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Pulmonary function and diffusion capacity are associated with pulmonary arterial systolic pressure in the general population: The Rotterdam Study

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ABSTRACT

Background: Pulmonary hypertension is a progressive heterogeneous syndrome, characterized by elevated pulmonary arterial pressure which can lead to right ventricular failure. Although the presence of elevated pulmonary arterial systolic pressure (PASP) in patients with a lung disease is a well-known occurrence, little is known about the association between pulmonary function and PASP in the general population. We hypothesized that pulmonary function and PASP are associated, irrespective of airflow limitation.

Methods: This study was performed within the Rotterdam Study, a prospective population-based cohort. We included 1660 participants with spirometry, performed and interpreted according to ATS/ERS-guidelines, and echocardiography performed according to the ASE/EAE/CSE-guidelines. We analyzed the association of Forced Expiratory Volume in 1 s (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC and diffusion capacity (DL_{CO}) with estimated PASP (ePASP). Furthermore, we investigated the association between spirometry measures, COPD, and echocardiographic pulmonary hypertension.

Results: A 10% absolute decrease in FEV_1 was associated with an ePASP increase of 0.46 mmHg (95%CI: 0.31; 0.61). Similarly, per absolute 10% decrease, FVC was significantly associated with an increased ePASP of 0.42 mmHg (95%CI: 0.25; 0.59). FEV_1/FVC showed an association of 1.01 mmHg (95%CI: 0.58; 1.45) increase in ePASP per 10% absolute decrease. A decrease in DL_{CO} (in mL/min/kPa) was associated with an increased ePASP (0.46 mmHg, 95%CI: 0.17; 0.76). We found significant associations for FEV_1 and FVC with echocardiographic pulmonary hypertension. Importantly, an increased ePASP was significantly associated with mortality (Hazard Ratio: 1.042 per mmHg [95%CI: 1.023–1.062; $p < 0.001$]).

Conclusion: We observed a clearly graded association between pulmonary function and ePASP and pulmonary hypertension, even in individuals without airflow limitation.

1. Introduction

Pulmonary hypertension is a progressive and in some cases fatal heterogeneous syndrome, characterized by elevated pulmonary arterial pressure and can lead to right ventricular failure [1]. Lung diseases and/or hypoxemia are important causes of pulmonary

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hypertension. Pulmonary hypertension is a common co-morbidity of lung disease, with a prevalence of up to 60% in patients with chronic obstructive pulmonary disease (COPD) [2]. Pulmonary hypertension in patients with COPD seems influenced by two mechanisms, obliteration of the vascular bed and hypoxia-induced vasoconstriction [3]. Its presence is associated with a progressive course of disease and decreased survival in comparison to patients with COPD without pulmonary hypertension [4]. Although the presence of elevated pulmonary arterial systolic pressure (PASP) in patients with lung disease is a well-known phenomenon, the relation between pulmonary function and PASP in the general population without lung disease is unclear.

We hypothesized that a decrease in lung function, as measured by spirometry and diffusion capacity, is associated with an increase in PASP, as measured by echocardiography, in the general population. Furthermore, we evaluated the association of ePASP with all-cause mortality.

2. Methods

This study was performed in the first cohort of the Rotterdam Study, an ongoing prospective population-based cohort study which started in 1990 in Ommoord, a suburb of Rotterdam. Main objectives and methods of the Rotterdam Study have been described elsewhere [5]. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. The cohort consists of 7983 participants, aged 55 years and older. At baseline, all participants were visited at home for a standardized interview, and underwent a wide array of examinations at the research center. These study rounds are repeated every 3–5 years. Participants are actively followed for the occurrence of clinical events and mortality as detailed previously [6]. All prescriptions dispensed to the participants are collected by linkage to the seven pharmacies covering the study area.

2.1. Study population

The study population consisted of all participants of the Rotterdam Study who underwent both spirometry and echocardiography. These were gathered during the fifth study round (2009–2011).

2.2. Echocardiography

Echocardiographs were made using a commercially available ultrasonography system (Vivid I, GE Healthcare, Little Chalfont, UK), with a 2.5 MHz transducer according to a standardized protocol. Extensive left- and right-sided measurements and measures of both systolic and diastolic function were obtained. All images obtained at echocardiography were digitally stored and assessed offline by experienced echocardiographists. ePASP (in mmHg) was calculated following the recommendations by the ASE/EAE/CSE as the sum of the estimated right atrial pressure (based on the diameter of the inferior vena cava and forced respiratory collapse) and the pressure gradient over the tricuspid valve. The pressure gradient was computed from the highest Doppler tricuspid regurgitation velocity (TRV) gathered from several windows using the simplified Bernoulli equation ($4v^2$, where v is TRV in m/sec)[8]. In those with sufficient tricuspid regurgitation to estimate ePASP, a 40-mmHg cut-off was set to define echocardiographic pulmonary hypertension. The definition of echocardiography-based pulmonary hypertension (ePH) is based on the measurements of TRV (elevated TRV is defined as TRV >3 m/sec, corresponding to a ePASP of >40 mmHg) and right ventricular end-diastolic dimension (RVEDD; elevated RVEDD is defined as RVEDD >42 mm) [7–10]. If the TRV was too small to measure, but a participant had an elevated RVEDD, this was considered to be indicative of PH (Supplementary Table 1). We assessed left ventricular (LV) systolic function through LV fractional shortening in the parasternal long-axis view using M-mode. LV fractional shortening (%) at the endocardium was calculated by: (LV end-diastolic diameter—LV end-systolic diameter)/LV end-diastolic diameter * 100% [11,12].

2.3. Spirometry and diffusion capacity

Spirometry and diffusing capacity were performed using a Master Screen® PFT Pro (CareFusion, San Diego, CA, USA) by trained paramedical personnel according to the ATS/ERS guidelines [13,14]. Using spirometry FEV_1, FVC and the ratio of FEV_1 over FVC (FEV_1/FVC) were measured. For the diffusion capacity, we measured the transfer factor using carbon monoxide in milliliters per minute per kilo Pascal (mL/min/kPA). Participants were asked to refrain from using any prescribed pulmonary medication one day before the center visit and were asked to refrain from smoking. The spirometry and diffusion capacity tests were analyzed by two researchers, and verified by a specialist in pulmonary medicine. Spirometry procedures that yielded results that did not meet ATS/ERS criteria for acceptability and reproducibility were classified as not interpretable [14]. Diffusion capacity procedures preferably attempted twice, if only one attempt was made, tests were scored on the basis of the quality of the curve. Multiple attempts yielding results that were not reproducible were not used in these analyses.

2.4. Mortality

Participants are actively followed for the occurrence of clinical events and mortality as detailed previously [6]. For the mortality analyses, the censor date was the date of last contact or date of death.

2.5. Statistical analyses

For cross-sectional analyses, we used linear and logistic regression. For mortality analyses, we used Cox proportional hazards analyses. Information on potential confounders included age, sex, height and weight, was gathered at the study in the same round as the spirometry and echocardiography. History of pulmonary embolism was determined on the basis of dispensing data of coumarin derivatives with pulmonary embolism as treatment indication through specialized monitoring centers. Furthermore, echocardiographic measures of systolic and diastolic function were collected, as well as use of medication, a history of heart failure, a history of coronary heart disease (i.e. a composite of myocardial infarction, percutaneous coronary intervention, and surgical coronary artery bypass graft), in order to adjust for left ventricular failure leading to an increased ePASP. Confounders were selected on the basis of their biologic plausibility [6]. The covariables were used in the final regression model according their influence on the effect estimate and/or statistical significance in the regression model.

3. Results

Within the Rotterdam Study, a total of 2903 individuals underwent echocardiography between 2009 and 2011 (44% male, mean