ORIGINAL ARTICLE

Is chest CT useful in newborn screened infants with cystic fibrosis at 1 year of age?

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ABSTRACT

Rationale Sensitive outcome measures applicable in different centres to quantify and track early pulmonary abnormalities in infants with cystic fibrosis (CF) are needed both for clinical care and interventional trials. Chest CT has been advocated as such a measure yet there is no validated scoring system in infants.

Objectives The objectives of this study were to standardise CT data collection across multiple sites; ascertain the incidence of bronchial dilatation and air trapping in newborn screened (NBS) infants with CF at 1 year; and assess the reproducibility of Brody-II, the most widely used scoring system in children with CF, during infancy.

Methods A multicentre observational study of early pulmonary lung disease in NBS infants with CF at age 1 year using volume-controlled chest CT performed under general anaesthetic.

Main results 65 infants with NBS-diagnosed CF had chest CT in three centres. Small insignificant variations in lung recruitment manoeuvres but significant centre differences in radiation exposures were found. Despite experienced scorers and prior training, with the exception of air trapping, inter- and intraobserver agreement on Brody-II score was poor to fair (eg, interobserver total score mean (95% CI) κ coefficient: 0.34 (0.20 to 0.49)). Only 7 (11%) infants had a total CT score $\geq$12 (ie, $\geq$5% maximum possible) by either scorer.

Conclusions In NBS infants with CF, CT changes were very mild at 1 year, and assessment of air trapping was the only reproducible outcome. CT is thus of questionable value in infants of this age, unless an improved scoring system for use in mild CF disease can be developed.

Key messages

What is the key question?

- Is chest CT a reliable surrogate outcome as a clinical tool or as an end-point in clinical trials in 1-year-old infants with cystic fibrosis (CF) diagnosed by newborn screening?

What is the bottom line?

- No, because structural changes detected on chest CT were generally very mild and, with the exception of air trapping, inter and intraobserver agreements on CT scores were poor using the standard Brody-II scoring system.

Why read on?

- Chest CT is of questionable value in infants of this age and thus should not be used routinely; development of an improved scoring system for use in mild CF disease is urgent.

INTRODUCTION

Widespread newborn screening for cystic fibrosis (CF) has resulted in early diagnosis and the potential for early intervention before changes in lung function and structure become irreversible. Sensitive outcome measures to quantify and track early abnormalities in infants and young children are needed both for clinical care and interventional trials. However, early intervention studies are likely to be of considerable duration and involve treatments with possible side effects. Such studies should therefore not be undertaken without ensuring that any risk is justified by a reasonable likelihood of obtaining useful information.

CT of the chest has been advocated as a sensitive surrogate measure of early lung disease,[1–4] since bronchiectasis and gas trapping have been detected in newborn screened (NBS) infants with CF,[5–7] and a recent international seminar concluded that chest CT was a useful outcome for interventional trials in very young children with CF.[8] Despite increasing publications in this field,[5–7 9 10] the challenges in obtaining standardised chest CTs at consistent lung volumes[11] with acceptable radiation exposure in infants, and also identifying a reproducible scoring system, sensitive to very mild lung disease, which can quantify severity of changes in NBS infants with CF, have received relatively little attention. The Brody-II CT score[12] is the most widely used and validated scoring system in CF[2 4 13–16] which quantifies lung disease objectively in school-aged children with good interobserver agreement,[2 12] but its usefulness in young infants with mild disease has not been established. Thus it is difficult to know whether changes identified in this population represent disease, normal variation or experimental error.

A longitudinal observational study of lung function and structure in NBS infants with CF by the London CF Collaboration (LCFC)[17 18] in which volumetric CT scans were obtained at 1 year of age, provided the opportunity to explore these challenges. Before starting the study, discussions were held with international experts, including those

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from the Australian Respiratory Early Surveillance Team for CF (AREST-CF), in order to standardise data collection. In the absence of any validated scoring system for use in NBS infants with CF, the Brody-II system was selected. We hypothesised that significant changes would be detected by 1 year of age but that interobserver agreement using Brody-II would be lower in NBS infants with CF than in older children, owing to the greater proportion of subjects with no, or only subtle, abnormalities.[2 15]

The aims of this study were to (a) standardise CT data collection across multiple sites to achieve consistent data quality with an acceptable radiation exposure, (b) ascertain the incidence of bronchial dilatation and air trapping in NBS infants with CF at 1 year and (c) assess the reproducibility of Brody-II in such infants by measuring inter- and intraobserver agreement of scores.

SUBJECTS AND METHODS

Study subjects

NBS infants with CF born between 2009 and 2011 were referred by one of six specialist LCFC centres for this study.[17 18] Chest CT scanning under general anaesthesia (GA) was performed at three of these centres using standardised protocols at ~1 year of age as part of the study protocol. The study was approved by the North Thames multicentre research ethics committee (#09/HO71/314). Informed written parental consent was obtained (section 1, see online supplementary data).

Protocol for controlled ventilation during GA

Infants were intubated and ventilated (section 2, see online supplementary data). Atelectasis was minimised by using slow inflations to a peak inspiratory pressure (PIP) of ~35 cmH_2O while maintaining a positive expiratory pressure (PEEP) of 5 cmH_2O[19] before the scan. Inspiratory scans were obtained during a breath-hold at 25 cmH_2O PIP, and expiratory scans at 0 cmH_2O. Initial adherence to protocols was variable across centres. Consequently, a team member monitored ventilation (see online supplementary table E3) using the $NICO_2$ respiratory monitor (Philips Respironics, USA).[20] (see online supplementary figure E3 and figure E4.)

Thin-section CT scan protocol

CT scans were performed using multidetector CT units (see online supplementary table E1). A predetermined technique for volumetric CT image acquisition was used (see online supplementary table E2; section 3, see online supplementary data). Scanning ranges for inspiratory and expiratory scans were tailored for each infant. The planned radiation dose range for the entire scan was ≤2.0 mSv with a target of ~1.5 mSv (annual background radiation exposure in the UK ~2.5 mSv).[21–23]

Scoring methodology

CT data collection was completed and scans anonymised before starting scoring. Studies were scored independently without clinical or laboratory information by two scorers (AB: 25 years' paediatric chest CT experience, 13 years' scoring CF lung disease; AC: 7 years' paediatric chest CT experience, 5 years' scoring CF lung disease) using Brody-II scores.[2 12] Using this scoring system, comprising five components, the maximum possible subscore is 72 for bronchial dilatation, 27 for air trapping and 243 for total CT; higher scores indicating more severe disease.[12] (see online supplementary figures E1 and E2)

The two scorers scored 12 training scans provided by AREST-CF, undertaken with similar protocols in young children with CF aged 1–4 years.[5–7] These 'training scans' were scored in two batches of six (section 7, see online supplementary data). Scoring of LCFC scans took place within 6 weeks of completing training; scores from both observers being analysed and compared by LPT who was not involved in scoring. LCFC scans with discrepant subscores were returned to both scorers (without details of prior scores allocated) for subsequent reassessment to investigate whether closer agreement might be achieved (section 7, see online supplementary data). A selection of LCFC scans was completely rescored after ~8 months to assess inter- and intraobserver agreement over time.

Statistical analysis

Data were inspected for distribution (PASW Statistics V.18, Chicago, Illinois, USA) and summarised using number (percentage), mean (SD) or median (IQR) as appropriate. Agreement between observers was assessed using Cohen's κ statistic with linear weighting (MedCal for Windows, statistical software V.12.3.0, Mariakerke, Belgium). κ Coefficients were similar whether analysed as non-weighted (results not shown) or with linear weighting. κ Results were interpreted as 0–0.2: poor agreement; 0.21–0.4: fair agreement; 0.41–0.6: moderate agreement; 0.61–0.8: strong agreement; 0.81–1.0: excellent agreement.[24] Ventilatory pressures and radiation doses between the centres were compared using Kruskal–Wallis with post hoc comparison using Mann–Whitney U tests; adjusted for multiple comparisons so that the family-wise error rate remained at 0.05.

RESULTS

Patient population

The study was conducted between January 2009 and May 2012[17 18 25]; chest CT scans at 1 year were performed in 65 NBS LCFC infants. Table 1 summarises clinical details of the infants. At the time of chest CT, all infants were clinically well with no respiratory symptoms.

Verification of adherence to protocols

PEEP during the recruitment inflations was slightly higher than intended (overall median (95% CI) PEEP 7.2 (5.4 to 8.8) cmH_2O, and was significantly higher in centre B than C ($p=0.012$; see online supplementary table E4). PIP during inflation manoeuvres and end-inspiratory breath-hold was close to protocol specifications, with no significant differences between centres.

Radiation doses

Median effective radiation exposure across all centres was 1.5 (1.2 to 1.8) mSv, with centres A and B achieving median doses close to the target dose of 1.5 mSv; exposure was significantly higher at centre C (see online supplementary figure E5 and table E5; overall Kruskal–Wallis $p<0.0001$). Exposures of ≤1.5 mSv were achieved in 58% of infants; 79% received an effective dose of ≤2 mSv. Three infants in centre C received ≥3 mSv; two owing to suboptimal positioning.

Training scan scoring

Interobserver agreement was, on average, fair for bronchial dilatation during training batch 1 ($\kappa=0.27$ (95% CI 0.08 to 0.46)) and, after a video conference to discuss discrepancies, moderate for training batch 2 ($\kappa=0.45$ (0.17 to 0.72)). During both training sessions greatest agreement was observed for air trapping ($\kappa=0.82$ (0.68 to 0.95) for training batch 1 and 0.79 (0.67 to 0.92) for batch 2) (see online supplementary table E6 and figure E6).

Table 1 Clinical features of infants with NBS-diagnosed CF undergoing CT at 1 year of age

Features	Value
N (% boys)	65 (48)
Age at diagnosis, weeks*	3.4 (3.0–4.4)
Pancreatic insufficiency, n (%)	61 (94)
Meconium ileus, n (%)	7 (11)
Delta F508†, n (%)	58 (89)
Age at time of test, weeks	52.7 (4.7)
Somatic growth	
Weight, z score‡	0.34 (0.10)
Length, z score‡	0.49 (0.97)
Body mass index, z score‡	0.09 (0.84)
Before 1 year CT assessments	
Respiratory symptoms, ever:	
Wheeze, physician-diagnosed	22 (34)
Crackles, physician-diagnosed	7 (11)
Bacterial growth on cough swab, ever§	
Pseudomonas aeruginosa¶	20 (31)
Other significant bacterial growth**	24 (37)
No growth††	21 (32)

Results expressed as mean (SD) or n (%) unless otherwise stated.
*Median (IQR).
†Homozygous or heterozygous.
‡Calculated according to Cole *et al*.[26]
§Based on the presence of bacteria ever isolated in the first year.
¶Definition of colonisation according to Lee *et al*[27]; only 2/65 (3%) infants had any evidence of *Pseudomonas aeruginosa* (*PsA*) on bronchoalveolar lavage or cough swab within 5 days of the CT scan.
**Significant bacterial growth consisted of those who had *methicillin-sensitive* or *methicillin-resistant Staphylococcus aureus (MSSA or MRSA*, respectively), *Haemophilus influenza (HI), Stenotrophomonas maltophilia, Acromobacter xylosidans* or *Aspergillus fumigatus* with no previous growth of *PsA*.
††No bacterial growth consisted of those with isolation of coliforms and upper respiratory tract flora only.
CF, cystic fibrosis; NBS, newborn screened.

LCFC scan scoring

The first round of scoring the LCFC scans (*initial LCFC*, n=65) started within 6 weeks of training and was completed within a month. Complete rescoring of a selected subset of LCFC scans (*rescoring LCFC;* n=22) occurred ~8 months after the initial scoring. As can be seen from table 2, changes were generally very mild, with only seven (11%) infants having a total CT score ≥12 (ie, ≥5% of maximum possible Brody score) according to scorer B, and only two (3%) according to scorer A.

Interobserver agreement between initial and rescoring LCFC rounds

Although discrepancies between scorers with respect to at least one subscore occurred in 50/65 scans, 90% of differences were between a score of 0 (normal), and 1 (minimal to mild disease) (table 2). There was fair agreement for bronchial dilatation and strong agreement for air trapping, both during initial scoring of all 65 LCFC scans and when rescoring (table 3). Scans selected for rescore were representative of those from the entire cohort for the number and severity of changes detected on CT (figure 1).

Scorer B identified more infants with CT changes and generally allocated higher scores than scorer A during initial scoring of LCFC scans, the reverse of that seen during training (see online supplementary figure E6). Scores for air trapping and total score were more similar between scorers during rescoring (figure 1). κ agreement between scorers was initially only fair for bronchial dilatation, with minimal improvement during rescoring, but agreement about the presence or absence of bronchial dilatation or air trapping was consistently achieved in >80% of the scans on initial and rescoring rounds (see online supplementary table E7).

Intraobserver agreement between study rounds

Intraobserver agreement after ~8 months was only fair for bronchial dilatation (scorer A: κ=0.24 (−0.13 to 0.60); B=0.35 (−0.06 to 0.76)) but strong for air trapping (A: κ=0.72 (0.59 to 0.85); B: κ=0.72 (0.55 to 0.88)). For total CT score, scorer A showed strong while scorer B showed moderate agreement (A: κ=0.66 (0.42 to 0.90); B: κ=0.51 (0.29 to 0.73)) (see online supplementary figure E7). Both scorers detected an identical proportion of changes when rescoring but those identified were not necessarily for the same infants. Challenges were faced in discriminating between very mild changes potentially attributable to bronchial dilatation or airtrapping and normal, even by those with considerable expertise, is illustrated in figure 2.

DISCUSSION

This is the first study specifically to assess the reproducibility, and hence validity, of CT evaluation of lung disease in infants with CF. Despite the scoring being undertaken by experienced observers with prior training, with the exception of air trapping, the Brody-II score was not reproducible in this age range. The obvious interpretation of these results is that the mild nature of any CT changes at 1 year of age precluded reproducible evaluation of most parameters. A label of bronchial dilatation in the presence of very mild lung disease should therefore be applied cautiously, at least using current methods and definitions. These findings, together with the technical difficulties in standardising acquisition of CT scans across sites, suggest that the use of CT both clinically and as an endpoint in multicentre trials of infants remains extremely challenging.

Strengths and limitations of the study

Standardised protocols for GA, scanning parameters and image acquisition were established to ensure consistent, reliable CT data were obtained between centres. This is the first study to monitor adherence to a specific CT ventilation protocol objectively. Use of both inspiratory and expiratory volumetric scans to evaluate lung disease (the first such study in NBS infants with CF at 1 year[28 29]) reduces the risk of missing subtle abnormalities, thereby increasing the likely accuracy of the reported changes.

We evaluated Brody-II in infants, as previously undertaken in older subjects with CF, by measuring inter- and intra-agreement of scores by two highly experienced scorers, who underwent training using scans from young children with CF immediately before scoring the LCFC scans in an attempt to ensure consistent interpretation.

The main limitation, as with similar studies, was the lack of normal CT scans for comparison owing to concerns about radiation exposure in healthy individuals. Since clinical CT scans in children with normal lungs (eg, screening for metastases) would not include expiratory images, even this group would not provide adequate controls. In addition, at the time of study, few training scans from 1-year-old NBS infants with CF were available. Owing to the time-consuming nature of the reproducibility studies, no other CT scoring system was used, but given that most use components which at least overlap with Brody-II, it is unlikely that the results would have been very different.

Radiological evidence of structural lung disease

Although AREST-CF detected structural abnormalities in 81% of NBS infants with CF at a median age of 3.6 months,

Table 2 Interobserver agreement for CT scores allocated to infants with NBS-diagnosed CF at 1 year of age during initial scoring of LCFC scans (n=65)

(a) Bronchial dilatation (maximum possible score=72)

κ=0.21 (0.05; 0.37)

Scorer B \ Scorer A	0	1	2	3	4	5
0	48	–	–	–	–	
1	6	–	–	–	–	–
2	4	3	1	–	–	–
3	1	–	–	–	–	–
4	1	–	–	–	–	–
5	–	1	–	–	–	–

(b) Air trapping (maximum possible score=27)

κ=0.66 (0.49; 0.83)

Scorer B \ Scorer A	0	1	2	3	4	5	7	8	15	16
0	37	–	1	–	–	–	–	–	–	–
1	6	3	–	–	–	–	–	–	–	–
2	3	–	1	1	–	–	–	–	–	–
3	1	1	1	2	–	–	–	–	–	–
4	–	–	–	–	2	–	–	–	–	–
5	–	–	–	–	2	–	–	–	–	–
7	–	–	–	–	–	1	–	–	–	–
8	1	–	–	1	–	–	–	–	–	–
15	–	–	–	–	–	–	–	–	1	–
16	–	–	–	–	–	–	–	–	–	–

(c) Total CT score (maximum possible score=243)

κ=0.34 (0.20 to 0.49)

Scorer B \ Scorer A	0	1	2	3	4	5	6	7	8	9	10	12	13	14	17	19	25	30
0	7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
1	5	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	7	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	5	–	2	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–
4	3	1	–	2	–	1	–	–	–	–	–	–	–	–	–	–	–	–
5	–	4	1	1	–	1	–	–	–	–	–	–	–	–	–	–	–	–
6	1	–	1	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–
7	1	1	1	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–
8	1	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–
9	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–
10	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–
12	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–
13	–	–	–	–	–	2	–	–	–	–	–	–	–	–	–	–	–	–
14	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
17	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–
19	–	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–
25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
30	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–

Shaded cells across the diagonals within each table represent identical results by scorers A and B using the Brody-II scoring system. For air trapping scores >5 and total CT scores >12, only those for which any values were obtained are shown. Although scorer B identified more abnormalities on scans than scorer A as indicated by values generally falling below the shaded diagonal cells (17 (26%) vs 5 (7%) for bronchial dilatation; 27 (42%) vs 17 (26%) for air trapping, the severity of changes were generally very minor, with only seven (11%) and two (3%) of patients having a total CT score ≥12 or 5% of the total possible score). κ=κ coefficient (95% CI) as a measure of agreement of CT subscores and total scores allocated by scorer A and B. It can be seen that the majority of discrepancies for bronchodilatation occurred when changes were deemed to be very minor[(1–3)] by one scorer and absent [0] by the other.
LCFC, London Cystic Fibrosis Collaboration; NBS, newborn screened.

bronchial dilatation was only found in 11/57 (19%) at this age,[6] and remained low through the first 2 years of life (~8% at both 1 and 2 years of age) before increasing markedly to ~36% by 4 years.[7] In the most recent publication from this group, prevalence of bronchial dilatation in children with CF during the first 4 years of life was ~60%,[10] ~80% of whom had evidence of bronchial dilatation at some time during the first 3 years. Bronchiectasis as classically defined refers to irreversible dilatation due to damaged bronchi. The 'apparent improvement' in bronchiectasis reported in some of the AREST children with CF

Table 3 κ Values between both scorers during the initial LCFC scoring round of the entire LCFC cohort, (n=65) and during initial and repeat scoring rounds of the subset of 22 scans

	Initial scoring (entire cohort: n=65)	Initial scoring* (subset: n=22)	Rescoring* (n=22)
Bronchial dilatation	0.21 (0.05 to 0.37)	0.38 (0.01 to 0.76)	0.24 (−0.27 to 0.75)
Air trapping	0.66 (0.49 to 0.83)	0.58 (0.37 to 0.79)	0.80 (0.67 to 0.93)
Total CT scores	0.34 (0.20 to 0.49)	0.38 (0.13 to 0.62)	0.67 (0.48 to 0.86)

Results presented as mean (95% CI) linear weighted κ coefficient.
*Scans from 22/65 LCFC infants were selected, results of which are summarised both for initial values and after rescoring.
LCFC, London Cystic Fibrosis Collaboration.

might be associated with mild and borderline normal bronchi (see below). The AREST-CF studies also report more air trapping (67% at ∼4 months,[6] 62% at ∼1 year[7] and 69% at ∼3 years[10]) than in this study. These discrepancies may be partially explained by the fact that in contrast to the AREST-CF study, LCFC children were only studied when asymptomatic. Bronchial dilatation was significantly more likely (60.0% vs 10.2% in asymptomatic) and more severe in AREST infants with CF with respiratory symptoms at the time of CT.[6]

Use of different scoring systems makes direct comparisons difficult, particularly when attempting to quantify severity of changes. While changes could be identified on at least one Brody-II subscore in 34/65 (52%) of the LCFC infants, the magnitude of these changes was often trivial. Important changes (defined either by visual inspection and/or a total CT score ≥5% maximum possible) were only detected in 2% of infants by scorer A and 11% by scorer B (table 2).

Comparing inter- and intraobserver agreement of CT scores with other studies

The interobserver agreement when using Brody-II in NBS infants with CF contrasts with previous studies in older subjects

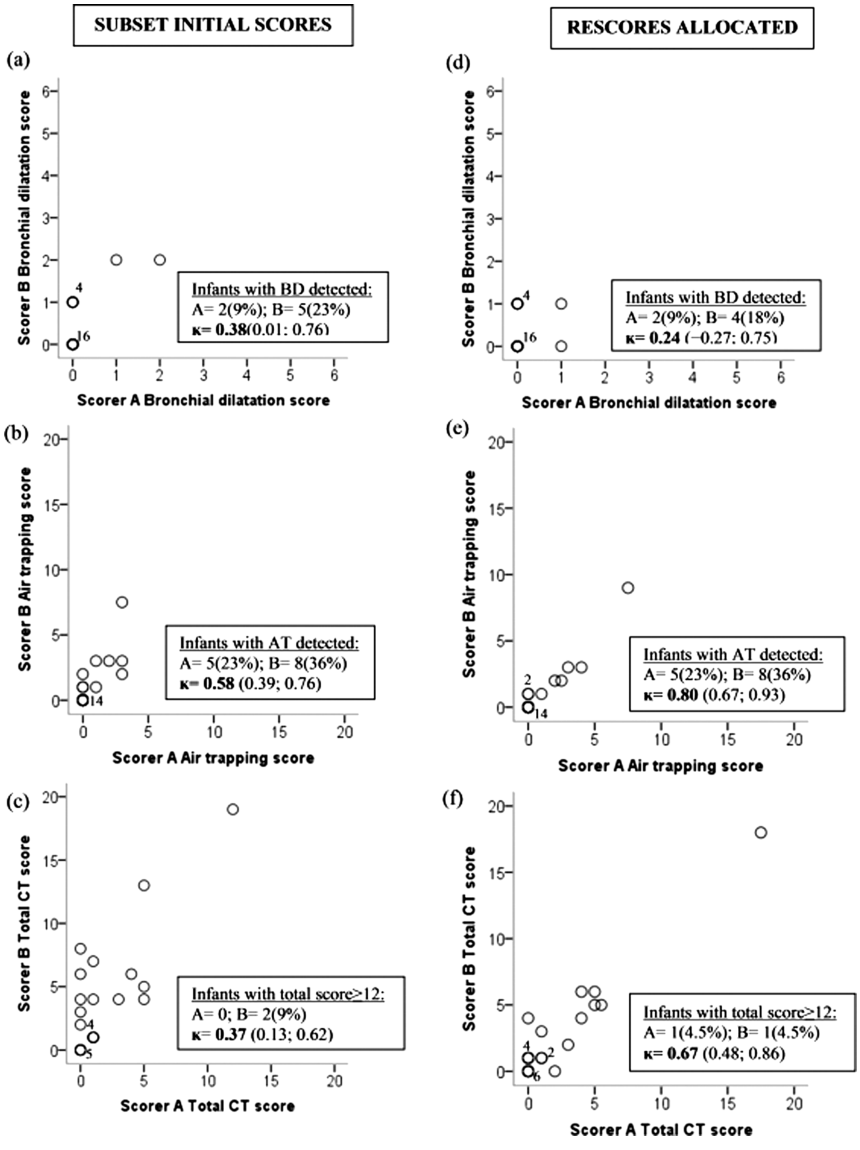

Figure 1 Interobserver agreement between initial and rescoring London Cystic Fibrosis Collaboration (LCFC) rounds. CT scores were allocated by scorers A and B for the subset of 22 scans during initial and rescoring rounds. While all 22 pairs of results have been plotted, overlap of some data, particularly those with zero scores means that not all results can be identified individually. Bold circles represent data that overlaid each other, the number in brackets representing the number of infants with each combination of scores. During *initial scoring of the subset*, scores allocated by scorer B were generally higher than those by scorer A for bronchial dilatation and total scores (A and C). More consistent scores with good agreement were seen for air trapping (B). During *rescoring of this subset*, scores were more similar, although only fair agreement was again seen for bronchial dilatation (D), while good agreement was seen for air trapping and total scores (E and F). κ=κ coefficient (95% CI). AT, air trapping, BD, bronchial dilatation.

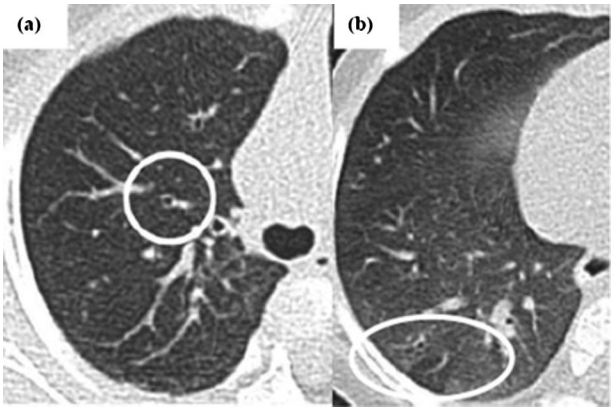

Figure 2 Examples of CT images from infants with cystic fibrosis (CF) showing mild abnormalities in bronchial dilatation and air trapping leading to discrepancy in scoring. (A) An example of thin section CT of the left lung in an infant with CF taken at 1 year of age showing discrepancies in scoring bronchial dilatation (circled). This was scored as normal by scorer A, but mild by scorer B during the initial study round, whereas during the subsequent rescoring round ~ 8 months later, scorer A scored this as mild bronchial dilatation, while scorer B scored it as normal. (B) Subtle tiny areas of hyperlucency in some of the scattered secondary pulmonary lobules of the lower lobes in keeping with air trapping (ringed by oval). During the initial scoring round, scorer A scored this as mild air trapping while scorer B labelled it as no air trapping. During the rescoring round, both scorers allocated mild air trapping.

(including those in which scorers A and B participated, see online supplementary table E8). Previous studies have found that bronchial dilatation is the most reliably reproducible element when evaluating CF lung disease.[12 15 30] The relatively poor agreement in this study probably reflects the subtlety of changes seen. A single scorer scored all the AREST-CF scans with good intraobserver agreement after a 6–12-month interval[7] (see online supplementary table E8). Separate assessments for younger children in whom bronchial dilatation was infrequent and milder were not, however, reported. While use of a single dedicated observer to score all scans[6 7 9] might provide more consistent outcomes, such an approach is impractical in clinical practice and unlikely to be either generalisable or feasible in large multicentre trials. In the absence of measures of repeatability, the extent to which inter- and intraobserver variation contributes to the reported CT findings cannot be established.

Definition of bronchial dilatation

Additional problems in interpreting CT scans relate to lack of international consensus on how to define bronchial dilatation, especially in infants. A bronchoarterial ratio (BAR) >1 as specified in Brody-II was used both in this study and CF-AREST. This speeds up evaluation, as judging whether the bronchus is bigger than the adjoining vessel can be assessed subjectively more easily than calculating a ratio. It has been suggested that a threshold of 0.76, rather than 1, should be applied in children,[31 32] but given the poor inter- and intraobserver agreement even when using BAR≥1 in infants with mild CF lung disease, it is unlikely that this would be effective. Furthermore, measuring changes in small bronchial luminal size to define bronchial dilatation may be beyond current CT spatial resolving ability. The accuracy of assessing BARs, especially in health, is also critically dependent on reliably achieving full lung inflations.[33]

Technical challenges in acquiring standardised CTs

We experienced several challenges in performing thoracic CT in this age group. Despite clear protocols and briefing the anaesthetic and radiology teams across all centres, variability in the image acquisition parameters—namely, airway pressures and radiation doses delivered was seen. The greater variability in radiation doses in centre C might be due to their slightly different type of scanner (see online supplementary table E1) and/or the fact that it was not possible to organise a dedicated radiographer to perform procedures within that hospital, the latter being a problem likely to be found in clinical practice as well as multicentre trials. The presence of an investigator to monitor all procedures improved compliance, but is unlikely to be feasible in clinical practice or most clinical trials.

To date there is no consensus on the optimal method of acquiring CT scans in young children to ensure maximum information with minimal radiation exposure. After discussions with the AREST-CF team, we adopted their approach of obtaining end-inspiratory scans at 25 cmH_2O PIP, and end-expiratory scans at 0 cmH_2O, together with recruitment manoeuvres to minimise procedure-related atelectasis. However, whereas we used a volumetric technique that images the entire lung volume, initial studies by AREST-CF consisted of three thin-slice scans during inspiration and expiration.[6 7 9] Limiting the dataset to three images, compared with ≥20 for the volumetric technique, severely limits the number of airways that can be evaluated. In addition, if bronchi were sampled and imaged at the point of bifurcation, this would overestimate the size of the bronchial lumen, potentially leading to overdetection of bronchial dilatation.

Clinical implications

Results from this study suggest that both the acquisition and interpretation of CT scans need further evaluation before being applicable either as a research outcome measure or clinical tool in NBS infants with CF at least at 1 year of age. Based on the incidence of bronchial dilatation detected by both scorers in this study, between 190 and 850 infants per group would be required if a randomised trial such as the recent Ivacaftor trial[34] were to be extended to infants, in order to detect a reduction in bronchial dilatation of 50% with 90% power at a 5% significance level at 1 year of age; this number would rise further after accounting for those ineligible for such a trial or whose parents decline.[35] Suggestions that such a study would be feasible with only 100/group were based on the incidence of bronchiectasis at 4, not 1 year of age.[7] Since there is neither knowledge about the long-term clinical significance of mild changes detected in young infants with CF, nor any data to suggest that mild changes lead to alterations in clinical management or long-term clinical outcomes, it is questionable whether the risks of exposing young infants to additional ionising radiation outweigh the benefits. Indeed, as a result of this study, without specific clinical indications, chest CTs are no longer performed in NBS infants with CF at 1 year within the LCFC group.

FUTURE DIRECTIONS

Before chest CT can be advocated for widespread use, especially in very young children, standardised CT scanning protocols, which demonstrably can be used in multiple centres, in combination with a reproducible scoring system with good intra- and interobserver agreement, are essential. Given the radiation burden and the expense of even limited, low-dose annual CT scans, it is essential to ensure that the information obtained is

useful; indeed there is a strong case for a randomised controlled study of whether CT improves outcome, analogous to the recent Australasian bronchoscopy study.[36] A more robust approach to CT scoring in infants with CF, in whom changes may be very mild, may be required; current relatively subjective methods could be augmented by publishing visual standards for comparison or by the more widespread use of formal airway measurements and quantitative assessment of air trapping.[37]

In conclusion, we do not believe that CT is ready for widespread clinical use or as a trial endpoint in the first year of life for NBS infants with CF. Until refinement of CT scoring has been established and validated, we recommend caution in reporting bronchial dilatation in NBS infants with CF, the incidence of which appears to be low in the first year of life.

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Collaborators London Cystic Fibrosis Collaboration (LCFC).

Contributors JS and AB were responsible for the conception and design of study; CMO, AC and ASB provided technical advice on imaging and scoring; AM provided anaesthetic advice. JS and LPT were responsible for supervision of the study and for research governance issues, including ethics committee approval. CY and YS supervised the CT imaging. LPT supervised and audited data collection and analyses. Infants with cystic fibrosis were recruited by the paediatric respiratory consultants participating in the London Cystic Fibrosis Collaboration, including AB and CW. LPT and AW performed statistical analyses; LPT, AC, ASB, AB and JS drafted the manuscript; all remaining authors revised and approved the manuscript for intellectual content before submission.

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Is Chest Computed Tomography Useful in Newborn Screened Infants with Cystic Fibrosis at One Year of Age?

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Data Supplement

Background

As part of a multicentre longitudinal research study of lung function and structure in infants with cystic fibrosis (CF) diagnosed by newborn screening (NBS),[E1,2] thin section CT scans under general anaesthesia (GA) were performed at 1 year of age in centres participating in the London Cystic Fibrosis Collaboration (LCFC) using similar GA and imaging protocols. With the same GA, infants underwent bronchoscopy with broncho-alveolar lavage after the performance of chest CT.

In this study we evaluated procedures required for a multi-institutional evaluation of lung disease in infants with CF. Specifically, we evaluated the use of a standardised protocol for CT scanning in infants under GA as well as the use of the Brody-II scoring system for quantifying lung disease in NBS CF infants at a year of age. We hypothesised that significant changes will be detected by 1 year of age but that inter-observer agreement using Brody-II scores will be lower in NBS CF infants than in older children, due to the greater proportion of subjects with no, or only subtle, abnormalities.[E3,4]

This online supplement (OLS) provides additional details regarding standardised GA protocol, CT scanning parameters, protocol for different image acquisition, verification of adherence to protocol through objective measures, radiation exposures, CT scores and other issues which could not be included in the main article due to space constraints.

1. Recruitment and Informed consent

The screening, recruitment, follow-up and parental attitudes to participating in this research study have been described in detail in previous publications.[E1,5] Families of eligible infants were provided separate written informed consent for each part of this observational study. With respect to the CT scan under GA, they were provided with written information augmented by verbal explanations about the potential risk associated with the small additional radiation exposure with having the CT scan at a year of age. They were advised that:

- All radiation (including the background environmental radiation to which we are all exposed) carries a small risk of damage to cells, which may lead to cancer after many years or decades.
- The extra radiation from having one CT scan using the proposed protocol for this study would be equivalent to about half that which their child would receive each year from background sources.

Of the 70 CF NBS infants who underwent lung function assessments at 3 months and 1 year of age,[E1,2] 65 infants agreed to chest CT scans. Remaining families declined due to concerns about GA and CT scanning.

2. General Anaesthesia protocol

- *Ventilate the child to maintain an appropriate end tidal CO_2 (4.5-5 kPa or 33.8-37.6 mmHg) with the addition of positive end expiratory pressure (PEEP=5 cmH_20), using a handheld pressure gauge/manometer.*
- *During initial mask bagging prior to intubation, there is a tendency for air to enter the stomach which could elevate the diaphragm and decrease lung volume. Pass a nasogastric tube and apply suction to reduce any gastric distension PRIOR to initial topogram/ scout.*
- *Maintain baseline ventilatory pattern prior to scan via anaesthetic machine using pressure controlled intermittent positive pressure ventilation (IPPV),*
    - *Respiratory rate 20 breaths per minute*
    - *Inspiratory: Expiratory (I:E) ratio 1:2*
    - *Tidal Volume (VT) 8-10ml/kg*
    - *PEEP: 5 cmH_2O*

- *To minimise the development of atelectasis, administer slow inflations with prolonged inspiratory phase, peak inspiratory pressure (PIP) of 25-35cmH_2O and PEEP of 5-6 cmH_2O using manual ventilation (recruitment maneuvers) prior to the scan.*

3. Scanning protocol and parameters

The following written protocol was given to all anaesthetists and radiologists after detailed explanations of the procedure and the importance of adhering to protocol in order to minimise anaesthesia-related atelectasis and obtain the CT scans at standardised volumes. Table E1 and E2 provide details of the different scanners used in the three centres and the scanning parameters used.

- *Radiographer to select and load the CF scan protocol and, once ready for topogram, to say 'READY FOR TOPOGRAM'.*
- *Anaesthetist to switch the child from being ventilated on the anaesthetic machine to using manual ventilation. The anaesthetist to ensure that patient breath-hold occurs on full inspiration at 25 cmH_2O and to say 'GO FOR TOPOGRAM' (while Topogram/scout was performed) until instructed to release by radiographer who will then say 'FINISHED'. This is essential to facilitate appropriate coverage of the entire lung fields when planning the inspiratory acquisition.*
- *Radiographer to set up both the inspiratory and expiratory acquisitions with coverage from lung apices to bases. Reduce coverage by 30mm at the lung bases for the expiratory acquisition to reduce over-irradiation in the abdomen. Include a 6sec delay prior to scan initiation to ensure lungs are at maximum expiration. Once ready, radiographer to say 'START INFLATIONS for INSPIRATORY SCAN'.*

- *Anaesthetist to perform:*
    - *6 deep slow inflations to 35- 40cmH_2O with a PEEP of 6 cmH_2O to reverse any anaesthetic-related atelectasis, followed by*
    - *4 deep slow inflations to 25cmH_2O with a PEEP of 5 cmH_2O to provide standard lung volume history.*
    - *During the inspiratory scan, the child's lungs are held in inspiration for 6s at 25 cmH_2O, until radiographer instructs 'FINISHED INSPIRATORY SCAN'.*
- *Anaesthetist to cease ventilation and decrease PEEP to zero to allow passive expiration to relaxed end expiratory volume.*
- *Once lung deflation completed (ZERO PEEP); anaesthetist to instruct radiographer by saying 'GO FOR EXPIRATION' (by which time the scanner will have moved into place ready to commence the expiratory acquisition). The aim of the subsequent 6 second delay before scan commencement is to ensure completely stable end expiratory level attained with no subsequent volume drift.*
- *Radiographer to inform anaesthetist when scan complete and that normal ventilatory support can be resumed.*

Table E1: Details of CT scanners used across the three centres

Centre	Multidetector CT scanner model
A	Somatom Definition Dual-Source (64 slice)*
B	Somatom Definition Flash (128 slice)*
C	Somatom Sensation (64 slice)*

Footnote: * Siemens Healthcare, Forchheim, Germany

Table E2: Details of scanning parameters used

	Topogram	**Inspiratory Spiral**	**Expiratory Spiral**
Tube voltage (kVp)	80	100	100
Tube current (mAs)	20	17	20
CTDIvol (mGy)		0.57	0.67
Detector collimation		64 x 0.6mm	
Tube rotation time		0.5 seconds	
Scan Pitch		1	1
Coverage	~ 256 mm	~140 mm	~ 30mm less than inspiratory range
Scan slice width		1mm	
Reconstructed slice thickness		1mm	
Reconstruction algorithm		• 1st reconstruction- B60 sharp kernel • 2nd reconstruction- B30 medium-soft kernel	• B60 sharp kernel
Reconstruction Window Setting		• 1st reconstruction - lung parenchyma setting (1200WW, -600WL) • 2nd reconstruction - mediastinum setting (400WW, 50WL)	• lung parenchyma setting
Post processing		2mm coronal reconstruction on B60 lung setting	

Using the CT parameters described in methods (main MS) and Table E2 in the OLS, the estimated target radiation dose is ~1.5 mSv for the combined volumetric inspiratory and expiratory scans, with an estimated dose range up to 2mSv.

4. CT scoring methodology

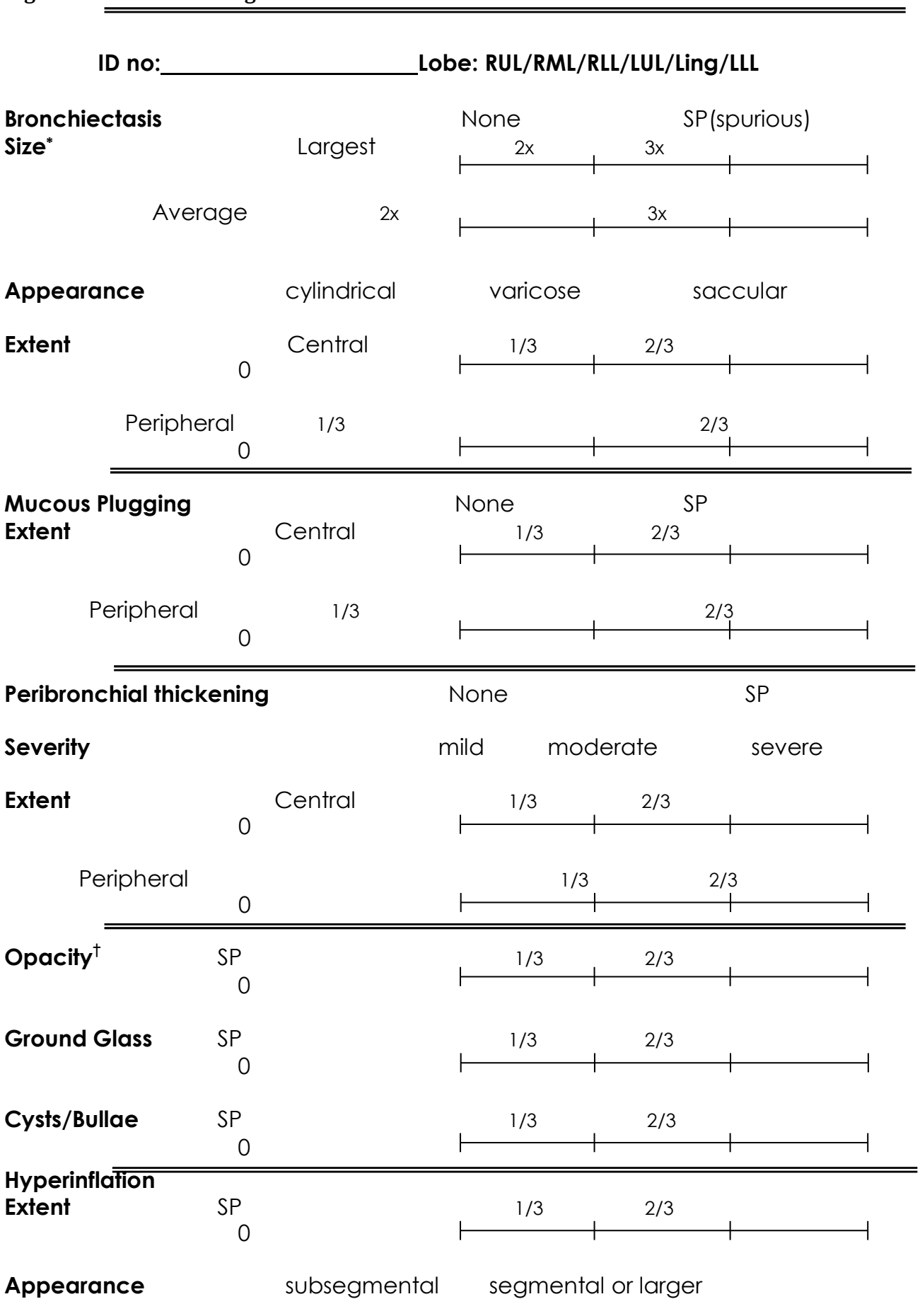
The Brody-II scoring system [6] assesses the severity and extent of bronchial dilatation and bronchial wall thickening, the extent of parenchymal changes of consolidation, ground glass opacification and cysts, extent of mucous plugging and finally the extent and location of air-trapping (based on expiratory scans), referred in Figure E1 as hyperinflation score, in each lobe. Distribution of each abnormality was described according to its central or peripheral location within each lobe. Peripheral lung was defined as the portion of lung within 2 cm of the costal or diaphragmatic pleura whilst central portion accounted for the rest of the lung. Each subject's lungs were divided into 6 lobes, three on each side. A score sheet was filled out for each lobe of the lung, including the lingula as a separate lobe. Therefore for an individual, there were 6 score sheets filled in. The sum of the sub-scores of each abnormality was calculated which, together with the total scores, form the basis of the results. (Figures E1 and E2).

Bronchial dilatation was assessed both in the central and peripheral lung, and rated from 0-3 for both severity and extent.[6] A broncho-arterial ratio (BAR) >1 specified in Brody II was used to define bronchial dilation in this study, as also used in CF-AREST. A critical nuance of this is whether bronchial diameter is evaluated from outer wall to outer wall, or as luminal diameter. While rarely specified in reports, when it is, it is the luminal, rather than external diameter that should be recorded, as was used in the present study.

Mucous plugging was similarly assessed in both central and peripheral lung, and scored from 0-3 for extent. Peribronchial thickening was assessed centrally and peripherally, rated from 0-3 for extent and rated mild, moderate or severe. Parenchymal changes not assessed elsewhere in the scoring system were also given a score from 0-3 for each of: ground glass, dense opacity and cysts or bulla. Finally, air-trapping was rated from 0-3 for extent, and classified as either segmental or sub-segmental. The overall severity score had a theoretical range from 0(normal) to

243(severe abnormality in all categories present throughout each lobe). The maximum ranges of bronchial dilatation and air trapping were 0 to 72 and 0 to 27 per scan respectively.

Figure E1: CFCT Scoring Sheet



Legend: Each score sheet was completed for each lobe i.e. six score sheets were completed for each infant.

*In this Brody-II scoring sheet, the term 'bronchiectasis', previously used in older children has been replaced by bronchial dilatation throughout this manuscript. Many of the bronchial luminal changes observed were mild and borderline and if the term bronchiectasis was used, it might suggest irreversible damage which in this age group with mild severity this may not be the case.

†The category of parenchyma changes consist of the sum of opacity seen, ground glass appearance and evidence of cysts or bullae.

Figure E2: HRCT scoring system

Bronchiectasis score (range 0 to 12)	= (	Extent of bronchiectasis in central lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	+	Extent of bronchiectasis in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	) x	Average bronchiectasis size multiplier 0.5 = 0 1 = 1 1.5 = 1.25 2.0 = 1.5 2.5 =1.75 3 = 2
where						
Average bronchiectasis size	= (	Size of largest dilated bronchus 1 = <2x 2 = 2x-3x 3 = >3x	+	Average size of dilated bronchi 1 = <2x 2 = 2x-3x 3 = >3x	) /	2
Mucous plugging score (range 0 to 6)	=	Extent of mucous plugging in central lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	+	Extent of mucous plugging in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe		
Peribronchial thickening score (range 0 to 9)	= (	Extent of peribronchial thickening in central lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	+	Extent of peribronchial thickening in peripheral lung 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	) x	Severity of peribronchial thickening 1 = mild 1.25 = moderate 1.5 = severe
Parenchyma score (range 0 to 9)	=	Extent of dense parechymal opacity 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	+	Extent of ground glass opacity 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	+	Extent of cysts or bullae 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe
Air Trapping score (range 0 to 4.5)		Extent of air trapping 0 = none 1 = 1/3 of lobe 2 = 1/3 to 2/3 of lobe 3 = >2/3 of lobe	X	Appearance of air trapping 1 = subsegmental 1.5 = segmental or larger		

5. Verification of adherence to protocol for manual ventilation during the procedure

In an attempt to standardise image acquisition across three different sites, training sessions were provided for the relevant anaesthetists and radiographers. Initial images displayed some dependent atelectasis and there were concerns that these may be related to the variation in ventilatory pressures or patterns used by different anaesthetists. To monitor adherence, inflation pressures and volumes were objectively measured through a respiratory monitor, $NICO_2$® [E7] during the procedure (Table E3). Screenshots of measurements recorded using $NICO_2$® during the different image acquisitions can be seen in Figure E3.

Table E3: The number (percentage) of scans performed, attendance of research team and objective monitoring in each centre.

	Total	Centre A	Centre B	Centre C
Number (%) scans performed/centre	65	10/65 (15%)	38/65 (58%)	17/65 (26%)
Number (%) attended by research team	50/65 (77%)	7/10 (70%)	28/38 (74%)	15/17 (88%)
Number (%) with objective monitoring	37/65 (57%)	5/10 (50%)	19/38 (50%)	13/17 (76%)

The research fellow (LT) attended 50 (77%) of the CT procedures in all three centres and objectively measured ventilation in 37 (57%) cases using the $NICO_2$® respiratory monitor. Of the 65 scans, 15% were performed at centre A, 58% at centre B and 26% at centre C.

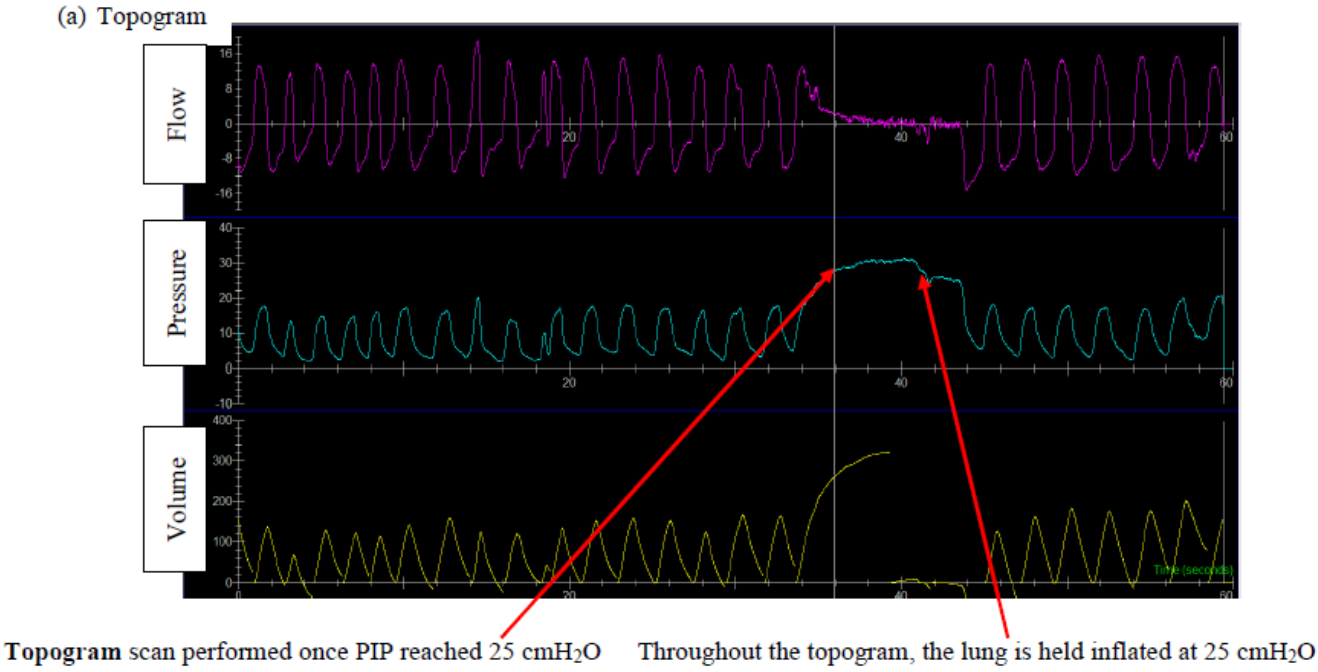
By using the respiratory monitor, ventilatory pattern was found to be similar across the three centres (Table E4). Figure E4 illustrates examples of when ventilatory protocol was not closely adhered to during the GA process for CT scanning.

Table E4: Ventilatory pressures monitored across the three centres using the $NICO_2^{®}$ respiratory monitor

	Centre A	Centre B	Centre C	Overall
PIP during recruitment	32.8(30.4;34.2)	32.6(30.1;35.5)	33.0(30.7;35.5)	32.9(30.6;35.1)
PEEP during recruitment	7.4(6.1;9.8)	8.0(6.5;9.1)*	5.2(2.9;7.6)*	7.2(5.4;8.8)
PIP during breath-hold	26.0(16.3;28.8)	27.6(25.5;29.0)	25.1(23.7;26.2)	26.2(24.5;27.9)

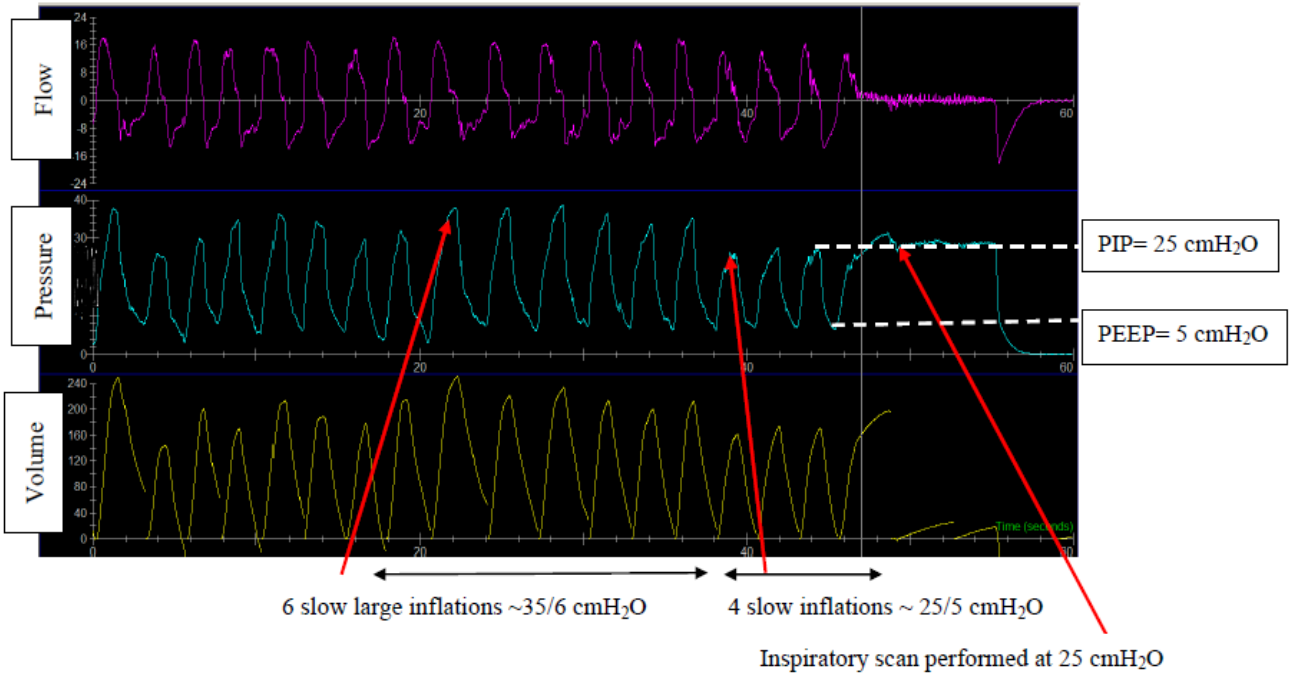
Footnote: Results expressed as median (inter-quartile ranges) cm H_2O. *significant diff $p<0.05$

Figure E3: Screenshot of $NICO_2$® measurements during GA for chest CT scan

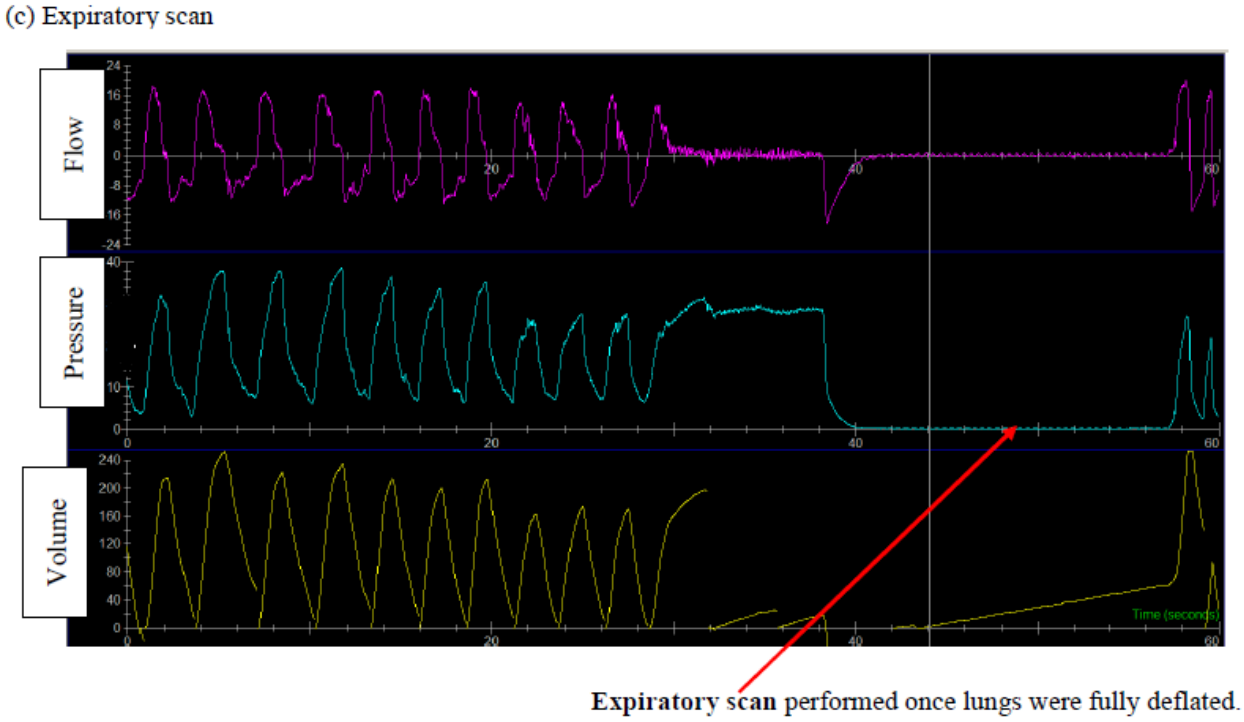


Legend: The top trace (purple) records the flow, the middle trace (turquoise) records the pressure and the bottom trace (yellow) records the volume of each inflated breath during GA. Prior to performing the topogram, baseline ventilation provided initially via the anaesthetic machine using tidal volume of 8-10 ml/kg and PEEP 5 cmH_2O. Once ready for topogram, ventilation was switched to manual ventilation. During topogram, the infant's lungs were inflated to a PIP of ~25 cm H_2O and when this pressure was attained, topogram was acquired during the breath hold at PIP 25 cmH_2O.

(b) During recruitment maneuvers and inspiratory scan

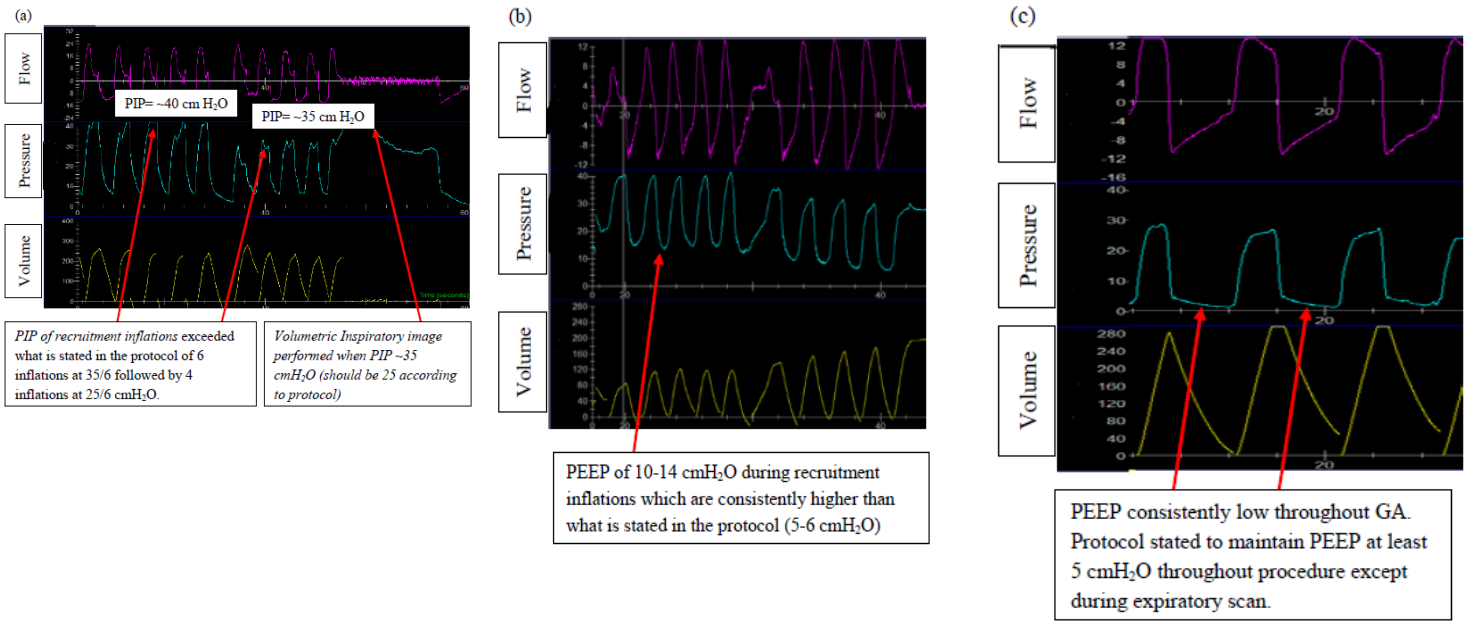


Legend: Prior to the inspiratory scan being acquired, 6 larger and slower inflations of PIP 35-40 cmH_2O were administered to reverse any GA-related atelactasis followed by 4 smaller and slow inflations of 25/5 cmH_2O. During the last of the 4 smaller inflations, the inflation was held at 25 cmH_2O and once attained, the inspiratory image was acquired.



Legend: Immediately following the acquisitionof the inspiratory scan, the inflation was released and the infant's lungs were allowed to deflate down to their elastic equilibrium volume, FRC (zero PEEP), before the expiratory scan was performed.

Figure E4: Examples of $NICO_2$® measurement screenshots, showing examples of when GA did not closely adhered to protocol.



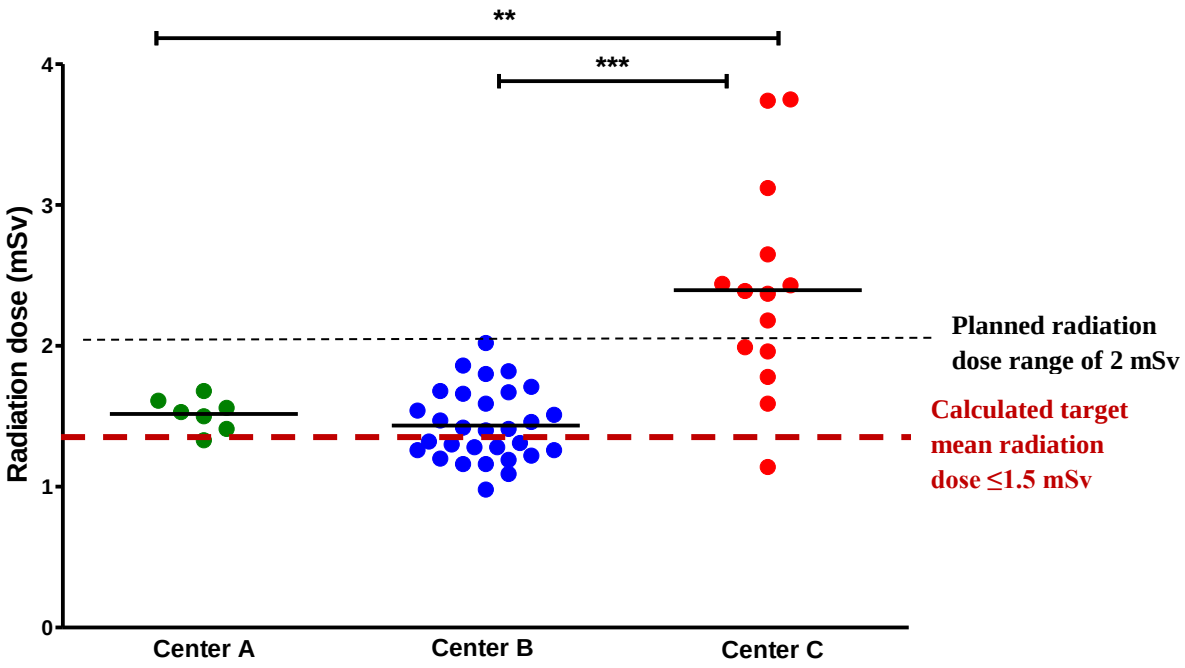
6. Radiation doses

Radiation exposure was minimised using automated dose modulation which performs a real time assessment of body thickness and adjusts tube current to provide consistent image quality. Patient dose information including CT dose index (CTDIvol, unit mGy) and dose-length product (DLP, unit mGy·cm) was recorded for each examination. The effective dose (E) was estimated from taking the DLP and applying a pediatric age specific conversion coefficient that is 0.026 for a child between 4 months and 1 year, and a correction factor of 2 to correct for the use of a 32 cm rather than 16 cm phantom. The formula used was: DLP x 2 x 0.026 = estimated effective dose milliSievert (EmSv).[E8,9]

Results of radiation doses across centres

The highest median radiation exposure was measured at centre C with a lower dose at centre A and the lowest dose at centre B (Table E5 and Figure E3). The greater variability in radiation doses observed in centre C may be due to the slightly different type of scanner (Table E1) and/or the fact that it was not possible to organise a dedicated radiographer to perform procedures within that hospital.

Figure E5: Radiation doses from chest CT across three centres



Legend: Solid horizontal line demonstrates the median radiation doses from each centre. mSv: milliSievert; a unit of measure for effective radiation exposure.**p<0.01; ***p<0.001

Table E5: Effective radiation doses from volumetric inspiratory and expiratory chest CT scans across three centres (n=53)*

	Centre A (n=7)	Centre B (n=31)	Centre C (n=15)	Overall dose
Median (mSv)	1.53	1.31	2.38	1.50
Inter- quartile range, IQR (mSv)	1.37- 1.65	0.86- 2.02	1.14- 3.75	1.24-1.84

Footnote: n= number of scans performed in each centre. mSv= milliSievert, unit of measuring ionising radiation. *The first eight scans performed were limited to 3-slices expiratory scans so have been excluded from these calculations. With these limited expiratory scans (n=8), median (IQR) radiation dose was 1.07(0.92;1.34) mSv. Of the remaining 57 full

volumetric scans, radiation dose for 4 of the later scans could not be calculated due to the lack of available qualified staff.

7. Scoring results

Training scans and scoring

Prior to the two observers commencing their scoring of study scans, they underwent two training sessions. Training scans were provided by the AREST-CF team from children with CF aged 1- 4 years in whom data had been acquired using a similar full volumetric inspiratory and expiratory imaging protocol standardised at an inspiratory lung volume of 25 cmH_2O as in this LCFC study; although in the early published reports of the AREST study, only 3 image slices were acquired at end expiration. Both observers independently evaluated the first 6 training scans (training batch 1) using the Brody-II scoring system.[E6] Scores were then compared and the cases with different scores were discussed by video-conference, with particular attention to differences in the identification of bronchial dilatation.

A second batch of six training studies was then independently evaluated and scores compared (training batch 2). The level of agreement for bronchial dilatation with this second training batch improved when compared to the first batch and was deemed acceptable by both observers (Table E6), who then progressed to the scoring of CT scans obtained for the definitive LCFC study of NBS infants with CF. Agreement for mucous plugging and parenchymal change sub-scores were lower with the second training batch leading to an overall lower Kappa agreement with the total scores of the second training batch. Figure E6 shows the range of sub-scores allocated by the two scorers during the two training batches.

Table E6: Inter-observer agreement of scores according to Brody-II scoring system during the two training batches

	Training batch 1 (n=6)	Training batch 2 (n=6)
Age of infants (years)*	2.0 (1.2; 2.6)	2.3 (1.4; 3.0)
Bronchial dilatation[#]	0.27 (0.08; 0.46)	0.45 (0.17; 0.72)
Air trapping[#]	0.82 (0.68; 0.95)	0.79 (0.67; 0.92)
Total CT scores[#]	0.75 (0.61; 0.90)	0.43 (0.10; 0.75)

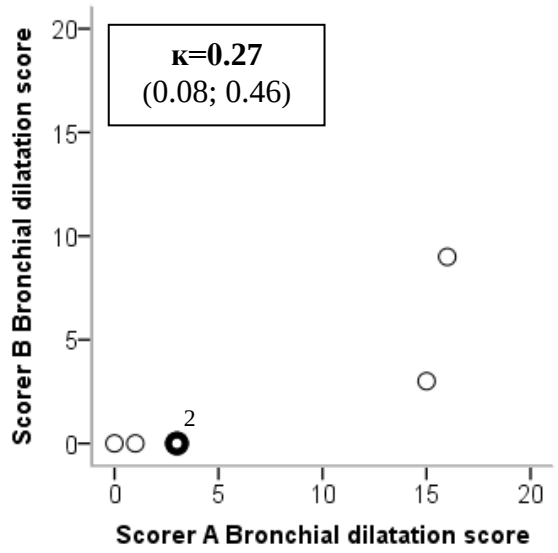
Footnote: * Age expressed as median (interquartile range) in years. [#] Agreement expressed as mean Kappa coefficient (95% confidence interval) using linear weighted Kappa statistics.

Figure E6: Scores allocated by scorers A and B for the two batches of training scans (n=12)

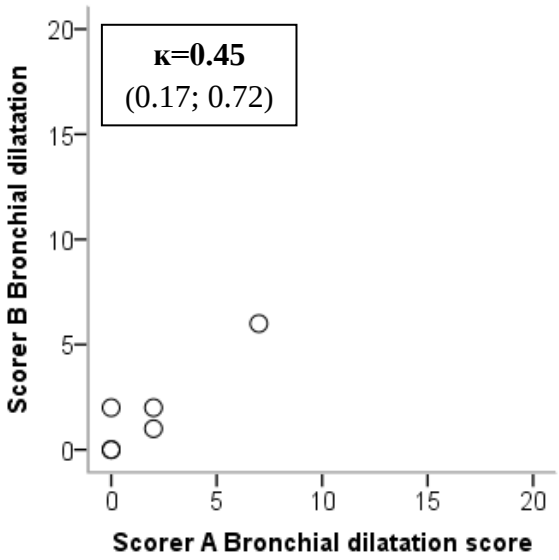
1st training batch (n=6)

2nd training batch (n=6)

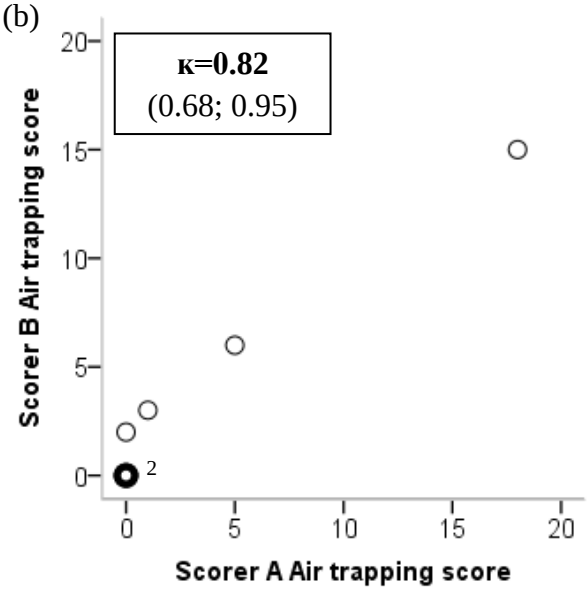
(a)



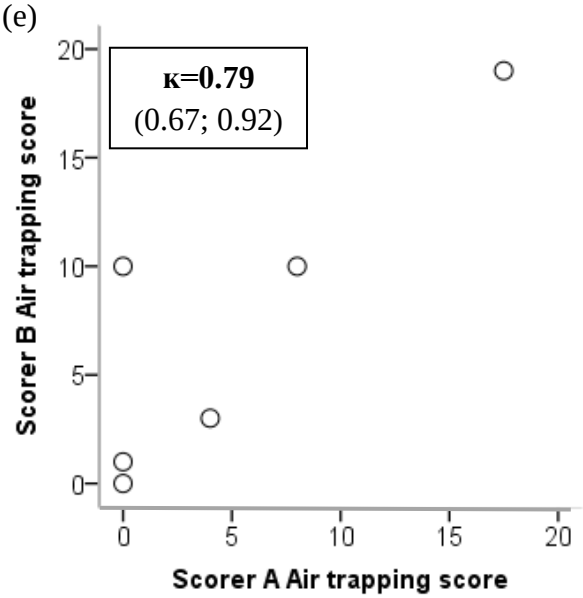
(d)



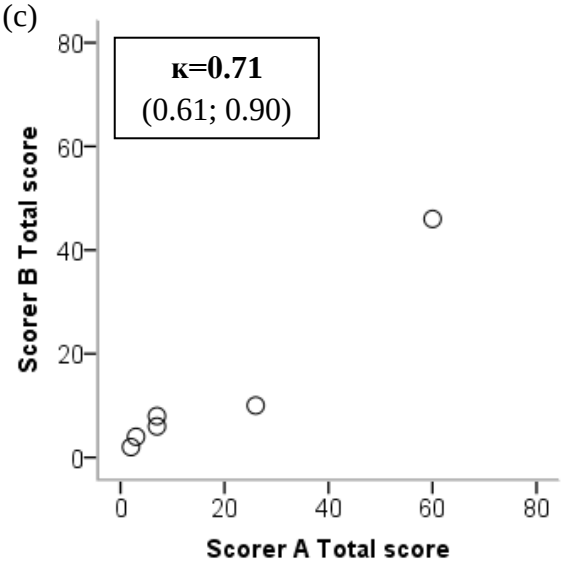
(b)



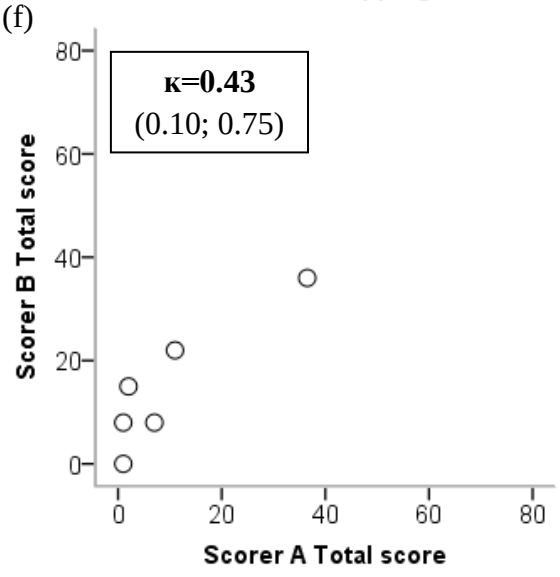
(e)



(c)



(f)



Legend: Scores allocated by scorers A and B for the two training batches with first batch scores represented by plots a to c and second batch scores represented by plots d to f. Bolder circles represent overlapping results with the number of overlapping data next to it. κ= Kappa coefficient (95% CI)

Panels (a-f) shows paired scores allocated by scorer A and B for each training scan in terms of bronchial dilatation and air trapping sub-scores and total CT scores during each of the two training batches. In (a & c): scorer A gave higher bronchial dilatation score and total score compared to scorer B at first training batch but subsequently allocated more similar scores during the second training batch (d & f). With air trapping (b & e), both observers were consistent with their scores at first and second training batches. Scans from both batches were similar in terms of severity for air trapping (median, range) [Batch 1: scorer A: 0.5(0-18) and scorer B: 2.5(0-15); Batch 2: scorer A: 2 (0-18) and scorer B: 6.5 (0-19)]. There appeared to be higher scores during the 1st than 2nd batch for both bronchial dilatation [Batch 1: scorer A (median, range): 3(0-16) and scorer B: 0(0-9) vs. Batch 2: scorer A: 1(0-7) and scorer B: 1.5(0-6)], and for total CT scores [Batch 1: scorer A 7 (2-60) and scorer B 7 (2-46) vs. Batch 2: scorer A: 4.5 (1-37) and scorer B 11.5 (0-36)].

Re-assessment of discrepant sub-scores following initial scoring of the LCFC scans

Of the 65 LCFC scans analysed, discrepancies were found in 50. A record of these was collated by LT. Following a short general discussion about the scoring system, both scorers independently re-scored these discrepant observations, blinded to their own and their counterpart's initial scores. Analysis of the discrepant cases showed that 90% of observed differences were between a score of 0 (normal), and 1 (minimal to mild disease). Following this rescoring of discrepant sub-scores, good agreement was observed for bronchial dilatation [Mean Kappa coefficient=0.62 (95% CI: 0.39; 0.86)] and excellent agreement for air-trapping [Mean Kappa coefficient=0.88 (95% CI: 0.81; 0.96)]. These Kappa coefficients for agreement were higher than those obtained during the initial scoring of the LCFC scans when the mean (95% CI) Kappa coefficient was 0.21 (0.05; 0.37) for bronchial dilatation and 0.66 (0.49; 0.83) for air trapping (see Table 3, main paper).

This reassured both scorers that improved inter-observer agreement could be achieved before undertaking complete rescoring of a selected sub-set of 22 LCFC scans 8 months after initial scoring, although subsequently this did not prove to be the case. The subset of 22 scans that underwent rescoring was selected by LT, who was not involved in the scoring process, and who selected every third scan from the list of study participants that had had CT scans, without any reference to scores previously allocated."

Intra-observer agreement of sub-scores during initial and re-scoring of LCFC scans

Both scorers only achieved fair intra-observer agreement for bronchial dilatation sub-score (Figure E7, panels a&b) but strong agreement for air trapping (Figure E7, panels c&d) after an interval of ~8m. Scorer A detected an identical proportion of changes when re-scoring as

did scorer B, with the exception of one less child with bronchial dilatation on re-score (Table E7).

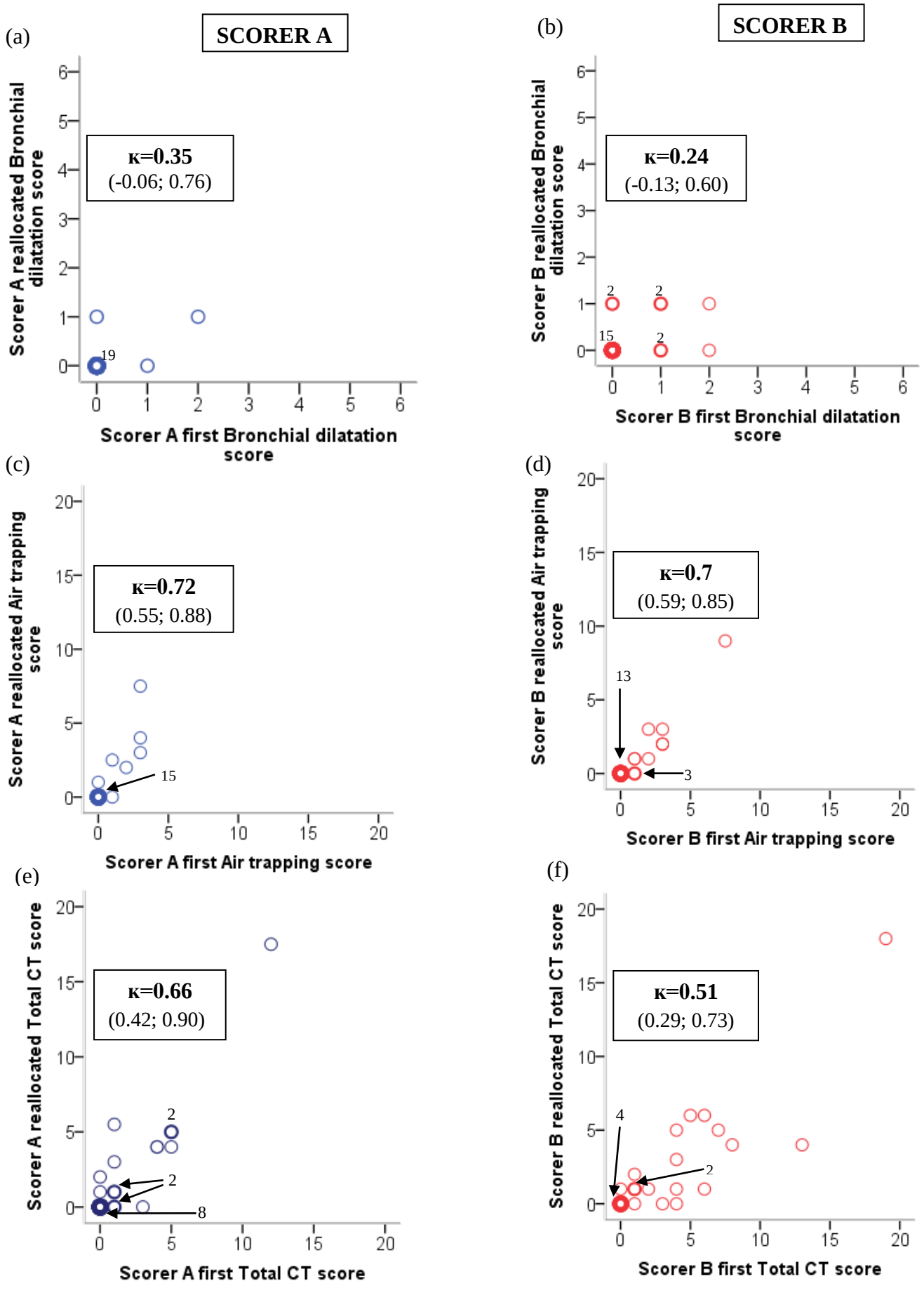
Although Kappa agreement between scorers was only fair for bronchial dilatation initially with minimal improvement during rescoring, agreement as to the presence or absence of bronchial dilatation or air trapping rather than the actual scores allocated was consistently achieved in >80% of the scans on initial and rescoring rounds. (Table E7).

Table E7: Inter-observer agreement with respect to presence or absence of bronchial dilatation and air trapping during initial and re-scoring rounds

	Bronchial Dilatation			**Air trapping**		
	Present	Absent	Total % agreed	Present	Absent	Total % agreed
initial scoring of all 65 scans	5 (8%)	48 (74%)	82%	16 (25%)	37 (57%)	82%
initial scoring of subset (n=22)	2 (9%)	17 (77%)	86%	5 (23%)	14 (67%)	90%
repeat scoring of subset (n=22)	1 (4.5%)	17 (77%)	81.5%	5 (23%)	14 (64%)	87%

The challenges faced, even by those with considerable expertise in the field, in discriminating very mild changes that could be attributed to bronchial dilation or air trapping from normal are illustrated in Figure 2 of the main paper in which discrepancies were observed both between and within observers with respect to scores allocated on two different occasions.

Figure E7: Intra-observer agreement for scorers A and B when rescoring bronchial dilatation, air trapping and total score after an interval of 8 months (n=22)



Legend: Scores allocated by scorer A represented as blue circles and by scorer B represented as red circles. Bolder circles represent overlapping results with the number of overlapping data next to it.

κ= Kappa coefficient (95% CI): fair intra-observer agreement for bronchial dilatation and total scores (panels a & b and e & f) and strong intra-observer agreement for air trapping (panels c & d). Although similar percentages of changes were detected on both occasions, the observers did not necessarily detect changes in the same infants during the two separate rounds.

Table E8: Comparison of measures of within- and between-observer variability used in the current and selected previous studies

Study	Current study		Brody et al[*][E6]		Owens et al[†][E4]	Brody et al* [E3]	De Jong et al [E10]	Stick et al [E11]
Population studied	NBS CF		NBS and clinically diagnosed CF		Clinically diagnosed CF	Clinically diagnosed CF	Clinically diagnosed CF	NBS CF
Age: years [‡]	1.0 (0.1)		10.5 (0.7)		7.8 (1.3)	6-10 [§]	5-52 [§]	1.1(0.3-3.3)[‖]
Scoring system	Brody-II		Brody-II		Brody-II	Brody-II	Brody-II	Specific[**]
Measure of variability	Between Obs kappa	Within Obs kappa	Between Obs variability	Within Obs variability	Between Obs Kendall's tau	Within Obs kappa	Between Obs ICC	Within Obs kappa
Bronchial dilatation	0.21	0.24/0.35	0.04	0.06	0.77	0.64	0.88	0.64
Air-trapping	0.66	0.72/0.72	0.07	0.04	0.59	0.55	0.27	0.55

Footnote: [*]Studies included scorer A as an observer. [†]Studies including scorer B as an observer. Obs = Observer; ICC = Intraclass correlation

[‡]Age at time of CT scan, expressed as mean (SD) unless otherwise stated. [§] Age expressed as range. [‖]Age as median (inter-quartile range) [**]

AREST-CF CT scoring system

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