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Reversibility of trapped air on chest computed tomography in cystic fibrosis patients

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ABSTRACT

Purpose: To investigate changes in trapped air volume and distribution over time and compare computed tomography (CT) with pulmonary function tests for determining trapped air.
Methods: Thirty children contributed two CTs and pulmonary function tests over 2 years. Localized changes in trapped air on CT were assessed using image analysis software, by deforming the CT at timepoint 2 to match timepoint 1, and measuring the volume of stable (TA_{stable}), disappeared ($TA_{disappeared}$) and new (TA_{new}) trapped air as a proportion of total lung volume. We used the difference between total lung capacity measured by plethysmography and helium dilution, residual volume to total lung capacity ratio, forced expiratory flow at 75% of vital capacity, and maximum mid-expiratory flow as pulmonary function test markers of trapped air. Statistical analysis included Wilcoxon's signed rank test and Spearman correlation coefficients.
Results: Median (range) age at baseline was 11.9 (5–17) years. Median (range) of trapped air was 9.5 (2–33)% at timepoint 1 and 9.0 (0–25)% at timepoint 2 ($p = 0.49$). Median (range) TA_{stable}, $TA_{disappeared}$ and TA_{new} were respectively 3.0 (0–12)%, 5.0 (1–22)% and 7.0 (0–20)%. Trapped air on CT correlated statistically significantly with all pulmonary function measures ($p < 0.01$), other than residual volume to total lung capacity ratio ($p = 0.37$).
Conclusion: Trapped air on CT did not significantly progress over 2 years, may have a substantial stable component, and is significantly correlated with pulmonary function markers.

1. Introduction

In cystic fibrosis (CF), the majority of the disease-related morbidity and mortality are determined by lung disease severity. CF lung disease starts early in life, evidenced by chest computed tomography (CT) studies showing structural lung abnormalities in infants [1,2]. Of these early abnormalities, trapped air, reflecting small airways disease, is considered an important finding [3]. At age 3 months, trapped air is present in nearly two thirds of children diagnosed by newborn screening, even in the absence of symptoms [4]. In addition, trapped air occupies a substantial lung volume in most patients with end stage CF lung disease [5]. Traditionally, trapped air was measured by pulmonary function tests. More recently, the volume and distribution of trapped air can be visualized using expiratory chest CT. To our knowledge, there is no gold standard to determine trapped air, and how CT measures relate to pulmonary function measures is not clear. A limited number of cross-sectional studies have been performed; these reported a correlation between pulmonary function markers and CT assessments of trapped air [6,7]. In addition, little is known

Abbreviations: CF, cystic fibrosis; CT, computed tomography; FEF_{75}, forced expiratory flow at 75% of vital capacity; HU, Hounsfield unit; MMEF, maximum mid-expiratory flow; MRSA, methicillian-resistant *Staphylococcus aureus*; RV/TLC, residual volume to total lung capacity ratio; $TA_{disappeared}$, trapped air (disappeared); TA_{new}, trapped air (new); TA_{PFT}, trapped air (assessed by pulmonary function test); TA_{stable}, trapped air (stable).

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about the change of trapped air over time. Studies using pulmonary function showed either progression [8], no change [9,10], or improvement [11]. Two studies using semi-quantitative scoring of CT to estimate trapped air showed progression over approximately 2 years' time [12,13]. The advantage of CT is that trapped air distribution can be determined in addition to extent. This enables the detection of even small, localized areas of trapped air. More recently, (semi-)automated systems have been developed to quantify the distribution of trapped air on CT [6,7]. These techniques are fast, objective, and provide a measure on a more continuous scale of extent. To our knowledge, these systems have never been used to study the natural course of trapped air in an unselected CF population. We know that in end stage lung disease, trapped air can occupy 20–80% of total lung volume [14]. This suggests that at some point during the course of disease, trapped air becomes irreversible. Previous intervention studies using CT suggest that trapped air is to some extent reversible. However, it is unknown what fraction reflects irreversible versus reversible small airway changes. We hypothesized that in a random subset of patients, a large fraction of trapped air would represent irreversible changes. To investigate this, we have developed new software that combines quantitative analysis with deformable image registration to assess local changes in trapped air on CT. Using this software, we performed a pilot study with the aims to assess: (1) the change in volume of trapped air over time; (2) changes in the distribution of trapped air over time; and (3) the relationship between trapped air assessed with CT and pulmonary function, as well as spirometric indicators of small airways disease.

2. Material and methods

2.1. Study population

In this retrospective study, we selected 30 consecutive children with CF, monitored at a single tertiary CF clinic, who could contribute two volumetric expiratory chest CT scans and pulmonary function tests between December 2006 and November 2009. All biennial CTs and annual pulmonary function were made as a part of routine care during annual check-up when clinically stable. Children on intravenous antibiotics were considered unstable and were excluded. The institutional review board approved the study protocol, and then informed consent from all subjects allowing use of anonymized data was obtained.

2.2. CT scanning protocol

Each child contributed two expiratory CT scans over two years. These routine scans were made biennially; hence the time between two scans was approximately two years for all patients. Scanning was performed from lung apex to base using a 6-slice CT scanner (Somatom Emotion, Siemens Medical Solutions, Forchheim, Germany) with the patient in the supine position. Scans consisted of inspiratory and expiratory images; however, only the expiratory images were used for this study. The baseline scan was made between December 2006 and October 2007 using a voluntary breath hold technique; patients were instructed to maximally exhale and hold their breath during the scan. The follow-up scan was made between January 2009 and November 2009. Scans were performed using spirometer control, as this had been introduced as a part of the clinical CT protocol. This was performed as follows: prior to scanning patients practiced the breathing maneuvers in the supine position, supervised by a lung function technician. Patients were trained with their arms raised above their shoulders using nose clip and spirometer. For the expiratory scan, patients were asked to inhale maximally starting at tidal volume level followed by a maximum slow expiratory vital capacity maneuver, and to hold their breath at the end of the expiration. These breathing maneuvers were repeated during CT scanning, supervised by the same lung function technician. The scanning protocol for expiratory CTs was volumetric (ultra low dose) using the following settings: rotation time 0.6-s, tube voltage 80 kV (weight < 35 kg) or 110 kV (weight ≥ 35 kg), pitch 1.5, 6×2 mm collimation, kernel B60s, and a fixed tube current of 25 mA, i.e. an effective tube current–time product of 10 mAs. Scans were reconstructed with a 2.5 mm slice thickness, and 1.2 mm increment.

2.3. Image analysis

Trapped air volume and total lung volume were computed using in-house developed software. First, the lungs were segmented automatically [15]. Second, a median filter (size $3 \times 3 \times 3$) was applied to reduce noise. Trapped air was defined initially as the lung tissue with an intensity value between thresholds of −975 and −850 Hounsfield units (HU) [6,16]. Third, a single, experienced observer visually checked the intensity thresholds. Per scan, the observer evaluated whether the thresholds covered most areas of trapped air appropriately. When needed, the thresholds were adjusted in steps of 25 HU. To evaluate the course of trapped air over time, we compared the volume of trapped air, expressed as a percentage of total lung volume, between CTs at each timepoint.

To investigate changes in the distribution of trapped air over time, we used a previously described deformable image registration method [17] to determine a transformation to match the CT at timepoint 2 to the CT at timepoint 1, such that the two scans could be overlaid. This process is illustrated in Figs. 2 and 3.

Then, for each voxel that was included in the lung segmentation in both CTs, it could be determined whether it was (1) part of trapped air in both CTs (stable trapped air), (2) part of trapped air only in follow-up CT (newly formed trapped air), (3) part of trapped air in baseline CT only (disappeared trapped air), or (4) not part of trapped air in either CT. These four parameters together make up the total volume of segmented lung present in both scans. These volumes were expressed as a percentage of the total volume within the lung segmentations, denoted by TA_{stable}, TA_{new}, and $TA_{disappeared}$.

Afterwards, all images were also visually checked to confirm successful lung segmentation, registration, and annotation of the changes in trapped air. This was done by comparing the baseline CT and the deformed follow-up CT, displayed side-by-side. First, we examined whether trapped air visually appeared to be stable, new or disappeared. Second, we switched on an overlay that showed TA_{new}, $TA_{disappeared}$, and TA_{stable} in different colors, and assessed whether the annotated areas matched our visual interpretation. Without further quantification, we documented for each scan whether large areas of trapped air were correctly indicated.

2.4. Pulmonary function tests

All pulmonary function tests were performed as per European Respiratory Society guidelines. Lung volumes were obtained using a Masterlab Body Plethysmograph (Erich Jaeger AG, Würzburg, Germany) using the panting technique. Spirometry was performed with a Jaeger diagnostic system (Erich Jaeger AG, Würzburg, Germany). All reference values were according to Zapletal et al. [18]. Only measurements obtained within 3 months of the matching CT were included for analysis. The following parameters were used as lung function parameters describing trapped air: (1) residual volume to total lung capacity ratio (RV/TLC); (2) difference in total lung capacity measured by body plethysmography and helium dilution, expressed as percentage of plethysmographic total lung capacity (TA_{PFT}). In addition, the following parameters of small airways