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Progression from respiratory dysfunction to failure in late-onset Pompe disease

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Abstract

To identify determinants of respiratory disease progression in late-onset Pompe disease (LOPD), we studied relationships between pulmonary function, respiratory muscle strength, gas exchange, and respiratory control. Longitudinal evaluation of 22 LOPD patients (mean age 38 years) was performed at 6-month intervals for 6–24 months. Measurements included vital capacity (VC), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), tidal volume (V_T), dead space (V_D), and ventilatory response to CO_2. Although reduction in VC correlated with MIP and MEP ($p < 0.0001$), some patients had normal VC despite reduced MIP and MEP (5 [23%] and 9 [41%] patients, respectively). Daytime hypercapnia was associated with reduced VC (<60% predicted) and MIP (<40% predicted). Moreover, chronic hypercapnia was associated with elevated V_D/V_T (≥0.44) due to falling V_T (≈300 ml), compatible with reduced efficiency of CO_2 clearance. The presence of hypercapnia and/or ventilatory support was associated with reduced ventilatory responsiveness to CO_2 (≤0.7 l/min/mmHg). We conclude that daytime hypercapnia, an indicator of chronic respiratory failure, is tightly linked to the degree of respiratory muscle weakness and severity of pulmonary dysfunction in LOPD patients. Reductions in CO_2 clearance efficiency and ventilatory responsiveness may contribute to the development of chronic daytime hypercapnia.

Keywords: Late-onset Pompe disease; Respiratory failure; Vital capacity; Maximum inspiratory pressure; Hypercapnia; Respiratory control

1. Introduction

Late-onset Pompe disease (LOPD) is a rare autosomal recessive neuromuscular disorder caused by lysosomal α-glucosidase acid (GAA) deficiency [1]. GAA deficiency induces a progressive glycogen accumulation (especially in skeletal muscles) that leads to severe proximal and respiratory muscle dysfunction [2]. Pulmonary dysfunction is prominent in LOPD, with 79% of adults and 59% of children having some degree of respiratory insufficiency [2,3] that eventually progresses to respiratory failure [4].

The etiology of pulmonary dysfunction in LOPD patients is related to weakness of the diaphragm and accessory muscles of respiration [2]. Physiologic evaluation reveals restrictive dysfunction that manifests as reduction in vital capacity (VC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) [2,5]. Over time, the progressive weakening of respiratory muscles is associated with development of respiratory failure and alveolar hypoventilation, which can be identified by daytime hypercapnia on blood gas evaluation [6]. The development of respiratory failure necessitates initiation of ventilatory support (nocturnal and daytime ventilation), which is associated with reduced quality of life. Moreover, respiratory failure is the most frequent cause of death in LOPD patients [7–10].

Despite numerous studies revealing progressive restrictive respiratory disease in patients [3,4,11–13], the determinants of progression from respiratory dysfunction to failure in LOPD have not been reported. Studies have shown an association between levels of respiratory impairment (reduction in VC and/or inspiratory pressure), development of sleep-disordered breathing, and the presence of respiratory failure [7,14–17]. However, the interrelationship between mechanical limitation

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of lung function, abnormalities in gas exchange, and measures of respiratory control has not been investigated in LOPD. Thus, we evaluated disease course, symptoms, respiratory function, and daytime hypercapnia in a cohort of 22 LOPD patients that were not receiving therapy. Our goal was to evaluate the evolution of respiratory function over time and study the relationships between measures of pulmonary function, respiratory muscle strength, gas exchange, and respiratory control to identify determinants of disease progression from respiratory dysfunction to failure. To accomplish these goals, data were reviewed from a cohort of patients studied prior to development of enzyme replacement therapy.

2. Methods

2.1. Study design

This was a 24-month observational study conducted in a cohort of untreated patients with LOPD that were studied from 1996 to 1999 at Bellevue Hospital, New York University School of Medicine, New York. After signing informed consent forms, patients completed a baseline evaluation. Longitudinal evaluation was performed at 6-month intervals for a maximum of 24 months. Diagnosis of Pompe disease was confirmed in all patients by a combination of endogenous GAA activity (either from leukocytes or cultured fibroblasts) and muscle biopsy.

2.2. Participants

Eligible patients had documented GAA enzyme deficiency (<75% of the lower limit of the normal adult range) or GAA gene mutation(s) in the medical record and were aged ≥18 years at the time of enrollment. Patients were excluded if they had previously received any experimental or approved therapy for Pompe disease or if they had a medical condition that, in the opinion of investigators, might compromise the subject's ability to comply with study protocol requirements.

2.3. Data collection

Patient data were collected on the following: 1) demographics; 2) presence of congenital abnormalities; 3) family history of Pompe disease; 4) data from respiratory assessments; 5) documented treatments and surgeries, including use of ventilatory assistance either during sleep or continuously throughout the day; 6) ability to ambulate and use of assistive devices; and 7) clinical laboratory data (creatine phosphokinase, thyroid function, arterial blood gas). Data were collected by the investigators, who transcribed medical records onto case report forms. There was no overlap between this patient cohort and previous literature reports.

2.4. Measurements

2.4.1. Pulmonary function and respiratory muscle strength

Pulmonary function testing was conducted with patients in the upright position using a spirometer and a plethysmograph (P.K. Morgan, Haverhill, MA, USA) to assess VC, inspiratory capacity (IC), and functional residual capacity. Respiratory muscle strength was evaluated by measuring MIP and MEP using a manometer (Physiodyne Inc, Quogue, NY, USA). Pressure was recorded in cmH_2O. The testing equipment was constant in all subjects at all assessments. The percentage of predicted normal values were calculated using published equations [18,19].

For the 2 patients with a tracheostomy tube, testing was performed after the tube was removed and the stoma was covered with an air tight dressing. This technique allowed for assessment of respiratory function without the confounding upper airway obstruction that would be present with the tracheostomy tube in place.

2.4.2. Resting ventilation and blood gas tensions

Resting ventilation was assessed in all patients to determine the resting respiratory pattern, effective dead space, and alveolar ventilation. Patients were studied in the upright position while breathing at their resting level for 20 minutes. The exhaled air was collected in a 120 liter spirometer (Tissot gasometer, W.E. Collins, Inc., Braintree, MA, USA). Measurements of respiratory rate and tidal volume (V_T) were obtained using the spirometer, while exhaled CO_2 and oxygen concentrations were determined using a metabolic cart (Fitco Max-1, Physiodyne, Farmingdale, NY, USA). Data were analyzed after stabilization of the ventilatory rate and pattern (final 3 to 5 minutes of the study). Patients were included in the final analysis only if steady state conditions were verifiable (n = 17) based on normal values for resting metabolic rate (oxygen consumption, CO_2 production, and respiratory quotient). The dead space volume (V_D) and dead space to tidal volume ratio (V_D/V_T) were calculated using standard equations [20]. Arterial blood was collected for analysis of $PaCO_2$ at the end of the study.

2.4.3. Respiratory control

The ventilatory response to CO_2 was assessed in all patients by a rebreathing technique [21]. Ventilation was measured as the subject rebreathed from a closed system containing increased CO_2 in a hyperoxic gas mixture. The partial pressure of carbon dioxide (PCO_2) was monitored by end-tidal level and was allowed to rise above the initial mixed venous level over 4 minutes. Automated custom software was utilized to perform this test and to acquire the ventilatory and gas signals. The ventilatory response to CO_2 was assessed as the slope of the relationship between minute ventilation and PCO_2. Valid data were obtainable in 20 patients.

2.5. Data analysis

Data are summarized as prevalence, mean, and standard deviation and/or range. Analysis of the relationship between inspiratory pressure to lung volume was performed using logarithmic regression, as previously described [16,22]. This approach accounts for the nonlinear relationship characteristic of normal subjects. The relationship between expiratory pressure and VC was assessed by linear regression. All analyses were conducted with either Microsoft Excel for Windows (v2010) or SigmaPlot for Windows (v12.0).

3. Results

3.1. Demographics and baseline characteristics

The demographic and baseline characteristics of patients are shown in Table 1. Mean age ± standard deviation (SD) was 38.0 ± 13 years (range, 19–60), and mean duration of disease was 10.2 ± 8.4 years (range, 1–30). Walking aids were used by 6 patients, and ventilatory support was used by 7 patients. At baseline, mean VC ± SD in the sitting position was 69 ± 27% predicted. Of the 22 patients, 10 (45%) had VC values in the normal range (>80% predicted). The remaining 12 patients (55%) had VC values <80%, indicating restrictive respiratory disease varying from mild to severe by American Thoracic Society standards. Clinical history did not reveal an explanation for the restrictive dysfunction other than neuromuscular weakness in any subject, and chest radiographs (n = 16) were either normal or revealed atelectasis and/or focal postinflammatory fibrotic changes. One subject had previously undergone surgery for scoliosis. Elevated $PaCO_2$ was noted in 5 patients; the serum bicarbonate concentration was elevated in all 5 patients (>31 mEq/l), indicating the presence of renal compensation and confirming persistence of the hypercapnic state. The arterial partial pressure of oxygen was reduced in the subjects with hypercapnia. However, calculation of the alveolar-arterial oxygen pressure difference revealed normal values in all patients, indicating that gas transfer across the alveolar air interface was within normal limits.

Table 1
Demographics and baseline characteristics of the patient population.

Characteristic	Data*
Number of patients enrolled, N	22
Age at enrollment, yrs	
Mean	38 ± 13
Range	19–60
Sex, n	
Male	9
Female	13
BMI†	
Mean	23.5 ± 4.8
n (%)	
<20	6 (32)
20–25	5 (26)
25–30	6 (32)
>30	2 (11)
Duration of disease, yrs	
Mean	10.2 ± 8.4
Range	1–30
Age of disease onset, yrs	
Mean	29 ± 13
Range	11–57
CPK (IU/L)	
Mean	645 ± 529
Walking aids‡, n (%)	
None	15 (68)
Cane/walker	2 (10)
Wheelchair	4 (19)
Ventilatory support, n (%)	
None	15 (68)
NIV	5 (23)
Tracheostomy	2 (9)
VC (% predicted)	
Mean	69 ± 27
n (%)	
>80	10 (45)
60–80	5 (23)
40–60	3 (14)
<40	4 (18)
$PaCO_2$ (mmHg)	
Mean	42 ± 11
n (%)	
<45	17 (77)
≥45	5 (23)

* Plus–minus values are mean ± SD.
† n = 19.
‡ n = 21.
BMI, body mass index; CPK, creatine phosphokinase; NIV, noninvasive ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; VC, vital capacity.

The top panel of Fig. 1 illustrates longitudinal VC data for the study cohort. Data were available for 18 of the 22 patients, and time points ranged from 6 to 24 months. VC, expressed as % predicted, was essentially stable and varied within 5% of baseline in 11 (61%) of the patients. A decline in VC >5% was seen in 3 (17%) patients. An increase >5% was seen in 4 (22%) patients; in 3 of these 4 patients, the increase in VC was not attributable to an increase in diaphragm strength since MIP and IC remained constant at all time points. In many cases, the longitudinal trend was not consistent and test-to-test variability was noted.

The bottom panel of Fig. 1 shows longitudinal MIP data for the study cohort. In contrast to the variable course of VC, the measured MIP remained essentially stable in the majority of subjects. Only 3 individuals demonstrated changes ≥10 cmH_2O.

3.2. Relationship between lung volumes and respiratory muscle strength

Fig. 2 illustrates the relationships between lung volume (VC and IC) and inspiratory muscle strength (MIP) in LOPD patients. The top panel plots VC as a function of the MIP; analysis of the data revealed a significant correlation ($r^2 = 0.71$, $p < 0.0001$). Although the observed data were similar to the predicted relationship (dotted line), the data were shifted downward (solid line), indicating that for any degree of inspiratory muscle weakness there was a disproportionate reduction in VC. These results suggest a decrease in either lung and/or chest wall compliance in patients with LOPD. Of note, 5 patients demonstrated normal VC (>80% predicted) despite reduction in MIP to values <80% predicted. The patients receiving ventilatory support (open symbols) demonstrated the most severe impairment in respiratory function; VC and MIP values were consistently below 60% and 40% predicted, respectively. The bottom panel illustrates similar data for IC, highlighting a respiratory restriction characterized by the inability to distend the lungs and chest cage ($r^2 = 0.63$, $p < 0.0001$).

The relationship between VC and MEP (a measure of expiratory muscle strength) is shown in Fig. 3. MEP was abnormal in all patients varying from borderline low to severely decreased values (range, 10–75% predicted). A linear

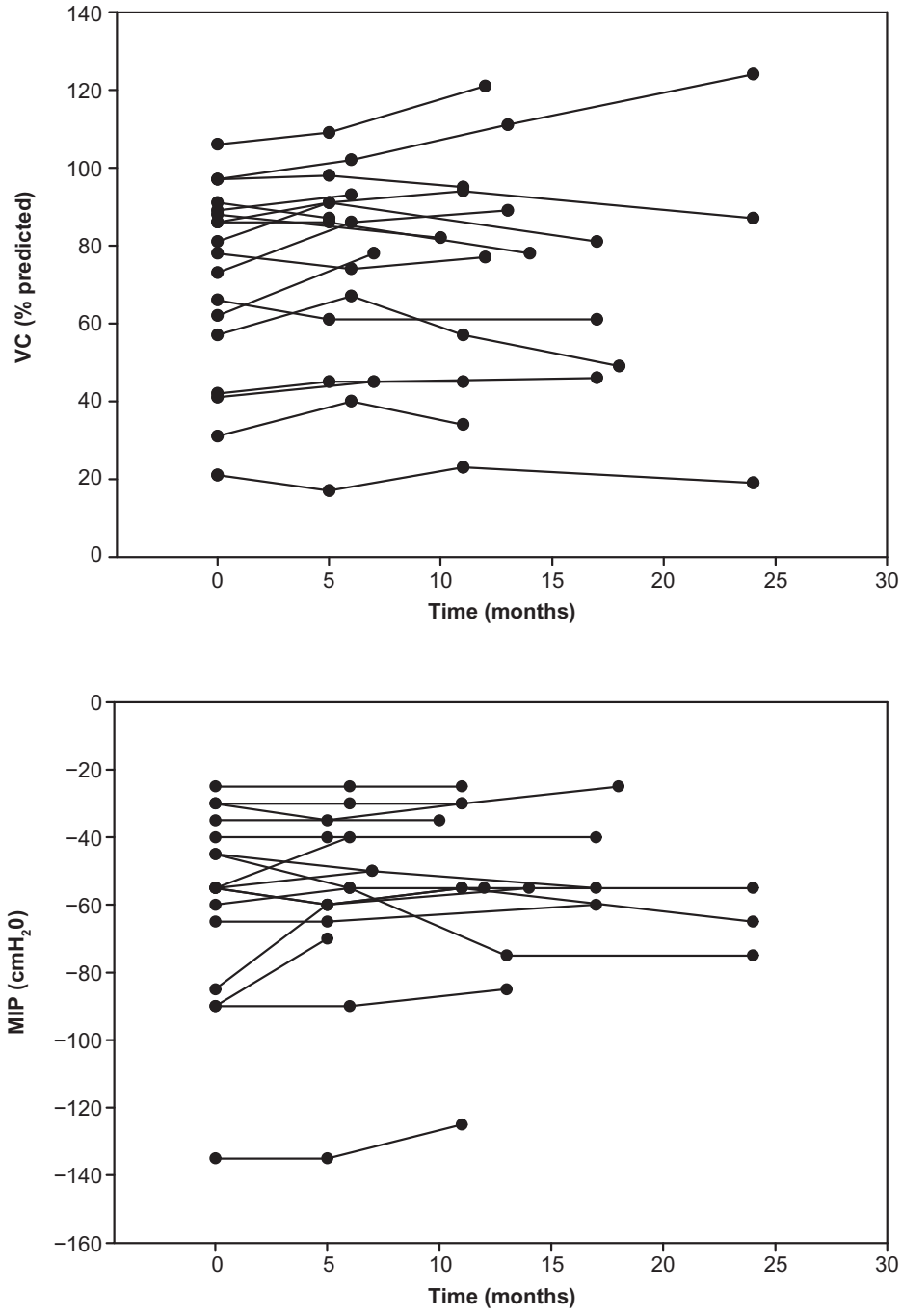

Fig. 1. Evolution of VC and MIP in the study cohort. Longitudinal data available and shown for 18 of 22 patients. VC, vital capacity; MIP, maximum inspiratory pressure.

relationship was observed between reductions in VC and MEP ($r^2 = 0.47$, $p < 0.001$). In 9 patients (41%), however, despite a reduction in MEP, VC remained in the normal range (>80% predicted). The patients receiving ventilatory support (open symbols) tended to have the most severely reduced % predicted MEP values.

3.3. Mechanism of respiratory failure in LOPD

Respiratory failure did not develop in any patient during the study, in accord with the stability of lung function demonstrated above; therefore, the mechanism for development of respiratory failure was evaluated from cross-sectional data, which integrates assessment of respiratory control and dead space to traditional clinical assessment of VC and MIP.

The relationship of arterial PCO_2 ($PaCO_2$) to VC and MIP are shown in Fig. 4. Daytime hypercapnia ($PaCO_2 > 50$ mmHg) was related to a reduction in both VC and MIP. The data were nonlinear, and hypercapnia was present only when VC and MIP were below thresholds of 60% and 40% predicted, respectively. In 2 patients, however, normal values for $PaCO_2$ were noted despite respiratory dysfunction below these thresholds, which

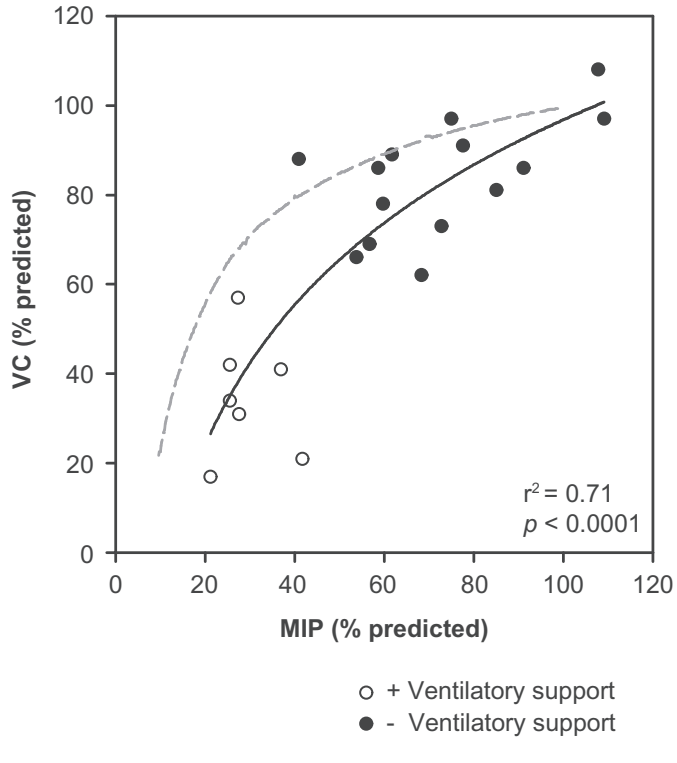

Fig. 2. Relationships between lung volume (VC and IC) and MIP. Dashed line indicates the predicted relationship assuming normal lung and chest wall mechanics. IC, inspiratory capacity; MIP, maximum inspiratory pressure; VC, vital capacity.

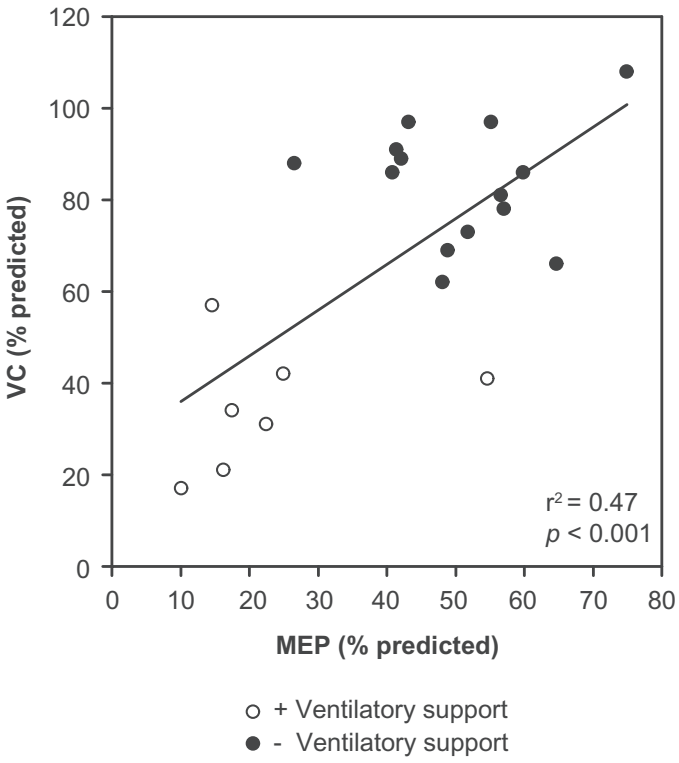

Fig. 3. Relationship between VC and MEP. A linear relationship between reductions in VC and MEP is shown. MEP, maximum expiratory pressure; VC, vital capacity.

likely reflects normalization of $PaCO_2$ after initiation of mechanical ventilatory support.

Fig. 5 illustrates the relationships of $PaCO_2$ to respiratory pattern and efficiency of CO_2 clearance. Data are illustrated for the 17 patients that successfully completed the assessments. The top panel illustrates the relationship between $PaCO_2$ and V_T. Variability of V_T was noted across patients, ranging from normal values >400–500 ml to values as low as ≈300 ml. A reduction in V_T was observed in 5 of the 6 patients with chronic hypercapnia ($PaCO_2 > 50$ mmHg) who required ventilatory support (open circles). The bottom panel illustrates the relationship between $PaCO_2$ and the dead space fraction (V_D/V_T). The V_D/V_T varied from normal values (<0.3) to markedly elevated values of >0.40. Normal $PaCO_2$ values of 35–40 mmHg were associated with normal V_D/V_T, while chronic hypercapnia was associated with elevated V_D/V_T, compatible with reduced efficiency of CO_2 clearance. The data are consistent with increased V_D/V_T due to falling V_T.

The relationship of $PaCO_2$ to ventilatory CO_2 responsiveness is shown in Fig. 6. Data are illustrated for the 20 patients that completed the assessment. The ventilatory response to CO_2 varied from normal in 8 patients (≥1.5 l/min/mmHg) to significant reductions in 10 patients (≤0.7 l/min/mmHg). The presence of hypercapnia and/or ventilatory support was associated with a reduced ventilatory responsiveness to CO_2. Two patients demonstrated reduced CO_2 responsiveness despite normal $PaCO_2$ below 40 mmHg.

4. Discussion

We evaluated the relationships between measures of pulmonary function, respiratory muscle strength, gas exchange, and respiratory control to identify determinants of disease progression from respiratory dysfunction to failure in LOPD patients. Since the study was designed to evaluate the natural history of Pompe disease, data were analyzed from patients that

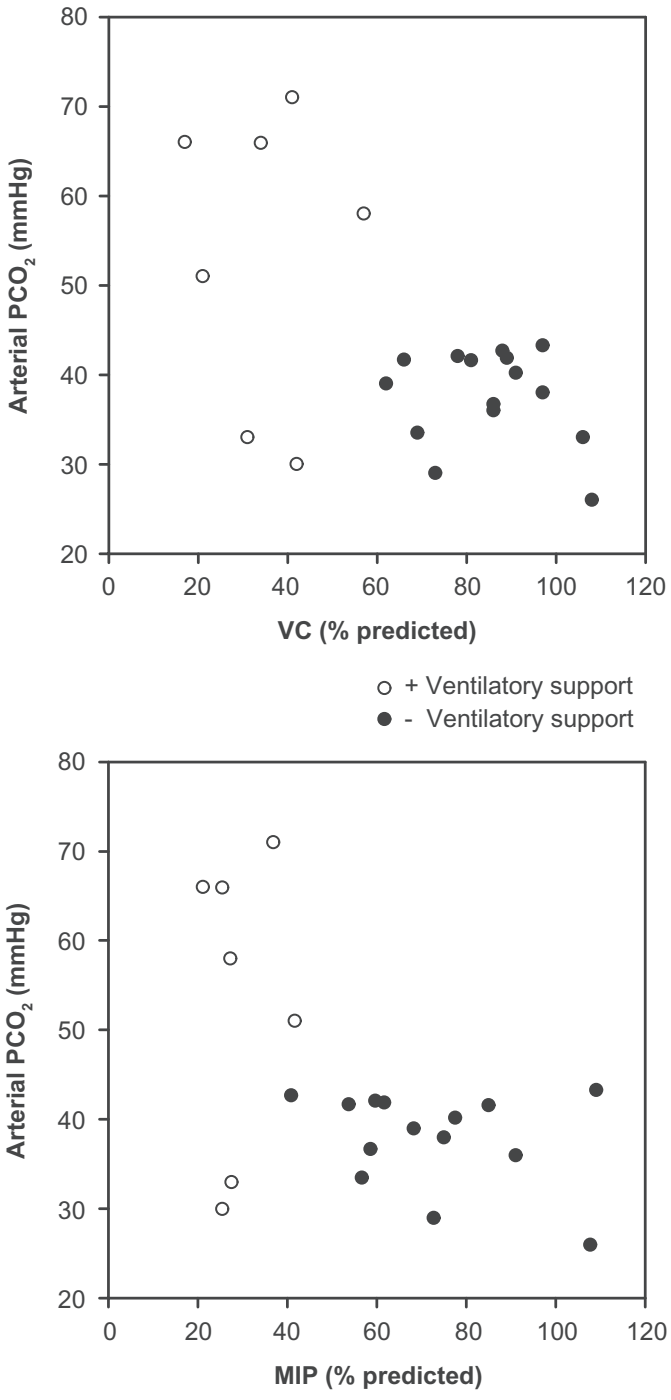

Fig. 4. Relationship of arterial PCO_2 to VC (left) and MIP (right). MIP, maximum inspiratory pressure; PCO_2, partial pressure of carbon dioxide.

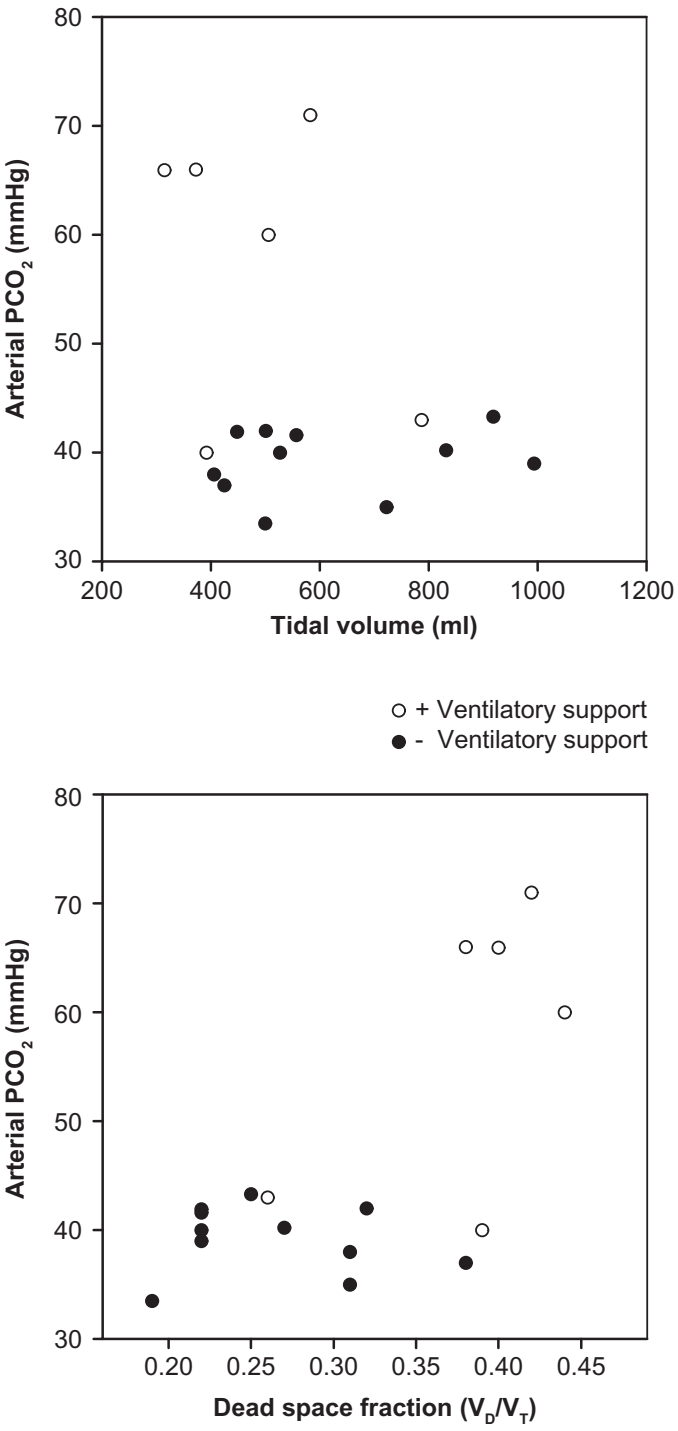

Fig. 5. Relationship of arterial PCO_2 to tidal volume (left) and dead space fraction (right). V_D, dead space volume; V_T, tidal volume; PCO_2, partial pressure of carbon dioxide.

were studied prior to approval of enzyme replacement therapy. Our results demonstrate that reduced CO_2 clearance efficiency as well as reduced ventilatory responsiveness may underlie the development of chronic daytime hypercapnia (ie, respiratory failure). The data also support the use of direct measures of respiratory muscle strength (eg, MIP) in combination with indirect measures (eg, VC) for the timely diagnosis of respiratory insufficiency in LOPD.

4.1. *Identification of respiratory insufficiency*

Prior studies show that respiratory insufficiency in neuromuscular diseases including LOPD manifests as a restrictive pattern on spirometry testing, primarily a decrease in VC [3,23–26]. A fall in VC in the supine position (compared with upright) is used as an indirect indicator of the role of

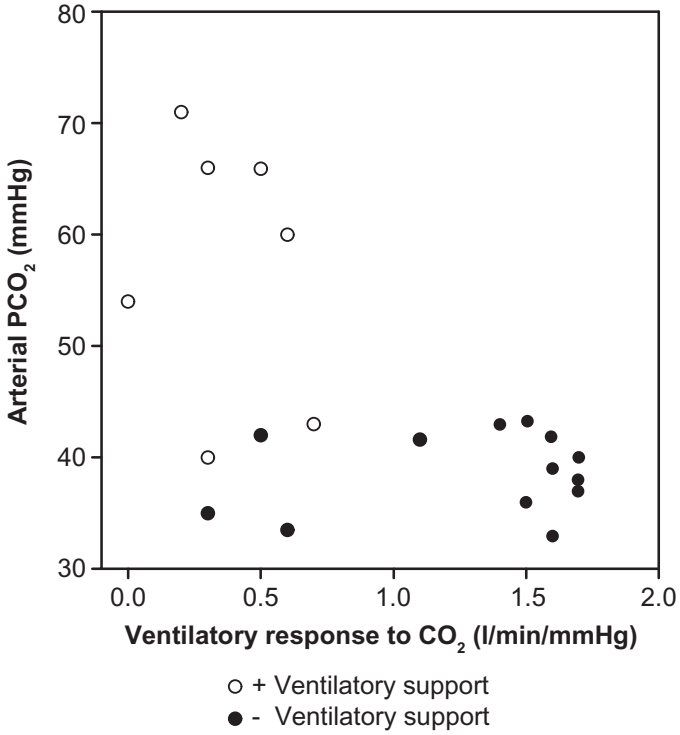

Fig. 6. Relationship of arterial PCO_2 to ventilatory CO_2 responsiveness. PCO_2, partial pressure of carbon dioxide.

diaphragm weakness [26–31]. Weakness of inspiratory as well as expiratory muscles has been confirmed with direct measurement of respiratory muscle output (MIP and MEP) [3,32]. Abnormal structure of the inspiratory and expiratory muscles was recently illustrated in patients with LOPD using computed tomography and magnetic resonance imaging techniques [5,33].

The present study confirms and augments these observations by demonstrating a nonlinear relationship between MIP and VC. A plateau of VC was noted in patients with mild respiratory dysfunction (ie, normal to mild reduction in MIP). This finding has implications for diagnosis of mild respiratory muscle weakness, as reduction in MIP likely precedes the fall of VC into the abnormal range. A role for the measurement of VC in the supine position, as an early marker of respiratory dysfunction, was not addressed in this study, but was demonstrated by van der Beek and colleagues [3].

The present study extends previous reports by demonstrating that the volume generated for any given degree of inspiratory muscle function is lower than predicted, which implies alteration in mechanical properties of either the lung or chest wall. For example, lung compliance may fall in LOPD due to development of microatelectasis, a common finding in patients with neuromuscular disease [34], or due to remodeling in lung parenchyma. Although the latter possibility seems unlikely, there are limited pulmonary histologic data in Pompe disease, and parenchymal changes have been suggested in other neuromuscular disorders [34]. Also, recent postmortem studies in LOPD patients demonstrated pulmonary fibrosis, veno-occlusive disease, and glycogen deposition in vascular smooth muscle [35,36]. Alternatively, chest wall mechanics can be altered by the presence of kyphoscoliosis, a frequent finding in patients with trunk weakness [37]. In either case, the degree of respiratory restriction in an individual may not be reliably predicted by measurement of respiratory muscle strength alone; this discrepancy would be further enhanced in a given patient if additional respiratory disease was present.

4.2. Longitudinal assessment of lung function

Few studies have published longitudinal data with respect to the natural history of respiratory function in untreated individual patients with LOPD. Although progressive decline would be expected in patients with a progressive neuromuscular disease, data obtained in the control group in the phase 3 trial of alglucosidase alfa suggest that lung function may have been stable in individual subjects. Specifically, while the mean change in VC was a 2.2% decline over 1.5 years, the confidence interval extended close to zero, consistent with stability of lung function in some subjects. Data in individual patients published by Pellegrini et al. [38] demonstrated stability or improvement in lung function in selected patients over time periods ranging up to 15 years. In accord with these findings, the present study demonstrated that the evolution of lung function was highly variable, with the majority of subjects demonstrating either stability or improvement in lung function during a time period ranging up to 2 years. Of note, evaluation of the subgroup that demonstrated an increase in VC >5%, showed no evidence for improved diaphragm strength since MIP and IC remained stable. These data imply improvement in either expiratory muscle function or improved technique of performing the testing maneuver. The above considerations are particularly of interest as new therapies for Pompe disease are being developed and clinical trials are likely in the near future.

4.3. Development of respiratory failure

The present study adds to our understanding of the mechanism of hypercapnia in patients with LOPD. Prior studies have focused on the role for respiratory muscle weakness and sleep-disordered breathing [6,39]. In general, hypercapnia develops when VC falls below ≈40% predicted [7,15,16]. However, while it is tempting to attribute the hypercapnia to this abnormality, hypercapnic patients in the present study demonstrated variable ventilatory reserve as assessed by the relationship between VC and the resting tidal volume. On average, the measured VC in these patients was 885 ml greater than their tidal volume and varied from low to high values (range 387–1744 ml). When ventilatory reserve is low, a rapid shallow breathing pattern would develop with consequent hypercapnia. The observed increase in dead space fraction for each breath (V_D/V_T) would further compromise alveolar ventilation and contribute to the development of respiratory failure. However, the reason for hypercapnia in patients with larger ventilatory reserve is unclear; chest radiographs did not reveal chest wall disease or diffuse parenchymal changes, indicating that these patients should have been able generate a larger tidal volume. We suggest therefore that development of

hypercapnia in patients with large ventilatory reserve may involve mechanisms related to the presence of sleep-disordered breathing and blunted ventilatory responsiveness.

Prior studies in patients with neuromuscular disease have indicated that nocturnal hypoventilation develops at VC levels similar to those noted with onset of daytime hypercapnia (≈40% predicted) [7,14,15,40,41]. This observation suggests that the acute hypercapnia that develops during sleep hypoventilation episodes is linked to the maintenance of chronic daytime hypercapnia. However, those studies do not address the mechanisms that underlie the perpetuation of the hypercapnic state throughout wakefulness when ventilation would presumably return to the baseline level. Maintenance of blood PCO_2 in the normal range in the presence of episodic hypoventilation requires a compensatory increase in ventilation upon awakening [42,43]. In fact, in amyotrophic lateral sclerosis the earliest manifestation of respiratory failure has been documented as a normal PCO_2 during wakefulness but with an elevated serum bicarbonate concentration. In these patients, CO_2 and bicarbonate retention likely occur during sleep, but there is adequate ventilatory compensation during wakefulness [23]. In patients with more severe limitation, the ventilatory reserve may be insufficient to accommodate the hyperventilation required to return daytime PCO_2 to the normal range. In addition, the observed reduction in ventilatory responsiveness in hypercapnic patients would further impair the compensatory hyperventilation despite the presence of adequate ventilatory reserve.

The mechanism for impairment of ventilatory control in LOPD is of interest. Reduction in respiratory muscle strength could explain blunting of respiratory responsiveness. In accord with this consideration, the subjects with the greatest degree of respiratory muscle weakness in the present study all demonstrated reduced ventilatory responsiveness. Of particular interest was demonstration of reduced ventilatory response in 2 additional patients that were not receiving ventilatory support and who demonstrated normal arterial PCO_2 values. Since these individuals had either normal or near normal MIP, MEP, and VC, respiratory muscle weakness was not the likely mechanism for the observed reduction in ventilatory response. One potential explanation may relate to accumulation of glycogen in the spinal cord and brain tissue, which has been shown both in patients with Pompe disease [44] and in a mouse model of Pompe disease [45]. Specific functional assessment of these mice demonstrated blunting of CO_2 response that was not attributable to diaphragm weakness and, therefore, was suggestive of a central control abnormality. The present study design could not distinguish a contribution of central control abnormalities to the development of chronic respiratory failure in LOPD. This mechanism may be relevant to an ongoing clinical trial investigating the utility of diaphragmatic pacing in LOPD [46].

In summary, the present study confirms prior observations that the development of daytime hypercapnia in patients with LOPD is tightly linked to both the degree of respiratory muscle weakness and the resulting severity of pulmonary dysfunction. Our results extend prior observations by demonstrating that hypercapnia is also linked to inefficiency in CO_2 clearance from either reduced ventilatory reserve or the inability to compensate for sleep-disordered breathing. Finally, an abnormality in respiratory control, identified in a subset of patients, may contribute to the development of chronic daytime hypercapnia. These observations suggest that development of hypercapnia may not be related to the muscle dysfunction per se, but may reflect inadequate compensatory hyperventilation in response to stressors of respiratory function (eg, exercise, sleep-disordered breathing, and infection).

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