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Case report

Effect of enterovirus D68 on Lung Clearance Index in patients with cystic fibrosis: A case report

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ABSTRACT

Cystic fibrosis (CF) causes airways obstruction and a decline in percent predicted forced expiratory volume in 1 s (FEV_1%). FEV_1% is an objective measure of a pulmonary exacerbation of CF; improvement in FEV_1% is the endpoint used often to determine success of treatment of these acute declines in pulmonary health. Lung Clearance Index (LCI), derived from multiple breath inert gas washout (MBW) test, measures ventilation inhomogeneity and small airways dysfunction. In the United States in 2014–2015, enterovirus D68 (EV-D68), a novel virus, led to hospitalizations in children because of respiratory distress. This report describes 2 patients with CF admitted for pulmonary exacerbations who were enrolled in an inpatient study to assess patient satisfaction and utility of MBW to measure LCI. Diagnostic testing indicated that these patients were infected with EV-D68. Although their FEV_1% improved to their previous baseline following treatment for pulmonary exacerbation, it was discordant with LCI. We discuss LCI as a novel measure of pulmonary function and hypothesize that, based on these cases, it may be a more sensitive indicator of ongoing post-viral airways dysfunction as compared to FEV_1%.

1. Introduction

Cystic fibrosis (CF) causes chronic, progressive airways obstruction. Acute worsening of disease is often accompanied by increased cough and sputum production, decreased exercise tolerance and increased obstruction. A decline in percent predicted forced expiratory volume in 1 s (FEV_1%) measured by standard spirometry is an objective measure of a pulmonary exacerbation of CF; improvement in FEV_1% is the endpoint used often to determine success of treatment of these acute declines in pulmonary health. Lung Clearance Index (LCI), derived from multiple breath inert gas washout test, measures ventilation inhomogeneity and small airway dysfunction. LCI is calculated as the number of lung volume turnovers needed to lower the end-tidal tracer gas concentration to $1/40^{th}$ of the starting concentration1. One of the benefits of LCI is that measurements are not dependent on age, height or gender, thus percent predicted values are not needed to normalize lung function to height growth in a disease such as CF that starts in childhood but progresses throughout life. A value above 6.8 to 7.41 indicates abnormal ventilation distribution [1]. LCI often, but does not always, inversely correlate, with FEV_1% or percent predicted forced expiratory flow in mid-range (FEF_{25-75}%) and it may be abnormal in young patients whose spirometry is still normal 2. LCI may be used to measure small airways dysfunction in children with cystic fibrosis (CF) who may have normal or minimally abnormal values using standard spirometry and LCI may correlate better with structural changes than does FEV_1% or FEF_{25-75}% [1,2]. The technique is easy to perform even for young children.

In the past decade, outbreaks of several novel respiratory viruses have been reported and new techniques for identifying viruses now enable us to define a cause of pediatric respiratory illness in up to 95% of cases [3]. During 2014–2015, many children in the United States developed acute, severe respiratory illness that was associated with a new strain of enterovirus (EV-D68). From mid-August 2014 to January 15, 2015, the Centers for Disease Control and Prevention or state public health laboratories confirmed a total of 1153 people in 49 states and the District of Columbia with respiratory illness caused by EV-D68; 14 patients who died and had samples submitted for testing were positive for EV-D68 [4]. Additionally, there were likely millions of mild EV-D68 infections for

Abbreviations: CF, Cystic Fibrosis; FEV_1%, Percent predicted forced expiratory volume in one second; LCI, Lung Clearance Index; MBW, Multiple breath inert gas washout; EV-D68, Enterovirus D68; FEF_{25-75}%, Percent predicted forced expiratory flow in mid-range; RT-PCR, Reverse transcription polymerase chain reaction.

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which people did not seek medical treatment and/or get tested. Almost all of the confirmed cases were among children, many whom had asthma or a history of wheezing, and the primary symptoms were those of lower respiratory tract disease with airways obstruction. Respiratory viral infections can be associated with long-term decreases in lung function [5]. However, appreciation of short-term effects of viral illness on pulmonary function may not be recognized using standard spirometry.

We report here the effect of EV-D68 on LCI in two patients with CF and near-normal spirometry at baseline who were admitted to the Women and Children's Hospital of Buffalo in 2014.

2. Materials and methods

The Institutional Review Board of the University at Buffalo, State University of New York had previously approved a study exploring patient satisfaction and utility of LCI compared to spirometry at the start and completion of inpatient treatment of pulmonary exacerbation of CF. The patients in this report provided assent and their guardians provided informed consent for that study.

Spirometry was performed using Medgraphics equipment. The technique met or exceeded American Thoracic Society criteria for reproducibility. Reference values are those recommended by the Cystic Fibrosis Foundation (Wang et al. method for females 6–15 years for Cases 1 and 2) [6].

Multiple breath washout was performed with the Exhalyzer-D (Eco Physics, Inc., Ann Arbor, MI). Using this open-circuit system, subjects breathe room air until baseline nitrogen (N_2) concentration is determined. Carbon dioxide (CO_2) is measured using a mainstream infrared analyzer and oxygen (O_2) is measured by side stream sampling to an internal laser O_2 analyzer. FN_2 (fraction of nitrogen) is then calculated using the following formula:

$$1 = FO_2 + FCO_2 + FN_2 + FAr$$

FAr (fraction of argon) is treated as a fixed proportion of FN_2 during the washout. During the washout phase the tracer gas is flushed from the lungs by having the subject inhale 100% oxygen while breathing normally. Respiratory flows and gas concentrations are measured breath-by-breath over time. The study ends when the first of three consecutive breaths falls below the set nitrogen target (1/40th of the starting concentration), followed by 5 additional breaths that fall below that target. LCI is calculated as the cumulative expired volume divided by the functional residual capacity. The Exhalyzer-D is calibrated each day and is synchronized on a weekly basis.

3. Results

3.1. Case 1

A 12 year old female with CF (F508del/F508del) had baseline FEV_1% predicted at or above 100. In October 2014 she complained of chest pain, increased productive cough and dyspnea, and was found to have a right middle lobe infiltrate; her FEV_1% predicted was decreased from baseline of 105 to 93. She was treated as an inpatient (17 days) with intravenous (IV) colistimethate, meropenem and linezolid to cover *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* and intensive airway clearance, including 7% hypertonic saline and rh-DNAse and chest vest 4 times per day, along with manual chest physiotherapy to the right middle lobe. She underwent flexible bronchoscopy which showed purulent secretions in the RML; these secretions grew EV-D68 by shell viral culture as well as moderate MRSA and few PA. Interestingly, her enteroviral RT-PCR from nasopharyngeal secretions at the beginning of the hospitalization was negative. The results of her spirometry and LCI are shown in the Table 1.

3.2. Case 2

A 15 year old female with CF (F508del/N1303K) had baseline FEV1% predicted of 80. In October 2014 she presented with cough and dyspnea with exercise; her FEV1% predicted had decreased from 80 to 73. She was treated as an inpatient for 10 days with IV levofloxacin, cefepime and oral minocycline to cover *Stenotrophomonas maltophilia* and *P. aeruginosa*, and intensive airway clearance, including 7% hypertonic saline and rh-DNAse, and chest vest 4 times per day. She was found to have enterovirus positive nasopharyngeal secretions by RT-PCR later confirmed as EV-D68. The results of her spirometry and LCI are shown in the Table.

4. Discussion

To our knowledge, this is the first report of EV-D68 infection and LCI in patients with CF before and after treatment for pulmonary exacerbation. During treatment for CF exacerbations, FEV_1% predicted improves in most patients [7]. However, even patients with a normal or near-normal FEV_1% may have ongoing CF lung disease [8], and this has prompted a search for better measures. Elevated LCI occurs from asymmetric narrowing of airway lumens due to inflammation, scarring, obstruction by mucus, secondary changes in airway tone or parenchymal changes in the subtended lung units resulting in changes in compliance and differing time-constants for filling and emptying [1], thus ongoing elevation of LCI despite improvement in FEV_1% may indicate ongoing pathology consistent with CF airways disease. LCI has the advantages of not exposing patients to ionizing radiation (as with computed tomography) and not needing adjustment to predicted normal values for age, height and gender as with standard spirometry. In the first case presented here, LCI remained markedly elevated despite a return to baseline normal FEV_1% above 100% and increase in FEF_{25-75}%. In the second case, FEV_1% and FEF_{25-75}% improved to the patient's baseline; LCI remained well above reported normal values. LCI was not measured in these patients at another time point after the end of hospitalization, at a period of further stability. A baseline measurement of LCI might be helpful in future CF research studies. The result of

Table 1
Spirometry and Lung Clearance Index results.

	Forced vital capacity (percent predicted)		Forced expiratory volume in one second (FEV_1) (percent predicted)		Forced expiratory flow in mid-range (FEF_{25-75}) (Percent predicted)		Lung Clearance Index	
	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge
Case 1	2.95 L (95)	3.19 L (102)	2.57 L (93)	2.75 L (100)	3.31 L/S (101)	3.83 L/S (117)	11.5	12.96
Case 2	2.43 L (77)	2.58 L (82)	2.07 L (73)	2.29 L (81)	2.38 L/sec (66)	2.91 L/S (81)	12.89	12.03

A change of >10% points in FEV_1% is considered to be significant.
A significant change in LCI has not yet been defined; values above 6.8–7.41 are considered abnormal [1].

persistent elevation of LCI after illness in these cases, however, is supported by a previous study of 63 patients with CF ages 5–19 years, in whom 42 (67%) had an abnormal LCI despite normal FEV_1% [9]. In a recent meta-analysis of 176 pulmonary exacerbations of CF in adults and children, LCI significantly decreased (was improved) by 0.40 units or 2.5% following treatment. However, results were discordant with FEV_1 in 42.5% of subjects [10]. Whether these exacerbations were correlated with viral infections is unknown.

Enteroviruses are common pathogens in humans and may cause gastrointestinal, respiratory or neurological symptoms. EV-D68 is uniquely associated with respiratory disease due to the fact that it grows at 33°, the temperature of the upper respiratory tract. EV-D68 shares some features of rhinoviruses and may shed for up to 3 weeks [4]. Animal and human data suggest that rhinoviral infections may result in an asthma phenotype in a genetically susceptible host [11]; whether EV-D68 may also have this effect is unclear. Although there is no seasonal difference in contracting viral respiratory symptoms in children with CF compared to matched healthy controls, the duration of symptoms and presence of lower respiratory tract symptoms is greater in those with CF, suggesting that viral illnesses contribute additively to the pulmonary dysfunction in these patients [12]. Detection of rhinovirus was significantly associated with the occurrence of an exacerbation in adults with CF [13]. Earlier studies suggest that both children and adults with cystic fibrosis have diminished levels of lung function during symptomatic or asymptomatic viral infections [14]. In the cases presented here, LCI remained elevated above normal values (abnormal), although FEV_1% and $_{FEF25-75}$%, which had declined from baseline during acute exacerbation associated with EV-D68, returned to normal levels after treatment with antibiotics and intensified airway clearance. LCI may be a more sensitive indicator of the impact of viral illness on lung function in patients with CF than standard spirometry.

5. Conclusion

This case report illustrates the finding of ongoing airway narrowing and ventilation inhomogeneity after pulmonary exacerbation associated with EV-D68 in two patients with CF that could not be detected by FEV_1% or FEF_{25-75}%, but which was demonstrated by LCI. Although it is still a research tool, LCI may be useful to detect subtle lung function decline after viral insults.

Conflict of interest

The authors do not have any conflict of interest to report in reference to this manuscript.

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