High altitude living and its relationship with Pulmonary Arterial Hypertension (PAH) symptom severity and clinical characteristics: The Pulmonary Hypertension Association Registry (PHAR).

Shoaib Fakhri MD[1]; Kelly Hannon RN[2]; Kelly Moulden RN[2]; Peter Hountras MD[2]; Ryan Peterson PhD[3]; David Badesch MD[2]; and the PHAR authors

University of Colorado Anschutz Medical Campus Department of Internal Medicine [1], Department of Pulmonary and Critical Care Sciences[2], Department of Biostatistics and Informatics[3]

Background

- Pulmonary Hypertension is a progressive and potentially fatal disease that often presents with exertional dyspnea and functional limitation.
- Pulmonary arterial hypertension (PAH) is a subtype of pulmonary hypertension that primarily affects the pulmonary arterial circulation. PAH is defined as a mean resting pulmonary artery pressure of 25 mm Hg or above, pulmonary capillary wedge pressure (PCWP) below 15 mm Hg, in the absence of significant left heart disease, chronic lung disease, or venous thromboembolism [1 2]
- Individuals living at high altitude are exposed to lower barometric pressure and hypobaric hypoxemia which can lead to pulmonary vasoconstriction in the acute setting and pulmonary vascular remodeling with chronic exposure [3]
- We sought to examine the relationship between high altitude living and PAH.

Methods

- Forty-two centers across the United States screened and enrolled adult patients (age ≥ 18) in the Pulmonary Hypertension Association Registry (PHAR) who met the definition of group I PAH.
- All PAH subgroups were included. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) where excluded.
- Upon enrollment patients and staff completed a baseline questionnaire reporting clinical characteristics, hemodynamic data, patient demographics and patient reported quality of life metrics.
- Patients were divided into two groups; defined as high elevation living (≥4000 ft) and low elevation living (<4000 ft) based on provided zip codes.

Results

- Among 1021 patients enrolled in the registry, 851 met the diagnostic definition for PAH and had elevation data available with 776 living at low altitude and 75 living at high altitude.
- Subjects at high elevation had a 6-minute walk distance (6MWD) 26 meters greater than those at low elevation (p=0.08), despite having a pulmonary vascular resistance (PVR) that was 2.1 Wood Units (WU) higher (p=0.002). Additionally, those at high elevation had 3.2 times greater odds of using supplemental oxygen (p<0.001).

	Unadjusted			Adjusted		
Response	**Difference (high –low elevation)**	**CI**	**p-value**	**Difference (high – low elevation)**	**CI**	**p-value**
Six minute walk distance (m)	42	(8.4, 75.6)	0.0145	26.2	(-3.3, 55.6)	0.0814
Mean pulmonary artery pressure	4.5	(1.2, 7.8)	0.0076	2.5	(-0.7, 5.7)	0.12
Right atrial pressure	0.2	(-1.3, 1.6)	0.84	0.1	(-1.3, 1.5)	0.86
PVR (Wood units)	2.6	(1.2, 3.9)	0.0002	2.1	(0.8, 3.5)	0.0024
Emph 10 score	-0.4	(-3.3, 2.6)	0.82	-0.9	(-3.7, 1.9)	0.53
Physical health score	0.1	(-1.5, 1.8)	0.87	0.2	(-1.4, 1.9)	0.78
Response	**Odds Ratio**	**CI**	**p-value**	**Odds Ratio**	**CI**	**p-value**
Use of supplemental oxygen	2.2	(1.3, 3.5)	0.0016	3.2	(1.9, 5.4)	< 1e-04

Table 1: Effect of elevation on response variables of interest (high compared to low elevation). Adjusted comparisons control for the potential confounding effects of age, BMI, sex at birth, supplemental oxygen medication use, race, cigarette use, meth use, alcohol use, and PH medication use.

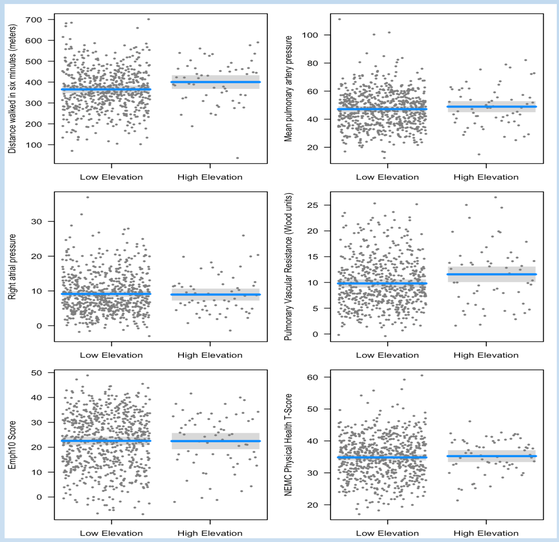

Figure 1: Effect of elevation group on response variables, adjusted for confounders. Points represent partial residuals (assuming median values for each confounding variable). Grey shading indicates the 95% confidence interval for the estimated mean value for the elevation group.

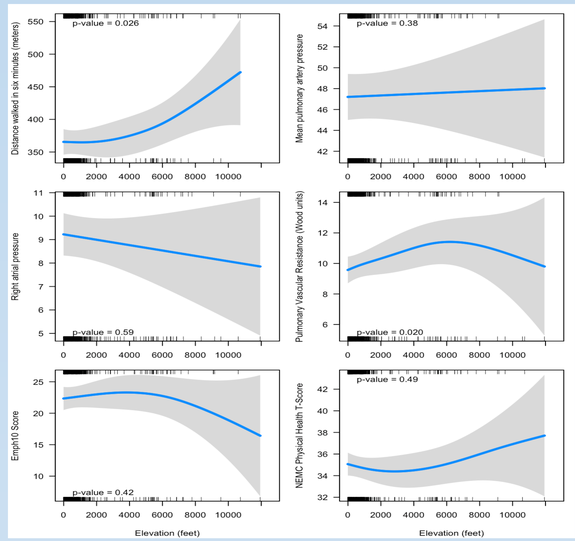

Figure 2: Nonlinear effects of elevation on outcomes of interest treating elevation as continuous. Effects are estimated using penalized thin plate regression splines, and adjust for confounding effects in the model.

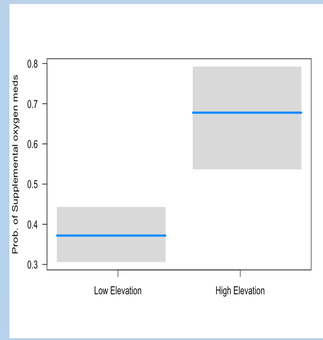

Figure 1b: Estimated probability (and 95% CI) of supplemental oxygen use by elevation group, adjusted for confounders.

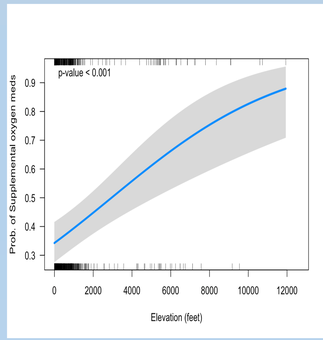

Figure 2b: Estimated probability (and 95% CI) of supplemental oxygen use by elevation (treated continuously), adjusted for confounders.

Conclusions

- Patients presenting with PAH who live at high altitude have a higher PVR, and are more likely to need supplemental oxygen.
- Despite their higher PVR, they appear to have a better 6MWD, which could be related in part to better overall conditioning.
- It is interesting to speculate that there might exist a “high-altitude phenotype” of PAH.

Future Directions

- More study is needed to further evaluate the relationship between chronic high-altitude exposure and PAH development and progression.

References

1. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J* 2019; 53 2018/12/14. DOI: 10.1183/13993003.01904-2018.
2. Thenappan T, Ormiston ML, Ryan JJ, et al. Pulmonary arterial hypertension: pathogenesis and clinical management. *Bmj* 2018; 360: j5492. 2018/03/16. DOI: 10.1136/bmj.j5492.
3. Young JM, Williams DR and Thompson AAR. Thin Air, Thick Vessels: Historical and Current Perspectives on Hypoxic Pulmonary Hypertension. *Front Med (Lausanne)* 2019; 6: 93. 2019/05/24. DOI: 10.3389/fmed.2019.00093

PHAR Pulmonary Hypertension Association Registry

School of Medicine UNIVERSITY OF COLORADO