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RESPIRATORY PHYSIOLOGY

Cough Effectiveness and Pulmonary Hygiene Practices in Patients with Pompe Disease

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Abstract

Purpose While factors leading to hypoventilation have been well studied in Pompe disease, cough effectiveness and airway clearance practices are less understood. We aimed to identify significant factors that influence peak cough flow (PCF) in Pompe, and to detect whether pulmonary hygiene practices were reflective of reduced PCF.

Methods This is a prospective observational study of 20 subjects with Pompe disease (infantile-onset: 7, juvenile-onset: 6, adult-onset: 14). Subjects performed spirometry, maximal respiratory pressures, and cough (voluntary: $n=24$, spontaneous: $n=3$). Subjects or their parents reported airway clearance and secretion management practices. Relationships between disease variables, pulmonary function, and cough parameters as well as group differences in cough parameters were evaluated.

Results Subjects with infantile-onset disease had significantly lower PCF ($p<0.05$) and tended to require more external ventilatory support ($p=0.07$). In juvenile- and adult-onset disease, PCF differed according to external ventilatory requirement [daytime: 83.6 L/min (95% CI 41.2–126.0); nighttime: 224.6 L/min (95% CI 139.1–310.2); none: 340.2 L/min (95% CI 193.3–487.6), $p<0.005$]. Cough inspiratory volume also differed significantly by ventilatory requirement [daytime: 5.5 mL/kg (95% CI 3.0–8.0); nighttime: 16.0 mL/kg (95% CI 11.8–20.2); none: 26.8 mL/kg (95% CI 11.9–41.7), $p<0.001$]. However, routine airway clearance or secretion management practices were only consistently reported among patients with infantile-onset disease (infantile: 86%, juvenile: 0%, adult: 14%, $p<0.005$).

Conclusions Cough weakness was detected in the majority of patients with Pompe disease and was influenced by both inspiratory and expiratory muscle function. Patients at risk for problems or with ineffective PCF should be urged to complete routine pulmonary hygiene.

Keywords Cough · Pulmonary hygiene · Pompe disease · Respiratory muscles

Abbreviations

FVC	Forced vital capacity
GAA	Acid alpha-glucosidase
IQR	Interquartile range
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
MV	Mechanical ventilation
PCF	Peak cough flow

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Introduction

Pompe disease is an inherited neuromuscular disease caused by mutations in the gene encoding acid alpha-glucosidase (GAA). Deficiency of GAA impairs the disassembly of lysosomal glycogen, and subsequently leads to glycogen accumulation in the internal organs, muscle, and neural tissues. The Pompe phenotype corresponds to residual GAA activity and can range from a rapidly progressive, severe infantile form to a later-onset, milder phenotype in which symptoms progress over years to decades [1, 2]. Across the phenotypic continuum, Pompe is characterized by respiratory weakness

that leads to sleep disordered breathing, ineffective airway clearance, and progressive ventilatory insufficiency [3]. The consequences are costly, and respiratory problems are the primary contributor to morbidity and mortality [4].

While effects of respiratory muscle weakness on hypoventilation are well documented for Pompe disease [5], impacts on airway clearance dysfunction and pulmonary hygiene practices are less clear. Clinically, the adequacy of a cough can be evaluated in a rapid, non-invasive manner by measuring peak airflows generated during the cough (PCF). In adults with other neuromuscular conditions, PCF values below ~ 160 L/min predicted an inability to extubate or decannulate [6, 7]. Additionally, a voluntary PCF between 160 and 270 L/min was associated with elevated risk for ineffective cough during respiratory illness [8]. These threshold values have been recommended as the basis for prescribing cough assistance therapies in Pompe disease [3].

Prior studies reported impaired cough strength in some patients with Pompe disease [9]. However, detailed evaluation of the relationships between the strength and timing of voluntary cough has not been completed. Further, it is not known whether the actual pulmonary hygiene practices of patients with Pompe disease correspond to published airway clearance guidelines [3]. Therefore, the purposes of this study were to evaluate factors that influence PCF in Pompe disease and to identify whether the proposed threshold PCF values corresponded to the airway clearance practices of the sample.

Materials and Methods

Subjects

Cough was evaluated in participants of two observational research studies of individuals with Pompe disease. The University of Florida Institutional Review Board reviewed and approved the study procedures (IRB #2016-0161, #2017-0087), which met standards set forth in the Helsinki Declaration. Individuals diagnosed with Pompe disease by genetic testing or enzyme activity assays were eligible to participate. Inclusion criteria included the ability to sit with support and the ability to breathe spontaneously without assisted ventilation for at least 1 min. Subjects or their designated guardians provided written informed consent, and school-aged children assented to participate.

Exclusionary criteria included (1) diagnosis of other neurological disorders (e.g., Parkinson's disease, stroke), (2) current or recent (≤ 30 days) respiratory infection, (3) current or recent (≤ 14 days) use of corticosteroid or antibiotic medications, (4) pregnancy, (5) recent surgery (≤ 30 days), or (6) uncontrolled hypertension.

Test Procedures

Tests included clinical pulmonary function tests (PFTs: spirometry, maximal respiratory pressures) and voluntary ($n = 24$) or spontaneous ($n = 3$) cough recordings. Test procedures were completed in a quiet clinic room with the participant seated upright with the back supported. When a tracheostomy was present, tests were completed via the tracheostomy tube with cuff inflated. For cuffless tracheostomies, subjects closed their mouth and wore a nose clip to minimize leaks through the upper airway.

Spirometry

Upright forced vital capacity (FVC) tests were conducted in accordance with ATS/ERS guidelines [10], using a filtered adaptor connected to a spirometer (KoKo, NSpire). After three to five tidal breaths, subjects inhaled to total lung capacity, followed by a sustained maximal forced exhalation to residual volume. Subjects received encouragement to provide a maximal effort. FVC tests were repeated until three efforts within 5% were obtained, and the best effort was reported.

Maximal Respiratory Pressures

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were tested with a filtered adaptor according to recommended guidelines [11]. Subjects used a digital manometer (Micro RPM, Care Fusion) placed in series with a disposable mouthpiece and filter. MIP was a 3-s, maximal static inspiratory contraction from residual volume. MEP was a 3-s, maximal static expiratory contraction from total lung capacity, with the oral muscles stabilized by the tester. Measurements were repeated three to five times with 20–30 s between attempts, to achieve three trials with < 5% variation. Of these, the best effort was recorded.

Voluntary Cough

Most participants completed 3–5 voluntary cough tests using a facemask. In tracheostomized participants, cough test equipment was connected directly to the tracheostomy tube. After ~ 4–6 tidal breaths, participants were instructed to take a deep breath and cough as forcefully as possible, "as if something went down the wrong pipe." Three participants were not old enough to follow instructions for voluntary cough. However, during sustained recordings of unassisted tidal breathing, each generated at least three technically

acceptable spontaneous coughs in an attempt to expel mucus from the airway.

Cough data were collected using a heated pneumotachograph (HR 3500B, 3700B, or 3813 Hans Rudolph, Shawnee, KS). The differential pressure signal from the pneumotachograph was transmitted to a digital spirometer and data acquisition system (S30-16, ADInstruments, Boston, MA) and recorded with a laptop computer. Data were sampled at 1 kHz and low-pass filtered at 40 Hz.

Pulmonary Hygiene Practices

Patients or their caretakers were interviewed to determine the type and frequency of pulmonary hygiene practices they employed. Cough augmentation included techniques to enhance a subject's cough force, such as manually assisted exhalation/cough, assisted insufflation (volitional or assisted), or the use of mechanical insufflation–exsufflation devices [12]. Secretion removal incorporated techniques to loosen and remove mucus from the airways such as manual chest physiotherapy, postural drainage, high-frequency chest wall oscillation, intrapulmonary ventilation, and suctioning [12]. Participants rated the frequency of each practice as routine (three or more days per week), occasional (only as needed and not more often than twice weekly), or not used.

Data Analysis

Cough data were analyzed off-line using Lab Chart Pro v7.2 (ADInstruments, Colorado Springs). The following cough parameters were measured: inspiratory phase peak flow, inspiratory phase duration, cough inspiratory volume, compression time, peak cough flow (PCF) (i.e., expiratory phase peak flow), expiratory phase rise time, cough volume acceleration (defined as PCF/expiratory phase rise time), cough expiratory volume, expiratory phase duration, and the number of cough expiratory efforts per cough epoch (Fig. 1). Each parameter was averaged from the subject's three best efforts.

Subjects were classified according to their clinical presentation (infantile-, juvenile-, or adult-onset) [2, 13], requirement for assisted ventilation [no support, nighttime support (invasive or non-invasive), or daytime support (invasive or non-invasive)], and cough effectiveness according to neuromuscular guidelines for adults (normal: > 270 L/min, at risk: 160–270 L/min, ineffective: < 160 L/min).

The distribution of the demographic data was tested, and group differences were analyzed with parametric or non-parametric ANOVA. Relationships between disease variables, pulmonary function, and cough parameters were evaluated with Pearson's correlation. Statistical analysis was completed with SPSS v24.0, using a significance threshold of $p < 0.05$. For non-normal distributions, median (interquartile range, IQR) is reported; otherwise means ± standard deviations (SD) or 95% confidence intervals are reported.

Results

Effect of Age on Cough

PCF was obtained from 27 patients (infantile-onset: $n = 7$, juvenile-onset: $n = 6$, adult-onset: $n = 14$), ranging in age from 1 to 70 years (Table 1). Subjects with the infantile phenotype tended to use ventilatory support for a greater proportion of the day [median (IQR) infantile: 24 (8–24)

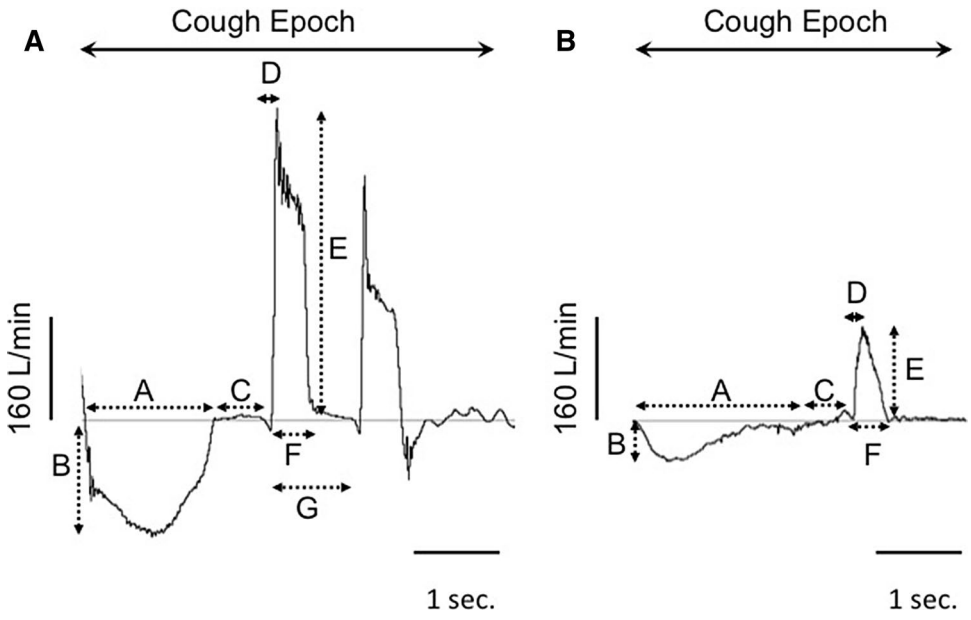

Fig. 1 The examples illustrate differences in cough magnitude in **a** a juvenile-onset patient with normal peak cough flow (patient 2) and in **b** an adult-onset patient with marginal peak cough flow who uses daytime non-invasive ventilation (patient 18). A cough epoch consists of a cough inspiration followed by the associated expulsive efforts, and it includes (A) cough inspiratory volume/duration, (B) inspiratory phase peak flow, (C) compression phase duration, (D) expiratory phase rise time, (E) peak cough flow, (F) cough expiratory volume/duration, and (G) total expiratory duration

Table 1 Demographics and clinical outcomes

Subject	Age (years)	Age Dx (years)	Ventilator status	Predicted FVC (%)	MIP (cm H_2O)	MEP (cm H_2O)	Cough PEF (L/min)	Airway clearance	Secretion management
6	1	0.25	MV	UA	−54	UA	49	ROU	ROU
11	2	0.40	NO	UA	−76	52	75	NO	OCC
10	3	0.30	NIV-N	UA	−54	30	49	ROU	ROU
7	4	0.25	MV	41	−49	32	41	OCC	ROU
4	6	0	NIV-D	UA	−10	11	101	ROU	NO
17	9	3	MV	UA	−12	24	29	ROU	ROU
26	9	1	MV	UA	−5	8	11	ROU	ROU
1	14	10	NO	87	−62	72	404	NO	NO
13	15	14	NO	74	−78	83	211	NO	NO
2	18	14	NO	86	−50	58	336	NO	NO
16	24	18	NIV-D	15	−29	24	111	OCC	NO
9	25	25	NIV-N	23	−30	30	117	NO	NO
23	26	12	NIV-D	11	−7	8	36	OCC	OCC
24	29	28	NO	145	−156	115	410	NO	NO
22	32	32	NO	96	−66	79	178	NO	NO
3	35	32	NIV-N	60	−52	47	185	NO	NO
5	42	41	NIV-N	79	−52	65	318	NO	NO
18	44	24	NIV-D	15	−22	20	95	NO	NO
8	46	40	NIV-N	89	−50	62	233	OCC	NO
12	49	35	NIV-D	10	−13	8	38	ROU	NO
14	54	50	NIV-N	19	−36	55	117	NO	NO
25	56	47	MV	21	−39	17	83	OCC	NO
15	60	59	NIV-N	51	−56	60	312	NO	NO
21	62	20	NIV-N	24	−32	38	172	NO	NO
19	63	28	NIV-N	22	−12	19	138	OCC	NO
20	63	45	NIV-N	53	−58	70	439	NO	NO
27	72	49	MV	31	−53	28	128	NO	ROU

Dx diagnosis, *FVC* forced vital capacity, *MIP* maximum inspiratory pressure, *MEP* maximum expiratory pressure, *PEF* peak expiratory flow, *NIV-N* non-invasive ventilation night, *NIV-D* non-invasive ventilation day, *MV* mechanical ventilation via tracheostomy, *UA* unavailable, *ROU* routine, *OCC* occasional

h, juvenile: 4 (0–13) h, adult: 9 (8–12.75) h, Kruskal–Wallis, $p = 0.07$], and they were more likely to be tracheostomized (infantile: 57%, juvenile: 0%, adult: 8%, Chi square, $p < 0.05$). Due to their smaller stature and more severe clinical presentation, PCF was significantly lower for infantile-onset subjects (50.8 ± 29.7 L/min, juvenile-onset: 202.7 ± 142.7 L/min, adult-onset: 209.1 ± 126.1 L/min, ANOVA, $p < 0.05$). In contrast, pulmonary function and PCF were not different between juvenile- and adult-onset patients. Further, cough assistance or secretion management was more frequently used in infantile patients (infantile: 86% routine, 14% occasional; juvenile: 0% routine, 33% occasional; adult: 14% routine, 29% occasional; Chi square, $p < 0.005$). Subsequent analyses focused on the juvenile- and adult-onset groups.

Among juvenile- and adult-onset patients, linear relationships between PCF and pulmonary function testing outcomes were strongly significant (Table 2). PCF had strong positive correlations with inspiratory volume ($r = 0.72$) and expiratory volume ($r = 0.71$), as well as moderate positive correlations with peak inspiratory flow ($r = 0.66$) and inspiratory time ($r = 0.65$).

Effect of Ventilatory Assistance on Cough

Among juvenile and adult-onset subjects, one newly diagnosed patient was excluded, pending pulmonary and sleep medicine consults. For the remaining subjects, we detected differences in cough, based upon their requirement for external ventilation (Fig. 2). PCF was significantly reduced in subjects who required daytime ventilatory support (83.6 L/min, 95% CI 41.2–126.0 L/min), compared to those who used support at nighttime (224.6, 95% CI 139.1–310.2 L/min) or not at all (340.4, 95% CI 193.3–487.6; $F = 9.946$,

Table 2 Relationships between cough peak flow and pulmonary function tests

	Peak cough flow (L/min)	Age (years)	Predicted FVC (%)	Predicted FEV1 (%)	MIP (cm H_2O)	MEP (cm H_2O)
Peak cough flow (L/min)		−0.159 ($p=0.5$)	0.768** ($p<0.001$)	0.841** ($p<0.001$)	−0.753** ($p<0.001$)	0.790** ($p<0.001$)
Age (years)	−0.159 ($p=0.5$)		−0.387 ($p=0.1$)	−0.305 ($p=0.2$)	0.377 ($p=0.1$)	0.234 ($p=0.3$)
Predicted FVC (%)	0.768** ($p<0.001$)	−0.387 ($p=0.102$)		0.969** ($p<0.001$)	−0.901** ($p<0.001$)	0.894** ($p<0.001$)
Predicted FEV1 (%)	0.841** ($p<0.001$)	−0.305 ($p=0.2$)	0.969** ($p<0.001$)		−0.863** ($p<0.001$)	0.897** ($p<0.001$)
MIP (cm H_2O)	−0.753** ($p<0.001$)	0.377 ($p=0.1$)	−0.901** ($p<0.001$)	−0.863** ($p<0.001$)		−0.933** ($p<0.001$)
MEP (cm H_2O)	0.790** ($p<0.001$)	0.234 ($p=0.321$)	0.894** ($p<0.001$)	0.897** ($p<0.001$)	−0.933** ($p<0.001$)	

Dx diagnosis, *FVC* forced vital capacity, *FEV1* forced expiratory volume in first second, *MIP* maximum inspiratory pressure, *MEP* maximum expiratory pressure

$p<0.005$). Cough differences according to ventilatory requirements were most clearly observed in cough volume acceleration and cough inspiratory volume. Cough volume acceleration was significantly different between each ventilatory assistance group [none: 81.5 (95% CI 45.8–117.1) L/s/s; nighttime: 45.0 (22.3–67.7) L/s/s; daytime: 12.8 (5.8–19.8) L/s/s, $F=10.49$, $p<0.005$]. Cough inspiratory volume also differed significantly between each ventilatory requirement [none: 26.8 (95% CI 11.9–41.7) mL/kg; nighttime: 16.0 (11.8–20.2) mL/kg; daytime: 5.5 (3.0–8.0) mL/kg; $F=16.84$, $p<0.001$]. Cough expiratory volume was significantly different between independent breathing [26.4 (95% CI 9.8–42.9) mL/kg], and use of any support [nighttime: 12.6 (7.8–17.4) mL/kg; daytime: 5.2 (2.3–8.0) mL/kg; $F=12.83$, $p<0.001$]. In addition, patients who required daytime support had significantly reduced inspiratory phase peak flow, compared to independent breathers ($F=5.425$, $p<0.05$). While inspiratory phase duration was significantly shorter with daytime ventilatory assist ($F=5.275$, $p<0.05$), ventilatory requirements did not significantly impact other aspects of cough timing.

Pulmonary Hygiene Practices

Among the juvenile and adult-onset patients, nine had an ineffective cough (PCF < 160 L/min), five were at risk (PCF 160–270 L/min), and cough PCF was normal (PCF > 270 L/min) in six [3]. None of the patients with normal PCF utilized secretion management, and one-third used occasional airway clearance. In those at risk for cough problems, none used secretion management strategies, and airway clearance was occasional ($n=1$) or not practiced ($n=4$). While a majority of patients with ineffective cough used airway clearance (routine: $n=1$, occasional: $n=6$), two reported no use. Four patients with ineffective cough reported routine use of secretion management, one used it occasionally, and four denied using secretion management.

Discussion

Here we report new findings that PCF generated by a majority of the adolescent and adult Pompe disease sample was ineffective or associated with an increased risk for respiratory problems during illness [6, 8]. Effectiveness of the PCF in the sample differed based upon the requirement for ventilatory assistance. The requirement for ventilatory assistance also distinguished the inspiratory and expiratory volumes generated during the cough maneuver. The majority of patients with reduced PCF did not report routine use of cough assistance or secretion management. In addition, this study reports novel data of PCF in patients with infantile-onset Pompe disease and in tracheostomized patients.

Published considerations for managing respiratory muscle weakness in Pompe disease include annual monitoring of spirometry, maximal respiratory pressures, and PCF [3]. For stable patients whose best PCF is < 270 L/min on one occasion, airway clearance and secretion management techniques should be instructed for use as needed, while patients with ineffective cough should incorporate airway clearance and secretion management into their daily routine [3]. In this sample, the requirement for ventilatory support also distinguished cough efficacy. Despite some variability, patients who required nighttime support generated an average PCF that placed them at risk for airway clearance problems. Therefore, a positive sleep study or new prescription for nighttime ventilation may necessitate a PCF evaluation. Assisted airway clearance techniques can improve PCF [14], yet many adolescent and adult subjects with reduced PCF reported no pulmonary hygiene routine. We acknowledge

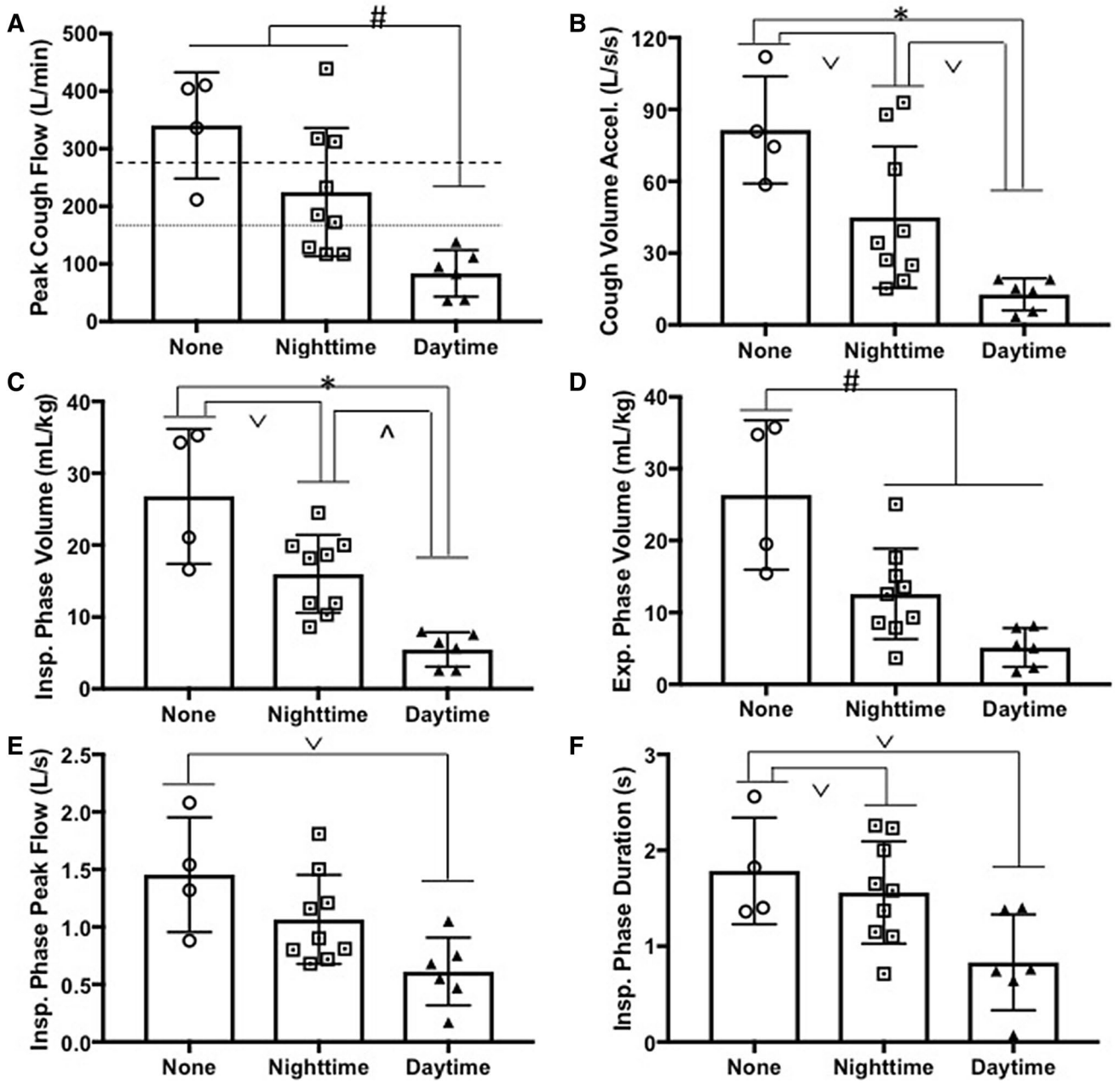

Fig. 2 Cough timing and magnitude in subjects with juvenile- and adult-onset Pompe disease who required no ventilatory support (open circles), support at nighttime or when sleeping (shaded squares), and those who required daytime ventilatory support (filled triangles). Peak cough flow (**a**) was significantly lower in subjects who required daytime support. The bottom line (160 L/min) represents the PCF associated with ineffective cough, while the top line (270 L/min) represents the level associated with risk for airway clearance problems during illness. Both cough volume acceleration (**b**) and cough inspiratory volume (**c**) differed significantly between each ventilator use group. Cough expiratory volume (**d**) was significantly greater in the independently breathing group than the groups who used any ventilatory support. **e** Peak inspiratory flow in the daytime ventilatory use group was significantly lower than those who did not use support. The only significant difference in cough timing was the inspiratory phase duration of independently breathing subjects (**f**), which was significantly longer than the groups who used support. $^{\vee}p<0.05$, $^{\wedge}p<0.01$, $^{\#}p<0.005$, $^{*}p<0.001$

that some patients may disregard the clinical recommendations and equipment distributed by their local providers. For example, some subjects reported owning an airway clearance device they did not use, because it was uncomfortable or required a large time commitment. However, when airway clearance devices and training are available to patients with neuromuscular disease, habitual use is a reasonable goal [15].

PCF and cough volume acceleration were significantly correlated with the magnitude of the inspiratory phase. During cough, inspiratory muscle contractions inflate the lungs toward inspiratory capacity. Larger inhaled volumes increase pulmonary elastic recoil and improve the length-tension of the expiratory muscles [16]. Cough inspiratory volume best differentiated patients according to their external ventilatory requirement. Early, preferential diaphragmatic paresis is a hallmark of Pompe disease [17, 18], and diaphragm dysfunction impacts PCF as well as ventilation [19]. Our results are consistent with previous reports that larger cough inspiratory volumes, whether through voluntary effort, air stacking, or assisted insufflation, generate significantly higher PCF [20, 21]. Although cough inspiratory and expiratory volumes differed according to respiratory muscle weakness and ventilator use, the timing of cough was stable until subjects required daytime support. This suggests that, while respiratory motor neuron loss occurs in Pompe disease [22], neural dysfunction did not alter coordination of the voluntary cough motor program until patients developed severe hypoventilation.

Technical Considerations

The sample included four children and two adults with a tracheostomy. PCF of the single tracheostomized adult who used nighttime support (subject 27) was below the published threshold for ineffective cough, along with two other non-invasively supported nighttime users. Glottic closure is not a requirement for cough, but its absence negatively impacts cough strength [23, 24] and decannulation or tracheostomy capping significantly increases PCF [25]. The sample of adults was too small to separately evaluate the effect of tracheostomy on cough timing and magnitude, but this issue warrants further study.

We report a lower PCF than some studies [26]. Patients with lower baseline function were eligible for the current study. Results may also have been affected by the use of the facemask. The chamber created by the facemask acts as a low-pass filter potentially reducing the peak expiratory flows, similar to a muffler on a car [27]. A facemask is preferred in patients with bulbar muscle involvement [28], and recent consensus guidelines recommend a facemask for PCF testing in neuromuscular disease [12].

While infantile-onset PCFs fell well below median age- and gender-matched reference values for children [29], subjects < 14 years of age were not included in the detailed cough analyses. Cough efficacy thresholds were largely derived in adults [6]. It appears that PCF < 160 L/min places children at risk for chest infections [30], but definitive efficacy thresholds are not validated in pediatric neuromuscular disorders [31]. We observed that, despite the severe phenotype of the infantile-onset patients, all could voluntarily or spontaneously initiate a cough. Three children were extremely young, and spontaneous coughing was incidentally recorded during monitoring of tidal breathing. Pressures generated during a spontaneous cough are less forceful than maximal voluntary efforts [32], which may also have influenced the PCF and corresponding volumes in the infantile sample. Therefore, we urge against generalizing these results to pediatric neuromuscular disease.

Conclusions

In this sample, the majority of patients with juvenile- and adult-onset Pompe disease had a PCF that placed them at risk for airway clearance problems, yet relatively few incorporated pulmonary hygiene into their daily routine. Since the inspiratory phase of cough and use of ventilatory support significantly impacted PCF, changes in inspiratory muscle function or ventilator use should trigger a comprehensive evaluation of cough effectiveness. Further study is needed to establish PCF values associated with risk for airway clearance problems in pediatric patients with Pompe disease.

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Compliance with Ethical Standards

Conflict of interest No conflicts exist for any of the authors.

References

1. Wens SC, Ciet P, Perez-Rovira A et al (2015) Lung MRI and impairment of diaphragmatic function in Pompe disease. BMC Pulm Med 15:54
2. American Association of Neuromuscular & Electrodiagnostic Medicine (2009) Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 40:149–160
3. Boentert M, Prigent H, Vardi K et al (2016) Practical recommendations for diagnosis and management of respiratory muscle weakness in late-onset Pompe disease. Int J Mol Sci 17
4. Gungor D, de Vries JM, Hop WC et al (2011) Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. Orphanet J Rare Dis 6:34
5. Schoser B, Fong E, Geberhiwot T et al (2017) Maximum inspiratory pressure as a clinically meaningful trial endpoint for neuromuscular diseases: a comprehensive review of the literature. Orphanet J Rare Dis 12:52
6. Bach JR, Saporito LR (1996) Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. Chest 110:1566–1571
7. Bach JR, Goncalves MR, Hamdani I, Winck JC (2010) Extubation of patients with neuromuscular weakness: a new management paradigm. Chest 137:1033–1039

8. Bach JR, Ishikawa Y, Kim H (1997) Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest 112:1024–1028
9. Jones HN, Crisp KD, Robey RR, Case LE, Kravitz RM, Kishnani PS (2015) Respiratory muscle training (RMT) in late-onset Pompe disease (LOPD): effects of training and detraining. Mol Genet Metab 117:120–128
10. Miller MR, Hankinson J, Brusasco V et al (2005) Standardisation of spirometry. Eur Respir J 26:319–338
11. European, Respiratory Society, American Thoracic Society (2002) ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med 166:518–624
12. Chatwin M, Toussaint M, Goncalves MR et al (2018) Airway clearance techniques in neuromuscular disorders: a state of the art review. Respir Med 136:98–110
13. Kroos M, Hoogeveen-Westerveld M, van der Ploeg A, Reuser AJ (2012) The genotype-phenotype correlation in Pompe disease. Am J Med Genet C 160:59–68
14. Morrow B, Zampoli M, van Aswegen H, Argent A (2013) Mechanical insufflation-exsufflation for people with neuromuscular disorders. Cochrane Database Syst Rev 2013:CD010044
15. Mahede T, Davis G, Rutkay A et al (2015) Use of mechanical airway clearance devices in the home by people with neuromuscular disorders: effects on health service use and lifestyle benefits. Orphanet J Rare Dis 10:54
16. Arora NS, Gal TJ (1981) Cough dynamics during progressive expiratory muscle weakness in healthy curarized subjects. J Appl Physiol 51:494–498
17. Prigent H, Orlikowski D, Laforet P et al (2012) Supine volume drop and diaphragmatic function in adults with Pompe disease. Eur Respir J 39:1545–1546
18. Smith BK, Corti M, Martin AD, Fuller DD, Byrne BJ (2016) Altered activation of the diaphragm in late-onset Pompe disease. Respir Physiol Neurobiol 222:11–15
19. LoMauro A, D'Angelo MG, Aliverti A (2015) Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. Ther Clin Risk Manage 11:1475–1488
20. Sarmento A, de Andrade AF, Lima IN, Aliverti A, de Freitas Fregonezi GA, Resqueti VR (2017) Air stacking: a detailed look into physiological acute effects on cough peak flow and chest wall volumes of healthy subjects. Respir Care 62:432–443
21. Trebbia G, Lacombe M, Fermanian C et al (2005) Cough determinants in patients with neuromuscular disease. Respir Physiol Neurobiol 146:291–300
22. Fuller DD, ElMallah MK, Smith BK et al (2013) The respiratory neuromuscular system in Pompe disease. Respir Physiol Neurobiol 189:241–249
23. McCool FD (2006) Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 129:48S–53S
24. Laghi F, Maddipati V, Schnell T, Langbein WE, Tobin MJ (2017) Determinants of cough effectiveness in patients with respiratory muscle weakness. Respir Physiol Neurobiol 240:17–25
25. McKim DA, Hendin A, LeBlanc C, King J, Brown CR, Woolnough A (2012) Tracheostomy decannulation and cough peak flows in patients with neuromuscular weakness. Am J Phys Med Rehabil 91:666–670
26. Gaeta M, Barca E, Ruggeri P et al (2013) Late-onset Pompe disease (LOPD): correlations between respiratory muscles CT and MRI features and pulmonary function. Mol Genet Metab 110:290–296
27. Yasuda T, Wu C, Nakagawa N, Nagamura K (2013) Studies on an automobile muffler with the acoustic characteristic of low-pass filter and Helmholtz resonator. Appl Acoust 74:49–57
28. Chatwin M, Ross E, Hart N, Nickol AH, Polkey MI, Simonds AK (2003) Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. Eur Respir J 21:502–508
29. Bianchi C, Baiardi P (2008) Cough peak flows: standard values for children and adolescents. Am J Phys Med Rehabil 87:461–467
30. Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U (2006) Predictors of severe chest infections in pediatric neuromuscular disorders. Neuromuscul Disord 16:325–328
31. Hull J, Aniapravan R, Chan E et al (2012) British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax 67(Suppl 1):i1–i40
32. Lee KK, Ward K, Rafferty GF, Moxham J, Birring SS (2015) The intensity of voluntary, induced, and spontaneous cough. Chest 148:1259–1267