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LETTER

PEDIATRIC PULMONOLOGY WILEY

Pilot study of nuclear scintigraphy to assess cough clearance in DMD

To the Editor,

Respiratory muscle weakness as a consequence of neuromuscular disease results in ineffective cough, atelectasis, and pneumonia. Augmented airway clearance treatments such as mechanical in exsufflation and high-frequency chest compression have been shown to decrease morbidity and mortality in children with neuromuscular disease, although the evidence supporting these therapies in the clearance of airway secretions is indirect.

We sought to explore the use of nuclear imaging of pulmonary secretions before and after voluntary coughing and airway clearance treatment to assess the role of pulmonary function tests to predict airway clearance. Pulmonary scintigraphy has been used for some time in patients with cystic fibrosis but has not been applied to patients with neuromuscular disease or to assess the utility of airway clearance devices. To this end, we recruited seven outpatient subjects (7.8–21 years of age) with Duchenne muscular dystrophy when clinically well and categorized as "early ambulatory" (requiring minimal assistive devices, $n = 4$); "early nonambulatory" (using wheelchair some of the time, $n = 2$); and "late nonambulatory" (always using a wheelchair, $n = 1$). This study was approved by the local Institutional Review Board (PRO11100704), registered with clinicaltrials.gov (NCT02034305), and funded by an unrestricted grant from Respirtech Inc.

Spirometry was performed according to ATS specifications and normalized using Global Lung Initiative equations. Peak cough flow (PCF) was measured from total lung capacity and data were normalized with previously published equations.[1] Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured at the mouth using a hand-held pressure manometer and maximal pressure from FRC was also be measured at the nares (SNIP) during a sniff maneuver[2] using a small nasal occluder and handheld transducer maximal static pressures[3] and SNIP pressures[4] were normalized using previously published data.

For imaging of mucus clearance, 4 mCi of Technetium [Tc-99m] sulfur-colloid particles in 2 ml of normal saline were delivered by nebulizer using a defined breathing pattern for 2 min.[5] During continuous imaging, subjects were asked to voluntarily cough every 10 s for 1 min using guidance from a metronome, and this sequence was repeated three times. The subject then received an airway clearance treatment for 30 min using a high-frequency chest compression device with pressure adjusted between 80% and 100% of device maximum, and compression frequencies gradually increased between 6 and 15 Hz over 2.5 min and then back to 6 Hz over 2.5 min, in a cyclical fashion. The device was paused every 10 min at which time the patient was asked to cough every 10 s over 1 min.

Image analysis was performed according to previously published methods.[6] Measurements of radioactivity in the right lung were corrected for background and radioactive decay and normalized by starting radioactive counts. A single retention curve was generated from the initial cough clearance (CC) period and the period during which the high-frequency chest compression device was operated. CC represents the percent of total deposited radioactivity cleared during the associated period. We designated the percentage cleared by 18 voluntary coughs over 18 min as CC_{vol}, and the percentage cleared during three 10-min periods of HFCC and 18 voluntary coughs over 40 min as CC_{HFCC}. CC_{vol} and CC_{HFCC} were correlated with physiologic measures including PCF, MIP/MEP, and SNIP using Spearman's correlation.

Pulmonary function was overall well-preserved (FVC 92 ± 35%). Respiratory muscle strength (in cmH_2O) decreased with disease severity (e.g., MIP EA 73.5 ± 26, ENA 62.5 ± 14.8, LNA 47). PCF (L/min) was relatively well preserved (EA 297 ± 56, ENA 286 ± 45, LNA 319) although three subjects had PCF below 270 L/min. Complete details are provided in the Supporting Information.

Representative imaging of two subjects is shown (Figure 1). Significant intrasubject differences were seen in clearance with voluntary cough and with cough augmented with HFCC vest (Figure 2). Voluntary cough was responsible for 46%–96% of the total clearance and HFCC-augmented clearance for 3%–53% of total clearance. For most patients, the kinetics of clearance with HFCC-augmented cough did not appear very different than for voluntary cough. No subjects expressed discomfort with the nebulization or imaging procedures or the HFCC treatment.

Statistical comparisons between disease stages were hampered by the small sample size in each group. Nonetheless, while there appeared to be a trend for decreasing CC_{vol} with the stage of disease (Figure 2), age, and PCF, we found no statistically significant correlations between voluntary CC and measures of pulmonary function, respiratory muscle strength, height, or weight (see Supporting Information). In addition, we did not find statistically significant correlations between

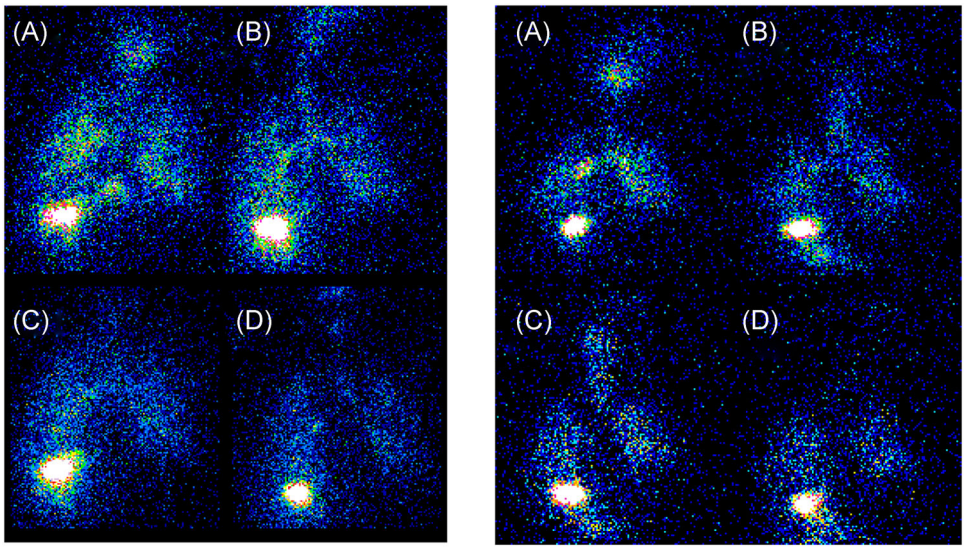

FIGURE 1 Left. Image montage from subject #4 (CC_{vol} 36%, CC_{HFCC} 5%). Right. Image montage from subject #8 (CC_{vol}: 0%, CC_{HFCC}: 25%). For both, (A) precoughing, (B) after 18 coughs in 18 min. (C) Before vest-augmented coughing. (D) After 30 min vest treatment and 18 coughs over 40 min. Images are posterior planar images depicting Tc-SC deposited in the lungs [Color figure can be viewed at wileyonlinelibrary.com]

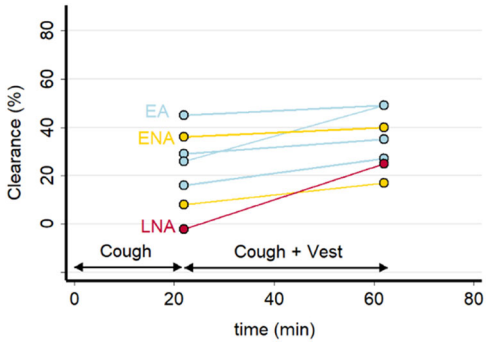

FIGURE 2 Clearance (%) of radiotracer in the lung after voluntary cough, and after a 30 min treatment with HFCC and intermittent voluntary coughing. [Color figure can be viewed at wileyonlinelibrary.com]

augmented CC and measures of pulmonary function, respiratory muscle strength, age, height, or weight.

This study is the first we are aware of to directly examine CC of secretions using nuclear scintigraphy in patients with DMD. Importantly, the measurements were well-tolerated by subjects. We did not find a relationship between CPF, respiratory muscle strength, spirometry, and voluntary CC. However, these results must be qualified based on the small number of enrolled subjects. We do note that many of the patients had good CC (23 + 11% after the spontaneous cough period). In addition, HFCC did not consistently alter the rate of secretion clearance above noted with voluntary cough.

While we were not able to demonstrate a relationship between CC and measures of respiratory muscle strength, PCF, or FVC, it is possible that this relationship exists and would be demonstrated in a larger population. The biggest limitation of our pilot study is the small sample size. We suspect enrollment was limited due to preference for interventional studies. Another limitation is that for our population, the impairment of respiratory muscle strength was mild for most subjects. Additional subjects with more advanced weakness may have helped clarify the relationship between respiratory muscle strength and airway clearance. Finally, there can be day-to-day variations of mucus clearance and subjects were studied on a single day.

There are now a number of airway clearance technologies being proposed for patients with neuromuscular and airway diseases (e.g., cystic fibrosis, ciliary dyskinesia). These include high-frequency chest compression vests, battery-powered vests, in exsufflation devices (with or without oscillation), intrapulmonary percussive ventilation devices, and handheld oscillating positive expiratory pressure devices. We propose that the imaging methodology used in this study could be utilized to compare these different techniques, some of which are costly and with limited or no comparison data. In addition, there are patients that will be unable to cooperate with pulmonary function measurements and an imaging assessment of airway clearance may be useful to determine optimal strategies.

In conclusion, we demonstrated that the use of nuclear scintigraphy is a feasible technique to examine airway clearance for patients with respiratory muscle weakness, as it has been used for patients with cystic fibrosis. Additional studies will be needed to further examine the relationship between pulmonary function measures and secretion removal.

AUTHOR CONTRIBUTIONS

Daniel J. Weiner: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Hoda Abdel-Hamid:** Conceptualization (supportive); data curation

(equal); formal analysis (supportive); investigation (supportive); methodology (supportive); project administration (supportive); writing – review and editing (supportive). **Timothy Corcoran:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.