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Left ventricular volume and wall stress are linked to lung function impairment in COPD

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ABSTRACT

Background: Cardiovascular comorbidities are common in chronic obstructive pulmonary disease (COPD). We examined the association between airflow limitation, hyperinflation and the left ventricle (LV).
Methods: Patients from the COPD cohort COSYCONET underwent evaluations including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), effective airway resistance (R_{eff}), intrathoracic gas volume (ITGV), and echocardiographic LV end-diastolic volume (LVEDV), stroke volume (LVSV), end-systolic volume (LVESV), and end-diastolic and end-systolic LV wall stress. Data from Visit 1 (baseline) and Visit 3 (18 months later) were used. In addition to comparisons of both visits, multivariate regression analysis was conducted, followed by structural equation modelling (SEM) with latent variables "Lung" and "Left heart".
Results: A total of 641 participants were included in this analysis. From Visit 1 to Visit 3, there were significant declines in FEV_1 and FEV_1/FVC, and increases in R_{eff}, ITGV and LV end-diastolic wall stress, and a borderline significant decrease in LV mass. There were significant correlations of: FEV_1% predicted with LVEDV and LVSV; R_{eff} with LVSV; and ITGV with LV mass and LV end-diastolic wall stress. The SEM fitted the data of both visits well (comparative fit index: 0.978, 0.962), with strong correlation between "Lung" and "Left heart".
Conclusions: We demonstrated a relationship between lung function impairment and LV wall stress in patients with COPD. This supports the hypothesis that LV impairment in COPD could be initiated or promoted, at least partly, by mechanical factors exerted by the lung disorder.

1. Introduction

Cardiovascular comorbidities are common in patients with chronic obstructive pulmonary disease (COPD) [1]. This has important clinical implications, since the coexistence of COPD and cardiovascular disease increases morbidity and mortality [2,3], and insight into the mechanisms underlying this association could provide additional therapeutic targets.

A number of studies have shown a correlation between COPD and increased rates of cardiovascular events including atherosclerotic

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plaque formation, myocardial infarction (MI) and stroke, in which systemic inflammation may play a role [4,5]. However, data are not unequivocal; for example, in a 10-year case-control study, the risk of atherosclerotic events was not increased in the COPD cohort compared with non-COPD controls [6]. Similar results were obtained in the VALIANT trial, in which COPD was not a predictor of atherosclerotic events [2], as well as in the Copenhagen City Heart Study, in which lung function correlated with fatal MI but not with non-fatal MI [7]. These findings suggest that multiple mechanisms are involved in the coexistence of COPD and cardiovascular disease.

The increased intrathoracic pressure oscillations during respiration in obstructive lung diseases have been shown to directly influence venous return through mechanical interaction [8]. Furthermore, the degree of emphysema or lung hyperinflation is associated with smaller cardiac chamber sizes, especially the left ventricle (LV) [9–11]. In addition, LV diastolic function appears to be correlated with hyperinflation in patients with COPD [12]. This suggests that the mechanisms underlying the increased frequency of cardiac events in COPD might well include mechanical interactions between lung and heart [13].

We hypothesized that airflow limitation and hyperinflation exert distending forces, particularly on the LV. We therefore examined the relationship between airflow limitation and LV function, morphology and ventricular wall stress (assessed by echocardiography). The study population was part of the German COPD cohort COSYCONET (*COPD and Systemic Consequences - Comorbidities Network*).

2. Methods

2.1. Study design

COSYCONET is a prospective, observational, multicenter cohort study in patients with COPD that is being conducted in major clinics and pulmonology centers across Germany [14]. The overall aim is to evaluate the pattern of comorbidities, their severity and their sequence over time, as compared to the course of lung disease. The present analysis used the baseline data from the recruitment visit (Visit 1) together with data from Visit 3 (which took place approximately 18 months after Visit 1). The study was approved by the Ethics Committee of the University of Marburg as coordinating center and the Ethics Committees of all study centers, and is registered on ClinicalTrials.gov (registration number NCT01245933).

2.2. Participants

Participants were recruited by the investigators, with no protocol-mandated recruitment method. The overall inclusion criteria for COSYCONET were: age 40 years or older; doctor diagnosis of COPD or chronic (non-obstructive) bronchitis; and availability for repeated study visits over at least 18 months. Exclusion criteria were: having undergone significant lung surgery in the past; moderate or severe exacerbation in the 4 weeks prior to entry; currently diagnosed lung tumor; and physical or cognitive impairment resulting in an inability to walk or understand the intention of the project. Other than the doctor diagnosis of COPD or chronic bronchitis, there were no spirometry-defined inclusion criteria. Patients were subsequently grouped according to Global Initiative for Obstructive Lung Disease (GOLD) airflow limitation criteria, as follows: in patients with a ratio of forced expiratory volume in 1 s [FEV_1] to forced vital capacity [FVC] <0.70, GOLD 1 is those with FEV_1 at least 80% predicted; GOLD 2, FEV_1 between 50 and 80% predicted; GOLD 3, FEV_1 between 30 and 50% predicted; GOLD 4, FEV_1 <30% predicted [15]. A proportion of patients had FEV_1/FVC >0.7 in the presence of symptoms and smoking history. These are described in this manuscript as "GOLD 0". All patients provided written informed consent prior to undertaking any study-related procedure.

In the presence of cardiac disease the relationship among cardiac parameters is likely to be intrinsically influenced by the disease itself. Therefore, in the current analyses we only included patients without aortic or mitral valve disease greater than mild, valve replacements, or implanted pacemakers or cardioverter-defibrillators. Moreover, criteria were applied regarding the completeness and plausibility of LV and lung function parameters (Supplementary Methods and Fig. 1). Patients with LV dilatation were excluded by the requirement that the left ventricular end-diastolic diameter (LVEDD) was ≤56 mm. This is the upper limit of normal, and was primarily motivated by the observation that the relationship of LVEDD to lung function appeared to be different beyond 56 mm as illustrated for FEV_1 percent predicted in Supplementary Fig. 2.

2.3. Evaluations

2.3.1. Spirometry/body plethysmography

Spirometry and body plethysmography were performed as recommended by the American Thoracic Society, European Respiratory Society and Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin [16–19]. The parameters used for this substudy were: FEV_1, FEV_1/FVC, effective airway resistance (R_{eff}), and intrathoracic gas volume (ITGV). Lung function was measured after bronchodilation using 400 μg salbutamol and 80 μg ipratropium bromide. As all reference equations were obtained in healthy subjects who show no or only a minor response to bronchodilators, they can be applied for GOLD classification irrespective of the requirement of post-bronchodilator measurements. Thus Global Lung Function Initiative values were used as reference values for FEV_1 [20], with European Coal and Steel Community value used for ITGV as determined from body plethysmography [21].

2.3.2. Echocardiography and wall stress

Echocardiography was performed using standard methodology (parasternal long- and short-axis and apical views using B- and M-mode techniques) to obtain LV wall and cavity diameters, and cardiac function [22]. The following standard echo parameters were obtained by experienced investigators at each center: LVEDD, left ventricular end-systolic diameter (LVESD), interventricular septum diastolic (IVSD), LV posterior wall thickness diastolic (LVPWD), LV ejection fraction (LVEF), LV end-diastolic and end-systolic volume (LVEDV and LVESV), LV stroke volume (LVSV), and LV mass. In addition, we analyzed end-diastolic and end-systolic LV wall stress, which is related to systolic and diastolic function [23] and results in cardiac hypertrophy [24,25]. LV cavity volume, myocardial mass and wall stress were calculated in the data processing center using the measured parameters (see Supplementary Methods) [26].

2.4. Sample size

For the overall COSYCONET study, the aim was to recruit 3500 patients of severity GOLD 1–4, together with 354 subjects of the former GOLD class 0. There was no formal sample size calculation for the cardiac substudy due to lack of prior information on variability.

2.5. Statistical methods

Standard descriptive statistics included mean and standard deviation (SD). Data were adjusted by taking them as percent predicted or normalized to body surface area except where indicated otherwise. In the descriptive analysis, group differences were analyzed using analysis of variance for continuous and chi-square test for categorical variables. Multivariate linear regression analyses were used to determine associations between the lung function indices as predictors and the echocardiographic measures as dependent variables, using SPSS (IBM SPSS Amos 22.0.0, Armonk, NY, US). In order to obtain a comprehensive picture of the relationship between parameters, structural equation modelling (SEM) was employed. Various models were constructed that made sense from a physiological perspective and these were compared regarding their ability to describe the data. Collinearities between the variables were implemented through the definition of constructs (latent variables) which are a natural feature of these models based on linear correlation coefficients. There was no adjustment for the differences between study centers (see supplementary file for a detailed explanation). Throughout the analyses, significance was assumed at $p < 0.05$.

3. Results

3.1. Patient disposition and baseline characteristics

Among 2741 participants enrolled in COSYCONET in 31 study centers, 2379 were examined by transthoracic echocardiography between September 2010 and December 2013, 1591 of whom fulfilled the predefined in- and exclusion criteria regarding completeness and quality of spirometry, body plethysmography, and echocardiography (Supplementary Fig. 1). Applying the Visit 1 criteria of completeness and plausibility to Visit 3, and excluding patients with LV dilatation, a total of 641 patients are included in the current analyses (who therefore had valid data at both visits). Their demographics, lung function and echocardiographic characteristics, as well as medication data (overall and stratified according to GOLD lung function criteria, based on Visit 1 data) are shown in Tables 1 and 2. Even though the indices of LV cavity size and function were largely normal, they correlated with GOLD grade. Right ventricular wall thickness also correlated with GOLD grade.

3.2. Changes in lung function and echocardiography from Visit 1 to Visit 3

Visit 3 took place a mean ± SD of 573 ± 45 days after Visit 1. As shown in Supplementary Table 1, there were small, but statistically significant declines in FEV_1 (both mean and percent predicted) and FEV_1/FVC ratio, and increases in R_{eff} and ITGV. These changes in lung function were accompanied by a statistically significant increase in LV