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Research article

Finding the right spot: Where to measure airway parameters in patients with COPD

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ABSTRACT

Purpose: The importance of spirometry for management of COPD was reduced in the 2017 revision of the GOLD report. CT derived airway measurements show strong correlations with lung function tests and symptoms. However, these correlations are specific to the airway localization, and currently there is no evidence for the ideal spot. Therefore, the aim of this prospective study was to systematically correlate CT derived airway measurements with extensive lung function testing.

Methods and materials: 65 patients with diagnosed COPD underwent body plethysmography, impulse oscillometry and dose optimized qCT examination (Somatom Force, Healthineers, Germany) in inspiration and expiration. Eight airway parameters (e.g. outer diameter, maximal wall thickness) were acquired for both scans in every lobe for the third to fifth generation bronchus and correlated with the lung function tests.

Results: The most significant correlations between airway parameters were found for the third generation bronchus of the upper left lobe during expiration (25 out of 48 correlation pairs, mean $r = -0.39$) and for the third generation bronchus of the upper right lobe during inspiration (9 out of 48 correlation pairs, mean $r = -0.25$). No significant correlations were for example found for the upper right lobe in expiration.

Conclusion: Correlations between airway parameters and lung function tests vary widely between lobes, bronchus generations and breathing states. Our work suggests that the third generation bronchus of the upper left lobe in expiration could be the preferred localization for airway quantification in future studies.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and largely avoidable disease that is characterized by irreversible airway obstruction, predominantly due to inhaled noxae and particles. COPD was listed as the third leading cause of death by the World Health Organization in 2012 and has surpassed epidemiological estimations by the Global Burden of Disease Project now causing over 3.1 million deaths per year [1,2].

Traditionally the diagnosis of COPD is based on spirometric measurements of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) as specified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [3]. Until recently the therapeutic decisions in patients with COPD were based on spirometry as well. With the new 2017 GOLD report spirometry should not be used for therapeutic decisions anymore and medication is thereby currently chosen by clinical criteria without objective quantifiable diagnostical tools [4].

In the past years several techniques have been evaluated against

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; D5-20, frequency dependency of resistance; ERS, European Respiratory Society; FEV_1, forced expiratory volume in one second; F_{res}, resonance frequency; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HIPAA, Health Insurance Portability and Accountability Act of 1996; ID, inner diameter; IOS, impulse oscillometry; LA, lumen area; maxWT, maximal wall thickness; minWT, minimal wall thickness; OD, outer diameter; (q)CT, (quantified) computed tomography; R5, resonance at 5 Hz; RV%TLC, ratio of residual volume to total lung capacity; sR_{tot}, specific total airway resistance; WA, wall area; WA%, percentage of wall area; WT, wall thickness

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spirometry and might become valuable diagnostical tools in patients with COPD in the future [5–7]. One of these techniques is quantified computed tomography (qCT). Already in the early stages of qCT Muller et al. were able to show that structural changes in the lung parenchyma such as emphysema can be detected and quantified. [8] Until today correlations between qCT parameters and several lung function tests such as spirometry, body plethysmography and impulse oscillometry have been identified [9–11].

In the context of COPD airways are of exceptional interest in qCT. This is due to the fact that local airway inflammation in patients with COPD can be detected and quantified via qCT [12]. Han et al. found that the bronchial wall thickness as well as the severity of the low attenuated volume are independently associated with the exacerbation rate in patients with COPD [13]. qCT can thereby be used to define bronchial and emphysema predominant COPD subtypes. These results are substantiated by the findings of Grydeland et al. who have been able to show that qCT airway measurements are independently related to symptoms like dyspnea cough and wheezing in patients with COPD [14].

One critical point in the examination of airway changes in qCT is the region of measurement. Hesegawa et al. calculated stronger correlations between airflow limitations and airway parameters for the lower right lobe rather than the upper right lobe [15]. Besides the location, breathing state is also important. In this regard, Matsuoka et al. have shown that expiratory measurements are more closely related to expiratory airflow limitations [16]. Nevertheless, most of these studies solely used single phase inspiratory qCT scans to correlate airway diameters with lung function tests. Further inconsistencies are found when reviewing the variety of applied airway measurement methods. Mair et al. combined measurements from the upper right and lower right airways to correlate them with lung function tests [17]. Other studies calculated mean values of different airway generations over all five lobes [12,18,19]. To overcome the problem of variable bronchus sizes and anatomical in homogeneities, virtually standardized parameters such as Pi-10 have been introduced [12]. However their clinical value is limited as separate and elaborate calculations are often required.

As demonstrated by the inhomogeneous methodology as well as the lack of homogenous data in existing literature, evidence regarding the exact location for airway measurement for correlation with lung function tests is missing. The mentioned differences in correlation regarding the region of measurement and breathing position of the patient suggest that the airway measuring procedure has a strong impact on the correlations. We hypothesized the existence of an ideal location to acquire airway parameters in qCT.

Therefore we aimed to evaluate the third- to fifth-generation airways of all five lobes from both an inspiratory and expiratory qCT with regard to elaborate lung function testing.

2. Materials and methods

2.1. Subjects

The HIPAA compliant study-protocol, which is in accordance to the Declaration of Helsinki was approved by our local ethics committee (**Medical Ethics Committee II of the Medical Faculty Mannheim, Heidelberg University, Germany**). The study was registered at clinicaltrials.gov (**NCT02826265**).

We prospectively enrolled 65 consecutive patients with previously diagnosed COPD and a clinical indication for unenhanced chest CT in a single center approach. Written informed consent was obtained from all patients following a full explanation of the purpose of the study and of potential risks and discomfort associated with their participation, with particular care given to the slightly increased radiation dose compared to a single breath-hold phase.

Table 1
Patient characteristics.

	Mean	SD	Minimum	Maximum
FEV_1 [% predicted]	55	24	16	117
RV/TLC [%]	59	16	16	87
sR_{tot} [% predicted]	280	222	34	1054
R5 [% predicted]	152	57.5	65	273
F_{res} [Hz]	22	7	6	37
D5-20 [%]	67	46	0	204

FEV1: forced expiratory volume in one second; RV/TLC: ratio of residual volume and total lung capacity; sR_{tot}: total specific resistance; R5: resonance at 5 Hz; F_{res}: resonance frequency of airways; D5-20: frequency dependency of resistance.

2.2. Study protocol

2.2.1. Lung function testing

All patients underwent whole-body plethysmography (MasterScreen® Body, CareFusion, Höchberg, Germany) yielding the following parameters: FEV_1, ratio of residual volume to total lung capacity (RV%TLC) and specific total airway resistance (sR_{tot}). Except for the RV%TLC all plethysmographic values are given as percent of predicted as calculated according to current ATS/ERS recommendations. [20,21] Prior to whole-body plethysmography we performed impulse oscillometry (IOS) using a commercially available system (MasterScreen® IOS, CareFusion Höchberg, Germany). The following parameters were acquired: resonance at 5 Hz (R5) in percent of predicted, resonance frequency (F_{res}) and frequency dependency of resistance (D5-20) in percent (Table 1).

2.2.2. CT examinations

A non-contrast chest scan was performed in maximum inspiration and maximum end-expiration using a 3rd generation dual source CT system (Somatom FORCE, Siemens Healthineers, Forchheim Germany) at 100kVp with a dedicated tin filter for dose reduction. [22,23] Additionally to a pre-imaging briefing the patients received voice commands for optimal inspiration and expiration results. Existing medication was not withheld prior to imaging. The scan parameters were as follows: 100 kVp tube voltage automated tube current modulation using 96mAs at 120 kVp as reference (effective mAs = 166.5 ± 105) 0.25 s rotation time, pitch 1.2, 192 mm × 0.6 mm detector collimation. All images were reconstructed with a slice thickness of 1.5 mm using a suitable reconstruction kernel for quantitative lung analysis (Br32) and a 3rd generation iterative reconstruction technique (Adaptive Model-based Iterative reconstruction [ADMIRE], Siemens Healthineers, Germany). The reconstruction algorithm was substantially explained in a recent publication by Gordic et al. [24]. An iterative strength level of four was chosen for the present study for optimum image noise as recommended by the CT vendor for quantitative lung analysis. The average CTDI was 0.48 ± 0.19 mGy and the mean DLP 17.2 ± 6.5 mGy cm.

2.2.3. Image analysis

Inspiratory and expiratory datasets were analyzed using dedicated semi-automatic software (SyngoViaVB10, Pulmo3D, Siemens Healthineers, Forchheim, Germany). The bronchial tree was detected automatically. Bronchial parameters were measured semi-automated once in the third fourth and fifth generation in every lobe for the inspiratory and expiratory scan by an experienced reader (6 years) as shown in Fig. 1. Thereby the software automatically measures the airway parameters. The reader supervised the correct position and airway lumen respectively wall detection but made no changes to the measured values. The middle lobe was rejected for quantification due to severe inconsistencies in the automated airway detection. The measured parameters acquired were: wall area (WA), lumen area (LA),