Validation of a Method To Screen for Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis*

David A. Zisman, MD, MS, FCCP; Arun S. Karlamangla, PhD, MD; Steven M. Kawut, MD, MS, FCCP; Oksana A. Shlobin, MD; Rajeev Saggar, MD; David J. Ross, MD; Marvin I. Schwarz, MD, FCCP; John A. Belperio, MD; Abbas Ardehali, MD; Joseph P. Lynch, III, MD; and Steven D. Nathan, MD, FCCP

Background: **We have developed a method to screen for pulmonary hypertension (PH) in idiopathic pulmonary fibrosis (IPF) patients, based on a formula to predict mean pulmonary artery pressure (MPAP) from standard lung function measurements. The objective of this study was to validate this method in a separate group of IPF patients.**

Methods: **Cross-sectional study of 60 IPF patients from two institutions. The accuracy of the MPAP estimation was assessed by examining the correlation between the predicted and measured MPAPs and the magnitude of the estimation error. The discriminatory ability of the method for PH was assessed using the area under the receiver operating characteristic curve (AUC).**

Results: **There was strong correlation in the expected direction between the predicted and measured MPAPs ($r = 0.72$; $p < 0.0001$). The estimated MPAP was within 5 mm Hg of the measured MPAP 72% of the time. The AUC for predicting PH was 0.85, and did not differ by institution. A formula-predicted MPAP > 21 mm Hg was associated with a sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 58%, 51%, and 96%, respectively, for PH defined as MPAP from right-heart catheterization > 25 mm Hg.**

Conclusions: **A prediction formula for MPAP using standard lung function measurements can be used to screen for PH in IPF patients.** ***(CHEST 2008; 133:640–645)***

Key words: idiopathic pulmonary fibrosis; prediction; pulmonary fibrosis; pulmonary hypertension

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; DLCO = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; MPAP = mean pulmonary artery pressure; NPV = negative predictive value; PFT = pulmonary function test; PH = pulmonary hypertension; PPV = positive predictive value; RHC = right-heart catheterization; Spo_2 = resting room air pulse oximetry; UCLA = University of California, Los Angeles

Pulmonary hypertension (PH) frequently complicates advanced idiopathic pulmonary fibrosis (IPF) and is associated with poor outcome.[1–7] Currently, right-heart catheterization (RHC) is the only accepted method for the diagnosis of PH in patients with IPF. However, RHC is invasive and expensive. Although echocardiography and CT-determined main pulmonary artery diameter are commonly used tests to screen for PH in patients with IPF, they are not reliable.[4,8,9] Reliable, noninvasive approaches to the diagnosis of PH in patients with IPF would improve patient safety, reduce costs, and enable the appropriate timing of RHC.

We recently demonstrated that the ratio of the FVC percentage of predicted to diffusing capacity of the lung for carbon monoxide (DLCO) percentage of predicted and room air resting pulse oximetry (Spo_2) data can be combined in a linear regression formula to screen for PH in patients with IPF.[4] It was shown that a cutoff of 25 mm Hg for the formula-estimated mean pulmonary artery pressure (MPAP) had sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for PH (defined as mean pulmonary artery pressure [MPAP] from RHC > 25 mm Hg) of 71%, 81%, 71%, and 81%, respectively. By selecting a lower cutoff of 21 mm Hg for the

formula-estimated MPAP, we maximized sensitivity (100%) for PH (defined as MPAP from RHC > 25 mm Hg) with the least compromise in specificity (40%).[4] The performance of the formula was assessed by bootstrap techniques; however, internal validation does not guarantee adequate performance in other populations.[10,11] Hence, independent external validation is essential before recommendations can be made for adoption in clinical practice.[12,13] Accordingly, the aim of this study was to validate the PH screening formula in an external population of IPF patients.

Materials and Methods

Validation Sample

We reviewed the medical records of all IPF patients from the Inova Fairfax Hospital between July 1997 and February 2007 and from University of California, Los Angeles (UCLA) Medical Center between July 2006 (following the close of the derivation study[4]) and June 2007. Hence, the group of patients in this study is totally separate from that used to develop the formula.[4] The Inova Fairfax Hospital and UCLA institutional review boards approved the study. All patients met accepted diagnostic criteria for IPF, and the majority (71%) had histopathologic evidence of usual interstitial pneumonia.[14] One hundred thirty-two 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 Spo_2 data while breathing room air within 3 months of the RHC. All RHCs were performed as part of standard lung transplant evaluation. Patients were excluded for the following reasons: (1) missing data (46 patients), and (2) PFT or Spo_2 not done within 3 months of RHC (26 patients). Sixty patients met the entry criteria and comprised the validation cohort (Inova Fairfax Hospital, 35 patients; UCLA, 25 patients).

Measurements

We defined PH as resting MPAP from RHC > 25 mm Hg.[15] Pulmonary artery occlusion pressure < 15 mm Hg and pulmonary vascular resistance > 3 Wood units were not required to define PH because these measurements do not provide prognostic information above and beyond MPAP in IPF patients.[1,7] Hence, we selected MPAP > 25 mm Hg from RHC as the outcome to screen for with our method and later confirm with RHC (when the rest of the hemodynamic variables would become available). Standard methodology was used for PFTs and pulse oximetry.[16,17] After at least 5 min of rest, Spo_2 was measured on room air. The equations of Crapo et al[16] were used to calculate predicted FVC values. The equations of Crapo and Morris[17] were used to calculate predicted Dlco values. To assess the impact of alternate predicted values on the discriminatory capacity of the method, we tested additional equations for predicted FVC[18] and Dlco.[19,20] The following equation, derived by our group,[4] was used to calculate predicted MPAP (in millimeters of mercury):

$$\text{MPAP} = -11.9 + 0.272 \times Spo_2 + 0.0659 \times (100 - Spo_2)^2 + 3.06 \times (\text{percentage of predicted FVC/percentage of predicted Dlco})$$

Statistical Analysis

Our objectives were to test the utility of the MPAP estimation formula by assessing both the accuracy of the MPAP prediction and the reliability of the PH prediction. First, the quality of the MPAP prediction was assessed by examining the percentage of MPAP estimates that fell within 5 and 10 mm Hg of the MPAP measured by directly RHC. This was also examined separately in the UCLA and Inova Fairfax Hospital samples. The Pearson correlation coefficient between the predicted MPAP and RHC-measured MPAP was examined. Second, the discriminatory ability of the PH-prediction method was assessed using the area under the receiver operating characteristic curve (AUC).[21,22] The AUC was also examined separately in the UCLA and Inova Fairfax Hospital samples, and we tested for a difference in the two AUC figures using the method published by Hanley and McNeil.[21] All tests were two tailed, and p values < 0.05 were required for statistical significance. All statistical analysis was performed using statistical software (SAS version 9.1; SAS Institute; Cary, NC; and MedCalc for Windows, version 9.2.0.0; MedCalc Software; Mariakerke, Belgium).

Results

Comparisons of Patients in the Validation and Excluded Cohorts

Patients in the validation sample (n = 60) were younger and had more advanced pulmonary disease than those excluded from the study (n = 72) but were similar to the rest of the cohort with respect to gender, race, and Spo_2 (Table 1). This is consistent

*From the Division of Pulmonary and Critical Care Medicine, (Drs. Zisman, Saggar, Ross, Belperio, and Lynch) and Division of Geriatrics (Dr. Karlamangla), Department of Medicine, and Division of Cardiothoracic Surgery (Dr. Ardehali), Department of Surgery, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA; Department of Medicine (Dr. Kawut), College of Physicians and Surgeons, Joseph L. Mailman School of Public Health, Columbia University, New York, NY; Advanced Lung Disease and Transplant Program (Drs. Shlobin and Nathan), Inova Fairfax Hospital, Falls Church, VA; and Department of Medicine (Dr. Schwarz), University of Colorado Health Sciences Center, Denver, CO.
All work was performed at the David Geffen School of Medicine, University of California, Los Angeles; and Inova Fairfax Hospital.
This work was supported in part by grants from the National Institutes of Health: 5U10HL080411 to D.A.Z.; 5P30 AG028748 to A.S.K.; and HL080206 and HL086491 to J.A.B.
Dr. Zisman received research grants from Intermune and Actelion Pharmaceuticals to do multicenter studies. Drs. Zisman and Schwarz are funded by the National Institutes of Health IPF Clinical Research Network, which includes participation in a pulmonary hypertension study with sildenafil. Dr. Nathan is a consultant for and received honoraria from Actelion, Encysive, and Gilead Pharmaceuticals. He has also received research funding from Actelion and United Therapeutics. Dr. Kawut received honoraria from Actelion, Encysive, Gilead, and United Therapeutics. None of the other authors have any other conflicts of interest to disclose.
Manuscript received October 8, 2007; revision accepted November 16, 2007.

Correspondence to: David A. Zisman, MD, MS, FCCP, Director, Interstitial Lung Disease Center, David Geffen School of Medicine at UCLA, 37–131 Center for Health Sciences, Los Angeles, CA 90095; e-mail: dzisman@mednet.ucla.edu
DOI: 10.1378/chest.07-2488