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ORIGINAL ARTICLE

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Using electrical impedance tomography to characterize lung impairment of children with primary ciliary dyskinesia: A pilot cross-sectional study

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Abstract

Background: In children with primary ciliary dyskinesia (PCD), measures more sensitive than spirometry are needed to characterize underlying pulmonary impairment. Electrical impedance tomography (EIT) is a promising noninvasive method for monitoring the distribution of lung ventilation, and it does not require patient collaboration. We aimed to provide an assessment of the feasibility and clinical usefulness of EIT in characterizing lung impairment in children with PCD, compared to spirometry and multiple breath nitrogen washout ($MBWN_2$) test.

Methods: Children and adolescents with PCD underwent $MBWN_2$ test as first respiratory assessment, followed by EIT monitoring and spirometry during outpatient follow-up.

Results: We included 12 out of 16 individuals regularly followed at our clinic. A total of 41.7% (5/12) showed abnormal forced expiratory volume in 1 s (FEV_1), whereas 11/12 (91.7%) had abnormal ventilation inhomogeneity measured with $MBWN_2$ test. Using EIT, the global inhomogeneity (GI_{TOT}) index showed moderate to strong correlation with FEV_1 ($\rho = -0.55$, 95% confidence interval [CI]: −0.87 to 0.02) and ranged from 37 to 44, with the highest inhomogeneity detected in the dorsal right quadrant. GI_{TOT} was moderately correlated with RV/TLC %predicted ($\rho = 0.38$, 95% CI: −0.17 to 0.74), while we detected a weak correlation between GI_{TOT} and lung clearance index ($\rho = 0.29$, 95% CI: −0.45 to 0.82).

Conclusion: EIT appears promising as a noninvasive technique to characterize ventilation distribution in children with PCD, thus providing a complementary assessment to static and dynamic lung function measures of PCD disease.

KEYWORDS

electrical impedance tomography, primary ciliary dyskinesia, respiratory function

1 | INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare and heterogeneous inherited disorder of motile cilia, characterized by impairment in mucociliary clearance, recurrent upper and lower respiratory infection, infertility and, in around 50% of cases, laterality defects (Kartagener syndrome [KS]). The progression of the disease leads to bronchiectasis.[1] Because of the lack of guidelines, respiratory management of PCD is still deduced from cystic fibrosis (CF) work-up and includes regular monitoring of lung function, surveillance sputum microbiology cultures, airway clearance techniques, and early treatment of infections.[2,3] PCD is characterized by some features (e.g., mucus plugging, ventilatory inhomogeneity, and atelectasis) which can be recognized using noninvasive respiratory equipment.[4] Spirometry, in particular the measurement of forced expiratory volume in 1 s (FEV_1), remains the most frequently reported clinical measure for detecting airway obstruction and monitoring disease progression. However, the feasibility of spirometry could be challenging in young children, who do not easily perform acceptable and repeatable respiratory maneuvers. Also, FEV_1 may not precisely indicate the site of airway obstruction. Some authors hypothesized that the measurement of static volumes by plethysmography could be more reliable in the assessment of air-trapping severity and pulmonary structural changes in patients with PCD. Nevertheless, plethysmography only shows low-to-moderate correlation with HRCT findings.[5] More recently, the measurement of lung clearance index (LCI), a parameter of ventilatory inhomogeneity derived from multiple breath nitrogen washout ($MBWN_2$), has been proven to be more sensitive than FEV_1 in the assessment of the small airways and can provide an earlier detection of lung function decline also in patients with PCD when spirometry is still normal.[6] Derivatives of $MBWN_2$, as a measure of ventilation inhomogeneity in conductive and acinar zones of the lungs, would be a further guidance to detect the degree and location of lung inhomogeneity compared to body plethysmography alone. Although LCI is performed during tidal breathing and requires mostly passive cooperation, the long washout time, especially in case of airways obstruction, could limit patient cooperation. Electrical impedance tomography (EIT) could overcome these limitations as a noninvasive imaging method for visualizing the distribution of lung ventilation, which does not require patient collaboration nor efforts. It is based on the distribution of electrical conductivity, delivered from a low intensity alternating current which circulates between electrodes applied on the chest circumference. The resulting cross-sectional images describe the impedance variation over a time interval, which, in turn, is strictly related to the amount of air that goes into the lungs.[7] EIT has been shown to provide reproducible regional ventilation, validated with CT images[8] and positron emission tomography[9] in the presence of atelectasis, air trapping, pleural effusion, and pneumothorax. EIT does not require patient collaboration and was historically used for the quantification of ventilation distribution and the titration of mechanical ventilation in patients with acute respiratory distress syndrome. More recently, EIT was applied in patients with CF and many studies documented that EIT changes in ventilation distribution during forced expiration have a good correlation with lung function parameters, highlighting the promising role of this diagnostic technique in the measurement of structural lung disease and in the assessment of disease progression and therapeutic response.[10,11] In particular, the EIT-derived measures distinguish between CF patients and healthy controls and between different disease states in CF.[11]

To date, EIT in children with PCD has not been studied yet, and we hypothesized that EIT could further characterize lung impairment of children with PCD, as a complementary respiratory tool to be used in a clinical setting. With this study, we aim to provide an assessment of the feasibility and clinical usefulness of EIT in monitoring ventilation distribution, by correlating the parameters provided by EIT with results of spirometry, plethysmography and $MBWN_2$ test.

2 | METHODS

We conducted this observational monocentric cohort study in the outpatient department of Pediatric High Intensity Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy. From July to October 2021, we enrolled children with diagnosis of PCD or KS, evaluated during an outpatient visit. Diagnosis of PCD was based on the presence of specific clinical features and confirmed by a range of specific tests, such as nasal nitric oxide measurement, ciliary beat pattern analysis through a high-speed video microscopy, ciliary ultrastructure examination through the transmission electron microscopy, and genetic testing. Subjects who were able to perform spirometry and $MBWN_2$ test were considered eligible. The exclusion criteria were a history of an ongoing or recent respiratory exacerbation (i.e., by 28 days), the use of pacemakers, presence of spinal fractures or injuries, and skin problems of the chest. The study was designed according to the principles of the Declaration of Helsinki (October 2013) and other guidelines, regulations, and Acts such as Good Clinical Practice. Written, informed consent signed by parents or guardians of the child was obtained, after Ethics Committee approval (no. 1376).

Data and medical history were obtained from the electronic clinical records; we considered the body mass index calculated and transformed into *Z*-score using Italian growth reference curves.[12] Children performed $MBWN_2$ as first respiratory assessment, followed by EIT monitoring and, finally, spirometric maneuvers.

2.1 | Pulmonary function measurements

An open-circuit MBW hard- and software package with nitrogen as tracer gas ($MBWN_2$) was used (Exhalyzer® D and Spiroware 3.2.2 Ecomedics AG, CH) and calibration and measurement procedures were performed as suggested.[13,14] Only results from three reproducible runs were considered, defined as a variation of functional residual capacity and LCI ($1/40^{th}$ of the starting concentration) values within 10%. LCI together with convective gas mixing in the

conducting airways (Scond*VT) and diffusion–convection interaction within the acinus (Sacin*VT), were therefore recorded, before patients performed spirometry. For children above 6 years old, upper limit of normal (ULN) equal to 7.91 was adopted, as recently published.[15] An adequate environment with enough distraction for younger children was assured during each test.

Lung volumes were measured by an 830 L plethysmograph (Vyntus Body 4.2, E. Jaeger GmbH) in the sitting position, according to ATS/ERS guidelines,[16,17] using SENTRYSUITE™ software. Flow and volume were measured by a pneumotachograph with a 0.036kPa L/-1s resistance and 160 ml dead volume. Values from spirometry and plethysmography are reported as a percentage of predicted values and as *Z*-score, according to Quanjer's equation developed under the Global Lung Function initiative.[18,19]

The EIT monitoring was performed with PulmoVista® 500 (Dräger Medical) by positioning an electrode belt consisting of 16-pediatric electrodes placed in the intermammillary region and a cable equipped with 16 clips numbered in series and evenly spaced applied to the special electrode buttons placed on the belt. In addition, a reference electrode was placed on the abdomen. At least 2 min of undisturbed tidal breathing was recorded in a semirecumbent position and afterwards, the first 10 tidal breaths have been extrapolated by the global relative impedance change curve obtained. The EIT data files were processed using the Dräger SW EITdiag Version 1.6. Analysis was focused on the global inhomogeneity (GI_{TOT}) index,[20] which represents the degree of heterogeneity of tidal volume distribution in the lung: disorders in ventilation distribution are reflected in higher GI_{TOT}. To assess regional ventilation, regions of interests (ROIs) were defined. For this purpose, the chest cross-section was divided into four equally sized quadrants (ventral right, ventral left, dorsal right, dorsal left). These ROIs reflect regional changes in ventilation distribution by calculating ventral and dorsal shifts during tidal breathing.

2.2 | Statistical analysis

Variables are presented as median and interquartile range or count and percentage (%). The relationships between the respiratory function variables derived from spirometry, plethysmography, $MBWN_2$, and EIT were explored using the Spearman correlation (ρ); precision was reported using 95% confidence interval (CI) based on 1000 bootstrap replications.

For all the analyses, a significance level of α 0.05 was considered. The analyses were carried out by using the R software[21] version 4.0.3, with *confintr* package added.

3 | RESULTS

Between July and October 2021, we enrolled 12 out of 16 children, who were regularly followed in outpatient clinic, 7 of whom were affected by KS (Table 1). Four children were excluded since they could not undergo spirometry and plethysmography measurements due to their young age. Six patients had received a PCD diagnosis by 3 years of age and one-third were chronically colonized by *Pseudomonas aeruginosa*. Genetic characteristics of included children with PCD are listed in Table 1.

Patients' pulmonary function tests are shown in Table 2. Five children (5/12, 41.7%) presented with FEV_1 below the 5th percentile (i.e., −1.64 *Z*-score), RV *Z*-score was normal in all patients (range −0.15 to −1.26) and in only one case RV/TLC was over 95th percentile (i.e., +1.64 *Z*-score). Overall, 11/12 (91.7%) showed abnormal LCI (LCI > ULN), and on average children showed more ventilation inhomogeneity in the most distal airways (Sacin*VT) compared to conductive airways (Scond*VT) (median value 0.184 and 0.074, respectively).

Based on the EIT analysis, the whole sample showed a narrow dispersion of the GI_{TOT} around the median, with values ranging from 37 to 44. By dividing the pulmonary area into four ROIs (Figure 1), the highest ventilatory inhomogeneity was detected in the dorsal right quadrant (Table 3 and Figure 2).

The relationship between GI_{TOT} and metrics derived by spirometry and plethysmography or $MBWN_2$ derivatives are

TABLE 1 Cohort' characteristics

Subjects (*n*)	12
Females, *n* (%)	6 (50.0)
Age (years)	12.0 (9.8; −14.2)
BMI (*Z*-score)	−0.3 (−1.1; −0.0)
Situs	
Solitus	5 (41.7)
Inversus totalis	5 (41.7)
Viscerum ambiguus	2 (16.7)
Genetic variants	
DNAH5	3 (25.0)
DNAH11	4 (33.3)
CCDC40	4 (33.3)
DAAF1	2 (16.7)
DNAI2	1 (8.3)
LRRC6	1 (8.3)
DNAAF3	2 (16.7)
DYX1C1	1 (8.3)
RSPH4A	1 (8.3)
RSPH1	1 (8.3)
HYDIN	2 (16.7)
Pseudomonas aeruginosa infection, n (%)	4 (33.3)

Note: Values are expressed as median with interquartile range (IQR) or absolute number with percentage (%)

Abbreviations: BMI, body mass index; IQR, interquartile range.

TABLE 2 Pulmonary characteristics

Subjects	FEV_1 % predicted	FEV_1 *Z*-score	LCI units	Sacin*VT	Scond*VT	RV % predicted	RV *Z*-score	RV/TLC % predicted	RV/TLC *Z*-score	GI_{TOT}
1	73.0	−2.29	11.36	0.191	0.063	123.3	0.52	129.5	0.82	42
2	72.7	−2.34	13.75	0.316	0.091	166.6	1.26	199.5	2.34	42
3	84.6	−1.33	12.81	0.177	0.086	112.2	0.26	140.4	1.02	37
4	70.1	−2.50	16.1	0.366	0.083	170.6	1.30	153.4	1.29	44
5	56.7	−3.58	12.31	0.261	0.068	144.0	0.87	162.9	1.55	41
6	86.7	−1.13	8	0.347	0.032	148.1	0.88	154.9	1.23	40
7	103.5	0.30	8.47	0.073	0.073	112.3	0.23	125.7	0.55	38
8	72.4	−2.28	10.93	0.121	0.1	153.1	1.09	163.1	1.63	42
9	97.1	−0.26	7.84	0.062	0.06	150.3	0.99	139.1	0.97	39
10	84.9	−1.31	13.51	0.511	0.075	93.1	−0.15	120.4	0.52	38
11	94.2	−0.49	7.94	0.113	0.08	93.4	−0.16	105	0.14	41
12	109.5	0.81	8.09	0.069	0.019	92.6	−0.15	102.7	0.06	41
Median	84.8	−1.32	11.15	0.184	0.074	133.7	0.70	139.8	1.00	41.0
IQR	72.6; 94.9	−2.30; −0.44	8.07; 12.9	0.103; 0.324	0.062; 0.084	107.0; 151.0	0.14; 1.01	124.4; 156.9	0.54; 1.36	38; 42

Abbreviations: FEV_1, forced expiratory volume in 1st s; FVC, forced vital capacity; GI_{TOT}, total global inhomogeneity; LCI, lung clearance index; RV, Residual Volume; RV/TLC, RV/total lung capacity; Sacin*VT, ventilation inhomogeneity in acinar airways; Scond*VT, ventilation inhomogeneity in conductive airways.

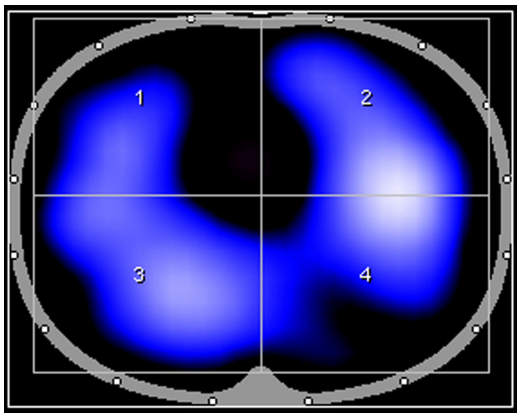

FIGURE 1 EIT image. Cross-section view of a 12-year-old boy's lungs, affected by primary ciliary dyskinesia with *situs solitus*. FEV_1 is 85% predicted and LCI 12.8; GI_{TOT} is 37. The image is divided into four quadrants showing the left dorsal (4) and left ventral (2), right dorsal (3), and right ventral (1) regions, to which correspond a GI of 7, 9, 14, and 6, respectively. Brighter (whiter) pixels denote a greater impedance change, equivalent to increased ventilation, in that area; where the lung remains closed to the passage of air, the region remains dark. FEV_1, forced expiratory volume in 1 s; GI_{TOT}, total global inhomogeneity; LCI, lung clearance index.

TABLE 3 EIT in the different ROIs

	N = 12
GI_{VL}	
Median (IQR)	10.0 (7.8; 11.0)
Range	7.0–13.0
GI_{DL}	
Median (IQR)	8.0 (7.0; 10.2)
Range	4.0–13.0
GI_{VR}	
Median (IQR)	9.5 (6.8; 11.0)
Range	2.0–13.0
GI_{DR}	
Median (IQR)	12.0 (10.8; 14.2)
Range	9.0–21.0

Abbreviations: GI_{DL}, global inhomogeneity dorsal left; GI_{DR}, global inhomogeneity dorsal right; GI_{VL}, global inhomogeneity ventral left; GI_{VR}, global inhomogeneity ventral right; IQR, interquartile range; ROIs, regions of interest.

represented in Figure 3. The strongest correlation was between FEV_1 %predicted and GI_{TOT} ($\rho = -0.55$, 95% CI: −0.87 to 0.02), followed by the positive correlation between RV %predicted and GI_{TOT} ($\rho = 0.58$, 95% CI: −0.06 to 0.91). GI_{TOT} was moderately correlated with RV/TLC % predicted ($\rho = 0.38$, 95% CI: −0.17 to 0.74). Overall, measures from $MBWN_2$ were weakly correlated with GI_{TOT}: LCI was 0.29 (95% CI: −0.45 to 0.82), Sacin*VT was 0.22 (95% CI: −0.50 to 0.77), and Scond*VT was 0.24 (95% CI: −0.51 to 0.70). It is worth also reporting that in the present sample the correlation between LCI and FEV_1 %predicted was −0.69 (95% CI: −0.94 to −0.37).

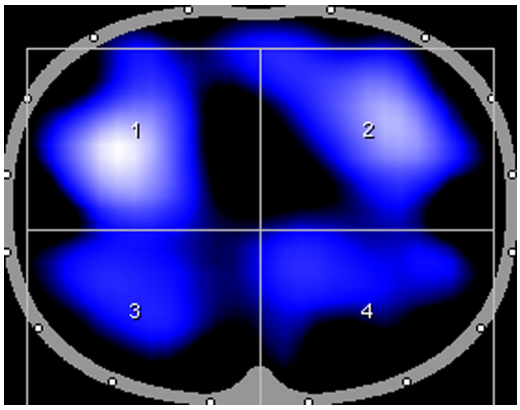

FIGURE 2 EIT image. Cross-section view of a 9-year-old boy's lungs, affected by Kartagener syndrome with *situs inversus totalis*. FEV_1 is 72.7% predicted and LCI 13.7; GI_{TOT} is 42. The image is divided into four quadrants showing the left dorsal (4) and left ventral (2), right dorsal (3), and right ventral (1) regions. The region 3 shows reduced passage of air. EIT, electrical impedance tomography; FEV_1, forced expiratory volume in 1 s; GI_{TOT}, total global inhomogeneity; LCI, lung clearance index.

4 | DISCUSSION

In this observational study on children with PCD and mild-to-moderate FEV_1 impairment, we documented that EIT has a good correlation with spirometric and plethysmographic findings, whereas metrics from $MBWN_2$ were weakly correlated with EIT.

EIT is a noninvasive, radiation-free functional imaging technique, that dynamically measures regional lung ventilation inhomogeneity by applying small alternating currents on the chest wall during breathing cycles. Even though EIT has been widely used at the bedside of mechanically ventilated patients to continuously monitor the distribution of lung ventilation during recruitment maneuvers,[22,23] it could be particularly promising for very young children because it does not require active patient collaboration. Indeed, EIT was well tolerated by children and adolescents included in the present study, and the time required to perform EIT was shorter than the whole $MBWN_2$ procedure, which required 10–15 min, on average.

Recent studies conducted within the CF pediatric population showed a good correlation of the EIT technique with lung function parameters and radiologic results.[10] These findings highlighted the ability of EIT to distinguish between patients with CF and healthy controls and to differentiate different disease states also in very young patients.[11] In the present study, we found a narrow dispersion of GI_{TOT} values, thus suggesting a good reliability of the average GI compared to a broad FEV_1 impairment.

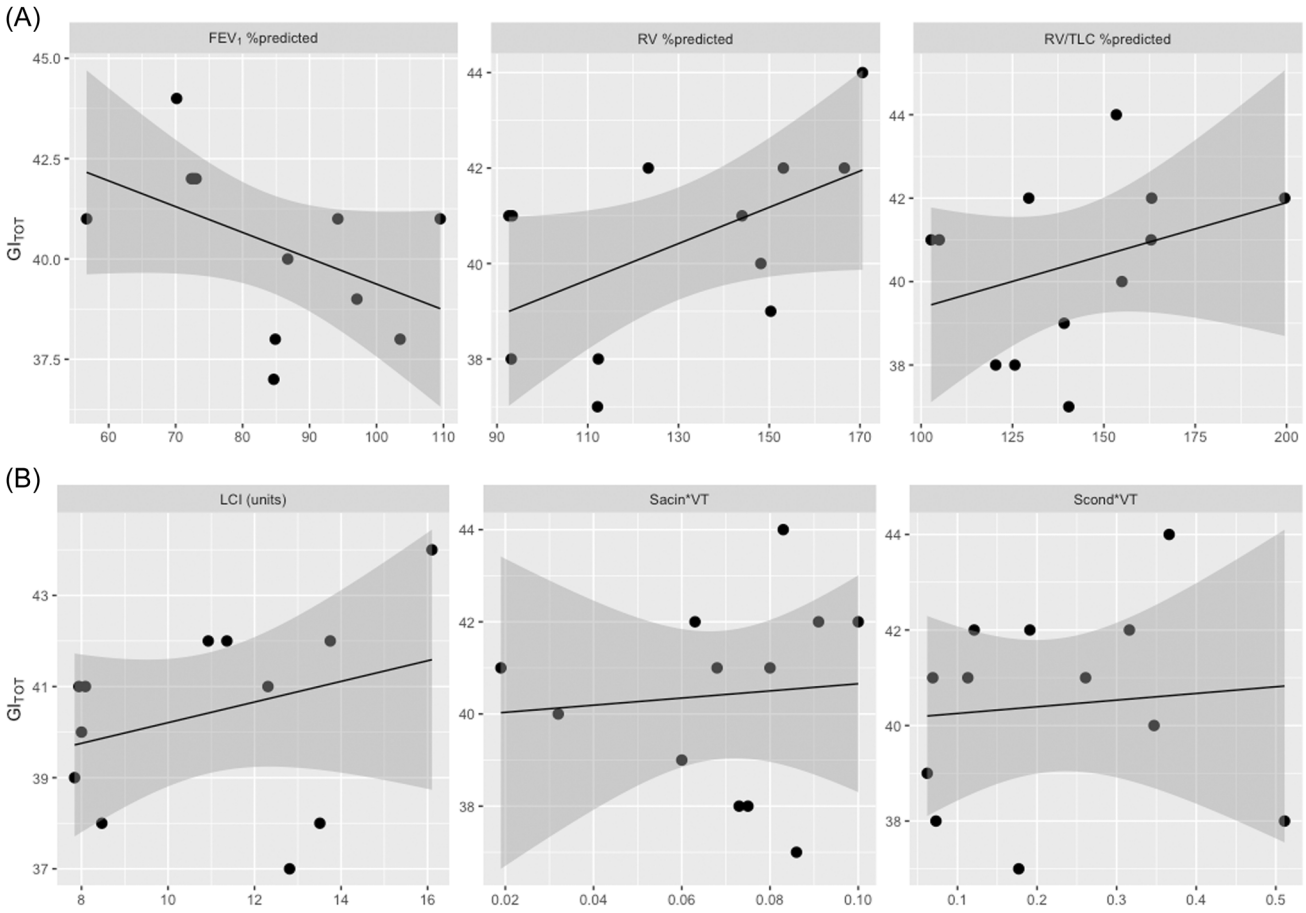

FIGURE 3 Correlation between GI_{TOT} and other respiratory parameters. Scatter plots of (A) spirometry and plethysmography metrics with EIT and (B) $MBWN_2$ derivatives with EIT. Solid line denotes regression line with 95% CI bands (gray). CI, confidence interval; EIT, electrical impedance tomography; GI_{TOT}, total global inhomogeneity; $MBWN_2$, multiple breath nitrogen washout.

Interestingly, the dorsal right quadrant showed the greatest inhomogeneity. The highest value belongs to a patient with KS, probably due to his low ventilation distribution, as depicted in Figure 2. This finding could be likely explained by the combination of poor movement of the ventral part of the diaphragm with an evident impairment of acinar and conductive ventilation distribution, which abnormally increased the regional inhomogeneity. Certainly, information about regional ventilation distribution in patients with PCD are lacking, and EIT is not able to provide accurate information as computed tomography or magnetic resonance imaging, because of its low spatial resolution; however, our results stress the clinical relevance of ventilation distribution while assessing young children with PCD. It is noteworthy to highlight that the availability of a noninvasive tool that provides real-time morphological information of lung ventilation is promising in optimizing respiratory physiotherapy and monitoring the efficacy of the treatment over time as well.[24]

In our sample, we showed a negative correlation between GI_{TOT} and FEV_1 and between GI_{TOT} and RV. While there is no information regarding the correlation between EIT and static volumes, there are several studies, conducted either in CF or in asthmatic children, that documented the significant correlation between spirometric measurements (e.g., $FEV_{0.5}$, FEV_1, FVC, FEV_1/FVC, MEF_{25}, MEF_{50}, MEF_{75}) and simultaneously performed EIT.[10,11,25] In the present work, the respiratory maneuvers were not performed simultaneously and EIT was carried out during tidal breathing because the measurement of EIT-derived FEV_1 was beyond our purpose. The good correlation between GI_{TOT} and FEV_1 supports the hypothesis that the global EIT measure could be a complementary tool to characterize pulmonary function. However, considering the number of individuals included, correlations show a broad range of plausible values, which require larger studies to gain precision and to inform clinical practice.

Early detection of lung impairment might have a significant effect in delaying the disease progression and the lung function decline. Spirometry is currently used in the clinical setting to monitor lung function as it is widely available and not expensive. Many authors suggested that abnormal lung function might develop early in life and a recent prospective, longitudinal study on 137 patients with PCD aged less than 19 years documented poor lung function and respiratory decline from 3 years of life, with a severity in lung function impairment related to ciliary ultrastructural defect and the corresponding genotype.[26] More recently, data on 333 children with PCD showed that the mean predicted FEV_1 was significantly lower in children with PCD compared with children

with CF, especially at an earlier age.[27] A recent multinational study on 991 patients from the international PCD Cohort documented that FEV_1 and forced vital capacity were significantly lower in all ages, including children, suggesting that lung function could be already impaired early in life.[28] Although FEV_1 shows a good correlation with lung structure changes documented with high-resolution computed tomography (HRCT),[29,30] FEV_1 has been shown to be quite insensitive in detecting early structural airway disease. On the contrary, LCI seems to be more reliable than FEV_1 in the early assessment of abnormal airway function and changes on HRCT.[6,31] Indeed, our study supports previous findings, considering that 5 out of 12 children (41.7%) showed FEV_1 below LLN, while abnormal LCI was present in nearly all patients, including those with normal FEV_1.

We documented that ventilation inhomogeneity was increased in both conducting and acinar airways, but we found more ventilation inhomogeneity in the most distal airways beyond terminal bronchioles (Sacin*VT), compared to the conducting airway zone (Scond*VT). The greatest increase in Sacin*VT has been already described in patients with chronic obstructive pulmonary disease (COPD) and this is not surprising since PCD and COPD share many common pathways in terms of airway inflammation and lung injury.[32] Our findings are also consistent with the results of a cross-sectional study on 27 children and adolescents with PCD, which demonstrated that this disease is characterized by marked peripheral airway dysfunction.[4] Interestingly, despite abnormal LCI and impairment in Sacin*VT and Scond*VT, we found that in our cohort, RV *Z*-score and RV/TLC *Z*-score were normal. We can speculate that in children with PCD small airway involvement and gas trapping due to mucus plugging might have intra- and interregional variability, resulting in overall normal static volumes. With increasing age, changes in ventilation inhomogeneity might become widespread and more pronounced, leading to higher static lung volumes and capacities.[33]

Our findings also showed a weak correlation between $MBWN_2$ test and EIT. Both methods show a significant association with FEV_1, however, it appears that they reflect different aspects of ventilation inhomogeneity. LCI detects peripheral airway dysfunction by measuring the gas mixing efficiency in the lungs, whereas EIT provides dynamic information about regional ventilation and lung aeration through the measurement of intrathoracic bioimpedance, which, in turn, varies with the air content. In the present study, we chose the EIT-based GI_{TOT} as an indicator of inhomogeneous ventilation, as it provides a numeric value from the overall pulmonary impedance distribution pattern during tidal ventilation and has been proven to be a reliable tool with good interpatient comparability.[20,34] So far, only a few studies have correlated the ventilation inhomogeneity assessed by EIT and $MBWN_2$ and the only pediatric study conducted on 17 healthy term-born and 15 preterm infants at a matched postmenstrual age of 44 weeks, demonstrated the superiority of EIT in detecting the differences in ventilation distribution between preterm and term-born infants.[35] However, EIT measurements assess ventilation distribution of a lung slice, so a comparison between EIT and LCI may be challenging. In addition, the limited number of participants and the width of confidence intervals lead to caution in drawing firm conclusions. It may be reasonable to consider EIT and LCI as complementary tools.

4.1 | Strengths and limitations

To our knowledge, this is the first study exploring the clinical usefulness of EIT in children with PCD, however, this study has several limitations. First, it is a pilot cross-sectional study based on a convenient sample, and no formal sample size calculation was done. So, further studies on a larger population are required to generalize our findings and to increase the precision of presented estimates. In addition, we arbitrarily decided the duration of EIT measurements, as there is no standardization of EIT procedures and data acquisition. This represents a common limit shared with the literature available on EIT.[36] Therefore, it may be possible that different EIT signal samplings and body positions may provide variable results. Finally, in the present study, no radiologic reference methods were used, and we were not able to calculate the accuracy of EIT, compared to FEV_1 and LCI, in the early detection of ventilation impairment, particularly in the youngest patients. Further investigation is, therefore, necessary for the clinical implementation of this diagnostic method.

5 | CONCLUSIONS

EIT looks promising as a complementary technique to assess ventilation distribution in children with PCD. It demonstrates a good correlation with the most common derivatives of spirometry and body plethysmography, and it could be further implemented in the clinic to characterize lung impairment in young patients with PCD.

AUTHOR CONTRIBUTIONS

Mariacarola Pensabene: Conceptualization; investigation; writing – original draft; software; data curation. **Simone Gambazza**: Methodology; formal analysis; visualization; writing – original draft. **Federica Carta**: Data curation; investigation. **Alessia Rocchi**: Investigation; supervision; writing – original draft. **Mara Lelii**: Investigation; supervision. **Barbara Madini**: Investigation; supervision. **Vittoria Hassan**: Investigation. **Marta Piotto**: Investigation. **Maria Francesca Patria**: Conceptualization; resources; project administration; writing – original draft; writing – review & editing; methodology.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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