

Residence at moderately high altitude and its relationship with WHO Group I pulmonary arterial hypertension symptom severity and clinical characteristics: the Pulmonary Hypertension Association Registry

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Abstract

Background: WHO Group I pulmonary arterial hypertension is a progressive and potentially fatal disease. Individuals living at higher altitude are exposed to lower barometric pressure and hypobaric hypoxemia. This may result in pulmonary vasoconstriction and contribute to disease progression. We sought to examine the relationship between living at moderately high altitude and pulmonary arterial hypertension characteristics.

Methods: Forty-two US centers participating in the Pulmonary Hypertension Association Registry enrolled patients who met the definition of WHO Group I pulmonary arterial hypertension. We utilized baseline data and patient questionnaire responses. Patients were divided into two groups: moderately high altitude residence (home \geq 4000 ft) and low altitude residence (home $<$ 4000 ft) based on zip-code. Clinical characteristics, hemodynamic data, patient demographics, and patient reported quality of life metrics were compared.

Results: Controlling for potential confounders (age, sex at birth, body mass index, supplemental oxygen use, race, 100-day cigarette use, alcohol use, and pulmonary arterial hypertension medication use), subjects residing at moderately high altitude had a 6-min walk distance 32 m greater than those at low altitude, despite having a pulmonary vascular resistance that was 2.2 Wood units higher. Additionally, those residing at moderately high altitude had 3.7 times greater odds of using supplemental oxygen.

Conclusion: Patients with pulmonary arterial hypertension who live at moderately high altitude have a higher pulmonary vascular resistance and are more likely to need supplemental oxygen. Despite these findings, moderately high altitude Pulmonary Hypertension Association Registry patients have better functional tolerance as measured by 6-min walk distance. It is possible that a "high-altitude phenotype" of pulmonary arterial hypertension may exist. These findings warrant further study.

Keywords

pulmonary arterial hypertension, elevation, 6-min walk distance, pulmonary vascular resistance, vascular

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Introduction

WHO Group 1 pulmonary arterial hypertension (PAH) is a progressive and potentially fatal disease primarily affecting the pulmonary arterial circulation that often presents with exertional dyspnea and functional limitation.¹ PAH is defined as having a resting mean pulmonary artery pressure (mPAP) of 25 mm Hg or above (based on 2015 definition), a pulmonary capillary wedge pressure (PCWP) below 15 mm Hg, and a pulmonary vascular resistance (PVR) above 3 Wood units (WU), in the absence of significant left heart disease, chronic lung disease, or venous thromboembolism.² Individuals living at moderately high altitude are exposed to lower barometric pressure and hypobaric hypoxemia. Alveolar hypoxemia can lead to pulmonary vasoconstriction and contribute to worsening pulmonary vascular remodeling with chronic exposure.³ These changes result in higher pulmonary artery pressures (PAP) at altitude compared to sea level, with increased afterload that may induce changes in right ventricular (RV) function.⁴⁻⁶ It is theoretically possible that increased PAP with associated changes in RV function may contribute to PAH disease progression in patients who reside at higher altitude. The Pulmonary Hypertension Association Registry (PHAR) is currently the largest longitudinal registry of PAH patients in the United States. Since its inception in 2015, it has grown to include 42 (at the time of this study) accredited Pulmonary Hypertension Care Centers. The PHAR not only captures important clinical and patient reported variables, but also permits geographic specificity through zip codes, which in turn allows estimation of the altitude at which patients live. We sought to examine the relationship between moderately high altitude living and PAH characteristics utilizing data from the PHAR.

Methods

Study population & data collection

Forty-two centers across the United States participating in the PHAR enrolled adult patients (age ≥ 18 years) who met the definition of WHO Group 1 PAH (hemodynamically defined by a mPAP at rest ≥ 25 mm Hg in the presence of a PCWP ≤ 15 mm Hg and PVR > 3 WU). All participants provided written informed consent. Analysis was performed on the cohort enrolled between 30 September 2015 and 30 August 2019. Patients were divided into two pre-specified groups: defined as moderately high altitude residence (≥ 4000 ft) and low altitude residence (< 4000 ft) based on patient-provided zip code, using the United States Geological Services TNM elevation tool. We had initially pre-specified two cut-offs at 4000 and 8000 ft, but since we did not observe sufficient data at > 8000 ft to perform our analyses, we abandoned this higher cut-off in the primary analysis. For patients residing at moderately high altitude, classification into WHO Group 1 PAH was made by the patients' pulmonary hypertension providers based upon

the standard definition, excluding WHO Groups 2 through 5, and clinical determination that their pulmonary hypertension was disproportionate to what might be expected due solely to the relatively mild hypoxemia that is often seen in patients exposed to moderately high altitude (WHO Group 3 pulmonary hypertension related to hypobaric hypoxemia). All WHO Group 1 PAH subgroups were included. Upon enrollment, patients and staff completed a baseline questionnaire reporting clinical characteristics, hemodynamic data, patient demographics and patient reported quality of life metrics. Registry data included age, gender at birth, race, use of supplemental oxygen, use of pulmonary hypertension medications for ≥ 6 months, lifetime use of ≥ 100 cigarettes, history of methamphetamine use, current alcohol use, 6-min walk distance (6MWD) in meters, PVR in WU, right atrial pressure (RAP), mPAP, and the results of vasoreactivity testing. Questionnaires were also utilized to calculate the validated emPHasis-10 (Emph-10) and the NEMC physical health short-form 12 (SF-12) survey.^{7,8}

Statistical analysis

To test for marginal relationships between the variables of interest in our sample with altitude group, Fisher's exact tests for categorical features and Welch's *t* tests for continuous variables were used. Six continuous response variables (6MWD, mPAP, RAP, PVR, Emph-10 score, and SF-12 score) were analyzed using multiple linear regression. In addition, two binary response variables were analyzed with logistic regression. Each model accounted for age, sex at birth, body mass index (BMI), supplemental oxygen use (yes/no), race (white/nonwhite), 100-day cigarette use, alcohol use, and PAH medication use (yes/no) as possible confounders. Due to small observed sample sizes at moderately high altitude, race was dichotomized (white/nonwhite). Each continuous confounder was first presumed to linearly relate to the response variable, but if any such relationship was found to exhibit lack of fit, polynomial terms were added to the model to adequately capture the relationship. While altitude was treated as a two-group categorical covariate in each of these models, we also investigated the possibility of a nonlinear effect of altitude (treated continuously) on each of the outcomes using generalized additive models with penalized thin plate splines. These models were fit using the *mgcv* package⁹ in R version 3.6.0,¹⁰ where the smoothing parameters were fit using restricted maximum likelihood.

We observed missing data in some of our response and independent variables. Elements with the highest percent missing were vasoreactivity testing (60%), 6MWD (14.5%), and PVR (13.3%). All other confounders and response variables had less than 6% missing data. Using the *mice* package¹¹ in R, we built chained equations and produced multiple ($m = 25$) imputed data sets. Analyses were performed on all imputed data sets and pooled, although only the complete cases are presented in Table 1

Table 1. Sample characteristics stratified by altitude.

	Low altitude (N = 782)	Moderately high altitude (N = 74)	p value	Overall (N = 856)
Age (years)				
Mean (SD)	55.2 (17.0)	47.8 (17.7)	<0.001	54.5 (17.2)
Missing	1 (0%)	0 (0%)		1 (0%)
Sex at birth				
Male	185 (23.7%)	27 (36.5%)	0.02	212 (24.8%)
Female	594 (76.0%)	47 (63.5%)		641 (74.9%)
Missing	3 (0%)	0 (0%)		3 (0%)
BMI				
Mean (SD)	29.5 (7.39)	29.0 (6.55)	0.52	29.5 (7.32)
Missing	30 (4%)	5 (7%)		35 (4%)
Distance walked in 6 min (m)				
Mean (SD)	334 (127)	390 (120)	<0.001	339 (127)
Missing	115 (15%)	9 (12%)		124 (14%)
White				
No	178 (22.8%)	10 (13.5%)	0.10	188 (22.0%)
Yes	561 (71.7%)	58 (78.4%)		619 (72.3%)
Missing	43 (5%)	6 (8%)		49 (6%)
Over 100 cigarettes smoked in lifetime				
No	404 (51.7%)	39 (52.7%)	0.71	443 (51.8%)
Yes	357 (45.7%)	31 (41.9%)		388 (45.3%)
Missing	21 (3%)	4 (5%)		25 (3%)
Used methamphetamine at least once				
No	648 (82.9%)	55 (74.3%)	0.22	703 (82.1%)
Yes	112 (14.3%)	14 (18.9%)		126 (14.7%)
Missing	22 (3%)	5 (7%)		27 (3%)
Presently drinks alcohol				
No	490 (62.7%)	51 (68.9%)	0.19	541 (63.2%)
Yes	273 (34.9%)	19 (25.7%)		292 (34.1%)
Missing	19 (2%)	4 (5%)		23 (3%)
PH medication for >6 months				
No	575 (73.5%)	52 (70.3%)	0.58	627 (73.2%)
Yes	207 (26.5%)	22 (29.7%)		229 (26.8%)
Supplemental oxygen meds				
No	472 (60.4%)	29 (39.2%)	<0.001	501 (58.5%)
Yes	306 (39.1%)	45 (60.8%)		351 (41.0%)
Missing	4 (1%)	0 (0%)		4 (0%)
Positive vasoreactivity test				
No	250 (32.0%)	35 (47.3%)	0.29	285 (33.3%)
Yes	47 (6.0%)	10 (13.5%)		57 (6.7%)
Missing	485 (62%)	29 (39%)		514 (60%)
Mean pulmonary artery pressure				
Mean (SD)	48.8 (13.5)	53.5 (16.4)	0.02	49.2 (13.8)
Missing	20 (3%)	2 (3%)		22 (3%)
Right atrial pressure				
Mean (SD)	9.86 (5.93)	9.96 (5.79)	0.90	9.87 (5.92)
Missing	34 (4%)	4 (5%)		38 (4%)

(continued)

Table 1. Continued

	Low altitude (N = 782)	Moderately high altitude (N = 74)	p value	Overall (N = 856)
Pulmonary vascular resistance (Wood units)				
Mean (SD)	9.81 (5.02)	12.4 (6.82)	0.003	10.0 (5.25)
Missing	106 (14%)	8 (11%)		114 (13%)
Cardiac output (thermodilution)				
Mean (SD)	4.29 (1.49)	3.94 (1.58)	0.08	4.26 (1.50)
Missing	78 (10%)	4 (5%)		82 (10%)
Cardiac Index (L/min/m ²)				
Mean (SD)	2.30 (0.769)	2.20 (0.841)	0.33	2.29 (0.776)
Missing	89 (11%)	5 (7%)		94 (11%)
Cardiac Index (calculated)				
Mean (SD)	2.31 (0.781)	2.13 (0.731)	0.06	2.29 (0.778)
Missing	90 (12%)	8 (11%)		98 (11%)
Emph10 Score				
Mean (SD)	25.0 (12.0)	25.4 (12.8)	0.81	25.1 (12.1)
Missing	26 (3%)	4 (5%)		30 (4%)
NEMC Physical Health T-Score				
Mean (SD)	34.1 (6.74)	33.9 (5.92)	0.85	34.1 (6.67)
Missing	25 (3%)	4 (5%)		29 (3%)
NEMC Mental Health T-Score				
Mean (SD)	48.2 (8.46)	48.9 (7.74)	0.49	48.3 (8.40)
Missing	25 (3%)	4 (5%)		29 (3%)

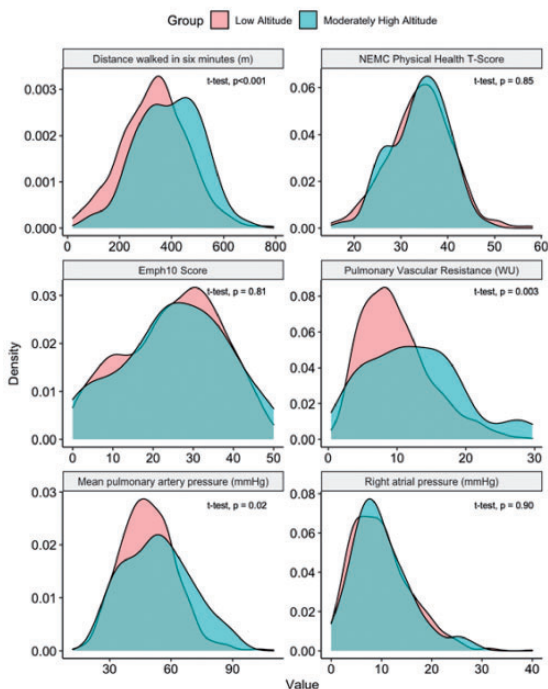


Fig. 1. Distributions of six response variables of interest by altitude group.

and all figures. Visualizations for Figs. 2 and 3 were generated with the visreg R package¹² using only the complete data. The p values listed in Fig. 3 for the spline terms represent the median p value for models across all multiply imputed data sets.

Results

Patient characteristics

Among 1021 patients enrolled in the registry, 856 met the diagnostic definition for PAH and had altitude data available, with 782 living at low altitude and 74 living at moderately high altitude. Table 1 shows sample characteristics stratified by altitude. Several significant bivariate relationships between altitude and examined variables of interest were identified. Specifically, altitude is associated with increased supplemental oxygen use ($p < 0.001$), male sex ($p = 0.0234$), higher mPAP ($p = 0.0221$), higher PVR ($p = 0.0031$), greater 6MWD ($p < 0.001$), and younger age ($p = 0.001$). We found no significant marginal (unadjusted) associations between altitude and any of the following: PH medication use, cigarette use, methamphetamine use, alcohol use, RAP, positive vasoreactivity, BMI, SF-12 score,

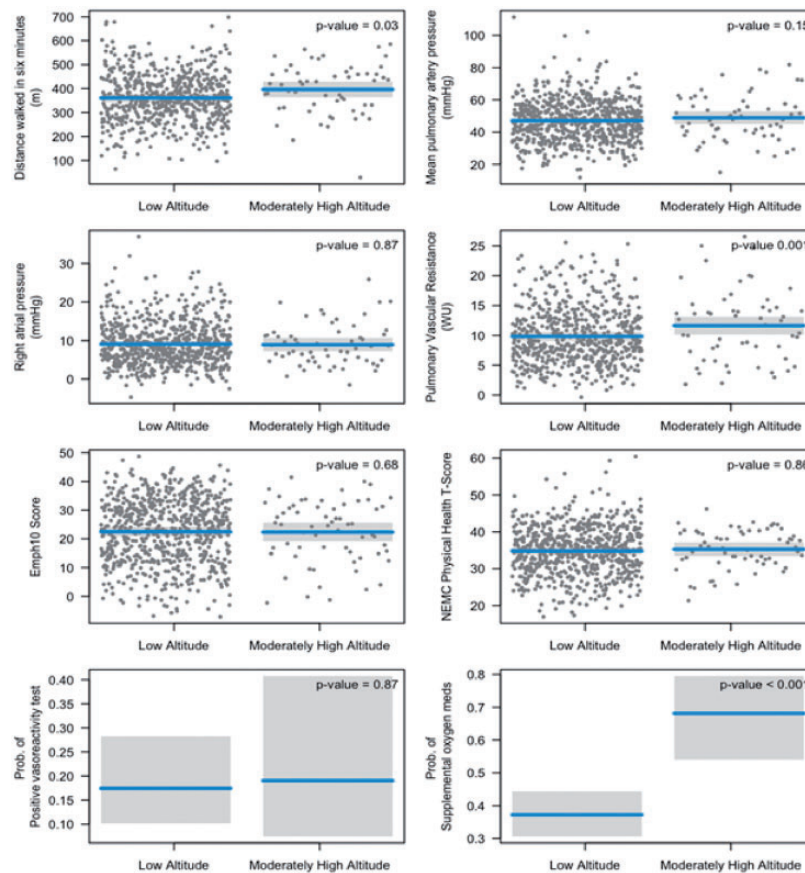


Fig. 2. Effect of altitude group on response variables, adjusted for confounders. Points represent partial residuals (assuming median values for each confounding variable). Grey shading indicates the 95% confidence interval for the estimated mean value (or probability) for the altitude group.

and Emph-10 score. Fig. 1 displays the distributions of some of the response variables of interest.

Relationship between altitude and variables of interest

Table 2 shows the unadjusted and adjusted relationships between altitude and each of our response variables of interest using pooled results from the multiply imputed data and controlling for the potential confounding effects of age, BMI, sex at birth, supplemental oxygen use, race, cigarette use, methamphetamine use, alcohol use, and PAH medication use. We found that controlling for these confounders, subjects at moderately high altitude residence had a 6MWD 32.2 m greater than those at low altitude residence (95% CI: [3.3, 61.1]; $p = 0.0294$), and had a PVR 2.2 WU higher (95% CI: [0.9, 3.5]; $p = 0.0011$). Additionally, those at moderately high altitude residence had 3.7 times the odds of using supplemental oxygen (95% CI: [2.2, 6.3]; $p < 1 \times 10^{-4}$) compared to those at low altitude residence. Fig. 2 shows the adjusted effects of altitude group on each of the outcomes, controlling for the confounders.

Fig. 3 shows the potentially nonlinear effects of altitude, treated continuously, for each outcome controlling for all confounders. For PVR, the expected value increases

somewhat linearly from sea level to about 6000 ft where it levels off. This relationship is statistically significant ($p = 0.020$). Above 7000 ft, the variance in the relationship between altitude and PVR increases substantially due to the data paucity at higher altitudes. As expected, the relationship between altitude and supplemental oxygen medication use is highly statistically significant in the nonlinear model, with the odds of supplemental oxygen use increasing with altitude.

Discussion

Our study shows that PAH patients who reside at moderately high altitude have a higher PVR. Previous studies have established that a hypoxic stimulus leads to diffuse pulmonary vasoconstriction of the arterioles and an increase in PVR.^{13,14} This increase in PVR is possibly attributable to the chronic effects of hypoxic pulmonary vasoconstriction due to hypobaric hypoxemia at altitude. Indeed, this increase in PVR has been shown with acute and sub-acute high/moderate altitude exposure. Hilty et al. showed that this increase in PVR remained persistent after four weeks of acclimation to high altitude in healthy individuals.^{15,16} When comparing healthy Peruvian adult individuals born

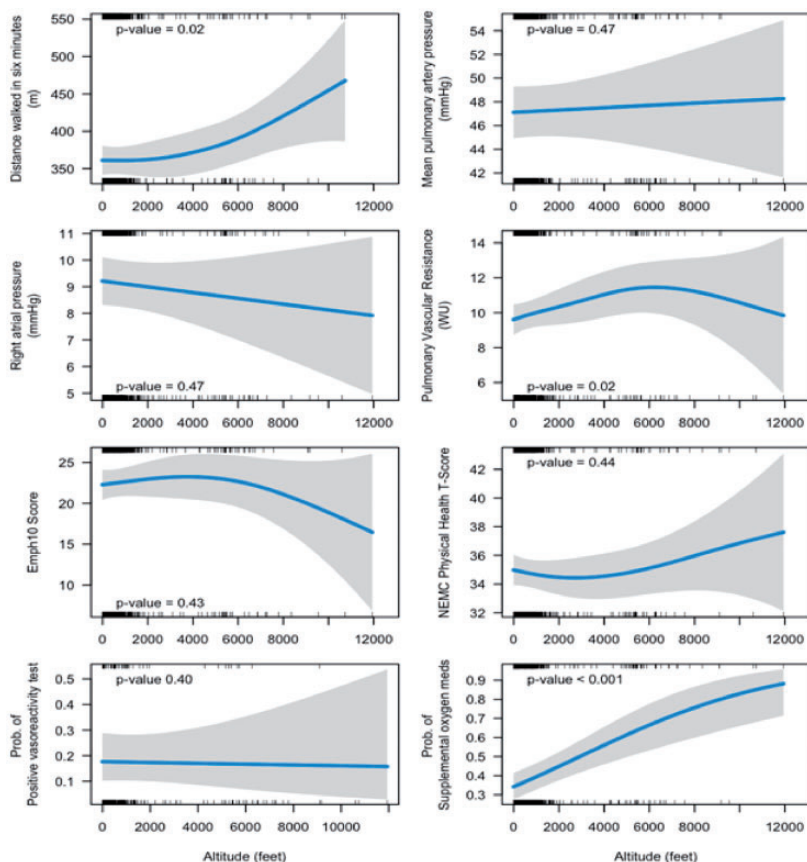


Fig. 3. Nonlinear effects of altitude on outcomes of interest treating elevation as continuous. Effects are estimated using penalized thin plate regression splines and adjust for confounding effects in the model.

Table 2. Effect of altitude on response variables of interest (moderately high compared to low altitude).^a

Continuous response	Unadjusted			Adjusted		
	Estimate	95% CI	p value	Estimate	95% CI	p value
6-Min walk distance (m)	46.5	(13.6, 79.5)	0.006	32.2	(3.3, 61.1)	0.03
Mean pulmonary artery pressure	4.6	(1.3, 8)	0.006	2.4	(-0.9, 5.8)	0.15
Right atrial pressure	0.0	(-1.4, 1.5)	0.97	-0.1	(-1.6, 1.3)	0.87
PVR (Wood units)	2.7	(1.4, 4)	<0.001	2.2	(0.9, 3.5)	0.001
Emph 10 score	0.2	(-2.8, 3.1)	0.91	-0.6	(-3.4, 2.2)	0.68
Physical health score	0.0	(-1.7, 1.6)	0.96	0.1	(-1.5, 1.7)	0.86
Binary response	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Positive vasoreactivity test	1.2	(0.6, 2.5)	0.60	1.1	(0.5, 2.5)	0.87
Use of supplemental oxygen	2.4	(1.5, 3.9)	<0.001	3.7	(2.2, 6.3)	<0.001

^aAdjusted comparisons control for the potential confounding effects of age, BMI, sex at birth, supplemental oxygen medication use, race, cigarette use, methamphetamine use, alcohol use, and PH medication use.

and living at high altitude to those at sea level, Penãloza et al. found that the calculated PVR was significantly greater in those residing at high altitude,¹⁷ suggesting the PVR remains elevated when at altitude. It is hypothesized that the persistent increase in PVR due to the chronic hypoxic

stimuli at elevation can result in permanent pulmonary vascular remodeling.¹⁸

In our study, those with PAH residing at moderately high altitude were found more likely to need supplemental oxygen. This is an expected result, as it has been established

with multiple studies that patients with underlying lung disease (chronic obstructive pulmonary disease (COPD), cystic fibrosis, restrictive lung disease) develop significant arterial hypoxemia when exposed to altitude.^{19–22} Patients with PAH may have a number of reasons to have hypoxemia, such as abnormalities in diffusing capacity; right-to-left shunts (whether intracardiac or intrapulmonary); ventilation/perfusion mismatch; pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; or any combination of these. Hypobaric hypoxia at altitude is likely to make this systemic arterial hypoxemia worse, increasing the need for supplemental oxygen.

Interestingly, despite their higher PVR, patients with PAH living at higher altitude have a greater 6MWD. This result does not appear to be due to differences in age, sex at birth, BMI, supplemental oxygen use, race, 100-day cigarette use, alcohol use, or PAH medication use as results were adjusted for these potential confounders. Although patients with PAH who use supplemental oxygen seem to have a higher symptom burden and shorter 6MWD,²³ those residing at moderately high altitude might have better overall conditioning and be more physically active than patients living at lower altitude.

Health-related quality of life measured by the SF-12 and Emph-10 scores did not significantly differ between the two groups. This is an important finding as it has been shown that aspects of health-related quality of life play an important role in clinical end points and predictors of prognosis.^{24,25}

We recognize that various limitations and unobserved confounders may impact our results. Limitations that we have identified include the number of subjects in the registry, particularly those that live at altitude (there are only two PHAR sites above 4000 ft, located in Denver and Salt Lake City, with each seeing patients from the surrounding regions). Given that there are only two sites at altitude, we are cognizant of the fact that there may be inherent differences at these two sites (such as access to care, provider practice differences and differences in demographics) that may confound our results. We therefore focused on patient data upon presentation to a PHAR site (baseline, enrollment questionnaires) to mitigate this confounder, and avoid comparing patient care and clinical outcomes across sites. We also recognize that our altitude cut-off of 4000 ft, though pre-specified, is somewhat arbitrary, which is why we investigated whether other cut-offs would be more appropriate in Fig. 3. Furthermore, given the small sample size at altitude we were unable to comment upon differences related to PAH diagnostic subgroups. Other limitations include inability to identify duration of residence at altitude, as this is not collected in the PHAR, and missing data points, as highlighted in our methods section. In addition, patients with lung disease, such as COPD, might have difficulties at higher elevations, and could out-migrate and self-select with respect to residence at higher altitude. Finally, it is possible that patients living at moderately high altitude have a higher hematocrit (unfortunately hematocrit values were not collected

in the PHAR), and that this could explain in part a better aerobic exercise capacity. A higher hematocrit might also increase viscosity and impact PAP and PVR.²⁶

Conclusion

This study highlights several differences in clinical characteristics between patients with PAH living at moderately high vs. low altitude. Patients presenting with PAH who live at moderately 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. This somewhat paradoxical finding warrants further study to better define the relationship between PAH characteristics and chronic exposure to higher altitude. It is interesting to speculate that there might exist a “high-altitude phenotype” of PAH.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

Ethical approval

The PHAR is IRB approved and all subjects were consented prior to enrollment. All subject data used in the PHAR are de-identified. This study is approved by Colorado Multiple Institutional Review Board under protocol #15-0882. The University of Pennsylvania IRB has also approved and primarily oversees the ethical conduct of this study under protocol #822830.

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