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Abstract

Chest tomography (CT) using the controlled ventilation technique (CTCV) is a sensitive method to detect features of lung cystic fibrosis (CF) disease in infants with CF. However, this technique needs sedation and is not easily applied for the clinician who may need, in the follow-up, to evaluate more precisely lung disease in infants with CF.

Thus, our study aims to evaluate if CT assessment of lung disease, without the need of sedation, during quiet breathing, using a semi-quantitative scoring system, is reproducible and may discriminate infants with CF from control infants at an early stage of the lung disease. 39 infants with CF underwent a first CT at 10.3 [9.4, 11.4] weeks of age. Among them, 33 underwent a second CT at 56.1 [53.1, 59.6] weeks of age. CF scoring images of the different scanner variables, i.e. bronchial wall thickening, bronchiectasis, mucus plugging and air trapping were compared to CT scoring obtained in 2 different groups of control infants of similar age without lung disease. Among all the constituents of the scoring, air trapping is the only parameter discriminating infants with CF from control infants at both ages in our study ($p \leq 0.01$). Moreover, air trapping explains 90% of the total score variability with $r^2 = 0.89$ with a good concordance after re-scoring in blind, 6 months apart, by the same operator for both infant populations: ICC = 0.98 [0.97, 0.99]. In this study, we propose that CT during quiet breathing could be a useful clinical tool to evaluate the early presence of gas trapping in infants with CF.

Keywords: Chest tomography; Cystic fibrosis; Infant; Scoring; Air trapping

1. Introduction

Chest CT using the controlled ventilation technique (CTCV) is a sensitive and extensively used method to detect, in infants with CF and young children, airway remodeling, bronchiectasis and gas trapping, i.e. the hallmark features of CF lung disease

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[1–8]. In this technique, sedation and positive pressure ventilation are necessary to minimize motion-related artifacts in infants who cannot hold their breath at end-inspiration or end-expiration, to obtain satisfactory images and reliable scores of airway abnormalities [9–11]. Moreover, two longitudinal studies, with successive CTCV, 10 months apart, observed in infants with CF, a constant increase of bronchiectasis prevalence exacerbated by the presence of free neutrophil elastase activity in BAL, a biological parameter linked to lung disease progression [7,12]. For all these studies, the Brody-II CT score was the most widely used: it is a validated semi-quantitative outcome in school-age children [3,13]. Recently in the CF community, CTCV has been proposed as a useful outcome for interventional trials in infants with CF [14]. However, CTCV scoring's poor reproducibility undermines it as a promising surrogate outcome to monitor early hallmark features of CF lung disease for clinical trials in this particular population, unless a new more efficient scoring system is developed [15]. Recently, a quantitative outcome measure has been proposed to score CTCV in children with CF younger than 6. This score seems more sensitive than the currently used score [16], but its usefulness in young infants with a mild disease has yet to be established.

Moreover, for ethical reasons, the sedation needed for CTCV may limit the potential usefulness of CTCV utilization in clinic for the follow-up of early-stage lung disease in infants with CF. Indeed, in regard to cancer risk [17–19], the use of Chloral Hydrate, frequently administered to sedate infants, has recently been prohibited for CT purposes in France, and other countries may follow suit.

Interestingly, constant technical progress of CT, whereby the rotation speed increases and the shooting duration decreases, should progressively reduce motion-related artifacts and improve the quality of CT images during quiet breathing. It is important to make CTCV a reliable primary outcome measure for clinical trials that may quantitatively score CF lung disease on CT images obtained under sedation. Conversely, there remains a need to develop and propose new tools easily applicable by the clinician to help him/her to better quantify the lung disease of CF infants diagnosed through newborn screening (NBS).

Thus, our study aims to evaluate if CT assessment of lung disease during quiet breathing using a semi-quantitative scoring system is reproducible and helps discriminate infants with CF from controls at the respective ages of 10 weeks and 13 months.

2. Methods

2.1. Study population

CF diagnosed through newborn screening (NBS) and disease surveillance conducted by the CF center federation has existed in France since 2002 and all infants receive an immunoreactive trypsinogen evaluation based on a heel prick-test in the first 48 to 72 h of life. Those above the 99th percentile undergo cystic fibrosis trans-membrane regulator gene mutation analysis, with confirmation of the diagnosis by means of a sweat chloride test.

Between 2008 and 2013, infants with CF diagnosed through NBS were recruited in the 6 centers participating in the study.

For gene mutation analysis in our study, the 30 most common mutations responsible for CF were investigated using a CF30 Kit (Elucigene CF30, Gen-Probe, San Diego, CA).

This study received the approval of the local research ethics committee "*Comité de Protection des Personnes Sud-Méditerranée IV*" and the agreement of the French Health Products Safety Agency (ANSM) before the start of the research.

The inclusion criteria covered infants diagnosed for CF through newborn screening, with a mean age of 10 ± 4. Infants were excluded if they were born at less than 35 weeks of gestation or had a coexisting heart, lung, metabolic, neuromuscular disease or had previously been mechanically ventilated.

In a longitudinal study with two visits (V1 and V2), infants with CF underwent 2 computed tomography sessions without any sedation during quiet breathing. V1 was performed at 10 ± 4 weeks and V2 at 13 ± 1 months of age. The infants were free of respiratory illness for at least 1 week before each visit and oxygen saturation was ≥ 94% on the day of the test.

Images obtained in infants with CF were compared at both visits with those obtained during a transversal study, in 2 different groups of control infants of similar age. All control infants, without history of lung disease, underwent a CT scan during quiet breathing for reasons presented in Table 2.

Body mass index was calculated, as well as standard deviation scores (Z-scores) for each measurement based on international growth reference data [20,21].

2.2. Chest CT during normal quiet breathing

Just after feeding, the infant was comfortably installed on the back then a clinical spotting with a lateral and median laser beam was performed.

All CT studies were spiral CT acquired using an exposure of 100 kV and a tube current of 80 to 150 mA, 0.4 s of exposition, SFVO small, pitch 1.375, matrix 512 × 512.

Then, images were read in each lung with a ×4 magnification and standard lung settings [1450; −500], in batches, in random order, on a soft copy reporting station, and were analyzed as previously published [4]. For each image analyzed, the scoring was performed twice in blind test at a 6-month interval by the same pediatric thoracic radiologist from one center (Montpellier).

2.3. CT analysis

CT lungs were subdivided in six zones (upper, mid, and lower; right and left) corresponding to each lobe. The presence of gas trapping, bronchial wall thickening bronchiectasis, mucus plugging was considered for each zone as present or absent in a binary fashion. Elements used to define the presence of bronchiectasis according to Hansell et al. [22] were: an internal diameter of the bronchus larger than the diameter of the adjacent pulmonary artery branch, an absence of normal tapering of the bronchus or the 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 geographic foci of reduced density. For bronchial wall thickening, the score for each zone was: 0 (absent) or 1 (present) (maximal score 6). For bronchiectasis, the score for each zone was: 0 (absent), 1 (mild bronchiectasis) or 2 (severe or distal bronchiectasis) (maximal score 12). A score of 2 was defined as presence of bronchial luminal diameter higher than 2 times the diameter of the vessel or presence of bronchiectasis in the distal third of the considered pulmonary lobe. For mucous plugging, atelectasis and air trapping, the extent of each abnormality was graded by determining the proportion of each zone affected (absent = 0, <50% = 1; >50% = 2) (maximal score 12 each). The final score over a maximum of 54 points was calculated by adding the scores for each zone.

2.4. Statistical analysis

Data were inspected for distribution and calculation of descriptive statistics. ICC criteria assess the reliability of the scanner values for two readings of the same picture after a 6-month interval by the same reader at blind. The Z-score of the descriptive statistics, weight, height and BMI was adjusted for age and sex [21].

The Shapiro test did not assess the normality of studied variables. Thus, data was presented as median [first quantile, third quantile] and comparison between groups was assessed by a Wilcoxon test. Significance was taken as $p < 0.05$.

The value of the quantile at 97.5% was used for scanner score threshold to define abnormality.

3. Results

3.1. Infants

In 42 infants with CF (20 boys and 22 girls), 39 (87%) CT under quiet breathing was successfully performed at the age of 10.5 ± 1.7 weeks. Indeed, in 3 infants with CF due to their constant movement which preclude any possibility to obtain good quality CT images.

None of our infants included in this study had presented clinical symptoms relating to their CF disease prior the first CT. Cough was reported by parents in 5 infants prior the second CT (15%). Among the 39 infants, 33 (73%) were also similarly evaluated at the age of 57.5 ± 6 weeks. The main reason for CT failure at the second visit was due to non-presentation of the infant at the appointment by the parents. In only 1 infant, the reason was presence of constant movement. Mean age at diagnosis of CF was 7 ± 2 weeks with 100% diagnosed through NBS. None of our infants included in this study presented meconium ileus or any history of respiratory disease before the first CT. Out of our 42 infants, 20 were homozygous and 18 were heterozygous for the 508 del mutation. All our infants with CF were treated according to CF national and European standards of care including bacterial infection prophylaxis and treatment [23,24]. Median and inter-quantile values of received radiation by child for each scan were 0.28 mSv [0.14; 0.51].

To compare the CT scores obtained in infants with CF with scores obtained in control infants, in a transversal study, 2 groups of 38 (22 boys and 16 girls) and 31 (18 boys and 13 girls) control infants of respectively similar age as the infants with CF at the first and the second visit, were explored by CT under quiet breathing for non-respiratory reasons.

The anthropometric data of the infants with CF and control infants included in our study are presented in Table 1. Clinical indications for CT in the control infants are presented in Table 2.

Table 2
CT indications and diagnosis for control infant.

Indication	Diagnosis	n
Annual follow-up for:	Heart disease	14
	Vascular malformation	14
Work-up for extension in:	Neuroblastoma	11
	Hepatoblastoma	2
	Lymphoma	3
	Nephroblastoma	3
	Genital tumor	3
	Mediastinal cysts	3
	Thoracic tumor	3
	Pelvic tumor	1
Dysphagia	Œsophageal atresia	2
	Œsophagitis	1
Stridor	Normal	2
	Vocal fold paralysis	1
	Laryngomalacia	2
BK suspicion	Normal	3
Cranial trauma	Normal	1

Table 1
Anthropometric characteristics of infants with cystic fibrosis (CF) and of control infants.

	Infant with CF at V1	1st control infant group	Infant with CF at V2	2nd control infant group
n	39	38	33	31
Age (weeks)	10.3 [9.4,11.4] [ba]	6.86 [2.29,13.71] [c]	56.1 [53.1,59.6] [a]	55.14 [51.86,62.71]
Weight (kg)	4.9 [4.4,5.2] [b]	4.55 [3.5,5.85] [c]	9.4 [8.7,10.0]	9.9 [9.05,10.55]
Height (cm)	56 [54,58] [b]	55.5 [51,60] [c]	75 [73,76] [a]	77 [75,78.5]
BMI	15.2 [14.3,16.1] [b]	15 [14,16] [c]	16.9 [16.2,17.7]	17 [16,18]
Weight (Z-score)	−0.67 [−1.55,−0.01] [b a]	0.08 [−0.5,0.66]	0.02 [−0.68,0.44]	0.3 [−0.39,0.8]
Height (Z-score)	−0.71 [−1.63,0.21] [b a]	0.06 [−0.44,0.67]	−0.39 [−1.36,0.45] [a]	0.45 [−0.1,1.16]
BMI (Z-score)	−0.60 [−1.13,0.22] [b]	−0.65 [−1.42,0.02] [c]	0.24 [−0.18,0.74]	0.62 [0.04,0.94]

V1: First visit for infant with CF. V2: second visit for infant with CF.
[a] Difference between control infant and infant with CF at each visit.
[b] Difference between V1 and V2 for CF infant.
[c] Difference between 1st and 2nd control infant group.

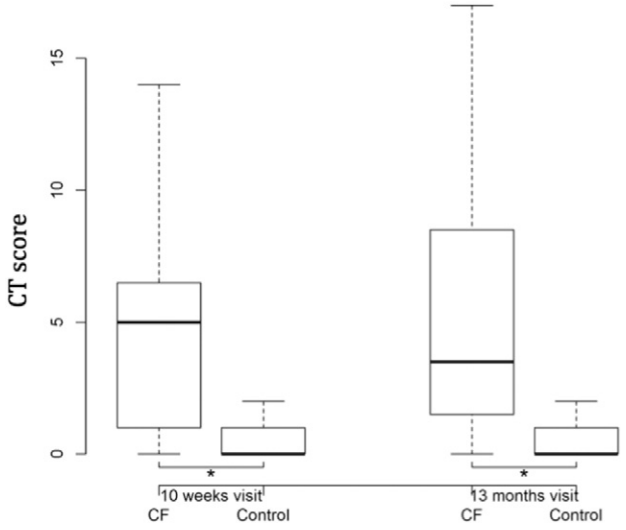

Fig. 1. CT scoring during quiet breathing in control infants and infants with CF at 10 weeks and 13 months. CF: Infant group with cystic fibrosis. Control: Control group of Control Infant. *: $p < 0.05$.

All CT have been re-scored 6 months apart in blind by the same operator and showed a good concordance between the 2 scores for both infant populations with ICC = 0.98 [0.97, 0.99].

As shown by Fig. 1, we observed a significant increase of the CT score in our infants with CF at 10 weeks compared to controls, (5 [1;6,5] vs. 0 [0;1]), with similar differences between CF and controls at 13 months (3.5 [1.5;8.75] vs. 0 [0;1]).

The total score value and each of its components are presented in Table 3 for infants with CF and control infants in absolute value compared to our control infants.

In our infants with CF, bronchiectasis was uncommon at V1 but not at V2. Indeed, we observed in only one infant with CF at V1 (2%) the presence of bronchiectasis, with a score at 2, and in 5 infants at V2 (15%) with a score at 2 [1,4] with minimum value at 1 and a maximum value at 6. None of our control infants presented with bronchiectasis.

Air trapping was the most common features of CF lung disease observed. Indeed, among all the constituents of the final score, air trapping is the main parameter which explains 90% of the total score variability with $r^2 = 0.89$ as shown in Fig. 2. Moreover, as shown in Table 3, only the air-trapping score discriminates infants with CF from control infants at both ages in our study ($p \leq 0.01$).

Fig. 3 shows a typical CT image during quiet breathing in control infants and infants with CF at 10 weeks and 13 months of age.

Considering that a score for CT scan higher than the 97.5% quantile of the normal population is statistically abnormal (>97.5th centile), 2.5% and 3% of our control population respectively at 10 weeks and at 13 months presented an abnormal score, while we found that at 10 weeks, 20 infants with CF (51%) presented abnormal CT scan in regard to airway trapping and 18 infants with CF (55%) at 13 months. In the normal population the quantile at 97.5% correspond to a score of 2.3 at V1 and 2.25 at V2. So we propose in the follow-up of infants with CF to consider for air trapping, that a score higher than 3 is abnormal.

Finally, we observed that the score obtained at 13 months is significantly predictable by the value obtained at 10 weeks ($P = 0.01$). Moreover, we observed that out of the 50% of infants who presented an abnormal score for air trapping at 10 weeks, the abnormality persisted in 72% of them at 13 months.

4. Discussion

The main result of our study is that when CT images are taken under quiet breathing without sedation in infants, from all the constituents of the Brody-II CT score [13], only air trapping allows early discrimination of infants with CF from control infants during the first year in infants as young as 10 weeks of age. Indeed, although the presence of bronchiectasis was the second most common feature of CF lung disease observed only in our CF population, the number of infants which presented this particular bronchial pathology was too low (2% at V1 and 15% at V2) for this feature to help discriminate infants with CF from control infants.

The radiological sign of airway obstruction was detectable in more than 70% of infants at 13 months of age despite an improvement of nutritional status, attested by a statistical BMI increase between the 2 visits. This BMI increase has been previously reported as the first clinical benefit observed after the instauration of NBS [25].

Yet, previous studies using CTVT [4–6,14,26] have observed and quantified in very young infants without any clinical symptoms, the presence of bronchiectasis and air trapping, the 2 major hallmarks of CF lung disease, which may serve as useful outcomes for interventional trials. But due to the sedation issue,

Table 3
Structural lung disease in infants with CF compared to control (CTL) infants at 10 weeks and 13 months.

	Infant with CF at V1	First CTL infant group	Infant with CF at V2	Second CTL infant group
n	39	38	33	31
Age (weeks)	10.29 [9.4;11.4] *	6.86 [2.43;14.29]	56.19[53.08;59.5]	55.14 [51.5;62.7]
Bronchial dilatation (min; max)	0 [0;0] (0;2)	0 [0;0] (0;0)	0 [0;0] (0;6)	0 [0;0] (0;0)
Bronchial wall thickness (min; max)	0.5 [0;1.5] (0;6)	0 [0;0] (0;2)	0.5 [0;2] (0;6)	0 [0;0] (0;1)
Air trapping (min; max)	2.5 [0.75;6] * (0;12)	0 [0;0] (0;6)	1.5 [0;5] * (0;12)	0 [0;0] (0;2)
Mucus plugging (min; max)	0 [0;0] (0;4)	0 [0;0] (0;0)	0 [0;0] (0;4)	0 [0;0] (0;1)
Atelectasis (min; max)	0 [0;2] (0;5)	0 [0;0] (0;1)	0 [0;1] (0;6)	0 [0;0] (0;1)
Total (min; max)	5 [1;6.5] * (0;29)	0 [0;1] (0;6)	3.5 [1.5;8.5] * (0;34)	0 [0;1] (0;3)

* Difference between healthy infant and infant with CF at each visit.

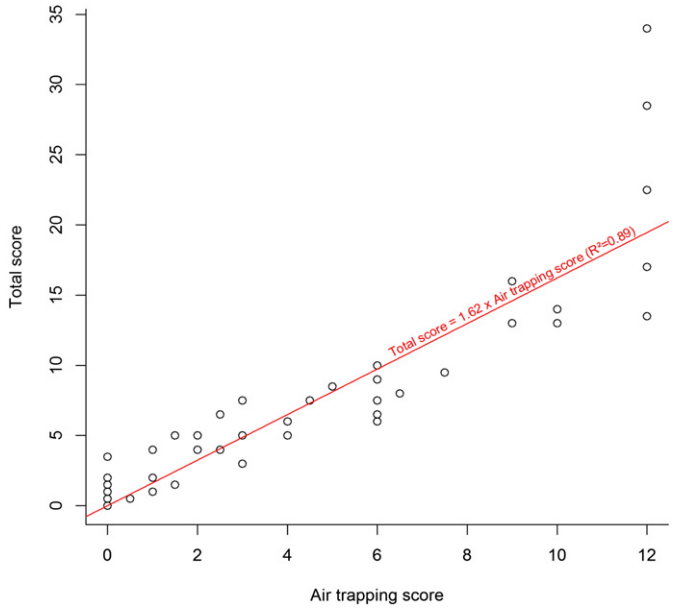

Fig. 2. Global CT scoring in relation to air-trapping scoring in infants with CF.

none of them have included a control population to evaluate the ability of their scoring to discriminate early infants with CF from controls.

Interestingly, a recent study observed that only air-trapping scoring with CTCV at end-expiratory level presented a satisfactory intra-observer agreement [15]. This particular level is similar to that of our study using CT during quiet breathing, considering that in both techniques, expiration is passive. Moreover, with the constant technical progress of CT, the initial rotation speed of 1 s previously used to compare CTCV and CT during quiet breathing in regard to score variability [26] is much higher than the current 0.4 s scan time used in our study. This time reduction may significantly reduce the negative effects of respiratory motion and thus optimize the relative differences in density that occur between normal regions and regions with air trapping, and thus, decrease the variability of the results. This may explain the accuracy of airway trapping scoring to discriminate infants with CF from control infants as young as 10 weeks of age, using CT during quiet breathing. The discriminating power of CT during quiet breathing is an important issue to consider. Indeed, although there is no doubt about the relevance of CTCV as a surrogate outcome in future clinical trials, its usefulness in the follow-up of infants with CF is difficult to consider in regard to the cumbersome procedure necessary for the sedation.

As also previously reported [4,6,7], to provide more consistent outcomes, this study used one single dedicated observer for scan scoring. Even if this choice cannot realistically be implemented for a large clinical practice, we observed good intra-observer reproducibility, an important factor to be considered in future clinical applications.

Nevertheless, we are aware that having a single radiologist reporting the scans is a limitation to our CT data. Although a second independent report would have been ideal, we were not able to achieve this. In the future, automated scoring systems should be developed to standardize the scoring procedure and minimize issues around inter-observer repeatability.

The quasi-totality of score variability explained by air trapping in our study clearly demonstrates that CT during quiet breathing may evaluate only one aspect of CF lung disease, namely, air trapping.

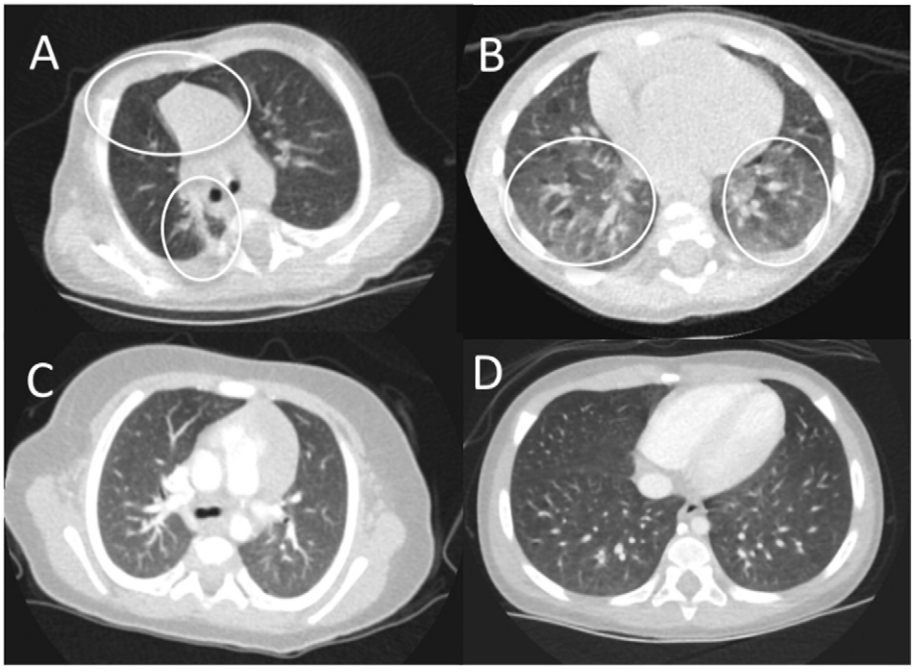

Fig. 3. Examples of CT images at respectively 10 weeks and 13 months from infants with CF (panels A and B) and control infants (panels C and D). Panel A shows, in a 10-week old infant with CF, important abnormalities in air trapping with distension and junction of the 3 anterior parts of the lung normally occupied by the thymus, and presence of atelectasis in the right posterior field of the lung. Panel B shows air trapping with mosaic in the 2 main posterior fields of the lung.

Indeed, we reported for the first time the presence of air trapping in infants with CF as young as 10 weeks of age, using CT during quiet breathing in comparison to a control infant group. The number of 50% of infants with CF presenting abnormal airway trapping scores is lower than the 67% previously found in similarly sedated and intubated infants with CF at 4 months of age [4]. Even if the younger ages or our infants with CF may partly explain the difference, we cannot exclude that our lower value is also related to the weaker accuracy of CT during quiet breathing to discriminate infants with CF from control infants in regard to air trapping. Early bronchiectasis may be more difficult to identify on low lung volume scans compared to CVCT [9]. Indeed, the detection of bronchiectasis is known to be volume dependent, as increased lung volume is associated with increased airway diameter and the number of airways that become visible.

This weakness should be set off by the fact that only 2.5% of our control infants at the same age presented an abnormal air-trapping score, with a score superior or equal to the 97.5% quantile. At 13 months, 55% of our infants with CF presented an abnormal air-trapping score, a finding consistent with the severity of the lung disease process.

In regard to the constant improvement of imaging techniques, which will further reduce the scan time, and, in view of ethical considerations, reduce the use of sedation to monitor a lung disease in infants, CT during quiet breathing could be an alternative, anesthesia-free method to evaluate the presence of gas trapping in young infants with CF. Although radiation induced when CT is programmed should remain a constant concern, the median dose delivered in our study was lower than in a previous study using CTCV procedures [4]. Indeed, to exclusively evaluate air trapping, only scan at end of passive expiration is needed. The dose received by our infants for each scan corresponds in France on average to 30 days of natural radiation exposure or 14 chest radiography [27]. Considering that CT during quiet breathing can only detect air trapping, the question whether CT offers a better evaluation of air trapping than chest X-rays should be addressed in further study. Nevertheless, in regard to our experience, chest X-ray seems less efficient to detect early presence of air trapping. Indeed, among our CF infants who only presented at V1 sign of air trapping attested by geographic foci of reduced density observed with CT during quiet breathing, chest X-ray, when performed, was always normal.

Lastly, thanks to continuous technical progress with shorter exposure, this dose is expected to constantly decrease in the future. Nevertheless, alternatives without radiation exposure must be developed, such as multiple breath washout measurements, which are correlated to air trapping [28]. But this test needs special equipment and skilled personnel devoted to this technique, not always available in the different institutions, which are in charge of the follow up of CF infant, which is not the case with CT, especially if automated scoring systems are likely to be developed.

Our study presents several limitations. All infants from our control group had some health issue that required evaluation by chest CT, and thus they cannot be considered as healthy. However, none of them presented pulmonary disease, and all infants with cardio vascular disease or stridor, which might affect CT, presented a score of air trapping of zero except one with air trapping scoring at 1.

Obtaining the chest CT during a post-feeding rest period is probably not practical after infancy, and it seems unlikely that this approach would be viable in older children. The data could still be meaningful if they could help the clinician identify infants at risk of more severe disease. But the usefulness of this technique in the follow-up of CF infant was outside the scope of this study. To address this issue, further studies will be needed to evaluate if chest CT during quiet breathing may predict lung disease at age 4 or 5. Moreover, correlations with infant lung function or CTCV score obtained in the same population are needed. We were unable to address this issue, considering that the necessary techniques were unavailable at the time of the study in the various participating institutions.

5. Conclusion

CT during quiet breathing may not represent an overly promising tool to quantify and monitor the severity of a lung disease for clinical trial purposes due to its greater inter-individual variability, and inefficiency to detect bronchiectasis. However, in this study we showed that this non-invasive procedure may provide the answer to whether or not air trapping exists in CF. Indeed, we propose in this study a semi-quantitative lung disease structural score to determine the presence of air trapping when the value obtained is equal or superior to 3. CT during quiet breathing may be useful in clinic for the follow-up of the early stages of lung disease in infants with CF considering that an image is better than a long explanation, and evidence of lung disease may help the clinician win over the parents in pursuing or intensifying an aggressive clinical management.

Funding

This work was supported by Montpellier University Hospital (PHRC) (PROM 8229).

Acknowledgement

We wish to thank Ms. RENAUD-MALLET Mireille, Interpreter–Translator, member of AMWA, EMWA and SFT, for her contribution in editing this paper.

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