Echocardiography, 6-Minute Walk Distance, and Distance-Saturation Product as Predictors of Pulmonary Arterial Hypertension in Idiopathic Pulmonary Fibrosis

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BACKGROUND: Pulmonary arterial hypertension (PAH) is frequently seen in patients with idiopathic pulmonary fibrosis (IPF). We sought to examine the performance of echocardiography, 6-min walk test (6MWT) distance, distance-saturation product (DSP), and pulse oximetry (S_{pO_2}) in detecting underlying PAH in IPF. METHODS: 626 lung transplanted patients from February 1990 to December 2007 were considered. Subjects with pre-transplant diagnosis of IPF were evaluated. Based on findings in pre-transplant right heart catheterization, the presence or absence of PAH was recorded. Right-ventricle systolic pressure, 6MWT distance, DSP, and lowest S_{pO_2} during 6MWT were compared in PAH and non-PAH groups. Receiver operating characteristic curves for each variable to assess prediction of PAH were constructed. RESULTS: 131 patients were transplanted due to IPF. Of these 131 patients, 58 (44%) were eligible. PAH was diagnosed by right heart catheterization in 25 (43%) of 58 eligible patients. The mean pulmonary arterial pressure in PAH patients was 33 mm Hg, and 19 mm Hg in non-PAH patients ($P = .001$). 6MWT distance was 321 m in the PAH group, and 346 m in the non-PAH one ($P = .38$). DSP in PAH subjects was 272 meters% and 286 meters% in those with no PAH ($P = .57$). The lowest S_{pO_2} in the PAH and non-PAH groups were 84% and 82%, respectively ($P = .38$). The diagnostic accuracy of the echocardiography exceeded that of the other variables (area under the curve 0.72). CONCLUSIONS: Right-ventricle systolic pressure measured by echocardiography, by 6MWT distance, by DSP, or by S_{pO_2} performs poorly in detecting PAH in IPF. Measured by right heart catheterization, right-ventricle systolic pressure performs better to predict PAH in IPF. *Key words: idiopathic pulmonary fibrosis; pulmonary arterial hypertension; echocardiogram; pulmonary function tests; oximetry.* [Respir Care 2010;55(5):584–588. © 2010 Daedalus Enterprises]

Introduction

Pulmonary arterial hypertension (PAH) in patients with idiopathic pulmonary fibrosis (IPF) has been the subject of growing attention since it was demonstrated that its presence carries high mortality.[1-4] In a retrospective study with IPF patients being evaluated for lung transplantation, Lettieri and colleagues,[2] at the end of the observation period, concluded that 60% of the patients with PAH had died, compared with 30% in the non-PAH group. Since then, various studies aimed to detect PAH with noninvasive cardiac imaging and pulmonary function tests (PFTs), obtaining variable results. Indeed, the aforementioned report revealed that the need of supplemental oxygen together with a diffusing capacity of the lung for carbon monoxide (D_{LCO}) < 40% identified the presence of PAH with a sensitivity of 65% and specificity of 94%.[2] In another report, Nathan and colleagues[5] studied the percent of predicted forced vital capacity (FVC%), the percent of predicted D_{LCO} (D_{LCO}%), and the ratio FVC%/D_{LCO}% in their ability to predict underlying PAH in IPF patients.

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These parameters demonstrated poor performance in detecting PAH. The value of echocardiography in diagnosing PAH has been examined in various settings, including idiopathic PAH,[6-8] PAH in systemic sclerosis,[9] and PAH associated with diffuse parenchymal lung disease.[10,11] Homma and colleagues[11] analyzed the correlation between right-ventricle systolic pressure (RVSP) determined by echocardiography, and the pulmonary artery systolic pressure measured by right heart catheterization (RHC). The study showed a poor correlation between these values in a subgroup of patients with IPF.

Despite this broad attention to the value of echocardiography and PFTs, important questions regarding the accuracy of noninvasive tests for predicting PAH in IPF patients still remain. Specifically, how do RVSP measured by echocardiography, 6-min walk test (6MWT) distance, distance-saturation product (DSP), and S_{pO_2} compare in their detecting PAH in patients with IPF? The current study addresses this question based on a consecutive series of transplanted patients for IPF at the Cleveland Clinic.

Methods

The study was approved by the Institutional Review Board of the Cleveland Clinic.

We conducted a retrospective review of a data set consisting of 626 consecutive lung transplantations performed at the Cleveland Clinic from February 1990 to December 2007. This data set was chosen based on the convenience of having data available from a recently implemented electronic database system (Epic, Epic Systems, Verona, Wisconsin). To determine the diagnosis of IPF, pathology reports of all 626 transplanted subjects were reviewed for the presence of usual interstitial pneumonia pattern in the explanted lung. Eligible subjects had to have echocardiography, 6MWT, and RHC as their initial evaluation prior to being listed for lung transplantation. PAH was defined as a pulmonary arterial pressure higher than 25 mm Hg with a concomitant pulmonary artery occlusion pressure lower than 15 mm Hg.[12]

To assure relatedness of the noninvasive tests to the RHC, eligible PFTs and echocardiography reports were restricted to those performed within 3 months before or after the RHC.

Measurements

Demographic, echocardiography, and 6MWT data, as well as resting S_{pO_2} with the patient's usual oxygen requirements were recorded.

The echocardiographic measure of interest was the RVSP. This variable was calculated through the quantification of the tricuspid regurgitant jet velocity and its utilization in the modified Bernoulli equation.[6]

6MWT was performed according to the American Thoracic Society protocol.[13] S_{pO_2} was monitored continuously with a wireless pulse oximeter. Total distance walked, expressed in meters, as well as the lowest S_{pO_2} observed during the test, were recorded. The patients were allowed to use their usual oxygen therapy, which had been determined by either a resting S_{pO_2} of $< 88\%$ or a P_{aO_2} of < 55 mm Hg. Distance-saturation product was calculated as reported in a prior study,[14] in which it was defined as the product of the final distance walked, in meters, and the lowest room air S_{pO_2}. RVSP, 6-minute walk distance, DSP, and lowest S_{pO_2} during 6MWT were compared in patients with and without PAH.

Statistical Methods

Continuous measurements were described as means and standard deviations. These variables were compared with the Student's *t* test. Categorical measurements were summarized using frequencies and percentages. These variables were compared with the Fisher's exact test. Receiver operating characteristic (ROC) curves under logistic regression were performed to assess the prediction ability of identifying positive PAH. We constructed ROC curves for each of the following variables: RVSP, 6MWT, S_{pO_2}, and DSP. ROC curves were compared via comparison of the area under the curve (AUC). In each curve, a cut-off value on the scale of the predicted probabilities from the logistic regression was used to classify patients into groups labeled "PAH" or "non-PAH." The objective was to select a cut-off with sufficiently high sensitivity and specificity for classifying PAH and non-PAH patients. The relationship between the sensitivity and the specificity for various cut-off points can be plotted as an ROC curve. SAS 9.1.3 software (SAS Institute, Cary, North Carolina) was used for all analyses.

Results

Of the 626 transplanted patients, 131 (21%) had IPF. Of these 131 evaluable patients, 58 (44%) were deemed eligible based on the availability of echocardiography, 6MWT, and RHC reports. Table 1 presents the demographic features of these eligible patients.

Seventy-three patients (56%) were excluded due to the lack of echocardiography or RHC reports in the electronic medical records.

The mean $\pm$ standard deviation intervals between performance of the RHC and the echocardiogram and 6MWT were 11 ± 27 d and 40 ± 30 d, respectively. Twenty-five patients (43% of eligible patients) had PAH confirmed by RHC. The mean pulmonary arterial pressure was 33 ± 8 mm Hg (range 26 to 57 mm Hg) among the patients with PAH and 19 ± 4 mm Hg (range 11 to 24 mm Hg) within the group of subjects with no PAH ($P = .001$).

The mean RVSP found in patients with PAH was 43 ± 30 mm Hg (range 16 to 93 mm Hg), whereas this variable was 20 ± 24 mm Hg (range 11 to 69 mm Hg) in

Table 1. Demographics and Baseline Physiologic Parameters (n = 58)

	PAH	Non-PAH	P
Patients (n, %)	25 (43)	33 (57)	NA
Age (mean y)	56 ± 7	56 ± 9	.95
Male (n, %)	17 (68)	23 (67)	> .99
Mean pulmonary arterial pressure (mean ± SD mm Hg)	33 ± 8	19 ± 4	.001
Cardiac output (mean ± SD L/min)	5.4 ± 1.0	5.8 ± 1.6	.36
F_{IO_2} (mean ± SD)	.60 ± .30	.50 ± .30	.69
S_{pO_2} at rest (mean ± SD %)	95 ± 1	96 ± 2	.19

PAH = pulmonary arterial hypertension
NA = not applicable
F_{IO_2} = fraction of inspired oxygen
S_{pO_2} = oxygen saturation measured via pulse oximetry

patients without it (95% confidence interval [CI] of difference 9 to 38, P = .01).

6MWT distance was 321 ± 114 m (range 81 to 518 m) in the group of patients with PAH and 346 ± 100 m (range 188 to 553 m) in subjects with normal pulmonary pressure (95% CI of difference −81 to 32, P = .38).

The mean oxygen concentration requirement (F_{IO_2}) in patients with PAH was .60 ± .30 (range .30 to 1.0) and .50 ± .30 (range .21 to 1.0) in patients without PAH (P = .69). Patients who had an F_{IO_2} requirement higher than .40 were administered O_2 through a transtracheal oxygen catheter. Rest S_{pO_2} was 95 ± 2% (range 93 to 99%) in subjects with PAH and 96 ± 2% (range 94 to 100%) in those without PAH (P = .19).

The analysis of the DSP in patients with PAH revealed a value of 272 ± 100 meters% (range 65 to 432 meters%), while it was 286 ± 89 meters% (range 142 to 504 meters%) in the group of patients with no PAH (95% CI of difference −64 to 36, P = .57). The lowest S_{pO_2} during the 6MWT in patients with PAH and with no PAH were 84 ± 9% (range 66 to 98%) and 82 ± 8% (range 67 to 95%), respectively (95% CI of difference −2.4 to 6.3, P = .38). Distance-saturation product was adjusted for F_{IO_2} (DSP/F_{IO_2}) to evaluate whether this parameter had a better performance than each of the aforementioned variables alone. The mean DSP/F_{IO_2} was 5 for both groups (PAH and non-PAH), with a standard deviation of ± 3 in each.

ROC curves were generated from logistic regression for each of the 4 aforementioned variables for detecting PAH. Values of the area under the ROC curves (AUC) for each of the 4 variables are shown in Table 2. The AUC for DSP was statistically lower (P = .04) than the AUC for RVSP. AUCs for 6MWT distance and S_{pO_2} were lower than the one for RVSP; however, this difference did not reach statistical significance (P = .07 and P = .15, respectively).

According to these results, RVSP shows a fair accuracy in detecting PAH. However, this parameter still performs

Table 2. Values of the Area Under the Receiver Operating Characteristic Curve for Each of the 4 Variables

	AUC	SE	95% CI
Right-ventricle systolic pressure	0.72	0.07	0.59 to 0.83
Distance-saturation product	0.53	0.08	0.39 to 0.66
6-min walk test distance	0.56	0.08	0.42 to 0.69
S_{pO_2}	0.59	0.08	0.45 to 0.72

AUC= area under the curve
SE = standard error
CI = confidence interval
S_{pO_2} = oxygen saturation measured via pulse oximetry

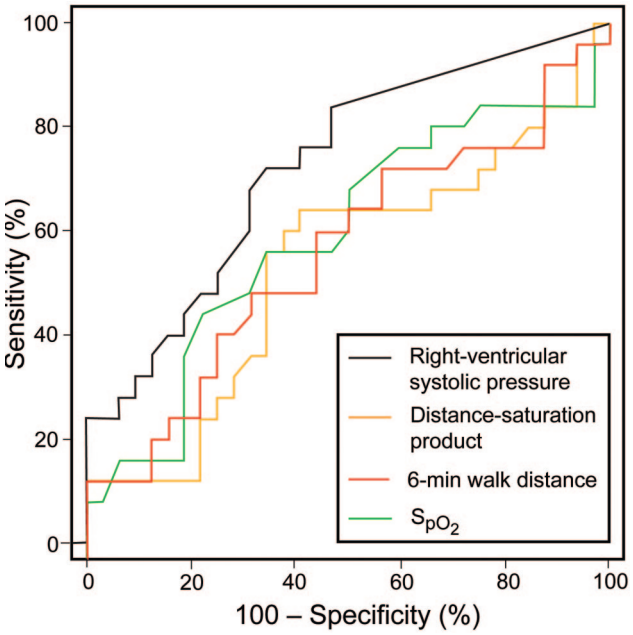

Fig. 1. Receiver operating characteristic curves for right-ventricle systolic pressure, 6-min walk test distance, distance-saturation product, and oxygen saturation measured via pulse oximetry (S_{pO_2}) as predictors of the presence of pulmonary arterial hypertension in patients with idiopathic pulmonary fibrosis.

better than 6MWT distance, DSP, and S_{pO_2}, which fail in detecting PAH. Because the AUC for each test falls well below 1.0, these variables remain an imperfect criterion for detecting PAH.

Through analysis of multiple points in the RVSP ROC curve (Fig. 1) and applying the Youden's index (sensitivity + specificity – 1), we identified a RVSP of 26 mm Hg as the threshold value with the highest pair sensitivity/specificity (sensitivity 72% and specificity 66%). The threshold value for 6MWT distance was 305 m, with sensitivity of 48% and specificity 67%, for DSP it was 285 meters%, with sensitivity of 64% and specificity of 57%, and for S_{pO_2} it was 88%, with a sensitivity of 44% and specificity of 76%. Table 3 shows the sensitivity, specificity, positive predictive value, and negative predictive

Table 3. Sensitivity, Specificity, and Positive Predictive Value, and Negative Predictive Value of RVSP, 6-Minute Walk Distance, Distance-Saturation Product, and S_{pO_2} for Detecting PAH in IPF Patients

	RVSP (%)	6-Min Walk Distance (%)	Distance-Saturation Product (%)	S_{pO_2} (%)
Sensitivity	72	48	64	44
Specificity	66	67	57	76
Positive predictive value	62	36	53	58
Negative predictive value	76	63	32	64

RVSP = right-ventricle systolic pressure
PAH = pulmonary arterial hypertension
IPF = idiopathic pulmonary fibrosis
S_{pO_2} = oxygen saturation measured via pulse oximetry

value of each of these parameters, utilizing the aforementioned cut-off points. Figure 1 shows the ROC curves for each of the aforementioned variables.

Discussion

The main findings of this study are: 1. Noninvasive diagnostic tests such as echocardiogram, 6MWT distance, DSP, and S_{pO_2} perform poorly in detecting PAH in IPF patients. 2. The diagnostic accuracy of the echocardiogram for the detection of PAH exceeds that of the other variables, with a sensitivity of 72% and a positive predictive value of 62%. 3. The prevalence of PAH in our cohort of patients with IPF was 43%.

Our findings extend the literature by offering an evaluation of a parameter recently described, the DSP,[14] as a predictor of PAH, and by directly comparing the diagnostic performance of various functional tests (6MWT, DSP, S_{pO_2}) with echocardiography. To our knowledge, only a few prior studies have compared PFTs with cardiac imaging in their accuracy of predicting PAH in IPF patients. Specifically, Zisman and colleagues[15] demonstrated, in a retrospective review, that FVC/D_{LCO} ratio can be used as a marker of PAH in IPF patients. In that study, an equation generated by linear regression utilizing the FVC/D_{LCO} ratio and resting S_{pO_2} at room air, showed a sensitivity of 71%, specificity of 81%, positive predictive value of 71%, and negative predictive value of 81% for the diagnosis of PAH. When this model was compared with the RVSP obtained by echocardiography (using a RVSP cut-off of 40 mm Hg), the equation had a better negative predictive value, with similar sensitivity. The limitation of applying this study to our series includes the fact that the estimation of RVSP by echocardiography was possible in only 54% of the patients, in concordance with other reports.[10] In our series, RVSP was estimated in all IPF patients.

In another report, Nathan and colleagues[5] assessed the ability of the $FVC\%/D_{LCO}\%$ ratio, FVC%, and $D_{LCO}\%$ to predict PAH in IPF patients. Via ROC curves, AUCs for each of these variables were obtained. As a result, the performance of all 3 parameters was poor, with AUC for $FVC\%/D_{LCO}\%$, $D_{LCO}\%$, and FVC% of 0.61, 0.64, and 0.51, respectively. In a landmark study mentioned earlier, Lettieri and colleagues[2] compared 6MWT distance and the lowest S_{pO_2} between patients with and without PAH. They found a statistically significant difference in the distance walked by subjects with PAH (143 ± 65 m) compared with those without PAH (366 ± 82 m). The S_{pO_2} was significantly lower as well in those subjects with PAH (80 ± 3.7% vs 88 ± 3.5%). Echocardiographic parameters (ie, RVSP) were not evaluated in these 2 studies; therefore, a comparison against the aforementioned functional variables was not performed.

The prevalence of PAH in our cohort was 43%, which coincides with the reported 20% to 46% described in other studies.[2,16-19]

Our study presented several limitations. First, this was a retrospective study, performed in a single center, which included only patients with IPF who underwent lung transplantation. We focused on this group due to the availability of RHC reports (obtained during the pre-transplant evaluation) and pathology reports from the explanted lungs, which confirmed the usual interstitial pneumonia pattern. However, we recognize that this cohort of patients was highly selected, as it included subjects that had survived long enough on a transplant list to undergo transplantation. It is conceivable that patients with more severe PAH were more apt to die while on the waiting list. We included younger patients, subjects without important medical comorbidities, and a group of patients with advanced IPF, leading to findings that may affect the generalizability of our results.

Second, 73 patients (56% of IPF patients) were initially excluded due to the lack of echocardiographic or RHC reports. Therefore, our study had a small total number of patients (58 patients). Additionally, this selection might have biased the results, as only patients having all of the tests were included. Patients for whom all studies were ordered were probably systematically different from those for whom physicians did not order these tests.

Third, a source of bias that could cause a miscalculation of the DSP was the fact that most of our patients had oxygen requirements at rest. In prior studies, DSP and S_{pO_2} were obtained from patients performing 6MWTs at room air.[2,14] Even though this shortcoming may affect the validation of our results, the fact that the entire cohort had comparable S_{pO_2} at baseline (whether using oxygen or not) might balance differences presented at baseline. This does not exclude a bias in the S_{pO_2} response to exercise.

Fourth, we selected cut-points for each of the evaluated variables (RVSP, 6MWT distance, DSP, S_{pO_2}) utilizing the Youden's index (sensitivity + specificity − 1). Based on this calculation, the perfect theoretical cut-point has an index of 1, whereas the worst possible index is −1. In our study, the best Youden's index was the one corresponding to a RVSP of 26 mm Hg (index of 0.3). We recognize that, although it was our "best" cut-point value, a RVSP of 26 mm Hg performed poorly, and future studies will hopefully find better noninvasive ways to discriminate the presence or absence of PAH.

Fifth, we have used RVSP as the echocardiographic measurement of choice to diagnose PAH. However, the skills and ability to detect a valid RVSP might have changed over 18 years (1990-2007). Indeed, the determination of RVSP is based on the modified Bernoulli equation, in which the sum of the tricuspid gradient is added to an estimated right atrial pressure. The problem with this equation is that in many centers the estimated right atrial pressure is assigned different values (5 to 20 mm Hg).[20] This might have happened over the course of the years in our institution as well, affecting the comparability of the echocardiography results. We also recognize that novel methods have been developed, such as pulse wave tissue Doppler imaging, 3-dimensional echocardiography, and tricuspid annular plane systolic excursion.[21,22] Unfortunately, this information was not available in the medical records; therefore, it was not included in this study.

Last, we were unable to include certain measurements on PFTs (such as D_{LCO}%, FVC%, FVC%/D_{LCO}%), which were studied in prior studies, due to lack of data in the medical records. Brain natriuretic peptide measurements were not widely available over the course of these 18 years.

Conclusions

In summary, available noninvasive diagnostic tests applied to patients with IPF perform poorly in detecting PAH. In this context, clinicians should pursue RHC when suspicion of PAH exists. Further study, including prospective validation of single or combined parameters, is warranted.

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