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Subclinical impairment of lung function is related to mild cardiac dysfunction and manifest heart failure in the general population

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ABSTRACT

Background: Lung function impairment has previously been related to heart failure, although no overt cardiovascular or structural heart disease is present. The extent to which pulmonary function is related to subclinical left ventricular impairment in the general population remains to be investigated.
Methods: 15010 individuals from the general population (mean age 55 ± 11 years, 50.5% men) in the Gutenberg Health Study underwent spirometry, transthoracic echocardiography and biomarker measurement. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) in percent of the predicted value and FEV1/FVC ratio were associated with echocardiographic measures of cardiac structure, systolic and diastolic function, biomarkers of cardiac necrosis (high-sensitive troponin I, hsTnI) and stress (N-terminal pro-B-type natriuretic peptide, Nt-proBNP) and heart failure with preserved (HFpEF) and reduced ejection fraction (HFrEF).
Results: Percent predicted FEV1 and FVC were significantly associated with hsTnI ($P < 0.001$) and Nt-proBNP ($P < 0.001$). Additionally, FEV1/FVC ratio was significantly related to hsTnI ($P = 0.0043$) and Nt-proBNP ($P < 0.001$). In the multivariable-adjusted linear regression analyses strongest associations were observed for percent predicted FEV1 and FVC with LVESD, E/e′, SV and EF. FEV1/FVC ratio was significantly related with SV and EF. The three lung function parameters were significantly ($P < 0.001$) associated with HFpEF and HFrEF. Associations remained statistically significant after exclusion of individuals with COPD.
Conclusions: FEV1, FVC and FEV1/FVC ratio were associated with systolic and diastolic function and manifest heart failure. Our observations could show, that subclinical lung function impairment is related to a measurable reduction of left ventricular filling and cardiac output in the general population.

1. Introduction

Lung and heart diseases share common risk factors. Chronic obstructive pulmonary disease (COPD) and heart failure are common comorbidities [1]. In both, dyspnea is the main clinical symptom. Impairment of lung function may cause symptoms of heart failure (HF), although no cardiovascular or structural heart disease is present. In patients with COPD, diastolic dysfunction seems to be frequent. It has

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EDV, end-diastolic volume; EF, left ventricular ejection fraction; ESV, end-systolic volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsTnI, high-sensitive troponin I; IVSd, interventricular end-diastolic septum diameter; LVESd, left ventricular end-systolic diameter; LVIDd, left ventricular end-diastolic diameter; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; SV, stroke volume.

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been explained by shortened diastolic filling due to medication-induced elevated heart rate (β2 agonists, theophylline), hypoxemia and reduced preload [2]. In severe COPD, parenchymal destruction and hypoxic vasoconstriction cause elevated pulmonary vascular resistance leading to right heart failure and consequently to a reduction of left ventricular filling, stroke volume and cardiac output [3,4]. In addition, the left ventricle may be directly compromised. Hyperinflation with consequent elevated intrathoracic pressure, as seen with increasing severity of COPD, is associated with decreasing cardiac chamber size [5]. Even in mild pulmonary impairment, an affection of left ventricular performance can be observed, e.g. a linear association of decreasing FEV1/FVC ratio and increasing emphysema with left ventricular end-diastolic volume (LVEDV), stroke volume (SV) and cardiac output has been shown [6].

Little is known about the relation of mild or subclinical lung function impairment with left ventricular measurements and heart failure. Some studies have reported, that moderately reduced FEV1 was associated with an increased incidence of HF in middle aged men [7], in older [8] and middle aged community-based individuals [9]. Impaired pulmonary function in young adulthood precedes left ventricular dysfunction in later life [10].

Since the cardio-pulmonary interplay is a continuum, we hypothesized that mild impairment of pulmonary function is related to echocardiographic measures of left ventricular systolic and diastolic dysfunction and heart failure in the general population. We further hypothesized that the associations would not change after exclusion of individuals with manifest COPD.

2. Methods

2.1. Study participants

The Gutenberg Health Study (N = 15010) started in 2007 as a population-based, prospective, single-center cohort study in the Rhine-Main region in western mid Germany [11]. Individuals between 35 and 74 years were randomly selected from the governmental local registry offices and equally stratified by sex and residence for each age decade and invited to take part in a five-hour study visit at the University Medical Center of the Johannes Gutenberg-University Mainz. Standardized interviews were performed to collect anthropometric data including information on cardiovascular risk factors and lifestyle. Risk factors comprised smoking status (current smokers versus never and former smokers), body mass index (body weight divided by height squared) (BMI), diabetes (physician diagnosis of diabetes or fasting blood glucose concentration of ≥126 mg/dL or ≥200 mg/dL at any time), dyslipidemia, arterial hypertension (mean systolic blood pressure ≥ 140 mm Hg or mean diastolic blood pressure ≥ 90 mm Hg or self-reported intake of medication prescribed for arterial hypertension).

Coronary artery disease was self-reported. COPD was defined clinically. Individuals who reported chronic bronchitis with sputum for more than 3 months in at least 2 consecutive years and/or had a physician-diagnosis of COPD were classified as having COPD. An individual was declared to have HF, if he/she fulfilled the criteria of HF with reduced (HFrEF) or preserved (HFpEF) ejection fraction. HFrEF was defined as (NYHA class ≥2 or medicated HF) and EF < 50%. HFpEF was defined adapting the Paulus et al. 2007 criteria [12]: (NYHA class ≥2 or medicated HF) and EF ≥ 50% and end-diastolic volume index (EDVI) < 97 ml/m^2 and at least one of the following:

- E/e′ ≥ 15
- 8 < E/e′ < 15 and Nt-proBNP > 220 pg/mL
- Nt-proBNP > 220 pg/mL and age > 50 years and decelaration time > 280 ms
- Nt-proBNP > 220 pg/mL and LADI > 3 cm/m^2
- Nt-proBNP > 220 pg/mL and left ventricular mass index (LVMI) > 122 g/m^2 & female
- Nt-proBNP > 220 pg/mL and LVMI > 149 g/m^2 & male
- Nt-proBNP > 220 pg/mL and atrial fibrillation
- 8 < E/e′ < 15 and age > 50 years and deceleration time > 280 ms
- 8 < E/e′ < 15 and left atrial diameter index (LADI) > 3 cm/m^2
- 8 < E/e′ < 15 and LVMI > 122 g/m^2 & female
- 8 < E/e′ < 15 and LVMI > 149 g/m^2 & male
- 8 < E/e′ < 15 and atrial fibrillation

The categories of diastolic dysfunction were defined as follows:

1. Normal: (0.75 ≤ E/A-ratio) and (deceleration time ≥ 0.140) and (E/e′ ratio < 10)
2. Mild: (E/A-ratio < 0.75) and (E/e′ ratio < 10)
3. Moderate: (0.75 ≤ E/A-ratio) and (deceleration time ≥ 0.140) and (E/e′ ratio ≥ 10)
4. Severe: (E/A-ratio > 2) and (deceleration time < 0.140) and (E/e′ ratio ≥ 10)

2.2. Spirometry

Spirometry was performed with the MicroMedical Spiro USB (MicroMedical, England). After detailed information about the course of the investigation, each individual performed at least three forced maneuvers in an upright sitting position. We used predictive equations for forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) derived from Global Lung Function Initiative (GLI) equations 2012 to obtain predicted lung function values taking account of age, sex, height and ethnicity [13]. FEV1 and FVC were presented as a percentage of their predicted values. Percent predicted FEV1 (%FEV1) = raw FEV1/predicted FEV1 and percent predicted FVC (%FVC) = raw FVC/predicted FVC.

2.3. Echocardiography

Cardiac function was assessed by multimodal echocardiography, performed with an iE33 echocardiography system with an S5–1 sector array transducer (Royal Philips Electronics, Amsterdam, The Netherlands), a phased array with 80 elements and a 5- to 1-MHz operating frequency range as described earlier [11]. Measurements were made by 2D-targeted M-mode echocardiography or directly from 2D images to determine the left ventricular internal diameters and the volume parameters. Diastolic function was assessed by pulsed wave and tissue Doppler imaging. The following echocardiographic variables were studied in the present investigation: interventricular end-diastolic septum diameter (IVSd), left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVESd), parameters of the transmitral velocity profile, i.e. ratio of the early to late ventricular filling velocities (E/A), ratio of peak early diastolic filling velocity of the mitral inflow to peak early diastolic velocity of the mitral annulus (E/e′), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and left ventricular ejection fraction (EF).

2.4. Biomarker measurement

HsTnI and Nt-proBNP measurements were available in 14006 and 14620 individuals for analyses. HsTnI was assessed with a high-sensitivity cardiac troponin assay (ARCHITECT STAT highly-sensitive Troponin I immunoassay, Abbott Diagnostics, USA, ARCHITECT i2000SR). The limit of detection (LoD) for the assay was 1.9 pg/mL (assay range 0–50000 pg/mL). The assay has a 10% coefficient of variation at a concentration of 5.2 pg/mL. Intra-assay and inter-assay coefficients of variation were 4.26 and 6.29%, respectively [14]. Nt-proBNP levels were measured on the ELECSYS 2010 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). The analytical reporting range is 5–35.000 ng/L. The functional assay