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Abnormal Infant Pulmonary Function in Young Children With Neuroendocrine Cell Hyperplasia of Infancy

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Summary. Rationale: Lung function in children with neuroendocrine cell hyperplasia of infancy (NEHI) and correlations with future clinical outcomes are needed to guide clinical management. Objective: To compare results of infant pulmonary function tests (IPFTs) in children with NEHI to disease control (DC) subjects and to correlate NEHI IPFTs with future outcomes. Methods: We performed a retrospective, single center study of IPFT in subjects diagnosed by lung biopsy (NEHI) or clinically (NEHI syndrome) and in DC subjects evaluated for cancer or pre-hematopoietic stem cell transplantation (HSCT). Raised volume rapid thoracoabdominal compression (RVRTC) and plethysmography were performed on all infants and evaluated for quality. Standard spirometry measures, room air oxygen saturations (RA O_2 sat), and weight percentiles were collected during follow up. Measurements and Main Results: Fifty-seven IPFTs were performed in 15 NEHI, 22 NEHI syndrome, and 20 DC subjects. RVRTC and FRC measurements were obtained in 85% or more of subjects in all groups. Significant airflow limitation ($FEV_{0.5}$ *P*-value ≤ 0.01) and air trapping (FRC *P*-value ≤ 0.01) were seen in NEHI and NEHI syndrome subjects compared to DCs. No significant correlations were found between IPFT, oxygen use, RA O_2 sat, and weight at the time of the IPFTs. Initial $FEV_{0.5}$ and FRC *z*-scores correlated with RA O_2 sat ($r = 0.60$ and -0.49) at short-term follow up (6–12 months). Most measurements of RVRTC correlated with FEV_1 ($n = 5$) measured 4–5 years later ($r > 0.50$). Conclusions: IPFTs in NEHI subjects are feasible, demonstrate significant obstruction and air trapping, and correlate with future RA O_2 sat and FEV_1. IPFTs may provide valuable clinical information when caring for NEHI patients. **Pediatr Pulmonol. 2013; 48:1008–1015.**

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INTRODUCTION

Neuroendocrine cell hyperplasia of infancy (NEHI) is a poorly understood rare disorder defined by clinical features, radiographic findings, and lung tissue bombesin staining.[1–3] Children with NEHI present at less than 2 years of age with pulmonary abnormalities including chronic hypoxemia, tachypnea, retraction, and crackles.[2,3] This impairment may last for years and usually resolves slowly over time, though limited data suggest that older patients may be persistently air trapped.[4] Recently, high resolution computerized tomography (HRCT) findings for NEHI have also been described to include ground glass opacity (GGO) and lower lobe air trapping.[1] Limited infant pulmonary function testing data from one center has suggested that NEHI patients may have airway obstruction and air trapping and that this may correlate with neuroendocrine cell prominence.[5]

As both clinical and imaging features in NEHI suggest major physiologic impairment in young children, we hypothesized that characteristic physiologic abnormalities could be defined by infant pulmonary function tests (IPFTs) when compared to disease controls (DCs) and correlated with future clinical outcomes. IPFTs have provided important physiologic insights in other chronic lung disorders in infants such as cystic fibrosis[6–8] and bronchopulmonary dysplasia.[9,10] We conducted a retrospective, single center study of subjects diagnosed with NEHI by lung biopsy or clinically compared with DC subjects. The objective of this investigation was to define physiologic patterns observed in this cross-sectional cohort as described by IPFTs and correlate initial IPFTs with pulmonary function testing, pulse oximetry, and weight in patients with follow-up data.

METHODS

Population

Subjects presented to Children's Hospital Colorado, National Jewish Health or Presbyterian-St. Luke's Hospital in Denver or Aurora, Colorado between September 2000 and June 2010 for clinical evaluation for childhood interstitial lung disease (chILD). All subjects received IPFTs at Children's Hospital Colorado. The DC subjects were tested for possible lung disease following referral from pediatric specialists. The study was approved by the Colorado Multiple Institutional Review Board. The subjects were separated into the following categories:

Neuroendocrine cell hyperplasia of infancy (*NEHI*): NEHI subjects (n = 15) had persistent tachypnea, crackles on examination and desaturation (O_2 sat <90% at 1609 m). Evaluation was done as clinically indicated by the physician to rule out other lung and cardiac diseases. Subjects in this group obtained a lung biopsy for clinical indications and had diagnostic bombesin tissue staining completed and read by pathologists experienced in this disorder. No other pathologic disease processes were found on lung biopsy. One subject was a sibling of a child previously diagnosed with NEHI by histology who presented with the identical clinical course and HRCT findings consistent with NEHI. The decision to obtain a biopsy was made by the clinician. Oxygen use and weight at the time of IPFTs and RA O_2 sat within 6 months prior to IPFTs were recorded.

NEHI syndrome: NEHI syndrome subjects (n = 22) had the same constellation of symptoms as NEHI subjects including persistent tachypnea, crackles on examination, and desaturation (O_2 sat < 90% at 1609 m). CT scans were reviewed by a radiologist experienced in recognizing NEHI. All subjects in this group had findings consistent with NEHI including ground glass opacities (GGO) and air trapping and no findings of nodules or bronchiectasis. Subjects in this group did not undergo a lung biopsy or have a family history of NEHI. Oxygen use and weight at the time of IPFTs and RA O_2 sat within 6 months prior to IPFTs were recorded.

Disease control (DC) subjects: DC subjects underwent an evaluation prior to hematopoietic stem cell transplantation (HSCT) or were undergoing chemotherapy for cancer and had clinical infant pulmonary function testing to evaluate for lung disease. These 20 subjects had the following underlying diagnoses: 6 acute lymphoblastic leukemia, 2 acute myeloid leukemia, 1 aplastic anemia, 1 beta thalessemia major, 1 germ cell tumor, 2 juvenile myelomonocytic leukemia, 1 lysosomal acid lipase deficiency, 2 neuroblastoma, 3 severe combined immunodeficiency, and 1 X-linked immunodeficiency with hyper-IgM. All leukemia patients received variable amounts of chemotherapy and had received no radiation therapy prior to testing. No patients received BCNU or CCNU. The germ cell tumor patient received bleomycin before testing. IPFT clinical encounter forms and medical records were reviewed to assure subjects had no evidence of lung disease by history and no oxygen use at the time of IPFT. The immunodeficiency patients may have had a prior history of pulmonary infections before testing.

Published normal lung function data: Subjects were compared to historic healthy control subjects previously published.[11–13]

Infant Pulmonary Function Testing (IPFT)

The IPFT data included represented the first research quality study for each patient.[7,14,15] After consent for

testing, the subjects were sedated with chloral hydrate (75–120 mg/kg by mouth or per rectum). A minority of subjects were alternatively given pentobarbital (3–7 mg/kg intravenously) for sedation. Testing was performed with the nSpire Infant Pulmonary Lab (IPL, nSpire, Inc, Longmont, CO) using updated software. IPFTs were performed as previously described based on published guidelines.[11,13–15] Testing sequence was tidal breathing, plethysomography, passive respiratory mechanics, raised volume rapid thoracoabdominal compression (RVRTC), and partial expiratory flows during tidal breathing (V'maxFRC). The measures analyzed for this manuscript were: functional residual capacity (FRC) obtained from plethysmography; forced vital capacity (FVC), forced expiratory volume at 0.5 sec ($FEV_{0.5}$), forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$), forced expiratory flow at 25% of FVC (FEF_{25}), forced expiratory flow at 50% of FVC (FEF_{50}), forced expiratory flow at 75% of FVC (FEF_{75}) and forced expiratory flow at 85% of FVC (FEF_{85}) obtained by RVRTC; and residual volume (RV), total lung capacity (TLC) and ratios RV/TLC and FRC/TLC obtained from a combined analysis of plethysmography and RVRTC measures as previously described.[11] Our personnel had previously been trained for participation in a multicenter trial sponsored by the Cystic Fibrosis Foundation.[7] All IPFTs were reviewed by one respiratory therapist (C.K.) for selection of acceptable measurements based on procedures used in the previous CF study[7] and based on published guidelines.[14,15]

Follow-Up Subject Data

A subset of subjects in this cohort had clinically indicated follow up with standard spirometry when acceptable results could be obtained,[16] pulse oximetry, and/or weight measurements. Time periods for analysis were chosen based on the maximum number of observations available. Data were analyzed for RA O_2 sat and weight percentiles 6–12 months after IPFT measurements (short-term follow up) and for spirometry 4 and 5 years after initial IPFT measurements (long-term follow up). The maximum value of the RA O_2 sat range recorded at rest was used.

Statistical Analysis

Descriptive statistics were calculated using the mean and standard deviation or the median and inter-quartile range for continuous variables, where specified. Percentages were used to describe categorical variables. The IPFT measurements from the DC group were compared to previously published values for normal infants[11–13] using two sample *t*-tests. *Z*-scores for the IPFT measurements were obtained by fitting a regression model to the DC group for each of the pulmonary function outcomes using age, gender, and gender–length interaction as covariates. The standard deviations for the model were weighted by age. *Z*-scores were computed by subtracting the predicted value and dividing by the matched standard deviation of prediction determined from the regression model. For each of the lung function *z*-score variables, a simple one-way analysis of variance (ANOVA) was used to test the differences in mean values across the three groups. As a sensitivity analysis, age, gender, and length were added to the model as covariates. Pearson correlation coefficients were used to quantify the associations between variables. All subjects had oxygen use and weight recorded at the time of IPFTs. As RA O_2 sat was not a routine measurement at the time of IPFT studies, RA O_2 sat recorded within 6 months prior to IPFTs was included. Only 22/37 (59%) NEHI and NEHI syndrome subjects had RA O_2 sat recorded prior to testing. Variables included the association between the IPFT *z*-score variables, weight and O_2 use at the time of testing and prior RA O_2 sat within the NEHI groups; between the IPFT values and follow-up PFTs; and between IPFT *z*-scores and follow-up weight and RA O_2 sat.

Fifteen (40%) NEHI and NEHI syndrome subjects had follow-up RA O_2 sat and weight measurements. There were 18 follow-up RA O2 sat measurements from 15 subjects taken within 6–12 months after the IPFT. Three patients had two measurements that fell within this time range so these were averaged, this was similarly performed for the weight percentiles. Five (13%) of the NEHI and NEHI syndrome patients had spirometry measurements analyzed. Five of the eight NEHI subjects with matching spirometry measurements had a research quality follow-up spirometry between 4 and 5 years after the IPFT measurements. Pearson correlation coefficients were calculated. All analyses were performed using SAS v9.2 (SAS Institute, Inc., Cary, NC, 2008).

RESULTS

Participants

The study populations consisted of a total of 57 infants studied for clinical indications at Children's Hospital Colorado between September 2000 and June 2010. There were 37 NEHI/NEHI syndrome patients studied out of 65 NEHI/NEHI syndrome patients seen at our center during this time period. Demographics and clinical characteristics are described in Table 1. Subjects were predominately male in the NEHI syndrome group and exclusively male in the NEHI group. All subject groups were predominantly Caucasian and the NEHI group was exclusively Caucasian. Patients ranged in age from 7.9 to 147.4 weeks of age

TABLE 1— Patient Demographics

Median (IQR) # (%)	Disease control (n = 20)	NEHI (n = 15)	NEHI syndrome (n = 22)
Female	14 (70%)	0 (0%)	6 (27%)
Caucasian	13 (65%)	15 (100%)	19 (86%)
Age, weeks	52.1 (55.5)	58.0 (46.1)	49.3 (24.9)
Length *z*-score	−2.16 (1.55)	−1.99 (0.95)	−1.24 (1.93)
Weight *z*-score	−1.70 (1.64)	−2.28 (1.17)	−1.44 (1.50)
O_2 use (LPM)[1]	0	0.50 (0.75)	0.50 (0.25)

[1]At time of IPFT measured at 1,609 m.

at the time of testing. The majority of the infants in all three groups were smaller in size compared to the general population matched for age, with *z*-scores for length and weight ranging from −1.24 to −2.28 at the time of initial IPFTs. The calculation of the *z*-score utilized differences in age, gender, and length in an attempt to adjust for these demographic differences across groups. The DC subjects did not require oxygen, and the NEHI and NEHI syndrome groups required on average 0.5 L (range 0 to 1.0 L) per minute of oxygen by nasal cannula at the time of the IPFT measured at 1609 m.

Feasibility of IPFTs

Table 2 displays the number of acceptable measurements, defined as meeting previously published criteria[11,13–15] obtained in each study group for each component of the IPFT. Tidal breathing was acceptably measured in almost all subjects. Acceptable FRC measurement was obtained for all DC subjects and a large majority (86%) of the NEHI and NEHI syndrome subjects. Acceptable RVRTC measurements (FVC, $FEV_{0.5}$, FEF_{25}, FEF_{50}, FEF_{75}, FEF_{85}, and $FEF_{25–75}$) and fractional lung volumes (RV and TLC) were obtained in the majority of all groups (range: 67–91%). Acceptable plethysmographic measurements were obtained in a higher proportion of subjects than acceptable RVRTC measurements or fractional lung volumes (which require both acceptable plethysmographic and RVRTC measurements).

Comparison of IPFT Measurements From DC Subjects and Historical Healthy Controls

Table 3 displays the comparison of IPFT measurements from DC subjects and previously published healthy control infants.[11,12] There are no significant differences between DCs and the previously published values. The measurements for our DC subjects are displayed in the online Supplementary Table (E-1).

Comparison of IPFT Measurements From NEHI, NEHI Syndrome, and DC Subjects

Figure 1 displays the distribution of four IPFT *z*-score RVRTC measurements across NEHI, NEHI syndrome, and DC subjects. Significant airflow limitation was seen in NEHI and NEHI syndrome subjects. For all RVRTC airflow measurements except FEF_{25}, the NEHI and NEHI syndrome groups were significantly lower when compared to the DC group (P-value ≤ 0.01, except FVC for NEHI syndrome and FEF_{85} for both NEHI and NEHI syndrome P-values $= 0.02$). NEHI and NEHI syndrome RVRTC measurements did not differ from each other. NEHI patients were significantly obstructed. The $FEV_{0.5}$/FVC ratio was lower for NEHI (P-value $= 0.04$) and NEHI syndrome (P-value $= 0.07$) groups when compared to DCs. Figure 2 displays the plethysmographic and fractional lung volume measurements from NEHI, NEHI syndrome, and DC subjects. Four lung volume measurements are shown. NEHI and NEHI syndrome patients were air trapped. For all lung volume measurements except TLC for NEHI subjects,

TABLE 2— Research Quality Data by group

# (%)	N	Tidal breathing	Plethysmography[1]	RVRTC measures[2]	Fractional lung volumes[3]
NEHI	15	15 (100%)	13 (87%)	13 (87%)	10 (67%)
NEHI syndrome	22	21 (95%)	19 (86%)	20 (91%)	17 (77%)
Disease control	20	20 (100%)	20 (100%)	17 (85%)	17 (85%)

[1]FRC.
[2]FVC, $FEV_{0.5}$, FEF_{75}, $FEF_{25–75}$.
[3]RV, TLC.

TABLE 3— Comparison of Infant PFT Measurements From Disease Control Subjects and Previously Published Normal Control Infants

	Disease control (% pred) (N = 17)	Goldstein[12] (% pred) (N = 41)	Disease control (ml/kg) (N = 17)	Castile[11] (ml/kg) (N = 33)
FVC				
Mean ± SE (95% CI)	100.3 ± 3.7 (92.6, 108.1)	95.8 ± 2.1 (91.7, 99.9)	43.9 ± 1.8 (40.1, 47.7)	42.1 ± 1.9 (38.4, 45.8)
FRC[1]				
Mean ± SE (95% CI)	93.7 ± 4.4 (84.4, 103.0)	95.9 ± 2.3 (91.1, 104.9)		
FEF_{50}				
Mean ± SE (95% CI)		90.0 ± 6.2 (76.9, 103.1)	79.1 ± 2.9 (73.4, 84.8)	
FEF_{75}				
Mean ± SE (95% CI)	120.0 ± 12.6 (93.3, 146.8)	94.3 ± 3.5 (87.4, 101.2)	46.9 ± 4.5 (37.4, 56.4)	39.3 ± 1.9 (35.6, 43.0)
$FEF_{25–75}$				
Mean ± SE (95% CI)	116.0 ± 8.8 (97.4, 134.6)	95.0 ± 2.9 (89.3, 100.7)		
$FEV_{0.5}$				
Mean ± SE (95% CI)	103.6 ± 4.3 (94.5, 112.7)	99.7 ± 2.9 (94.0, 105.4)		
RV/TLC				
Mean ± SE (95% CI)	88.7 ± 5.2 (77.6, 99.7)	85.6 ± 3.0 (79.7, 91.5)		
RV				
Mean ± SE (95% CI)	87.0 ± 6.1 (74.2, 99.9)	83.9 ± 3.5 (77.0, 90.8)	15.3 ± 1.2 (12.8, 17.8)	17.6 ± 0.7 (16.2, 19.0)
TLC				
Mean ± SE (95% CI)	95.1 ± 3.4 (87.8, 102.3)	96.2 ± 1.8 (92.7, 99.7)	58.8 ± 2.3 (53.9, 63.8)	60.1 ± 1.9 (56.4, 63.8)

[1]All 20 disease controls had FRC measurements.

the NEHI and NEHI syndrome groups were significantly higher than the DC group (P-values < 0.01) but not different from each other. The IPFT measurements that most distinguished NEHI and NEHI syndrome from DC subjects were RV/TLC from the fractional volume measurements and $FEF_{25–75}$ from the RVRTC measurements. As a sensitivity analysis, the mean z-scores were calculated after adjusting for the potential confounding effects of age, gender, and length in the regression model. The results for all measurements remained robust except for the FVC comparisons between the NEHI and DC groups, which were no longer statistically significant (NEHI comparison P-value = 0.06 and NEHI syndrome comparison P-value = 0.07). This indicates that FVC and TLC may have some residual differences in z-scores due to the gender differences across groups even after the z-score calculation.

Post-bronchodilator studies were planned for all the IPFT studies on NEHI and NEHI syndrome subjects. However due to difficulty in maintaining sedation, only 26 (70%) subjects had post-bronchodilator measurements attempted, 19 (51%) subjects had some post-bronchodilator results but only 9 (24%) subjects produced research quality post-bronchodilator results. Of those

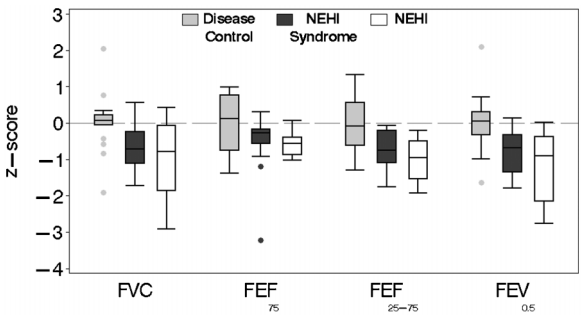

Fig. 1. Distribution of the *z*-scores for raised volume rapid thoracoabdominal compression (RVRTC) measurements for disease control subjects (light gray), NEHI syndrome subjects (dark gray), and NEHI subjects (white) are displayed. Bars represent the 25th and 75th percentiles, the whiskers designate 1.5 interquartile ranges, and the points represent values outside this range. The lines in the bars correspond to the median values.

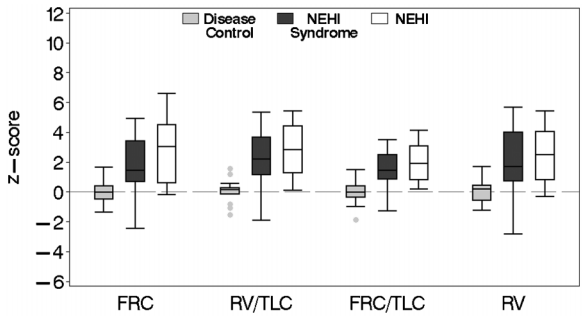

Fig. 2. Distribution of the *z*-scores for plethysmographic and fractional lung volume measurements for disease control subjects (light gray), NEHI syndrome subjects (dark gray), and NEHI subjects (white) are displayed. Least square means from the ANOVAs are represented by the central horizontal bar and 95% confidence intervals are shown. Bars represent the 25th and 75th percentiles, the whiskers designate 1.5 interquartile ranges, and the points represent values outside this range. The lines in the bars correspond to the median values.

nine subjects, only one subject has a significant response to bronchodilator as defined by Goldstein et al.[12]

There were no statistically significant correlations between any IPFT measures and oxygen use (correlation coefficients ranged from 0.27 to −0.16, all *P*-values > 0.05), or weight by *z*-score (correlation coefficients ranged from 0.33 to −0.05, all *P*-values > 0.05) obtained at the time of IPFTs or RA O_2 sat prior to testing (correlation coefficients ranged from 0.14 to −0.32, all *P*-values > 0.05). Lower FEF_{75} and FEF_{85} measurements trended toward significant correlation with lower weight *z*-score [r (*P*-value) 0.33 (0.06) and 0.31 (0.08), respectively]. The correlations between oxygen use and weight were also not significant [r (*P*-value) weight *z*-score: −0.06 (0.71); weight in kg: 0.14 (0.41)].

Comparison of IPFT Measurements With Longitudinal Follow-Up Spirometry, Pulse Oximetry, and Weight

A subset of subjects in this dataset followed longitudinally for clinical indications with standard spirometry, pulse oximetry, and weight were studied. There were strong correlations and significant *P* values between follow-up O_2 sat and IPFT *z*-scores for $FEV_{0.5}$, FVC, FRC, RV/TLC, and FRC/TLC (Table 4). There were 15/37 (40%) subjects with follow-up RA O_2 sat and weight measurements taken within 6–12 months after the IPFT. No correlation was seen between IPFT *z*-scores and follow-up weight percentiles (Fig. 3). Five (5/37; 13%) subjects had matching acceptable follow-up spirometry measurements 4 and 5 years after the IPFTs. Figure 3 shows positive correlations (all r value > 0.50; range 0.54–0.72) between the IPFT values of $FEV_{0.5}$, FVC, and $FEF_{25–75}$, and follow-up FEV_1, FVC, and $FEF_{25–75}$.

DISCUSSION

NEHI is increasingly recognized worldwide as a chronic disease of infants and young children characterized by impressive clinical findings.[17] This is the largest series of NEHI subjects from one center ever published. We report marked pulmonary function impairment in NEHI subjects when compared to DC subjects and published normal values in infants. We found evidence of significant airway obstruction and air trapping which is consistent with air trapping reported on CT scans of our patients and published findings for NEHI in the literature.[1] These physiologic findings are equally important as there is little histologic evidence of small airway obstruction on lung histology and yet air trapping and obstruction are noted, raising questions about mechanism of disease in NEHI.

Our IPFT data also substantiates, with a larger sample size and a comparison DC group, a previously reported small cohort of patients with NEHI who were also reported to have airway obstruction and air trapping.[5] The most distinguishing measures between DCs and NEHI or NEHI syndrome subjects are RV/TLC and $FEF_{25–75}$. When compared to other children with a more common chronic lung disease such as bronchopulmonary dysplasia,[9] NEHI patients have similar degrees of airway obstruction but increased air trapping. These data substantiate that NEHI creates pulmonary function abnormalities that are equally severe to other known obstructive lung diseases in young children. In the limited number of IPFT measurements obtained after albuterol, there was a significant bronchodilator response in only one subject. The response to bronchodilators is an important question for future studies.

Many of these children required oxygen and had significant pulmonary findings characteristic of NEHI such as tachypnea and retractions. We sought to determine if research quality measurements could be reliably obtained in children with this degree of pulmonary derangement compared to controls. Table 2 demonstrates that in many children we could achieve acceptable measurements for tidal breathing, plethysmography, and RVRTC measurement. The feasibility of obtaining infant PFTs in NEHI subjects is similar to the feasibility

TABLE 4— Associations Between Initial Infant PFTs and Follow-Up RA O2 sat

IPFT	N	RA O_2 sat r	*P*-value
$FEV_{0.5}$ *z*-score	13	0.60	0.03
FVC *z*-score	13	0.61	0.03
$FEF_{25–75}$ *z*-score	13	0.36	0.23
FRC *z*-score	14	−0.49	0.08
RV/TLC *z*-score	11	−0.65	0.03
FRC/TLC *z*-score	11	−0.67	0.02

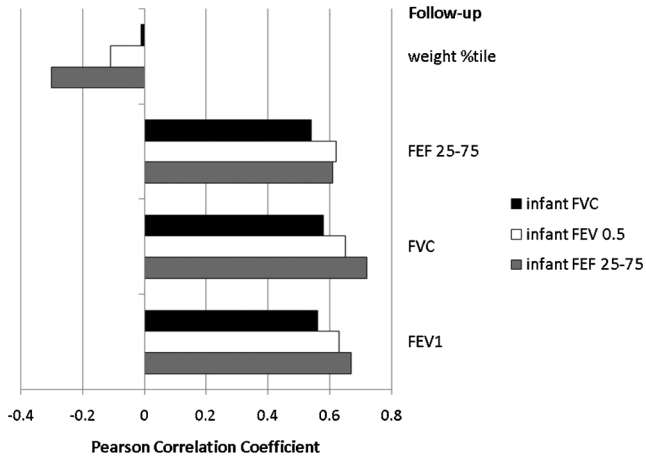

Fig. 3. Pearson correlation coefficients for infant PFT measurements (FVC (black), $FEV_{0.5}$ (white), $FEF_{25–75}$ (gray)) with follow-up weight percentile within 6–12 months after the IPFT and spirometry (FVC, FEV_1, and $FEF_{25–75}$) 4–5 years after initial IPFTs.

noted in a multicenter study of subjects with cystic fibrosis.[7] We believe that quality IPFTs are feasible in this population.

The gold standard for diagnosis of NEHI has been elevated numbers of pulmonary neuroendocrine cells seen with specialized bombesin staining of lung tissue in the right clinical context and without evidence of other known lung disease.[18] Recently, Brody et al.[1] described characteristic HRCT findings in 23 subjects with NEHI that included GGO as the most common finding, usually involving the right middle lobe and lingula, and a mosaic pattern of air trapping, frequently in lower lobes. Some centers, including ours, may now forgo lung biopsies in patients with the characteristic clinical and imaging findings, resulting in a diagnosis of NEHI syndrome. There is still considerable debate about the need for lung biopsies in children with possible NEHI but most would agree that a lung biopsy should be pursued in a significantly symptomatic child if the clinical and imaging findings are atypical. Our data show similar degrees of obstruction and air trapping between NEHI and NEHI syndrome subjects compared with controls. This similarity indicates that those diagnosed with NEHI syndrome had similar physiologic patterns compared to those with a biopsy confirmed diagnosis of NEHI. Though obstruction and air trapping are not specific to NEHI, IPFTs with a normal or restrictive pattern in a symptomatic NEHI patient are atypical of our cohort. We suggest that evaluating IPFTs may provide another non-invasive diagnostic measure to consider when weighing the pros and cons of obtaining a lung biopsy in a child that has characteristic clinical and imaging findings of NEHI. More study is needed to further define the role of IPFTs in the diagnostic evaluation of NEHI.

NEHI and NEHI syndrome subjects required oxygen and were smaller than the general population. There were no major correlations between IPFT measurements and oxygen use at the time of testing or RA O_2 sat prior to testing. There was a trend for correlation between flows at low lung volumes and the patient's weight. We had hypothesized that IPFTs would correlate in some degree to these other measures frequently assessed and be related to degree of pulmonary impairment such as oxygen use. The reason for this disconnect may be that IPFTs are measuring a different variable of lung impairment not reflected in the oxygen use at the time of testing. Oxygen use may be driven by physician or family comfort and thus, may not be quite as quantifiable as lung function. The lack of correlation between RA O_2 sat prior to testing and IPFTs and yet significant correlation with RA O_2 sat at 6–12 months after testing is difficult to explain and will require further study. The poor weight gain, frequently reported in children with chILD[3] and also seen in our population, may also be driven by variables other than lung function, but our data suggest there is some relationship between flows at low lung volumes and weight. As IPFTs may be a unique quantifiable measurement of pulmonary status that does not correlate strongly with more commonly used markers believed to be related to poor lung function, IPFTs may have important and different prognostic value.

We report for the first time IPFT data associations with longitudinal follow-up RA O_2 sat, weight and spirometry in a small number of NEHI subjects. When we assessed RA sat at 6–12 months after initial IPFTs, significant correlations were found; whereas, weight was not correlated. Though only available in five children, IPFTs were correlated with future spirometry measurements over a 4–5 year time frame from initial testing. These data are preliminary and limited by small numbers and sample bias. Regardless, it provides important preliminary information in this rare disease and strongly suggests further study is needed with a larger sample and longer longitudinal follow up. It further suggests that IPFTs may have a prognostic role in this disease, especially when combined with the observation by Young and Deustch[5] that physiologic obstruction may correlate with neuroendocrine cell prevalence.

We also report that young children who have undergone chemotherapy or treatment for genetic or oncologic conditions have normal airflow and lung volumes on IPFTs when compared to published healthy controls. Most of these children were evaluated before HSCT to assess pulmonary risk. Recently, a pre-transplant lung function score that included a combined measurement of FEV_1 and diffusing capacity (DLCO) was found to predict survival following pediatric HSCT in older children, suggesting pulmonary function may have an important role in pre-transplant assessment in children.[19] However, we found that pulmonary function in our young DC children were collectively normal unlike some older children who have been reported to develop significant pulmonary morbidity after conditioning regimens for HSCT.[19] We were not able to address DLCO with our IPFTs. This cohort of children without obvious lung disease provided DCs for this study to assure that our IPFTs were technically sound and comparable to published literature. Additionally, our published measures (Supplementary Table E-1) may be of benefit as baseline data for future studies investigating pulmonary abnormalities in young children associated with chemotherapy or HSCT.

There are limitations of the current study. This is a retrospective, cross-sectional study performed at a single center, thereby decreasing the generalizability across other centers. Both IPFTs and PFTs were performed for clinical indications and subjects followed up based upon clinical need, creating significant variability

in follow-up time and assessment. As with most rare disease studied in one center, sample size for the follow-up PFTs was very small, limiting the interpretation of these data. Furthermore, our study population was predominantly male and Caucasian. Whether this is more characteristic of NEHI requires further study, but it does impact our ability to generalize to other ethnic groups and female subjects. It will be important to collect multi-center IPFT data as part of a Database for Children's Interstitial and Diffuse Lung Disease to further define these issues. Finally, though we recommend IPFT to most of our NEHI patients, not all patients seen in our center with NEHI had IPFT testing completed due to different clinical circumstances and not all patients had prolonged patient follow up at our center, thus raising the potential of selection bias.

In conclusion, we report that NEHI and NEHI syndrome patients have significant pulmonary obstruction and air trapping when compared to DCs and published healthy control subjects. NEHI and NEHI syndrome were not significantly different from each other on any pulmonary function measurement. Moreover, initial IPFTs were correlated with follow-up RA O_2 sat and PFTs in a small number of follow-up patients. We suggest that IPFTs can be reliably obtained, determine the degree of physiologic impairment, and may have clinical prognostic value in children with NEHI. Further studies are clearly needed.

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