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Early follow-up of lung disease in infants with cystic fibrosis using the raised volume rapid thoracic compression technique and computed tomography during quiet breathing

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Abstract

Background: Among the different techniques used to monitor lung disease progression in infants with CF diagnosed by Newborn screening (NBS), raised volume-rapid thoracic compression (RVRTC) remains a promising tool. However, the need of sedation and positive pressure ventilation considerably limits its clinical use. We recently described a semi-quantitative method to evaluate air trapping by chest tomography during quite breathing without sedation (CTqb score). This parameter is the radiological sign of airway obstruction and could be also used for lung disease follow-up in infants with CF. However, its discriminative power compared with RVRTC and correlation with lung function parameters are not known.

Objectives: To compare the discriminative powers of the CTqb score and RVRTC parameters and to determine their correlation during the first year of life of infants with CF.

Methods: In this multicenter longitudinal study, infants with CF diagnosed by NBS underwent RVRTC and CT during quite breathing at 10 ± 4 weeks (n = 30) and then at 13 ± 1 months of age (n = 28).

Results: All RVRTC parameters and the CTqb score remained stable between evaluations. The CTqb score showed a higher discriminative power than forced expiratory volume in 0.5 s ($FEV_{0.5}$; the main RVRTC parameter) at both visits (66% and 50% of abnormal values vs 30% and 28%, respectively). No correlation was found between CTqb score and the different RVRTC parameters or the plethysmographic functional residual capacity, indicating that they evaluate different aspect of CF lung disease.

1 | INTRODUCTION

Early Cystic Fibrosis (CF) lung disease is characterized by airway remodeling and airway obstruction associated with bacterial infections and inflammation. The functional result is a reduced forced expiratory flow, presence of gas trapping, bronchiectasis, and alveolar ventilation inhomogeneity, which may be reduced by therapeutic intervention.[1–5] To this aim, newborn screening (NBS) programs for CF have been

implemented in many countries during the last decade, based on the possible long-term benefit of early medical management to delay or prevent irreversible airway damage that ultimately leads to illness and death.[6–9] To optimize CF follow-up in infants, outcome measures are needed to allow the identification of children who present early disease abnormalities and who would best benefits from preventive therapies. Different methods exist to evaluate the early consequence of airway remodeling in CF. The raised volume rapid thoracoabdominal compression (RVRTC) technique and plethysmographic lung volume assessment allow quantifying the functional consequences of airway obstruction. They are used to quantify, respectively, two hallmark features of early CF lung disease that are frequently present prior to symptom onset: (i) the reduction in forced expiratory flow (FEF) and (ii) the increase in functional residual capacity (FRC), which is an indicator of hyperinflation in the context of gas trapping.[10,11] Multiple-breath inert-gas washout with the measurement of the lung clearance index (LCI) also is a promising tool to quantify ventilation inhomogeneity, as an indicator of gas trapping and bronchiectasis.[10] Moreover, LCI has been proposed as clinical endpoint in one study on infants with CF that showed an improvement of this parameter after daily hypertonic saline nebulization.[2,5] However, in countries where non-resident gases, such as sulfur hexafluoride, are prohibited, the only available alternative (ie, washout of resident gases by breathing 100% oxygen) has important technical limitations due to the negative effect of 100% oxygen on infant breathing patterns.

Among the different RVRTC parameters, forced expiratory volume in 0.5 s ($FEV_{0.5}$) is less specific for small airway obstruction detection compared with forced vital capacity (FVC) or the mean FEF between 25% and 75% of the FVC ($FEF_{25\text{-}75}$). However, $FEV_{0.5}$ presents the better discriminative power between infants with CF and controls[10–16] and the best responsiveness to therapeutic interventions.[2] Therefore, $FEV_{0.5}$ is still considered among the main endpoints for clinical trials in infants with CF, even if it should be used only as a secondary endpoint, due to the difficulties to obtain reproducible results and the near-normal values obtained in infants with CF.[4,17]

Controlled-ventilation chest CT (CV-CT) also is a promising outcome measure for interventional trials in infants with CF.[18] It is a sensitive and efficient method to detect the early presence of airway remodeling, bronchiectasis and gas trapping.[19–26] Moreover, the ratio of bronchial wall area to lumen area, a lung damage parameter evaluated by this technique, has been negatively correlated with $FEV_{0.5}$.[26] This emphasizes the consequence on lung function of the airway remodeling detected by CV-CT. However, CV-CT in infants requires sedation and positive pressure ventilation to minimize motion-related artifacts.[27–29] This, like for RVRTC, considerably limits its routine use in the clinic for CF monitoring in infants.

Therefore, the development of less invasive and less constraining procedures to evaluate lung disease in infants with CF and to improve their early follow-up remains a significant challenge. Indeed, clinicians need objective and quantifiable parameters of lung disease to improve CF follow-up and management and to identify at early stages infants with the most severe lung disease. We recently described a reproducible and efficient semi-quantitative lung disease score to discriminate patients with CF from healthy controls based only on air trapping measurement by CT during quite breathing without sedation (CTqb score).[30] Indeed, the other structural changes relevant for CF lung disease monitoring (ie, increased bronchial wall thickness and bronchiectasis) are poorly detectable with this method.

As a CTqb score equal or higher than three indicates the presence of gas trapping, which is one of the feature airway obstruction,[30] we wanted to evaluate whether it could be used for the follow-up of infants with CF, and to compare its discriminative power with parameters routinely used in the clinic for monitoring CF lung disease progression in young children. To this aim, we evaluated the RVRTC parameters ($FEV_{0.5}$, FVC, and $FEF_{25\text{-}75}$), FRC and the CTqb score in a French cohort of infants with CF at 10 weeks and 13 months of age.

2 | METHODS

2.1 | Study population

Between 2008 and 2013, 39 infants (mean age: 10 ± 4 weeks) with CF diagnosed by NBS and followed in six French CF centers were enrolled to take part in a recently published study showing that a semi-quantitative score evaluated with chest CT during quiet breathing (CTqb score) can be used to follow CF lung disease progression. This study demonstrated that air trapping explains 90% of CTqb score variability.[30] During this study, some children also underwent RVRTC testing, which was available only in four of the participant centers. Only children who underwent both RVRTC and CT assessments ($n = 35$) were included in the present study. This study was approved by the Comité de Protection des Personnes Sud-Méditerranée IV and the French National Agency for Medicines and Health Products Safety (ANSM). All parents received and signed an informed consent.

All infants underwent NBS (heel prick test for the measurement of immunoreactive trypsinogen) during the first 48–72 h after birth. When results were above the 99th percentile, CF transmembrane conductance regulator (*CFTR*) gene mutation screening was performed followed by the sweat chloride test for CF diagnosis confirmation.

Infants born before week 35 of gestation or with a coexisting heart, lung, metabolic, or neuromuscular disease, or previously mechanically ventilated were excluded.

Two visits were programmed at 10 ± 4 weeks (V1) and 13 ± 1 months (V2) of age. Infants needed to be free of respiratory illness for at least 1 week before each visit and to have oxygen saturation values ≥94% on testing day. At each visit, infants underwent a chest CT during quiet breathing and a lung function evaluation with the RVRTC technique.

2.2 | Clinical assessment and follow-up during the study

During the study, infants with CF were normally treated according to the French and European standards of care, including bacterial infection prophylaxis and treatment.[31,32] For each infant, *CFTR* genotype, family history of lung diseases, antenatal or postnatal

presence of maternal smoking, and anthropometric data at birth were reported. At each visit, the history of current and past respiratory symptoms, prior hospital admissions, respiratory symptoms and clinical data, available cough swab microbiological results, date of the first culture positive for *Pseudomonas aeruginosa* or *Staphylococcus aureus*, and use of medications or physiotherapy were noted. Weight, crown–heel length and body mass index and the standard scores (Z-scores), adjusted for age and sex, for each measurement based on international growth reference data[33,34] were calculated.

2.3 | Lung function testing

Lung function was evaluated using the RVRTC technique, with the same apparatus in all four centers (Jaeger MasterScreen™ BabyBody Pletysmograph; CareFusion, Höchberg, Germany). Measurement were carried out according to international recommendations,[35] and an inflatable jacket was used to rapidly compress the thorax and abdomen, producing forced expiratory flow volume curves. For this test, infants were sedated with oral chloral hydrate (75–100 mg/kg) and monitored by pulse oximetry.

Breathing pattern at rest (breathing frequency (Bf) and tidal volume (Vt)), functional residual capacity measured by pulmonary plethysmography (FRCpleth) and tidal rapid thoracic compression (RTC) were first evaluated according to international guidelines.[36,37] During the last test, the pressure applied by the inflatable jacket was progressively increased until a plateau of forced expiratory flow was obtained, indicating flow limitation. Then, RVRTC measurement was performed according to international guidelines.[38] Repeated synchronized positive pressure inflation breaths were used for lung inflation to a pressure of 30 cm H_2O. After reaching the maximal inflation, rapid thoracic compression was performed at the "optimal" jacket pressure, as determined during the tidal RTC maneuvers.[39]

The flow volume curves were carefully analyzed. The criteria for acceptable flow volume curves included acceptable transmission pressures at airway opening, a rapid rise to peak flow, expiration to residual volume, absence of glottis closure, and absence of flow transients. The lung function parameters were: FVC, $FEV_{0.5}$, and FEF_{25-75}. Values were extracted from the best curve defined as a technically acceptable curve with the greatest sum of FVC and $FEV_{0.5}$. The maneuver was repeated until obtaining at least another curve with values 10% lower than those of the best curve.

Particular attention was taken to harmonize the procedure and quality control in the four centers to reduce result variability. To be selected, each curved had to meet the control criteria required by the Standard Operating Procedures (SOPs) of the European Cystic Fibrosis Society for Clinical Trial Network (ECFS-CTN)[17] and was then validated by the two main investigators (R.G. and S.M.).

2.4 | Chest CT during normal quiet breathing

As previously described,[30] just after feeding, the infant was comfortably installed on the back, and proper chest positioning was checked with a lateral and median laser beam. When the infant showed a quite breathing pattern, the radiologist manually triggered image acquisition during expiration (visually monitored).

All CT examinations were performed by helical CT image acquisition with 100 kV, tube currents from 80 to 150 mA, 0.4 s of exposure, scan field of view (SFOV) small, pitch 1.375, and matrix 512 × 512.

For each lung, images were analyzed in batches in random order at ×4 magnification and standard lung settings [1450-500], on a soft copy reporting station. As described in our previous study,[30] lung images were subdivided in six zones (upper, mid, and lower; right and left) that corresponded to each lobe. The presence of gas trapping, bronchial wall thickening, and bronchiectasis, or mucus plugging was assessed in each zone and marked as present or absent. The elements used to define the presence of bronchiectasis, according to Hansell et al,[40] were: internal diameter of the bronchus larger than the diameter of the adjacent pulmonary artery branch, absence of normal bronchus tapering or visualization of a bronchus in the lung periphery. The presence or absence of bronchial wall thickening, mucus plugging, and atelectasis was assessed subjectively. Air trapping was defined as a geographic focus of reduced density. Bronchial wall thickening in each zone was scored as: 0 (absent) or 1 (present) (maximum score: 6). For bronchiectasis, the score for each zone was: 0 (absent), 1 (mild bronchiectasis), or 2 (severe or distal bronchiectasis; bronchial luminal diameter two times higher than the diameter of the vessel or presence of bronchiectasis in the distal third of the considered pulmonary lobe) (maximum score: 12). The extent of mucous plugging, atelectasis and air trapping was graded by determining the percentage of the affected area in each zone (absent = 0, <50% = 1; >50% = 2; maximum score: 12). The final score was calculated by adding the scores for each zone (maximum score: 54).

3 | STATISTICAL ANALYSIS

Descriptive data were presented according to data distribution and sample size. The Z-score values for weight, height, and BMI were adjusted for age and sex.[34] The Intra-class Correlation Criteria (ICC) were used to assess the reliability of the CT results from two analyses of the same image performed by the same operator in blind conditions after a 6-month interval. For CT scoring, the Shapiro-Wilk test did not confirm the normal distribution of the studied variables. Therefore, data were presented as medians [first quantile, third quantile] and between-visit comparisons were done with the Wilcoxon test for paired samples. CTqb scores ≥3 were considered abnormal.[30]

Lung function results were reported as Z-scores calculated from the raw lung function parameter values and the recently published reference equations[41] and presented as medians [first quartile and third quartile] due to the sample size and the non-normal distribution (Shapiro-Wilk test). Between-visit differences were assessed using the Wilcoxon test for paired samples. Abnormal lung function was defined by a Z-score outside the 95th percentiles. The distribution of abnormal values was assessed using the chi-square test. Changes over time were modeled using a linear mixed model.

The Kruskal-Wallis test was used to assess the inter-center repeatability for $FEV_{0.5}$, based on the assumption that infants with CF at V1 were similar.

Multivariable linear regressions were used to investigate whether the CTqb score and the RVRTC parameters evaluated at V1 could predict the results obtained at V2, and how they were correlated with other variables (clinical symptoms, antibiotic treatment and microbiological results). Statistical analyses were performed with R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ denoted statistical significance.

4 | RESULTS

4.1 | Infants

For this longitudinal study, 35 infants with CF were included (mean age at diagnosis 7 ± 2 weeks). None presented meconium ileus or any history of respiratory disease before the first visit. The anthropometric details of these infants are presented in Table 1. Moreover, 48% of infants were homozygous and 45% heterozygous for the F508del CFTR mutation; 42% had a positive history of exposure to maternal smoking during pregnancy or after birth and 23% during pregnancy. The weight and BMI Z-scores increased significantly between V1 and V2.

During the study, a cough swab was satisfactorily obtained only in 26 infants at both visits. *S. aureus* was isolated in 18 infants (69%), and the first detection occurred before V1 in 10 infants (38%). *P. aeruginosa* was isolated in eight infants (30%), and the first detection occurred before V1 in two infants (7%). All infants were treated according to the French and European standards of care for CF, including bacterial infection prophylaxis and treatment,[31,32] and 88% of them received intravenous antibiotics. Despite the treatment, based on cough swab cultures, 14 infants (50%) were still infected, intermittently or chronically, by *P. aeruginosa* or *S. aureus* at V2. Viruses were detected in 10 infants (33%).

TABLE 1 Age, anthropometric characteristics, lung function parameters, and CTqb score of children with cystic fibrosis at the first (V1; 10 weeks of age) and second visit (V2; 13 months of age)

	V1	V2
N	30	28
Age (months)	11 [9.9, 11.9]	56.29 [54.9, 60.3]*
Weight (kg)	4.7 [4.3, 5.4]	9.4 [8.7, 10.0]*
Height (cm)	56 [54.0, 58.1]	75 [72, 77]*
BMI	15.2 [14.4, 16.1]	17.1 [16.1, 17.5]*
Weight z-score	−0.62 [−1.3, 0.1]	0.0 [−0.6, 0.8]*
Height z-score	−0.7 [−1.5, 0.3]	−0.4 [−1.0, 0.5]
BMI z-score	−0.5 [−1.1, 0.3]	0.2 [−0.2, 0.6]*
Bf (cpm)	41 [37, 46]	32 [29, 36]*
Vt (mL/kg)	9 [8.3, 9.6]	9.7 [9.0, 10.5]*
FRC (mL/kg)	20 [18.6, 22.9]	23.2 [19.2, 25.8]
Bf z-score	0.22 [−0.6, 1.1]	0.7 [0.3, 1.7]
Vt z-score	−0.4 [−1.1, 0.2]	−0.3 [−0.7, 0.4]
FRC z-score	0.6 [0.2, 1.5]	1.1 [0.5, 2.1]
$FEV_{0.5}$ (mL)	132.0 [121.1, 143.5]	275.0 [254.0, 303.8]*
FVC (mL)	153.0 [138.0, 182.7]	361.5 [309.7, 408.7]*
FEF_{25-75} (mL/s)	250.0 [196.4, 288.0]	464.0 [395.5, 503.7]*
$FEV_{0.5}$ z-score	−1.1 [−1.7, −0.3]	−1.0 [−1.7, −0.2]
FVC z-score	−1.1 [−1.9, 0.2]	−0.9 [−1.5, −0.1]
FEF_{25-75} z-score	−1.72 [−2.76, −0.49]	−1.74 [−2.24, −1.08]
CTqb z-score	5.0 [1.0, 6.5]	3.7 [1.4, 8.6]

BMI, body mass index; Vt, tidal volume; Bf, breathing frequency; FRCpleth, functional residual capacity; FVC, forced vital capacity; $FEV_{0.5}$, forced expiratory volume in 0.5 sec; FEF_{25-75}, mean forced expiratory flow between 25% and 75% of FVC. Data are presented as medians [first quartile and third quartile].

*$P < 0.05$ (comparison between V1 and V2).

4.2 | Lung function

Among the 35 infants with CF, satisfactory RVRTC results were obtained in 30 at both visits. The main reasons for lung function testing failure were: insufficient sedation (one infant; 3%), and technically non-acceptable measurements at the secondary analysis (four infants; 13%). The ventilatory parameters at rest (Bf and Vt) and FRCpleth at V1 and V2 are presented in Table 1 (raw values and Z-scores). These three parameters (Z-scores) did not significantly change between visits.

Similarly, the RVRTC parameters ($FEV_{0.5}$, FVC, and FEF_{25-75}), expressed as Z-scores,[41] remained stable between visits (Table 1 and Figure 1 for $FEV_{0.5}$ variations).

$FEV_{0.5}$ was not significantly different between centers ($P = 0.08$), which indicates an acceptable inter-center repeatability for this RVRTC parameter. As a Z-score lower than −1.64 was considered to be statistically abnormal (>95th percentiles), 30% of infants had an abnormal $FEV_{0.5}$ (the most discriminative RVRTC parameter[32]) at V1 and 28% at V2. Multivariate analyses showed that age, sex, weight, BMI, bacterial colonization, antibiotic treatment, and $FEV_{0.5}$ Z-score at V1 were not associated with the $FEV_{0.5}$ Z-score at V2. The same negative result was obtained for the $FEV_{0.5}$ Z-score variation between visits.

4.3 | CTqb score

Among the 30 infants with satisfactory lung function testing, only 28 underwent a successful CT evaluation at V2. The reasons for CT failure at V2 were non-attendance (one infant) and constant movement during the CT scan (one infant). As previously described,[30] all CT data were re-scored after an interval of 6 months in blind by the same operator and the two scores showed a good concordance (ICC = 0.98 [0.97, 0.99]). The CTqb scores were not significantly different between visits (Table 1 and Figure 1).

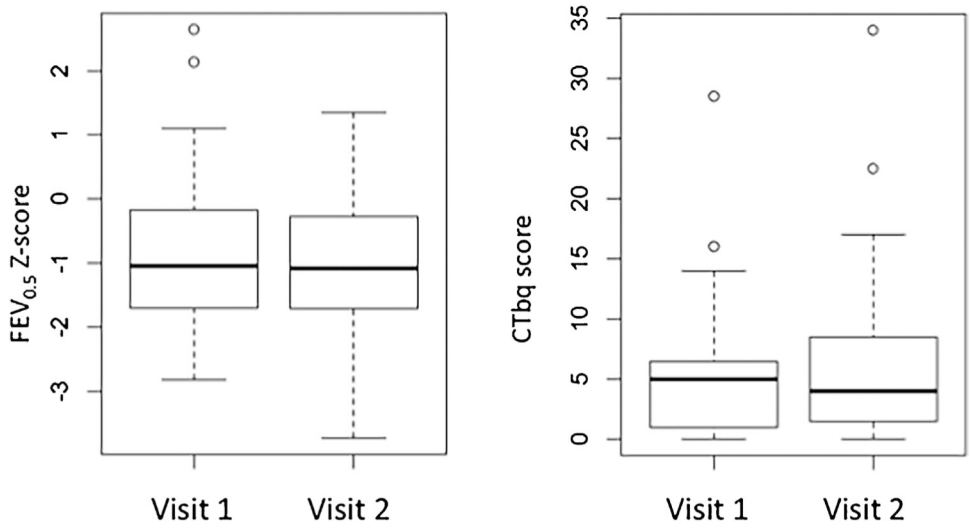

FIGURE 1 $FEV_{0.5}$ z-score and CTqb score (median, first quartile and third quartile) in infants with cystic fibrosis at 10 weeks (visit 1), and 13 months of age (visit 2); $^*P < 0.05$

In a normal population, CTqb Z-scores higher than three correspond to a quantile higher than 97.5% (and thus indicate abnormal presence of air trapping in lungs).[30] At V1, 66% of infants had a CTqb score >3 and 50% at V2.

No correlation was found between $FEV_{0.5}$ and the CTqb score at V1 and V2 (Figure 2), although the CTqb score showed a higher discriminative power than $FEV_{0.5}$ ($P < 0.01$). Similarly, no correlation was detected between the CTqb score and more specific parameters of airway obstruction, such as $FEF_{25\text{-}75}$, FVC, and FRCpleth ($P = 0.2$, $P = 0.18$, and $P = 0.34$, respectively).

5 | DISCUSSION

In this study, we evaluated lung disease changes in 30 infants with CF diagnosed by NBS, at 10 weeks, using two techniques: pulmonary lung function testing with RVRTC and CT imaging during normal breathing. Among them, 28 CF infants were similarly evaluated at 13 months of age.

The main result of our study is that the CTqb score at 10 weeks of age present a higher discriminative power than RVRTC, and particularly $FEV_{0.5}$, for lung disease in infants with CF (66% of abnormal CTqb values vs 30% of abnormal $FEV_{0.5}$ values). However, we did not find any correlation between these parameters, suggesting that they measure different pathological processes. Other RVRTC parameters ($FEF_{25\text{-}75}$, FVC, and FRCpleth) are more specific for peripheral airway obstruction; however, they present lower discriminative power compared with $FEV_{0.5}$ in infants with CF due to their higher coefficient of variation.[10,17] This could also partly explain the lack of correlation between these parameters and the CTbp score.

Using CV-CT, Martinez et al[26] observed a negative correlation between the ratio of wall to lumen area and $FEV_{0.5}$. However, they did not find any correlation between $FEV_{0.5}$ and lung density, which should accurately reflect air trapping, similarly to our CTqb score. Therefore, our results and this study suggest that $FEV_{0.5}$ reduction reflects remodeling of bronchial tree areas that are different from those where abnormal air trapping is observed by CT. Moreover, the less discriminative power of the RVRTC technique we observed in very young infants with CF suggests that $FEV_{0.5}$ is a less sensitive parameter of small airway remodeling in comparison with the radiological sign of air trapping.

We did not observe any between-visit change in RVRTC parameters. $FEV_{0.5,}$ the main RVRTC parameter expressed as Z-score,[41] was stable, despite the BMI increase at V2, which is the first clinical benefit of NBS programs.[6] This result is in accordance with recent studies on infants with CF diagnosed by NBS showing minimal and stable lung function deficit.[10,11,14,41,42] In agreement, the number of infants with abnormal lung function ($FEV_{0.5}$ Z-score lower than −1.64) was low in our study. The lower discriminative power of $FEV_{0.5}$ in young infants and the technical difficulties have been clearly identified previously. Indeed, $FEV_{0.5}$ is only considered as a secondary endpoint in many clinical trials.[4,17]

In this study, we detected *S. aureus* or *P. aeruginosa* infections in 46% of infants with CF at V1, as previously reported with bronchoalveolar lavage (BAL).[43] However, we did not find any correlation between lung function and the presence of airway pathogens in cough swabs. We did not perform BAL, which is considered the "gold standard" for microbiological culture.[44] Previous studies have shown a link between lower respiratory infections by *S. aureus* or *P. aeruginosa*, evaluated by BAL, and lung function.[43] The absence of correlation between lung function and cough swab results in our study indicates that induced sputum analysis is less relevant than BAL for the follow-up of this population. Indeed, although a positive cough swab is strongly predictive of lower airway infection, a negative cough swab does not rule out the presence of lower airway infections.[45]

In our study, we observed radiological signs of airway obstruction in 66% of infants with CF at V1 and in 50% at V2.

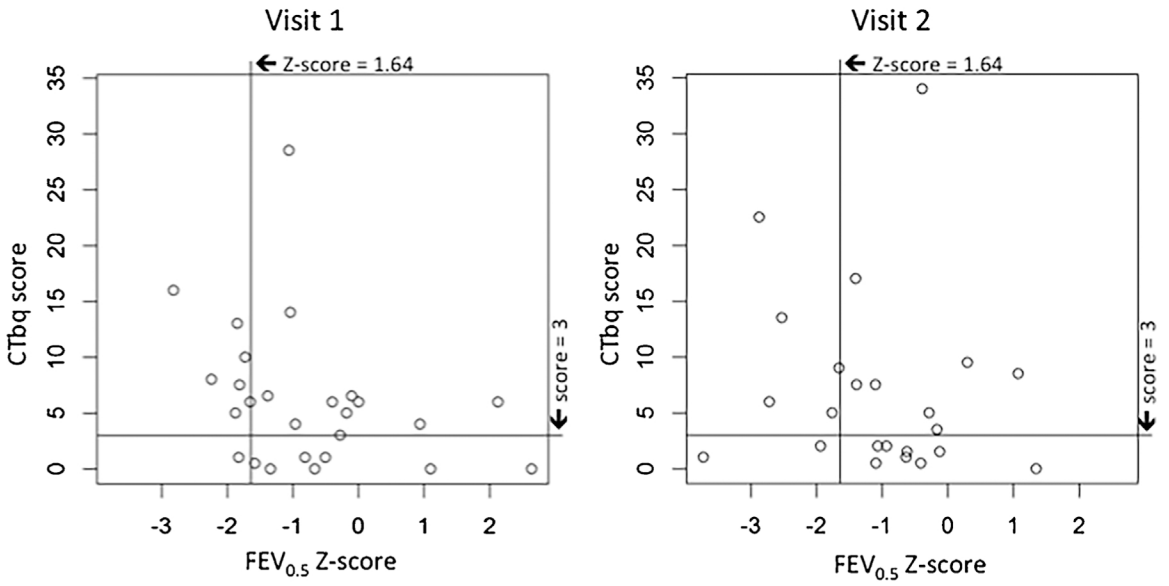

FIGURE 2 Relationship between pulmonary function at 10 weeks (visit 1) and 13 months (visit 2) of age in infants with cystic fibrosis detected by newborn screening. The upper limits (95th percentiles) of the "normal range" for the $FEV_{0.5}$ z-score (−1.64) and CTqb score (3) are represented by a vertical and horizontal line, respectively. At both visits, infants with normal $FEV_{0.5}$ z-score and CTqb score are in the lower right quadrant. Infants with abnormal CTqb score and normal $FEV_{0.5}$ z-score are in the higher right quadrant, while those with abnormal $FEV_{0.5}$ z-score and normal CTqb are in the left lower quadrant.

These results are comparable with those found in sedated and intubated infants with CF at four months of age,[22] and are significantly higher than those obtained with pulmonary lung function testing (30% and 28% at V1 and V2, respectively). Technical progress has decreased considerably the time necessary for end-expiratory image acquisition. This could explain the good accuracy of airway trapping scoring with CT during quite breathing and consequently the better discrimination, compared with RVRTC, in infants with CF at 10 weeks of age. Indeed, the shorter image capture time significantly reduces the respiratory motion artifacts that can increase the CT score variability.[46] On the other hand, due to its greater inter-individual variability and inefficiency in detecting bronchiectasis, the CT score is not optimal to quantify and monitor CF lung disease severity for clinical trial purposes. However, RVRTC is not available in all CF centers because of the cumbersome procedure necessary for sedation and the technical challenges to obtain reproducible data. Conversely, CF lung disease evaluation by CT during quiet breathing without sedation does not need special equipment and skilled personnel devoted to this technique. The easy access to CT emphasizes its usefulness in the follow-up of infants with CF. Nevertheless, the lack of correlation with $FEV_{0.5}$ and its higher discriminative power suggest that the air trapping score, quantified with CT during quiet breathing, represents remodeling of more peripheral airways than $FEV_{0.5}$. In agreement with this hypothesis, a previous study in infants with CF found a relationship between air trapping evaluated by chest CT under sedation and abnormal ventilation distribution based on the multiple breath washout technique, which is a peripheral airway marker.[47]

6 | STRENGTHS AND WEAKNESSES

A major weakness of the CTqb method to evaluate air-trapping is that the volume is not standardized. With CV-CT, air-trapping is evaluated at end expiration, which may roughly correspond to the volume of our study, considering that in both techniques, expiration is passive. Moreover, the initial rotation speed used in our study was 0.4 s, which is certainly insufficient to standardize the end expiratory level when acquisition is manually triggered. Nevertheless, the CTqb score is reproducible and is an efficient tool to discriminate CF from healthy infants based on air trapping measurement.[30] Technical progress, particularly reduction of the rotation speed and development of automatic shooting coupled to ventilatory motion, will allow, in the near future, end-expiratory lung volume standardization with CT during quiet breathing.

Another limitation of the current study is that we did not include a healthy control group for lung function testing and CT during quite breathing. Indeed, the French national ethics committee does not allow sedation of healthy infants with chloral hydrate for functional or radiological tests because of the potential cancer risk,[48–50] although the only longitudinal study on this issue did not find any effect.[51]

Therefore, we used recent published reference equations derived from a cohort of 429 healthy infants (4–118 weeks of age)[41] to express our RVRTC result as Z-scores and the semi-quantitative structural lung scoring system we recently validated[30] for CT during quite breathing, to determine the prevalence of abnormal values with both techniques in infants with CF. Indeed, both can discriminate infants with CF from healthy controls and this is the first study to compare these two scores in the same CF population.

We obtained acceptable RVRTC data for 80% of infants with CF at both visits during the first year of life. The main reason of failure was related to technical difficulties (inadequate sedation or not compliance with the American Thoracic Society/European Respiratory Society quality control criteria). Our technical failure rate is in line with previous studies reporting a success rate between 62% and 96%.[1,2,10–12,26,43,52–55] These values highlight the high technical skills required to perform RVRTC according to the SOPs to ensure good quality data collection. The participant centers in our study underwent harmonization procedures according to the ECFS-CTN SOPs, and test re-reading by two designated experts (SM and RG) was performed to retain only technically satisfactory RVRTC tests. In comparison, we could not obtain an acceptable CTqb score only in one infant with CF, due to the presence of constant movement.

Finally, although our results emphasize the importance of evaluating the correlation between CTqb and CV-CT, we could not address this issue because CV-CT requires sedation, which is not allowed by our national ethics committee.

7 | CONCLUSION

In this longitudinal study in which pulmonary lung function testing and CT scan during quite breathing were performed at 10 weeks and 13 months of age, we observed minimal and stable lung disease in infants with CF. We also show that the CTqb score has a higher discriminative powers to detect lung abnormalities than $FEV_{0.5}$. Therefore, due to its lower technical constraints, it is an interesting tool to help the clinician win over the parents in pursuing or intensifying an aggressive clinical management of CF. However the lack of correlation with lung function parameters implies that the CTqb score and $FEV_{0.5}$ measure different aspects of CF lung disease.

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REFERENCES

1. Davis SD, Rosenfeld M, Kerby GS, et al. Multicenter evaluation of infant lung function tests as cystic fibrosis clinical trial endpoints. *Am J Respir Crit Care Med*. 2010;182:1387–1397.
2. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA*. 2012;307:2269–2277.
3. Amin R, Subbarao P, Jabar A, et al. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. *Thorax*. 2010;65:379–383.
4. Davis SD, Ratjen F, Brumback LC, et al. Infant lung function tests as endpoints in the ISIS multicenter clinical trial in cystic fibrosis. *J Cyst Fibros*. 2016;15:386–391.
5. Subbarao P, Stanojevic S, Brown M, et al. Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis. A pilot study using inhaled hypertonic saline. *Am J Respir Crit Care Med* 2013;188:456–460.
6. Farrell PM, Lai HJ, Li Z, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough! *J Pediatr*. 2005;147:S30–S36.
7. Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics*. 2007;119:19–28.
8. Balfour-Lynn IM. Newborn screening for cystic fibrosis: evidence for benefit. *Arch Dis Child*. 2008;93:7–10.
9. Martin B, Schechter MS, Jaffe A, Cooper P, Bell SC, Ranganathan S. Comparison of the US and Australian cystic fibrosis registries: the impact of newborn screening. *Pediatrics*. 2012;129: e348–e355.
10. Hoo AF, Thia LP, Nguyen TT, et al. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. *Thorax*. 2012;67:874–881.
11. Nguyen TT, Thia LP, Hoo AF, et al. Evolution of lung function during the first year of life in newborn screened cystic fibrosis infants. *Thorax*. 2013.
12. Lum S, Gustafsson P, Ljungberg H, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. *Thorax*. 2007;62:341–347.
13. Lum S, Hoo AF, Hulskamp G, Wade A, Stocks J. Potential misinterpretation of infant lung function unless prospective healthy controls are studied. *Pediatr Pulmonol*. 2010;45:906–913.
14. Linnane BM, Hall GL, Nolan G, et al. Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med*. 2008;178:1238–1244.
15. Ranganathan SC, Stocks J, Dezateux C, et al. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med*. 2004;169:928–933.
16. Kozlowska WJ, Bush A, Wade A, et al. Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178:42–49.
17. Matecki S, Kent L, de Boeck K, et al. Is the raised volume rapid thoracic compression technique ready for use in clinical trials in infants with cystic fibrosis? *J Cyst Fibros*. 2015.
18. Stick S, Tiddens H, Aurora P, et al. Early intervention studies in infants and preschool children with cystic fibrosis: are we ready? *Eur Respir J*. 2013;42:527–538.
19. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. *J Pediatr*. 2004;144:154–161.
20. de Jong PA, Nakano Y, Lequin MH, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. *Eur Respir J*. 2004;23:93–97.
21. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. *J Pediatr*. 2004;145:32–38.
22. Sly PD, Brennan S, Gangell C, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med*. 2009;180:146–152.
23. Mott LS, Gangell CL, Murray CP, Stick SM, Sly PD. Bronchiectasis in an asymptomatic infant with cystic fibrosis diagnosed following newborn screening. *J Cyst Fibros*. 2009;8:285–287.
24. Stick SM, Brennan S, Murray C, et al. Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening. *J Pediatr*. 2009;155:623–628 e1.

25. Mott LS, Park J, Murray CP, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. *Thorax*. 2012;67:509–516.
26. Martinez TM, Llapur CJ, Williams TH, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. *Am J Respir Crit Care Med*. 2005;172:1133–1138.
27. Mott LS, Graniel KG, Park J, et al. Assessment of early bronchiectasis in young children with cystic fibrosis is dependent on lung volume. *Chest*. 2013;144:1193–1198.
28. Long FR, Williams RS, Castile RG. Inspiratory and expiratory CT lung density in infants and young children. *Pediatr Radiol*. 2005;35: 677–683.
29. Long FR, Castile RG, Brody AS, et al. Lungs in infants and young children: improved thin-section CT with a noninvasive controlled-ventilation technique–initial experience. *Radiology*. 1999;212: 588–593.
30. Saguintaah M, Cabon Y, Gauthier R, et al. A simplified, semi-quantitative structural lung disease computed tomography outcome during quiet breathing in infants with cystic fibrosis. *J Cyst Fibros*. 2017;16:151–157.
31. Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. *Eur Respir J*. 2000;16:749–767.
32. Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros*. 2005;4:7–26.
33. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med*. 1998;17:407–429.
34. Cole TJ, Wright CM, Williams AF. Designing the new UK-WHO growth charts to enhance assessment of growth around birth. *Arch Dis Child Fetal Neonatal Ed*. 2012;97:F219–F222.
35. Frey U, Stocks J, Sly P, Bates J. Specification for signal processing and data handling used for infant pulmonary function testing. ERS/ATS task force on standards for infant respiratory function testing. european respiratory Society/American thoracic society. *Eur Respir J*. 2000;16:1016–1022.
36. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS task force on standards for infant respiratory function testing. European Respiratory Society/American Thoracic Society. *Eur Respir J*. 2001;17:302–312.
37. Sly PD, Tepper R, Henschen M, Gappa M, Stocks J. Tidal forced expirations. ERS/ATS task force on standards for infant respiratory function testing. European Respiratory Society/American Thoracic Society. *Eur Respir J*. 2000;16:741–748.
38. ATS/ERS statement: raised volume forced expirations in infants: guidelines for current practice. *Am J Respir Crit Care Med*. 2005;172: 1463–1471.
39. Lum S, Hoo AF, Stocks J. Effect of airway inflation pressure on forced expiratory maneuvers from raised lung volume in infants. *Pediatr Pulmonol*. 2002;33:130–134.
40. Hansell DM. Bronchiectasis. *Radiol Clin North Am*. 1998;36:107–128.
41. Lum S, Bountziouka V, Wade A, et al. New reference ranges for interpreting forced expiratory manoeuvres in infants and implications for clinical interpretation: a multicentre collaboration. *Thorax*. 2016;71:276–283.
42. Thia LP, Calder A, Stocks J, et al. Is chest CT useful in newborn screened infants with cystic fibrosis at 1 year of age? *Thorax*. 2014; 69:320–327.
43. Pillarisetti N, Williamson E, Linnane B, et al. Infection, inflammation, and lung function decline in infants with cystic fibrosis. *Am J Respir Crit Care Med*. 2011;184:75–81.
44. de Blic J, Midulla F, Barbato A, et al. Bronchoalveolar lavage in children. ERS Task Force on bronchoalveolar lavage in children. European Respiratory Society. *Eur Respir J*. 2000;15:217–231.
45. Equi AC, Pike SE, Davies J, Bush A. Use of cough swabs in a cystic fibrosis clinic. *Arch Dis Child*. 2001;85:438–439.
46. Long FR, Williams RS, Adler BH, Castile RG. Comparison of quiet breathing and controlled ventilation in the high-resolution CT assessment of airway disease in infants with cystic fibrosis. *Pediatr Radiol*. 2005;35:1075–1080.
47. Hall GL, Logie KM, Parsons F, et al. Air trapping on chest CT is associated with worse ventilation distribution in infants with cystic fibrosis diagnosed following newborn screening. *PLoS ONE*. 2011;6: e23932.
48. Ikbal M, Tastekin A, Dogan H, Pirim I, Ors R. The assessment of genotoxic effects in lymphocyte cultures of infants treated with chloral hydrate. *Mutat Res*. 2004;564:159–164.
49. Seng JE, Agrawal N, Horsley ET, et al. Toxicokinetics of chloral hydrate in ad libitum-fed, dietary-controlled, and calorically restricted male B6C3F1 mice following short-term exposure. *Toxicol Appl Pharmacol*. 2003;193:281–292.
50. Leakey JE, Seng JE, Latendresse JR, Hussain N, Allen LJ, Allaben WT. Dietary controlled carcinogenicity study of chloral hydrate in male B6C3F1 mice. *Toxicol Appl Pharmacol*. 2003;193:266–280.
51. Haselkorn T, Whittemore AS, Udaltsova N, Friedman GD. Short-term chloral hydrate administration and cancer in humans. *Drug Saf*. 2006;29:67–77.
52. Ranganathan SC, Bush A, Dezateux C, et al. Relative ability of full and partial forced expiratory maneuvers to identify diminished airway function in infants with cystic fibrosis. *Am J Respir Crit Care Med*. 2002;166:1350–1357.
53. Nixon GM, Armstrong DS, Carzino R, et al. Early airway infection, inflammation, and lung function in cystic fibrosis. *Arch Dis Child*. 2002;87:306–311.
54. Subbarao P, Balkovec S, Solomon M, Ratjen F. Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis. *Pediatr Pulmonol*. 2007;42:471–476.
55. Brumback LC, Davis SD, Kerby GS, et al. Lung function from infancy to preschool in a cohort of children with cystic fibrosis. *Eur Respir J*. 2013;41:60–66.