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Blunted Hypercapnic Respiratory Drive Response in Subjects With Late-Onset Pompe Disease

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BACKGROUND: Patients with late-onset Pompe disease develop progressive hypercapnic respiratory failure that can be disproportionate to the respiratory muscle compromise and/or thoracic restriction. Although recent studies have reported the presence of a blunted hypercapnic respiratory response in some subjects with neuromuscular disorders and chronic hypercapnia, no study has evaluated the integrity of the respiratory drive in subjects with late-onset Pompe disease. Thus, we endeavor to determine the CO_2 rebreathing response in subjects with late-onset Pompe disease. METHODS: Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure, and the maximum expiratory pressure. The maximum inspiratory pressure reflects the strength of the diaphragm and other inspiratory muscles, whereas the maximum expiratory pressure reflects the strength of the abdominal muscles and other expiratory muscles. We studied the hypercapnic drive response (measured as the ratio of the change in airway-occlusion pressure 0.1 s after the start of inspiration and end-tidal P_{CO_2} in 13 subjects with late-onset Pompe disease and 51 healthy controls. RESULTS: Overall inspiratory muscle strength was within normal limits or slightly diminished in the late-onset Pompe disease group. Five subjects (38.5%) were chronically hypercapnic, and 9 (69.2%) had an increased breath-holding time. Compared with controls, the change in airway-occlusion pressure 0.1 s/change in end-tidal CO_2 pressure slope (hypercapnic respiratory drive) was lower in the late-onset Pompe disease group (median 0.050 [interquartile range 0.027–0.118] vs 0.183 [0.153–0.233], $P < .001$). Nine subjects (69.2%) had a blunted change in airway-occlusion pressure 0.1 s/change in end-tidal carbon dioxide pressure slope. CONCLUSIONS: Subjects with late-onset Pompe disease had an impaired hypercapnic respiratory drive response. The clinical impact of this phenomenon in this subject subset deserves further investigation. *Key words: late-onset Pompe disease; control of breathing; hypercapnic respiratory drive; central chemoreception; hypercapnia; respiratory under responsiveness to hypoxia and hypercapnia.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive inherited disorder, due to a reduced activity of the lysosomal acid α-glucosidase.[1] This enzyme deficiency results in failure of lysosomal glycogen degradation, leading to progressive glycogen accumulation in various tissues.[2] There are 2 distinct clinical presentations of Pompe disease: a severe infantile one with cardiomyopathy, respiratory distress, and muscle hypotonia and a late-onset form characterized by a progressive myopathy.[2] Age of onset and phenotype in late-onset Pompe disease can vary greatly, but most typically, patients present with symptoms secondary to skeletal muscle weak-

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ness, whereas clinical prognosis mainly depends on the degree of respiratory involvement.[1]

Patients with neuromuscular disorders, including patients with late-onset Pompe disease, may present with CO_2 retention out of proportion to the degree of respiratory muscle weakness and the alterations of lung mechanics.[3,4] In subjects with neuromuscular disorders, some studies have reported a blunted central respiratory drive as the culprit for chronic hypercapnia; however, specifically in subjects with late-onset Pompe disease, no study has evaluated the integrity of the central respiratory drive.

The aim of the present study was to determine the integrity of the central respiratory drive in subjects with late-onset Pompe disease by measuring the occlusion pressure response to CO_2 rebreathing, a parameter that is independent of respiratory muscle strength and lung mechanics.[5,6]

QUICK LOOK

Current knowledge

Several studies have identified a blunted central respiratory drive in subjects with neuromuscular disorders. However, it is not known whether such an anomaly occurs in subjects with late-onset Pompe disease.

What this paper contributes to our knowledge

In the present study, subjects with late-onset Pompe disease had chronic hypercapnia that appeared disproportionate to the degree of respiratory muscle weakness and mechanical defect. In these subjects, we found a low response to inhaled CO_2, which confirmed the presence of a blunted central respiratory drive.

Methods

Population

We included 13 subjects with late-onset Pompe disease and 51 healthy subjects. We used previously collected data from a control group to find reference values for the technique. Normal subjects who worked or studied at our university medical center participated as healthy controls. The subjects with late-onset Pompe disease were assessed at the pulmonary laboratory of neuromuscular disorders in an out-patient setting. We defined healthy subjects as individuals with no prior pulmonary or cardiac medical history, absence of respiratory or cardiac complaints, normal chest radiographs, and an end-tidal CO_2 (P_{ETCO_2}) of $\leq$45 mm Hg. The present study was reviewed and approved by the institutional ethics committee, and informed consent was obtained in all cases from the subjects and healthy controls.

Measurements and Procedures

Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure (P_{Imax}) and the maximum expiratory pressure (P_{Emax}). The P_{Imax} reflects the strength of the diaphragm and other inspiratory muscles, whereas the P_{Emax} reflects the strength of the abdominal muscles and other expiratory muscles. These static maximum pressures at the mouth were obtained with a snorkel-like mouthpiece coupled with a unidirectional Hans Rudolph valve connected to a pressure transducer (Validyne MP 45, Validyne Engineering, Northridge, California). Data were recorded in a digital format (MP100 Workstation, Biopac Systems, Goleta, California). For acquisition, the signals were passed through an analog-to-digital conversion board (Biopac Systems) at a 60-Hz sampling rate. The signals from the pressure transducers were filtered with low-pass filters ($\leq$30 Hz). Maximum static pressures were considered normal according to Evans equations.[7]

S_{pO_2} and P_{ETCO_2} were measured (Oscar Oxy, Datex, Helsinki, Finland). Arterial blood gas samples were obtained from the radial artery while the subject was at rest in the sitting position and breathing room air. Analyses of P_{O_2} and P_{CO_2} were made with standard equipment (ABL 800, Radiometer, Copenhagen, Denmark).

Although it appeared not to be a reference with this cut-off value, P_{ETCO_2} is a measure of end-tidal CO_2 as an estimate of P_{aCO_2}. $P_{ETCO_2} \approx$ alveolar partial pressure of $CO_2 \approx P_{aCO_2}$. In normal conditions, P_{ETCO_2} is a close approximation change by very similar P_{aCO_2}. The normal values of P_{ETCO_2} are around 5%, or 35–37 mm Hg. According to the 2010–2015 American Heart Association Guidelines for Advanced Cardiovascular Life Support, normal P_{ETCO_2} in the adult patient should be 35–45 mm Hg.[8]

In order to measure breath-holding time, following a few sighs, subjects were asked to perform maximum inspiration and then hold respiration for as long as possible. We performed the test twice and registered the highest value.[9] A prolonged breath-holding time may suggest impaired CO_2 chemosensitivity.

CO_2 Chemosensitivity Response Test

This test was performed using the Read re-inhalation technique described by Whitelaw et al.[5,6] Briefly, subjects sat comfortably on a chair. After determining the baseline occlusion pressure during the first 0.1 s of inspiration ($P_{0.1}$), the subjects re-inhaled from a rubber bag a progressively increasing mixture of CO_2 (7% CO_2, balanced to oxygen) during 4 min in a closed circuit. Flow at the mouth was

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Table 1. Baseline Demographics and Respiratory Function

Characteristics	Pompe Disease Group (n = 13)	Control Group (n = 51)	P
Age, median (IQR) y	45.0 (29.7–58.5)	34.0 (28.0–39.7)	.57
Age at onset, median (IQR) y	20.0 (15.0–26.2)	NA	NA
Female sex, n (%)	8 (61.5%)	22 (43.1%)	.19
Weight, median (IQR) kg	67.0 (59.7–79.0)	65.0 (60.0–71.7)	.57
Height, median (IQR) cm	1.69 (1.55–1.80)	1.69 (1.65–1.72)	.99
BMI, median (IQR) kg/m^2	23.8 (20.9–28.9)	23.2 (21.9–24.8)	.51
P_{ETCO_2}, median (IQR) mm Hg	40.4 (38.4–46.8)	39.1 (37.6–40.2)	.09
$\Delta P_{01}/\Delta P_{CO_2}$, median (IQR) cm H_2O/mm Hg	0.050 (0.027–0.118)	0.183 (0.153–0.233)	.001

IQR = interquartile range
NA = not applicable
BMI = body mass index
P_{ETCO_2} = end-tidal P_{CO_2}
$P_{0.1}$ = occlusion pressure obtained during the first 0.1 s during the subsequent inspiration (zero flow)
$\Delta P_{01}/\Delta P_{CO_2}$ = hypercapnic drive response

obtained by means of a pneumotachograph connected to a medium size Hans Rudolph valve.

Both pneumotachograph catheters were connected to a differential pressure transducer, and another catheter was connected to an oxicapnograph that measured P_{ETCO_2} while a fourth catheter was used to measure mouth pressure (MP-45). Consequently, one catheter measured mouth pressure, another measured P_{ETCO_2}, and the remaining 2 catheters were connected to the pneumotachograph for the assessment of pressure differential (flow). All signals were amplified and passed via an analog-digital board to a computer running Acknowledge software (Biopac Systems). Subjects were asked to breath for 4 min while we occluded the silent pneumatic valve during expiration. The pressure obtained during the first 0.1 s during the subsequent inspiration (zero flow) was the $P_{0.1}$. After that, we immediately reopened the pneumatic valve and assessed the P_{ETCO_2} before occlusion.

Two CO_2 rebreathing tests were performed on each subject. Each consisted of about 15 occlusions. Each test was visually analyzed, and slope $P_{0.1}/P_{CO_2}$ (cm H_2O/mm Hg) was obtained. After that, a single slope with all occlusions was obtained. Slope values reported reflect the CO_2 chemosensitivity.

Statistical Analysis

Statistical analysis was performed with the SPSS 12.0 package (SPSS, Chicago, Illinois). Categorical data are presented as frequencies and percentages. After checking for normal distribution with Shapiro-Wilk test, continuous variables were reported as mean ± SD or median (interquartile range). Statistical comparison for continuous variables was performed using the Student t test or Mann-Whitney rank-sum test and Fisher exact test for binary variables. P values $<.05$ were considered significant. Correlations between blood gas parameters and $\Delta P_{0.1}/\Delta P_{ETCO_2}$ are expressed in terms of Pearson or Spearman coefficient when appropriate.

Table 2. Respiratory Parameters in the Late-Onset Pompe Disease Group

Variables	Values
FVC-seated, mean ± SD, L	2.84 ± 0.92
FVC-seated, mean ± SD % predicted	69.65 ± 23.09
FVC-supine, median (IQR) L	1.46 (1.27–3.37)
FVC-seated, mean ± SD % predicted*	51.17 ± 27.59
FVC, mean ± SD % fall	29.95 ± 18.11
P_{Imax}, mean ± SD mm Hg	55.23 ± 16.45
P_{Imax}, mean ± SD % predicted	60.30 ± 16.19
P_{Imax}, mean ± SD % lower limit of normal range	111.78 ± 35.20
P_{Emax}, mean ± SD mm Hg	77.70 ± 21.49
P_{Emax}, mean ± SD % predicted	69.56 ± 23.78
P_{Emax}, mean ± SD % lower limit of normal range	107.49 ± 31.06
Breath-holding time, mean ± SD s	93.5 ± 40.3

N = 13.
* P = .048 with seated.
IQR = interquartile range
P_{Imax} = maximum inspiratory pressure
P_{Emax} = maximum expiratory pressure

Results

Baseline demographics, P_{ETCO_2}, and $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope values are summarized in Tables 1 and 2. There were no significant differences in terms of age, sex, weight, height and P_{ETCO_2} as well as body mass index between groups (see Table 1). Compared with controls (see Table 1), $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope was lower (median 0.050 [interquartile range 0.027–0.118] vs 0.183 [0.153–0.233], P = .001) in the late-onset Pompe disease group (Fig. 1).

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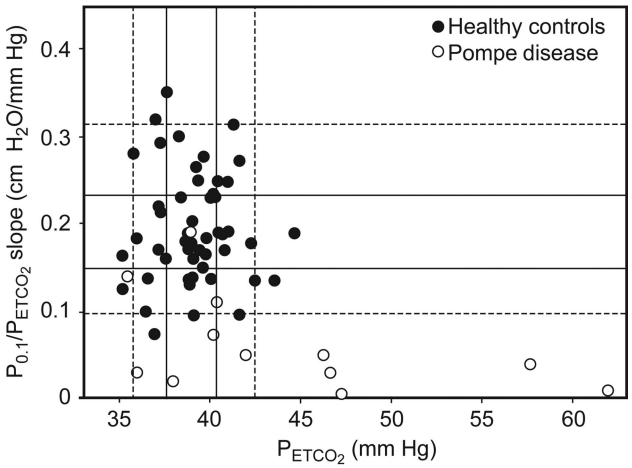

Fig. 1. Relationship between the $\Delta P_{0.1}$/end-tidal CO_2 ($\Delta P_{0.1}/\Delta P_{ETCO_2}$) slope and the ΔP_{ETCO_2} in subjects with late-onset Pompe disease and healthy controls. Note that 11 late-onset Pompe disease subjects (84.6%) showed a reduced hypercapnic drive response (slope below the 25% interquartile level), whereas 9 (69.2%) had a slope below the 5% interquartile level.

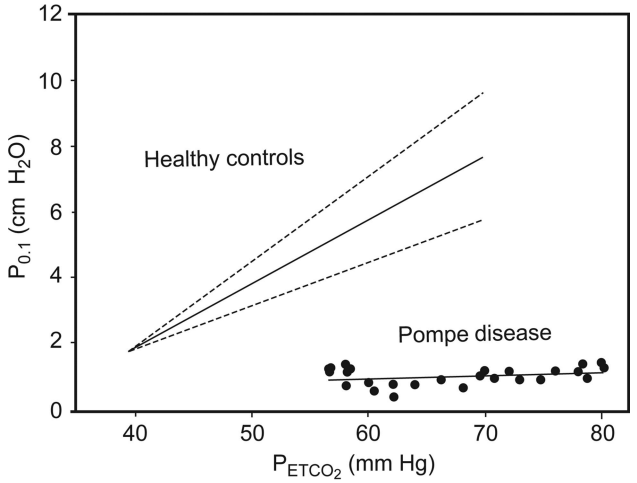

Fig. 2. The median $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope value for healthy controls is shown along with their 25th to 75th percentiles (dotted lines). The group of points and its corresponding regression line depict a flat CO_2 response of a subject with late-onset Pompe disease.

Nine subjects with late-onset Pompe disease (69.2%) had a blunted $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope, and 5 (38.5%) had chronic hypercapnia. Of note, 9 subjects (69.2%) had an increased breath-holding time (see Table 2).[9]

Arterial blood gases were drawn in the late-onset Pompe disease group. Mean serum pH was 7.39 (range 7.32–7.44) in subjects with late-onset Pompe disease. Mean P_{CO_2} was 43.8 ± 8.2 mm Hg (range 35.0–62.0) with 5 subjects presenting hypercapnia (≥45 mm Hg), which is concordant with P_{ETCO_2} values. Mean serum bicarbonate level was 25.9 ± 2.9 mmol/L (range 22.0–32.2), and 6 subjects presented a serum bicarbonate level >26 mmol/L.

As shown in Table 2, the percent-of-predicted FVC seated was 69.95% and decreased to 51% in the supine position. P_{Imax} values were above the lower limit of the normal range in 7 subjects (53.8%), and the remaining 6 had values that were slightly lower than the lower limit of the normal range. Eight subjects (61.5%) had P_{Emax} values above the lower limit of the normal range, and the rest had values that were slightly lower than the lower limit of the normal range.

In the late-onset Pompe disease group, there was a trend toward an inverse relationship between serum P_{CO_2} levels and the $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slopes ($r = 0.47$, $P = .11$), whereas no relationship was observed between P_{Imax} and P_{Emax} and the $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slopes. There was no relationship between P_{ETCO_2} and the slopes in the controls ($r = 0.008$, $P = .96$). Figure 2 illustrates an example of a flat $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope.

Discussion

In the present study, we found a blunted hypercapnic drive response in subjects with late-onset Pompe disease. The degree of hypercapnia found in these individuals seemed disproportionate to their respiratory muscle weakness. There was a trend toward an inverse relationship between the levels of serum P_{CO_2} and the $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope in these subjects, whereas there was no association between the hypercapnic drive response and the degree of respiratory muscle weakness in these individuals. The latter findings may reflect 2 different pathophysiological mechanisms that can affect respiratory status in a given patient. Thus, respiratory muscle weakness is only partly responsible for the respiratory deterioration witnessed in subjects with late-onset Pompe disease. Evaluation of the respiratory drive response in patients with neuromuscular disorders, such as late-onset Pompe disease, can be difficult in the presence of extreme respiratory muscle weakness and alterations of lung mechanics. Central drive is diminished in some patients with neuromuscular disease but not in the majority of cases. Before 1975, central breathing response was based on the ventilatory response, the latter being a parameter influenced by respiratory system resistance and compliance, and respiratory muscle weakness, which may cause variations in ventilation that do not reflect variations in the activity of the respiratory centers.[5] Since then, determination of $P_{0.1}$ has allowed the clinical assessment of central chemosensitivity.[5,6,10] According to Holle et al,[11] respiratory muscle weakness does not affect the $P_{0.1}$ response to hypercapnia, as evidenced by the absence of changes of the $P_{0.1}/P_{CO_2}$ slope with various degrees of inspiratory muscle weakness (up to 23 ± 1%). In

addition, mild to moderate generalized respiratory muscle weakness in healthy subjects due to pharmacologic skeletal muscle paralysis does not affect ventilatory and mouth occlusion pressure response to hypercapnia. In a similar situation, in the presence of generalized respiratory muscle weakness, as observed in subjects with neuromuscular disorders, ventilatory response can be affected, but the mouth occlusion pressure response to CO_2 remains intact.[10,12-15] In our study, none of the subjects had muscle weakness comparable with Holle et al.[11] Furthermore, we did not find a relationship between P_{Imax} percentage and $\Delta P_{0.1}/\Delta P_{ETCO_2}$ slope values ($r = 0.550$, $P = .052$).

Respiratory muscle weakness alone is sufficient to account for hypercapnia when respiratory muscle strength is <30% of normal. A reduction of FVC below 55% of predicted in patients with neuromuscular diseases is likely to be associated with hypercapnia. If, however, CO_2 retention takes place with a FVC above this level or with respiratory muscle strength >30% compared to normal values, coexisting lung disease and/or abnormality of ventilatory control may be present and are probably also contributing factors.[16,17] These observations underscore the large reserve capacity of the respiratory system, which may, in turn, mask involvement of the respiratory muscles until late in the course of neuromuscular disease.

Consequently, prior studies focusing on the hypercapnic respiratory drive response in subjects with neuromuscular disorders have reported conflicting results.[18] Some investigators have reported a normal hypercapnic respiratory drive response in subjects with neuromuscular disorders[10,19]; however, they only included normocapnic subjects. Others evaluated breathing control by measuring the hypercapnic ventilatory drive,[14,20] a parameter affected by respiratory muscles weakness and impaired lung mechanics. Recently published data from our group demonstrated a flat hypercapnic drive response in subjects with myotonic dystrophy (Steinert disease) and chronic hypercapnia.[3] Of note, in both studies, we found a prolonged breath-holding time, which also suggests the presence of a blunted respiratory drive.

The fall in FVC in the recumbent position was present in 3 of 13 cases (23%). In Pompe disease, in contrast with other neuromuscular disorders, there is early diaphragmatic involvement, which may help orient diagnosis. A decrease in FVC of 30–50% when the patient is supine supports the diagnosis of bilateral diaphragmatic paralysis, whereas a decrease in FVC of 10–30% when the patient is seated may be seen with mild diaphragmatic weakness or unilateral diaphragmatic paralysis. When there is little or no reduction in supine vital capacity, the presence of clinically important diaphragmatic weakness is unlikely. The mechanism related to the reduction in supine FVC is the cephalic displacement of abdominal contents in concert with ineffective activity of the accessory inspiratory muscles. Regarding the relationship between ventilatory control and hypercapnia, a chicken and egg question then becomes important: Is CO_2 retention secondary to an underlying ventilatory control abnormality in these patients, or is the diminution in ventilatory sensitivity merely secondary to chronic CO_2 retention?

Patients with chronic compensated respiratory acidosis have higher levels of plasma (as well as cerebrospinal fluid) bicarbonate because of bicarbonate retention by the kidneys. Therefore, for any increment in P_{CO_2}, the effect on pH at the medullary chemoreceptor is attenuated by the increased buffering capacity available.[21] The brain-CO_2 buffering capacity increases in respiratory acidosis and decreases in respiratory alkalosis.[22] The central drive is influenced by the acid/base status. In chronic respiratory acidosis, the central response to acute CO_2 inhalation is reduced. This finding has been described in subjects with chronic obstructive pulmonary disease and hypercapnia.[23]

In normal subjects, the slope of the CO_2 response line during steady-state CO_2 inhalation was unaffected by chronic alkalosis and acidosis.[24-26] Using the rebreathing technique, there was no significant change in intercept in acidosis and alkalosis, but the slope ($\Delta \dot{V}_E/\Delta P_{CO_2}$) varied from the control values. The mean slope value during alkalosis (pH 7.44 ± 0.02, plasma HCO_3^- 28.5 ± 3.0 mmol/L) was 0.6 times the average baseline.[26] To our knowledge, a flat $\Delta P_{0.1}/\Delta P_{CO_2}$ slope response has not been described in the setting of metabolic alkalosis. Thus, a combination of factors can lead to abnormal patterns of breathing and hypoventilation in these disorders; no single pathophysiologic mechanism can explain all of the abnormalities. Clinically, it is important to appreciate the prevalence of ventilatory control disorders and include appropriate evaluations when assessing patients with neuromuscular diseases and offering therapeutic options.[19]

In our study, 69.2% of subjects had a flat CO_2 response, which could be attributed to alterations in the acid/base state. However, 4 of 9 subjects with a flat CO_2 response were normocapnic. Therefore, it appears that hypercapnia may not be the main factor responsible for a flat CO_2 response.

To our knowledge, this is the first study evaluating the control of breathing using the $P_{0.1}$ response to CO_2 in subjects with late-onset Pompe disease. The potential clinical interest in evaluating the CO_2 response test in these patients could be the ability to improve risk stratification during a concomitant unrelated medical problem or before an invasive diagnostic or therapeutic procedure. The presence of a blunted respiratory drive, regardless of the degree of respiratory muscle compromise, may call for closer monitoring in these individuals to limit pulmonary complications.

Although our study included a small number of subjects with late-onset Pompe disease, our findings appear con-

clusive, since the majority (84.6%) of subjects showed a reduced hypercapnic drive response (a slope below the 25% interquartile level) despite mild impairment of respiratory muscles and lung mechanics and normal bicarbonate levels. Mean serum bicarbonate level was 25.9 ± 2.9 mmol/L (range 22.0–32.2), and only 5 subjects had bicarbonate >26 mmol/L. A larger sample size may confirm our findings and help identify factors that may influence hypercapnic respiratory drive. We have not performed autonomic function tests to evaluate the integrity of the autonomic nervous system. In that sense, several studies have found glycogen deposition in the brain in subjects with the infantile form of Pompe disease, causing overt autonomic neuropathy and other neurological derangements,[27-29] whereas no data are available so far in subjects with late-onset Pompe disease.[30]

Conclusions

Subjects with late-onset Pompe disease had a reduced hypercapnic drive that may contribute to carbon dioxide retention. The clinical repercussion of this phenomenon in this subject subset deserves further investigation.

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