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Acinar ventilation heterogeneity in COPD relates to diffusion capacity, resistance and reactance☆

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ABSTRACT

The aim of this study was to investigate heterogenic ventilation in the acinar (Sacin) and conductive (Scond) airways of patients with varying chronic obstructive pulmonary disease (COPD) severity and how these relates to advanced lung function parameters, primarily measured by impulse oscillometry (IOS). A secondary aim was to investigate the effects of a short acting beta2-agonist and a muscarinic antagonist on the heterogenic ventilation.

Eleven never smoking controls, 12 smoking controls, and 57 COPD patients (7 GOLD 1, 25 GOLD 2, 14 GOLD 3 and 11 GOLD 4) performed flow-volume spirometry, IOS, body plethysmography, single breath carbon monoxide diffusion, and N2-multiple breath washout. Six smoking controls and 13 of the COPD patients also performed double reversibility test by using salbutamol and its combination with ipratropium.

Sacin was significantly higher in GOLD 2–4 compared to never smoking controls and smoking controls, but showed similar levels in GOLD 3 and 4. A factor analysis identified 4 components consisting of; 1) IOS parameters, 2) volume parameters, 3) diffusion parameters, Sacin and some IOS parameters and 4) Scond with central obstruction/air trapping. Salbutamol and its combination with ipratropium had no effect on Sacin and Scond.

Increased Sacin in COPD was strongly related to diffusion capacity and lung volumes, but also weakly to resistance and reactance, showing a link between ventilation heterogeneity in the acinar airways and parameters measured by IOS.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is often diagnosed and graded based on spirometric disease severity according to forced expiratory volume in 1 s (FEV_1) and the ratio of FEV_1/forced vital capacity (FVC) [1]. FEV_1 mainly measures the degree of obstruction in large and intermediate airways [2] while COPD is a disease mainly residing in the peripheral airways. It is generally accepted that FEV_1 is not an optimal parameter for describing the complexity of COPD and that other lung function assessments are necessary to describe the disease pattern [1,3–6]. To get a more complete picture of the disease, additional techniques measuring lung volumes, diffusion capacity, resistance and reactance are of importance.

A method becoming more common is inert gas washout, which gives information about the ventilation heterogeneity in the airways. It is used together with nontoxic inert gases, such as N_2, and can be performed either as a single breath washout (SBW) or as a

Abbreviation list: AX, reactance area; COPD, Chronic obstructive pulmonary disease; $D_{L,CO}$, diffusing capacity for the lungs measured using carbon monoxide; FEV_1, Forced expiratory volume in 1 s; Fres, resonance frequency; FVC, Forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; IC, inspiratory capacity; IOS, impulse oscillometry; LLN, lower limit of normal; MBW, multiple breath washout; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, difference between R5 and R20; Rex, expiratory resistance; Rin, inspiratory resistance; RV, residual volume; Sacin, Heterogenic ventilation in acinar airways; SBW, Single breath washout; Scond, Heterogenic ventilation in conductive airways; TLC, total lung capacity; V_A, alveolar volume; VC, vital capacity; X5, reactance at 5 Hz; %p, Percent of predicted normal.

☆ **Summary at glance:** Sacin in COPD has been related to diffusion capacity, but the relationship to peripheral airways measured with IOS has not been investigated. We found that increased Sacin in COPD was strongly related to diffusion capacity and lung volumes, but also to resistance and reactance.

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multiple breath washout (MBW). When used as a MBW, this method can separate ventilation heterogeneity in the conductive (Scond) from the acinar airways (Sacin) [7–9], which could be used in the characterization of COPD patients. MBW is more time consuming but can be used on patients that cannot perform a vital capacity (VC) manoeuvre.

Another interesting, easy to perform method is Impulse Oscillometry (IOS), which measures the reactance (the capacitive and inertive properties) and resistance of the airways which can give information about the peripheral airways [10–12].

In previous studies, nitrogen SBW have been used to measure heterogenic ventilation in COPD showing correlations to FEV_1, FVC, residual volume (RV), inspiratory capacity (IC) and resonance frequency (Fres) [13,14]. Another study demonstrated increased Sacin and Scond measured by nitrogen MBW in COPD patients compared to controls [15], as well as a lack of response to either the bronchodilators salbutamol [16] or tiotropium bromide [17] in these parameters. It has been shown that Sacin in COPD patients relates to diffusion capacity, while Scond relates to specific airway conductance and FEV_1 percent predicted (%p) [18]. Another study was done using a different forced oscillometry technique and N_2 MBW in COPD patients [18], but the direct relationship between resistance and reactance and ventilation heterogeneity was not investigated. The relationship between Sacin and Scond and peripheral airway measurements obtained by IOS therefore needs to be further explored. This information is important for understanding the ventilation heterogeneity in relation to airway resistance and reactance to gain a deeper understanding about the COPD disease.

The aim of this study was to investigate the conductive and acinar ventilation heterogeneity's (measured by nitrogen MBW) relationship to the peripheral airway measures obtained by IOS in patients with varying degrees of COPD. A secondary aim was to investigate the effect of optimal bronchodilation, using a combination of both a short acting $beta_2$-agonist and a muscarinic antagonist, on the conductive and acinar heterogenic ventilation.

2. Methods

2.1. Study subjects

Eighty subjects were recruited from a patient cohort used in previous studies at our Research unit at the Lung clinic. They were classified as either never smoking controls (n = 11), smoking controls (n = 12), or COPD (n = 57) according to Global Initiative for Obstructive Lung Disease (GOLD [1], with the exception that classification was done without bronchodilation).

Study subjects had no history of asthma, lung cancer, or any cardiorespiratory disease and both COPD patients and smoking controls had a smoking history of ≥15 pack years. Patients experienced no exacerbations or respiratory infections three weeks prior to the study.

Study participants were asked to refrain from inhaled bronchodilators before their visit (long acting β2 agonist, long acting muscarinic antagonist for 48 h and short acting β2 agonist, short acting muscarinic antagonist for 8 h). Eleven patients (3 GOLD 3, 8 GOLD 4) had inhaled long-acting muscarinic antagonists (18 μg tiotropium, Spiriva®) at baseline due to dyspnea. Inhaled corticosteroids were allowed for patients in the study.

This study was approved by the Regional Ethical Review Board in Lund (431/2008) and all study participants signed informed consent.

2.2. Study design and methods

Subjects performed flow-volume spirometry and IOS (MasterScreen, Erich Jaeger GmbH, Würzburg, Germany), body plethysmography [19] (MasterScreen Body, Erich Jaeger GmbH), single breath helium dilution carbon monoxide diffusion [20–22] (MasterScreen Diffusion, Erich Jaeger GmbH) and MBW of N_2 (Exhalyzer D, Eco Medics, Switzerland) in the given order. Lung function measurements were performed according to manufacturer's instructions and European Respiratory Society (ERS)/American Thorax Society (ATS) recommendations [21,23,24]. The reference values used were established by Crapo et al. [25] (spirometry), from ECCS [26] (Body plethysmography and DLCO) and Vogel [27] (IOS).

MBW of N_2 was performed with 1 L tidal breathing superimposed. Measurements were performed to >6 turn overs to gain valid information for correctly calculated Sacin and Scond and each SnIII curve was first automatically generated (Spiroware®, Eco Medics), then manually confirmed [7].

The subjects used nose clips and supported their cheeks with their hand palms to decrease the upper airways shunt. Oscillometric pressure impulses were superimposed to the tidal breathing for about 30 s, with a pulse sequence of 5 per second and a frequency spectrum between 5 and 35 Hz [12]. Resistance at 5 Hz (R5) reflects total respiratory resistance of the airways and resistance at 20 Hz (R20) reflects resistance of the proximal airways. The difference between R5 and R20 (R5-R20) parameter is an indicator of peripheral properties of the respiratory tract. Low frequent reactance is usually reported as reactance at 5 Hz (X5). X5 reflects changes to the lung periphery and is non-specific. Increased negative values can be seen both in restrictive and obstructive disease. Resonant frequency (Fres) is the frequency where the inertance and capacitance are equal in magnitude and opposite in sign (phase), and is measured in Hz. The reactance area (AX) is a quantification of the respiratory reactance between 5 Hz and Fres, thus it will mostly reflect the capacitance part of the reactance. This makes AX a good index of changes of the degree of peripheral involvement.

All subjects were asked to also perform a reversibility test. A subgroup of the COPD patients (n = 13; 3 GOLD 1, 6 GOLD 2, 4 GOLD 3) and smoking controls (n = 6) accepted. The others declined due to dyspnea or lack of time. The reversibility test was performed by using salbutamol and then additional ipratropium (lung function measurements at baseline, 10 min after salbutamol (400 μg) and 40 min after ipratropium (80 μg). Salbutamol and ipratropium were administered with dry powder inhalation using Easyhaler® and Handihaler® respectively.

2.3. Statistical analysis

Factor analysis was performed in SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL). Principal-components factor analysis was used to extract as few independent factors as possible from 18 variables to explain maximum variance in the variables. Only factors with an eigenvalue > 1 were extracted and the Varimax orthogonal rotation option was selected. The other statistical analyses were performed using Graph Pad Prism 5 and a p-value < 0.05 was considered significant. Paired and unpaired data were analyzed using Wilcoxon t-test and Kruskal–Wallis test with Dunn's Multiple Comparison post-test, respectively. Correlations were performed using Spearman's correlation test. All data are presented as median (interquartile range).

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