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Pulmonary function and adverse cardiovascular outcomes: Can cardiac function explain the link?

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ABSTRACT

Background: The complex interaction between pulmonary function, cardiac function and adverse cardiovascular events has only been partially described. We sought to describe the association between pulmonary function with left heart structure and function, all-cause mortality and incident cardiovascular hospitalization.

Methods: This study is a retrospective analysis of patients evaluated in a single tertiary care medical center. We used multivariable linear regression analyses to examine the relationship between FVC and FEV1 with left ventricular ejection fraction (LVEF), left ventricular internal dimension in systole and diastole (LVIDS, LVIDD) and left atrial diameter, adjusting for baseline characteristics, right ventricular function and lung hyperinflation. We also used Cox proportional hazards models to examine the relationship between FVC and FEV1 with all-cause mortality and cardiac hospitalization.

Results: A total of 1807 patients were included in this analysis with a median age of 61 years and 50% were female. Decreased FVC and FEV1 were both associated with decreased LVEF. In individuals with FVC less than 2.75 L, decreased FVC was associated with increased all-cause mortality after adjusting for left and right heart echocardiographic variables (hazard ratio [HR] 0.49, 95% CI 0.29, 0.82, respectively). Decreased FVC was associated with increased cardiac hospitalization after adjusting for left heart size (HR 0.80, 95% CI 0.67, 0.96), even in patients with normal LVEF (HR 0.75, 95% CI 0.57, 0.97).

Conclusion: In a tertiary care center reduced pulmonary function was associated with adverse cardiovascular events, a relationship that is not fully explained by left heart remodeling or right heart dysfunction.

1. Introduction

Pulmonary disease including chronic obstructive pulmonary disease (COPD) and asthma account for a sizable portion of the burden of chronic disease in the United States affecting 11.8 and 24.6 million people, respectively [1,2]. While the association of severe COPD with co-morbid cardiovascular disease has been well described, individuals with asthma and mild and moderate reductions in pulmonary function have also been found to be at increased risk of adverse cardiovascular outcomes, including incident coronary artery disease, cerebrovascular disease and heart failure [3–8]. Reduced forced vital capacity (FVC) and reduced forced expiratory volume in 1 s (FEV1) have been associated with increased cardiovascular mortality, fatal and nonfatal coronary events, case-fatality after myocardial infarction, stroke and incident heart failure independent of tobacco use [9–16]. However, no prior study has incorporated echocardiographic data in order to better elucidate how alterations in cardiac structure and function might explain the relationship between reduced pulmonary function and cardiovascular outcomes.

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While none of the longitudinal studies of pulmonary function and incident cardiovascular outcomes incorporated cardiovascular imaging, such as transthoracic echocardiography, cardiac magnetic resonance (CMR) imaging has been used to study cardiac structure and function in a cross-sectional study of individuals with differing degrees of obstructive airway disease. A substudy of the Multi-Ethic Study of Atherosclerosis (MESA) examined the relationship between percent emphysema by chest computed tomography, airway obstruction by pulmonary function testing and cardiac structure and function measured by CMR [17]. However, the pulmonary function testing in this study was completed 4 years after CMR and no measures of right heart function or lung hyperinflation were incorporated into the analysis. The complex interaction between pulmonary function, right heart function, left heart structure and function and adverse cardiovascular events has only been partially described.

The primary objective of this study was to describe the relationship between FVC and FEV1 with echocardiographic measures of left ventricular function, left ventricular size and left atrial size in patients seen at a tertiary care center. The secondary objective of this study was to determine the association of baseline FVC and FEV1 with all-cause mortality and incident cardiovascular hospitalization.

2. Methods

2.1. Study design

This study is a retrospective, observational analysis of patients evaluated in a single tertiary care medical center. Using the Duke Echocardiography Laboratory Database (DELD) and the Duke Pulmonary Function Testing Database we identified patients with transthoracic echocardiograms performed within 7 days of pulmonary function testing from January 2012 to April 2013. Patients with a prior history of lung or heart transplant were excluded from the database. Baseline characteristics consisting of demographics, medical history and comorbidities were identified using the Duke Enterprise Data Unified Content Explorer (DEDUCE) [18,19]. This study was approved by the Duke University School of Medicine Institutional Review Board and no informed consent was required.

2.2. Variable definitions

FVC and FEV1 were determined by spirometry in the Duke University Medical Center Pulmonary Function Laboratory using the Vmax 22 (CareFusion, San Diego). Spirometry was done without the administration of bronchodilators. Total lung capacity (TLC) was determined by either plethysmography or nitrogen washout (CareFusion Model 6200, CareFusion, San Diego). Plethysmography was the preferred method in patients with obstructive airway disease, given the possibility of air trapping, while nitrogen washout was generally utilized in patients who demonstrated no airway obstruction by spirometry. Transthoracic echocardiography was completed in the Duke Cardiac Diagnostic Unit. The echocardiograms were performed using either Philips IE33 (Philips Medical Systems, Foster City, CA) or General Electric Vivid (General Electric Healthcare, Sunnyvale, CA) machines and read on the Philips Xcelera platform (Philips Medical Systems, Foster City, CA). The following measurements were performed from 2D and M-mode echocardiography images: left ventricular ejection fraction (LVEF), left ventricular internal dimension in systole and diastole (LVIDS, LVIDD), right ventricular systolic pressure (RVSP), tricuspid annular plane systolic excursion (TAPSE) and left atrial anterior-posterior diameter. LVEF was determined quantitatively using 3D echocardiography. When a quantitative left ventricular ejection fraction was not available ejection fraction was determined qualitatively [20,21]. For the analysis of this study, left ventricular ejection fraction was parameterized into categories of 5% intervals. Right ventricular systolic pressure (RVSP) was estimated by the tricuspid regurgitant jet velocity using the modified Bernoulli equation.

All-cause mortality and cardiovascular hospitalization were captured from multiple sources in DELD with follow-up through February 2014. In patients without events, follow up was censored at their last known alive date based on clinic visits. Cardiovascular hospitalization was captured from DEDUCE using ICD-9 codes and included the following incidences: acute myocardial infarction, ischemic heart disease other, stroke, congestive heart failure, coronary artery bypass surgery and percutaneous coronary intervention. Clinical characteristics adjusted for in the regression analyses were also extracted from DEDUCE using ICD-9 codes.

2.3. Statistical methods

Baseline characteristics of the study population were compared by LVEF ($\leq$50% vs >50%). Continuous covariates were compared using Wilcoxon rank-sum tests and categorical covariates compared by Pearson chi-square tests. Spearman's Rank Correlation was used to determine the correlation between FVC and FEV1 with LVEF, LVIDD, LVIDS and left atrial diameter. To further describe the relationship between FVC and FEV1 with these echocardiography variables, we conducted regression analyses, adjusting for baseline patient characteristics/comorbidities. Normality of the distributions of the pulmonary function and echocardiography variables were assessed by visual inspection of histograms and q-q plots for symmetry and normality.

Adjusted regression models were created by using a backward stepwise selection method where in all baseline characteristics and comorbidities of interest were placed into the model and only those significant at the alpha = 0.10 level remained in the final adjusted model. Candidate variables included the following: Age, gender, race, body mass index, tobacco smoking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, renal disease, congestive heart failure, prior myocardial infarction, prior percutaneous intervention, and prior coronary artery bypass grafting surgery. For each of the left heart echocardiographic variables, a total of three adjusted models were created. The first regression model was a baseline-adjusted model, which included only baseline characteristics and comorbidities selected from the backward stepwise procedure. The second regression model included RVSP and TAPSE in addition to the variables included in the baseline-adjusted model in order to adjust for right heart function in the subset of patients with available data. The third regression included TLC in addition to the variables included in the baseline-adjusted model in order to adjust for lung hyperinflation. This analysis was restricted to participants for whom TLC was performed. In a sensitivity analysis the baseline only adjusted regression models were also conducted using the percent predicted PFT variables rather than the measured PFT variables.

As a secondary analysis, all adjusted models described above were conducted in patients with normal ejection fraction. For this analysis, normal ejection fraction was defined as LVEF greater than or equal to 50%.

In an additional secondary analysis, we evaluated the association between measured FVC and FEV1 with all-cause mortality and cardiovascular hospitalization using Cox proportional hazards models, adjusting for baseline characteristics and echocardiographic characteristics. Time zero was defined as the date of the initial echocardiogram or pulmonary function testing. We restricted this analysis to patients with more than one Duke