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Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis ☆

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Summary
Background: Reliable, noninvasive approaches to the diagnosis of pulmonary hypertension in idiopathic pulmonary fibrosis are needed. We tested the hypothesis that the forced vital capacity to diffusing capacity ratio and room air resting pulse oximetry may be combined to predict mean pulmonary artery pressure (MPAP) in idiopathic pulmonary fibrosis.
Methods: Sixty-one idiopathic pulmonary fibrosis patients with available right-heart catheterization were studied. We regressed measured MPAP as a continuous variable on pulse oximetry (SpO_2) and percent predicted forced vital capacity (FVC) to percent-predicted diffusing capacity ratio (% FVC/% DL_{co}) in a multivariable linear regression model.
Results: Linear regression generated the following equation: $MPAP = -11.9 + 0.272 \times SpO_2 + 0.0659 \times (100 - SpO_2)^2 + 3.06 \times (\%\ FVC/\%\ DL_{co})$; adjusted $R^2 = 0.55$, $p < 0.0001$. The sensitivity, specificity, positive predictive and negative predictive value of

Abbreviations: ABG, arterial blood gas; CI, confidence interval; DE, Doppler echocardiography; DL_{co}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IRB, institutional review board; MPAP, mean pulmonary artery pressure; NPV, negative predictive value; PH, pulmonary hypertension; PaO_2, arterial blood oxygen tension; PFT, pulmonary function tests; PPV, positive predictive value; RHC, right-heart catheterization; RV, residual volume; RVSP, right ventricular systolic pressure from echocardiography; SpO_2, resting room air pulse oximetry; TLC, total lung capacity; VA, alveolar volume; 6 MWD, 6-min walk distance.

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model-predicted pulmonary hypertension were 71% (95% confidence interval (CI): 50–89%), 81% (95% CI: 68–92%), 71% (95% CI: 51–87%) and 81% (95% CI: 68–94%).
Conclusions: A pulmonary hypertension predictor based on room air resting pulse oximetry and FVC to diffusing capacity ratio has a relatively high negative predictive value. However, this model will require external validation before it can be used in clinical practice.

Introduction

Pulmonary hypertension (PH) is common in patients with idiopathic pulmonary fibrosis (IPF) and its presence has a significant adverse impact on survival.[1,2] Echocardiography is commonly used to diagnose PH; however, echocardiography is frequently inaccurate in patients with interstitial lung disease (ILD).[3] Right-heart catheterization (RHC) is the gold standard for diagnosis of PH in IPF patients.[3,4] However, it is an invasive method with significant risks for complications.

Noninvasive approaches to the diagnosis of PH in IPF would improve patient safety and reduce cost. The ability to predict which IPF patients have PH using noninvasive measures could guide the selection of patients for RHC to confirm its presence.

In ILD patients, the diffusing capacity for carbon monoxide (DL_{co}) falls because of fibrosis, emphysema and pulmonary vascular disease.[5,6] In these patients, a reduction in DL_{co} out of proportion to the reduction in lung volumes might indicate underlying pulmonary vascular disease. For instance, in patients with scleroderma, when there is a mixture of both fibrosis and pulmonary vasculopathy, the forced vital capacity (FVC) is moderately decreased but the DL_{co} is even lower and the FVC to DL_{co} ratio is often greater than 1.8.[7–12] We therefore hypothesized that a high FVC/DL_{co} ratio might be a marker for increased pulmonary artery pressures in IPF.

Chronic hypoxia causes pulmonary vasoconstriction through a diversity of actions on pulmonary artery endothelium and smooth muscle cells, including downregulation of endothelial nitric oxide synthase and reduced production of the voltage-gated potassium channel alpha subunit.[13,14] Although initially reversible, the pathologic changes induced by hypoxia-induced vasoconstriction ultimately result in irreversible vascular remodeling.[15,16]

The independent associations of FVC/DL_{co} ratio and chronic hypoxia with PH in ILD patients, raise the possibility that these factors may be combined to improve the prediction of PH in IPF patients.

Methods

Study sample

We retrospectively reviewed the medical records of all IPF patients who were seen at our institution between July 1999 and June 2006. During their initial visit, all patients provided written informed consent to use their clinical and demographic information for research purposes. All patients met accepted diagnostic criteria for IPF and the majority (61%) had histopathologic evidence of usual interstitial pneumonia.[17] Two hundred and ninety-eight IPF patients were candidates for inclusion in this study. To be included in the study, participants had to have had RHC and have pulmonary function test (PFT) and resting pulse oximetry data while breathing room air (SpO_2) within 1 month of the RHC. Fifty five patients met this entry criterion. Six other patients had RHC and PFTs and were known to require supplemental oxygen; however, their actual SpO_2 was not available. We included these six patients and used the imputed value of 85% for their SpO_2. We used 85% because it was the mean SpO_2 in the 15 patients requiring supplemental oxygen who had measurements of SpO_2. Thus, our study sample consisted of 61 patients.

Measurements

RHC data included measurements of pulmonary arterial pressures with the patient at rest. We defined PH as a resting mean pulmonary artery pressure (MPAP) of >25 mmHg.[18]

SpO_2 measurements were conducted in agreement with a clinical protocol: after at least 5 min of rest, SpO_2 was measured on room air. All SpO_2 measurements were done with the same oximeter (Digital Handheld Pulse Oximeter, Nonin Medical, Inc.).

Standard methodology was used for obtaining PFT, ABG, 6 MWD, and RVSP from Doppler echocardiography.[19–25]

Statistical analysis

We compared patients in the study sample with those excluded with respect to the variables of interest, using standard tests for comparing means (Student's *t*-test), medians (Wilcoxon rank-sum test) and proportions (Chi-square test or the Fisher's exact test, if cell sizes are small).

We regressed the MPAP (obtained from RHC) as a continuous variable on SpO_2 and % FVC/% DL_{co}, both as continuous predictors in a multivariable linear regression model. Examination of the model residual indicated that the model underestimated MPAP in patients with high MPAP and overestimated MPAP in patients with low MPAP. We therefore added a quadratic term $(100-SpO_2)^2$ to the model. Given the moderately small sample size, no attempt was made to further refine the model, to avoid overly optimistic results.[26]

We compared this final model's prediction ability with alternate models that included other predictors or alternate predictors. MPAP prediction ability was assessed by model R^2