Journal of Cystic Fibrosis 16 (2017) 151 – 157

www.elsevier.com/locate/jcf

Original Article

A simplified, semi-quantitative structural lung disease computed tomography outcome during quiet breathing in infants with cystic fibrosis

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Received 20 May 2016; revised 29 September 2016; accepted 31 October 2016
Available online 23 November 2016

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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http://dx.doi.org/10.1016/j.jcf.2016.10.014
1569-1993/

[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