後就會出現症狀，而晚發型的龐貝氏症病發時間較不一定，但症狀會漸進式發生。本病例報告為一對姊妹，分別於 11 歲與 14 歲時診斷龐貝氏症。兩者在診斷後都接受兩週一次的酵素替代治療。兩位姊妹在接受酵素替代治療的過程中，分別於 2013 及 2015 年接受運動心肺測試。心肺測試的結果顯示，酵素替代治療可穩定甚至改善晚發型的龐貝氏症中的限制性肺疾病情形。除了傳統肺功能測試之外，心肺運動測試具有可在短時間內偵測細微的有氧能力下降的價值，能夠幫助臨床醫師為這類病患及早進行適當的心肺復健計畫。（台灣復健醫誌 2016; 44(4): 211 - 217）

關鍵詞：肝醣儲存疾病(glycogen storage disorder)，龐貝氏症(Pompe disease)，酵素替代療法(enzyme replacement therapy)，心肺運動測試(cardiopulmonary exercise testing)，肺功能測試(pulmonary function test)，有氧能力(aerobic capacity)