ERJ Express. Published on August 9, 2018 as doi: 10.1183/13993003.01015-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Exercise Pulmonary Hemodynamic Response Predicts Outcomes in Fibrotic Lung Disease

Arun Jose, Christopher S. King, Oksana A. Shlobin, A. Whitney Brown, Cheng Xi Wang, Steven D. Nathan

Please cite this article as: Jose A, King CS, Shlobin OA, *et al*. Exercise Pulmonary Hemodynamic Response Predicts Outcomes in Fibrotic Lung Disease. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01015-2018).

Exercise Pulmonary Hemodynamic Response Predicts Outcomes in Fibrotic Lung Disease

Authors:

[1]Arun Jose, MD

[2]Christopher S. King, MD

[2]Oksana A. Shlobin, MD

[2]A. Whitney Brown, MD

[3]ChengXi Wang, MD

[2]Steven D. Nathan, MD

Author Affiliations

1 – Pulmonary, Critical Care and Sleep Medicine Division, The George Washington University MFA, Washington, District of Columbia
2 – Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Inova Fairfax Hospital, Falls Church, Virginia
3 – Internal Medicine Division, Inova Fairfax Hospital, Falls Church, Virginia

Corresponding Author: Arun Jose, MD
Pulmonary, Critical Care, and Sleep Medicine Division
The George Washington University MFA
Suite 8-404
2150 Pennsylvania Avenue NW
Washington, D.C.
Email: ajose.mdgg@gmail.com

Summary – Hemodynamic changes with exercise including **Δ** mPAP/**Δ**CO predicted clinical worsening in fibrotic lung disease patients

Introduction

Pulmonary hypertension (PH) is diagnosed by an elevated mean pulmonary arterial pressure (mPAP) during resting right heart catheterization (RHC). (1) Although "exercise-induced PH" is no longer a distinct clinical entity, recently there has been renewed interest in the prognostic value of pulmonary hemodynamic responses to exercise, particularly in patients with fibrotic lung disease. (1-4) As the optimal use of exercise RHC in this cohort remains unknown, our main objective in this study was to study the relationship between exercise hemodynamics and outcomes in fibrotic lung disease patients. (3-7)

Methods

All consecutive fibrotic lung disease patients at our center undergoing exercise RHC testing over a 7-year period, regardless of the mPAP at rest, were included in the study. Fibrotic lung disease, scored by one observer (AJ) using the method of Goh et al., was defined as >10% fibrosis on CT imaging at the time of exercise RHC. (8) Subjects without fibrotic lung disease, with missing data, and those with an elevated pulmonary artery wedge pressure (PAWP > 15mmHg) at rest were excluded.

Measurements at rest included heart rate, right atrial pressure (RAP), mPAP, digital mean PAWP, thermodilution cardiac output (CO), and pulmonary artery oxygen saturation. Pressures were measured as the digital mean across several respiratory cycles. Pulmonary vascular resistance (PVR) was calculated in the standard fashion. After baseline hemodynamic measurements, the patients underwent supine bicycle ergometer exercise to (subjective) maximal exertion and hemodynamic measurements were repeated.

The total pulmonary resistance was calculated both at rest (TPR = mPAP/CO) and at peak exercise (TPRex). The exercise-*induced* TPR (ΔTPRex = ΔmPAP/ΔCO) was calculated from the difference between rest and peak exercise hemodynamics. (1, 3, 5-7) An *abnormal precapillary ΔTPRex*, reflecting pulmonary arterial response to exercise, was defined as ΔTPRex ≥ 3 mmHg•L^{-1}•min with concomitant PAWP < 20mmHg at peak exercise. This cutoff was used to definitively exclude patients with occult left heart disease. (1,7) Demographic, laboratory, functional testing (including six-minute walk test, 6MWT), and pulmonary function testing (PFT) were collected within 3 months of index exercise RHC.

The primary outcome was defined as the first of three clinical worsening events: hospitalization for cardiopulmonary decompensation, lung transplantation, or death. Information on the primary outcome was obtained from the medical record and review of patient's charts. Time zero was the date of the index RHC, and patients were followed until either an event occurred or the study period ended. Patients lost to follow-up were censored at the time of their last clinical encounter. This study was reviewed and approved by the Inova Institutional Review Board (IRB 15-2025).

Statistical Analysis

Differences in clinical and hemodynamic characteristics between groups were compared using the Wilcoxon rank-sum test for continuous variables and the X^2 test for categorical variables. A two-tailed P-value < 0.05 was considered significant. Cox proportional hazard models were used to assess the relationship between variables and time to clinical worsening. (9) The Variance Inflation Factor was used to test for

collinearity, with variables being retained on the basis of their univariable p-value. Non-collinear individual variables with a p-value less than 0.1 in the univariable analysis were incorporated into the final multivariable model, subsequently adjusted for age, gender, RAP, resting mPAP, resting CO, baseline 6MWT, and the presence of targeted PAH therapy. Subsequently, an unadjusted multivariable analysis excluding patients with an exercise PAWP $\geq$ 20mmHg was performed, to exclude those patients with occult post-capillary disease. This model was constructed using forwards and backwards selection, retaining variables based on the Likelihood Ratio Test.

The proportional hazards assumption was examined for all models using scaled Schoenfeld residuals. All analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 119 patients underwent exercise RHC, of whom 49 had fibrotic lung disease and were included in the final analysis. The most common etiology of lung disease was connective-tissue disease associated (39%), followed by nonspecific interstitial pneumonitis (18%) and combined pulmonary fibrosis and emphysema (14%).

The baseline characteristics of patients are shown in Table 1. Patients were predominantly older Caucasian females. As expected, all patients displayed physiologic restriction and diffusion capacity impairment on PFTs. A number of patients (55%) had PH at rest, and 35% were on targeted PAH therapy at the time of the exercise RHC testing. The median observation period was 11 months, and a total of 25 patients (51%) experienced the primary outcome of clinical worsening. The most common primary

outcome event was hospitalization, the majority (80%) driven by ILD exacerbations. A total of four patients died during the study period, and one patient underwent lung transplantation.

As compared to stable patients, those with clinical worsening had a significantly higher resting PVR, lower resting RAP and PAWP, and lower 6MWT. Additionally, the presence of diabetes mellitus was significantly more common. Although there were no significant differences in exercise hemodynamics, a greater proportion of patients with clinical worsening (40% versus 17%) had an abnormal precapillary ΔTPRex.

The final multivariable models are shown in Table 1. After adjustment, only an abnormal precapillary ΔTPRex was significantly predictive of clinical worsening (hazard ratio 3.81, p=0.042). When limiting the analysis to patients with an exercise PAWP < 20mmHg, the ΔTPRex had the strongest association with clinical worsening.

Discussion

Our study demonstrates that abnormal pulmonary exercise parameters, specifically an abnormal precapillary ΔTPRex, may predict clinical outcomes in patients with fibrotic lung disease. This variable may reflect the underlying pulmonary vascular abnormalities present in some patients with fibrotic lung disease. (10-12) Functionally, abnormal elevations in the ΔTPRex with exercise may reflect an impaired relationship between mPAP and CO, due to a limited pulmonary vascular reserve, recruitment, and compliance. Independent of the pulmonary vasculature, these abnormalities may also be a consequence of hypoxic pulmonary vasoconstriction during exercise and fibrotic destruction of the pulmonary capillary bed. (5-6, 10-13) Interestingly, our results

suggested that the presence of diabetes mellitus might also be associated with worse outcomes. While our study was not designed to study this specific relationship, we suggest that the association between exercise hemodynamics, metabolic dysfunction, pulmonary vascular remodeling, and clinical outcomes warrants further study. (14)

In contrast to previous studies in patients with idiopathic pulmonary fibrosis, we found no association between the PFT measures of disease severity and outcomes. (15) This may be due to the small numbers and heterogeneous etiologies of lung fibrosis in our study.

Our study has a number of strengths, including a well-described population of patients undergoing exercise RHC and accounting for known markers of clinical worsening in our final model. However there are also some limitations. The study population included patients from a single tertiary referral center, some also predisposed to PAH due to conditions like scleroderma, and thereby on targeted PAH therapy. This could potentially have introduced a certain selection bias and limits the generalizability of our findings.

In conclusion, exercise pulmonary hemodynamic response in the form of an abnormal precapillary ΔTPRex is significantly and independently predictive of adverse clinical outcomes in patients with fibrotic lung disease. Utilization of hemodynamic information obtained during exercise RHC testing might be a useful tool to risk-stratify patients with fibrotic lung disease. Further studies are encouraged to validate our findings.

References

1. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37(1):67-119.
2. Kovacs G, Herve P, Barbera JA, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J 2017;50(5):pii:1700578.
3. Hasler ED, Muller-Mottet S, Furian M, et al. Pressure-Flow during exercise catheterization predicts survival in pulmonary hypertension. Chest 2016;150(1):57-67.
4. Chaouat A, Sitbon O, Mercy M, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. Eur Respir J 2014;44(3):704-13.
5. Stamm A, Saxer S, Lichtblau M, et al. Exercise pulmonary haemodynamics predict outcomes in patients with systemic sclerosis. Eur Respir J 2016;48(6):1658-67.
6. Degani-Costa LH, Levarge B, Digumarthy SR, et al. Pulmonary vascular response patterns during exercise in interstitial lung disease. Eur Respir J 2015;46(3):738-49.
7. Herve P, Lau EM, Sitbon O, et al. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015;46(3):728-37.
8. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177(11):1248-54.

9. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187-220.
10. Caminati A, Cassandro R, Harari S. Pulmonary hypertension in chronic interstitial lung diseases. Eur Respir Rev 2013;22(129):292-301.
11. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008;31(6):1357-67.
12. Awano N, Inomata M, Ikushima S, et al. Histological analysis of vasculopathy associated with pulmonary hypertension in combined pulmonary fibrosis and emphysema: comparison with idiopathic pulmonary fibrosis or emphysema alone. Histopathology 2017;70(6):896-905.
13. Godinas L, Lau EM, Chemla D, et al. Diagnostic concordance of different criteria for exercise pulmonary hypertension in subjects with normal resting pulmonary artery pressure. Eur Respir J 2016;48:254-57.
14. Abernethy AD, Stackhouse K, Hart S, et al. Impact of diabetes in patients with pulmonary hypertension. Pulm Circ 2015;5(1):117-123.
15. Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183(4):431-40.

Table 1: Baseline Demographic, Clinical, and Hemodynamic Characteristics and Cox Proportional Hazards Models

Variable	Median/Frequency	Interquartile Range/%
Age (years)	65	51 – 72
Race, White	30	61%
Gender, Female	36	73%
On PAH Therapy	17	35%
BMI (kg/m^2)	29.6	24.2 – 34.3
Hypertension	28	57%
Diabetes Mellitus	11	22%
Obstructive Sleep Apnea	12	24%
CAD	11	22%
6MWT (meters)	314	215 – 396
Pulse-rate recovery	21	12 – 29
Borg dyspnea scale value	4	3 – 5
FVC (L)	1.96	1.49 – 2.33
%FVC	61	53 – 74
FEV_1 (L)	1.45	1.15 – 1.70
$\%FEV_1$	60	49 – 73
FEV_1/FVC	77	68 – 84
TLC (L)	3.04	2.59 – 3.61
%TLC	59	47 – 69
DLCO (mL/mmHg/min)	8.3	7.2 – 10.5
%DLCO	32	24 – 39
Rest RAP (mmHg)	3	2 – 6
Rest sPAP (mmHg)	40	35 – 55
Rest dPAP (mmHg)	15	11 – 20
Rest mPAP (mmHg)	25	21 – 34
Rest PAWP (mmHg)	10	7 – 13
Rest CO (L/min)	5.0	4.5 – 6.5
Rest PVR (WU)	2.6	1.8 – 3.9
Rest HR (bpm)	70	66 – 85
Rest PAsat (%)	72	69 – 74
proBNP (pg/mL)	38	20 – 125

Unadjusted Final Proportional Hazard Model

Variable	HR	95% CI	P Value
Diabetes Mellitus	2.53	1.05 – 6.07	0.039
6MWT (meters)	0.99	0.99 – 1.00	0.261
Abnormal precapillary ΔTPRex	3.09	1.22 – 7.85	0.018

Adjusted Final Proportional Hazard Model *

Variable	HR	95% CI	P Value
Diabetes Mellitus	2.29	0.86 – 6.11	0.098
6MWT (meters)	1.00	0.99 – 1.00	0.320
Abnormal precapillary ΔTPRex	3.81	1.05 – 13.79	0.042
Global Scaled Schoenfeld Residuals p = 0.111			

Unadjusted Final Hazards Model – Peak Exercise PAOP < 20mmHg (n=22)

Variable	HR	95% CI	P Value
ΔTPRex (mmHg·min/L)	1.14	1.02 – 1.27	0.025
Global Scaled Schoenfeld Residuals p = 0.759			

Abbreviations: PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, BMI = body mass index, CAD = coronary artery disease, 6MWT = six-minute walk test, FVC = forced vital capacity, %FVC = percent-predicted FVC, FEV_1 = forced expiratory volume in one second, $\%FEV_1$ = percent-predicted of FEV_1, TLC = total lung capacity, %TLC = percent-predicted TLC, DLCO = diffusion capacity for carbon monoxide, %DLCO = percent-predicted DLCO, RAP = right atrial pressure, sPAP = pulmonary artery systolic pressure, dPAP = pulmonary artery diastolic pressure, mPAP = mean pulmonary artery pressure, PAWP = pulmonary artery wedge pressure, CO = cardiac output, PVR = pulmonary vascular resistance, HR = heart rate, PAsat = pulmonary artery saturation, WU = woods units, bpm = beats per minute, TPR = total pulmonary resistance (mPAP/CO), TPRex= TPR at peak exercise, ΔTPRex = exercise-induced change in TPR, Abnormal precapillary ΔTPRex = ΔTPRex > 3 *with* exercise PAOP < 20mmHg,

HR = hazard ratio, 95% CI= 95-percent confidence interval,

*Adjusted for age, gender, resting RAP, resting mPAP, resting CO, resting 6MWT, and stratified on the presence of PAH therapy.