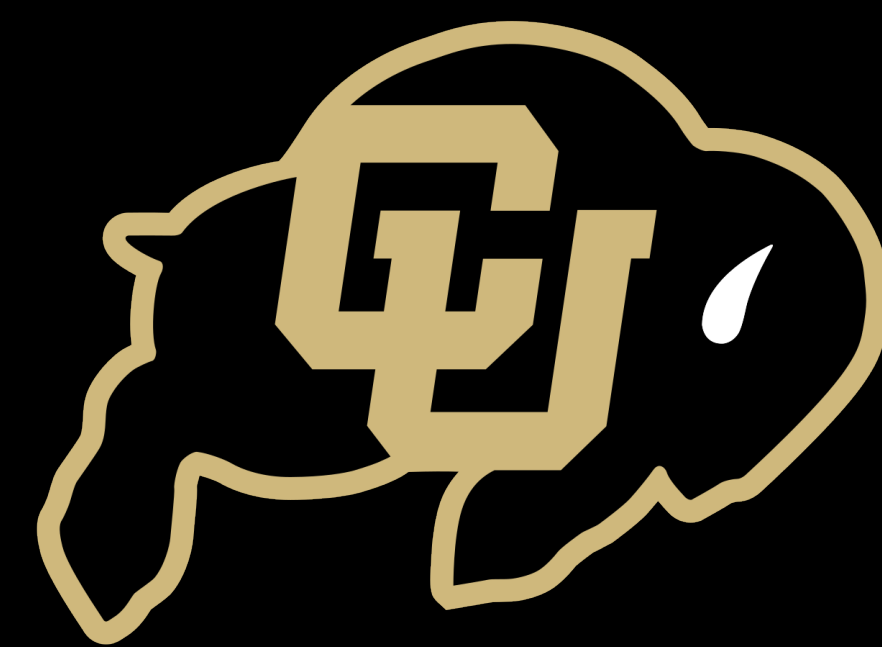


# Lowering Cutoffs A Mile High: Assessing the Impact of a New Definition of Pulmonary Hypertension

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## Introduction

- Pulmonary Hypertension (PH) has historically been defined by a mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg.
- Precapillary PH, a subgroup of PH that benefits from targeted therapies, has been defined by a mPAP  $\geq 25$  mmHg, a pulmonary capillary wedge pressure (PCWP) of  $\leq 15$  mmHg, and a pulmonary vascular resistance (PVR) of  $> 3$  Wood Units (WU).<sup>1</sup>
- In 2018, the 6<sup>th</sup> World Symposium on Pulmonary Hypertension (6WSPH), proposed a lower diagnostic threshold for precapillary PH: mPAP  $>20$ , PCWP  $\leq 15$ , PVR  $\geq 3$  WU.<sup>2</sup>
- This definition was based on a meta-analysis of 882 healthy subjects from 47 studies, showing the average mPAP of healthy individuals to be 14.0,  $\pm 3.3$  mmHg, as measured at sea level.<sup>3</sup>
- Controversy has arisen around whether or not to treat patients that have been "recategorized" as having precapillary PH, as the clinical significance of a mPAP of 20-24 mmHg is unknown.
- A concern that has not been addressed is the generalizability of this definition to patients at altitude, as elevation has well-known effects on mPAP.<sup>4,5</sup>

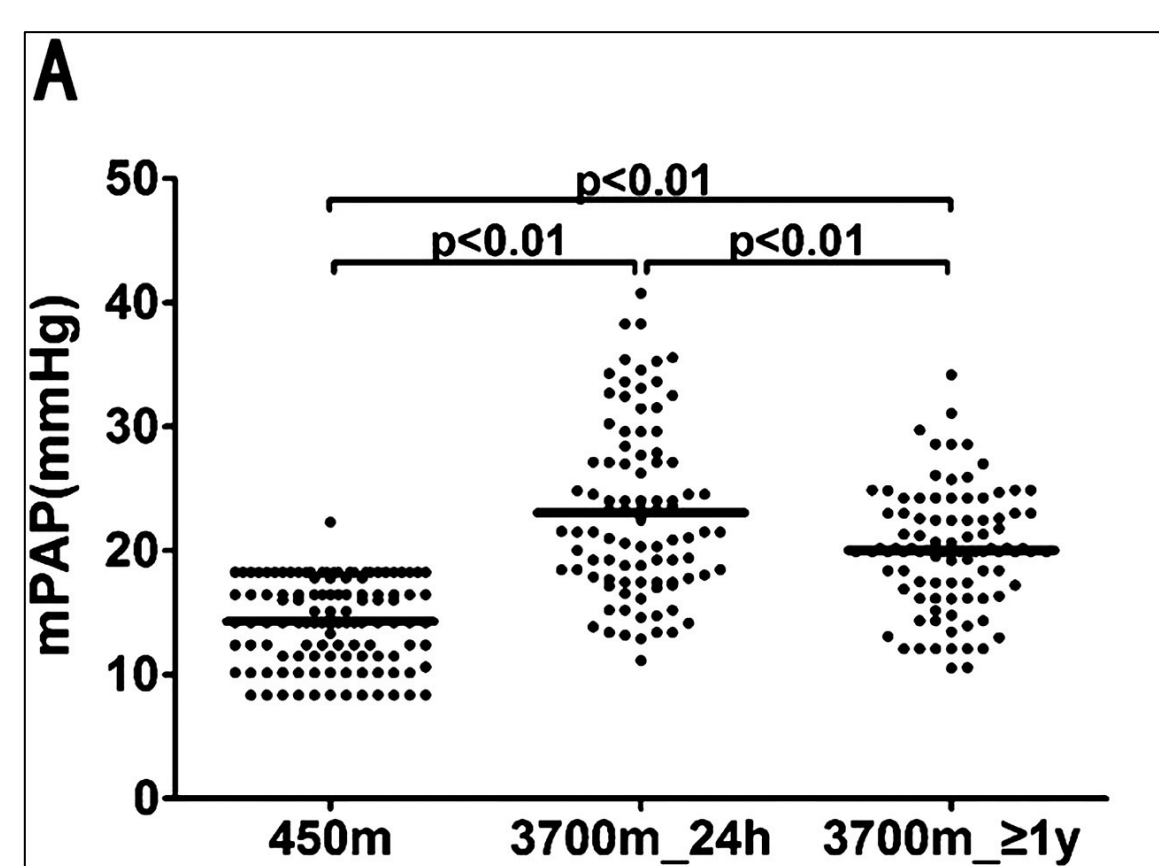


Figure adapted from Yang et al., demonstrating the effects of increased elevation on mPAP.

- Our study examined whether the 6WSPH definition of PH would result in a significant increase in PH diagnosis and precapillary PH in Denver.

## Methods

- Data including mPAP, PCWP, and PVR, as well as age, BMI, and gender were collected were automatically abstracted from the EMR for all patients undergoing right heart catheterization for any indication at the University of Colorado Hospital between the years of 2015 and 2017.
- Municipal information was used to calculate the mean elevation of patients' home counties based on zip code.
- All patients with a mPAP  $> 20$  mmHg were included in the analysis.
- This population was categorized according to the ERS definition, then re-categorized according to the 6WSPH Definition.
- Number and proportion of PH diagnoses were recorded, and significant differences determined by 1-sample proportions test with continuity correction, with significance set at .05.

Pulmonary Hypertension Definitions		
PH Category	ERS Definition (mmHg)	6WSPH (mmHg)
Precapillary PH	mPAP $\geq 25$ & PCWP $\leq 15$ & PVR $>3$	mPAP $> 20$ & PCWP $\leq 15$ & PVR $\geq 3$
Combined PH	mPAP $\geq 25$ & PCWP $>15$ & PVR $> 3$	mPAP $> 20$ & PCWP $> 15$ & PVR $\geq 3$
Postcapillary PH	mPAP $\geq 25$ & PCWP $>15$ & PVR $\leq 3$	mPAP $> 20$ & PCWP $>15$ & PVR $\leq 3$
Other PH	mPAP $\geq 25$ & PCWP $\leq 15$ & PVR $\leq 3$	mPAP $> 20$ & PCWP $\leq 15$ & PVR $< 3$

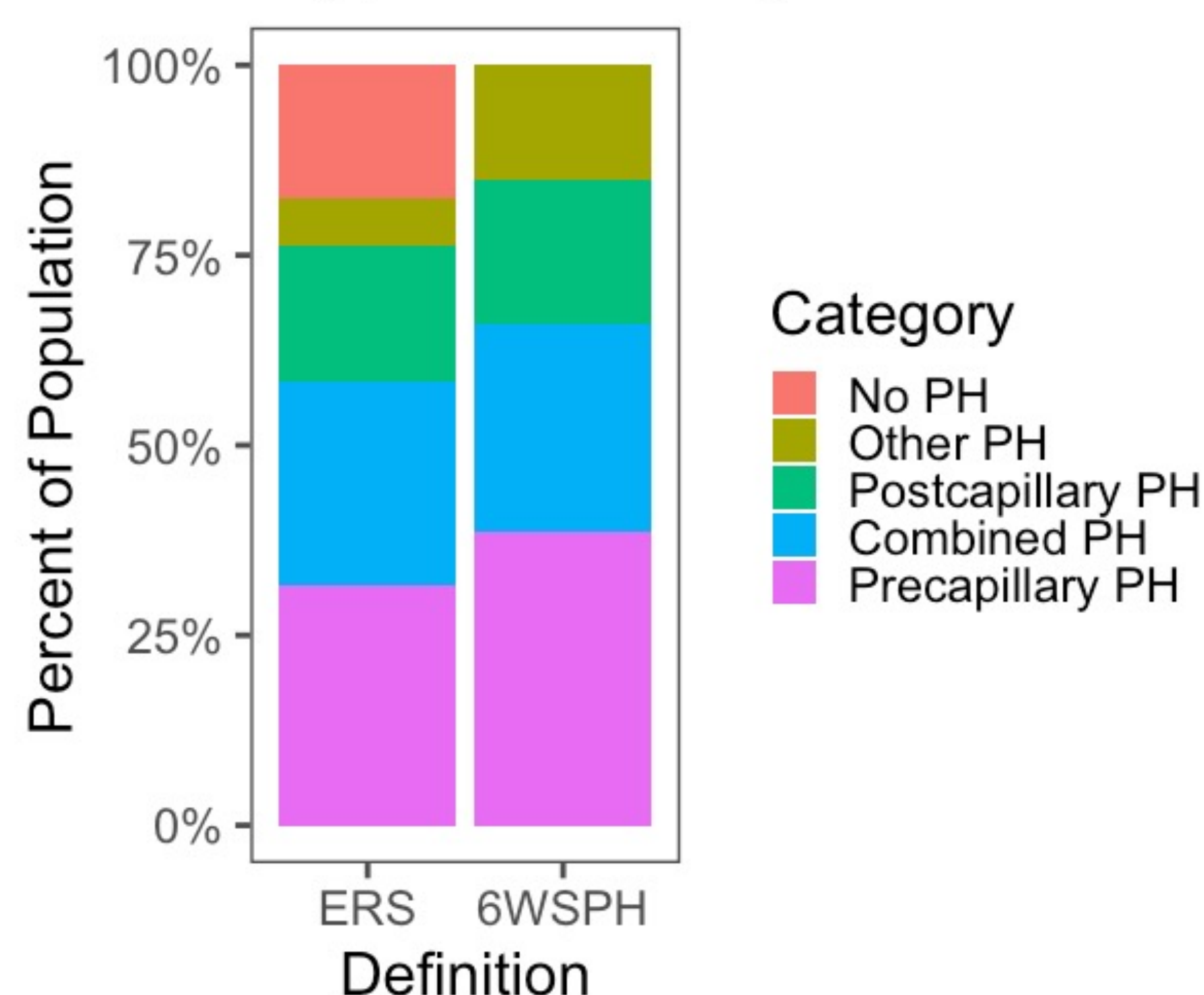
Definitions used to categorize patients<sup>1,2</sup>

## Results

Patient Characteristics (n = 1641)	
Gender: n (%)	Male: 751 (46) Female: 598 (36) Undisclosed: 292 (18)
Age (years)	60.2 (15.3)
BMI (kg/m <sup>2</sup> )	29.1 (8.7)
Home Elevation (meters)	1681.6 (645.2)
Right Heart Catheterization Measurements (mmHg)	
Mean Pulmonary Artery Pressure	34.9 (11.4)
Pulmonary Capillary Wedge Pressure	16.1 (7.5)
Pulmonary Vascular Resistance	76.1 (215.6)

Continuous variables recorded as mean (SD). Patients were predominantly male, in the 6<sup>th</sup> decade of life, with elevated pulmonary artery pressures

### Diagnoses of Pulmonary Hypertension by Definition



Proportional representation of each PH subcategory based on the ERS and 6WSPH definitions. "No PH" under the ERS definition represents patients with an mPAP 20 -24 mmHg.

Changes in PH Diagnosis Following 6WSPH Recategorization			
PH Category	ERS Definition	6WSPH Definition	Change in Proportion
Pre-capillary PH	517	632	(.32, .38, p < .01)
Combined PH	442	449	(.27, .27, p = .76)
Post-capillary PH	294	314	(.18, .19, p = .24)
Other PH	102	246	(.06, .15, p < .01)
No PH	286	0	(.17, 0, p < .01)

Using the 6WSPH definition resulted in a statistically significant increase in the proportion of patients diagnosed with precapillary PH and Other PH, as well as an increase of 17% in patients diagnosed with PH increased overall.

## Discussion

- The results of this study suggest that use of the 6WSPH definition result in an increase in the diagnosis of PH overall, with a particular increase in the diagnosis of precapillary PH.
- This study builds on prior cohort studies examining the effects of the new definition on different populations.
- The increase in PH by 17% was higher in this cohort than in other similar studies in Sao Paolo (2%)<sup>6</sup>, Giessen (8%),<sup>6</sup> and Turkey (9.8%),<sup>7</sup> all of which are lower in elevation than Denver, CO. This may suggest that patients living at altitude have higher baseline mPAP than those at sea level, limiting the generalizability of the 6WSPH definition.
- The significant increase in precapillary PH of 6% is consistent with another Turkish cohort study showing a greater-than-expected increase in precapillary PH after application of the 6WSPH.<sup>8</sup>

## Future Directions

- Clinical significance of mPAP 20 - 24 remains unclear, prospective data on the impact of PH treatment in this population is lacking.
- Several studies have shown that borderline mPAP values are associated with poor prognosis.<sup>9,10</sup>
- No causative link has been established
- An important question is whether any link between morbidity and mPAP is observed at altitude.
- A future study is planned to follow this cohort from 2017 -2021, evaluating trends in mortality and development of PH or associated diagnoses, and any association with baseline mPAP.

## References

- Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langen D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl):D42-50. doi: 10.1016/j.jacc.2013.10.032. PMID: 24355641.
- Gérald Simonneau, David Montani, David S. Celermajer, Christopher P. Denton, Michael A. Gatzoulis, Michael Krowka, Paul G. Williams, Rogerio Souza. *European Respiratory Journal* 2019 53: 1801913; DOI: 10.1183/13993003.01913-2018
- Kovacs G, Berghold A, Scheidl S, et al. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888-894.
- Mirrahimov AE, Strohl KP. High-altitude Pulmonary Hypertension: an Update on Disease Pathogenesis and Management. *Open Cardiovasc Med J*. 2016;10:19-27. Published 2016 Feb 8. doi:10.2174/1874192401610010019
- Yang T, Li X, Qin J, Li S, Yu J, Zhang J, Yu S, Wu X, Huang L. High altitude-induced borderline pulmonary hypertension impaired cardiorespiratory fitness in healthy young men. *Int J Cardiol*. 2015 Feb 15;181:382-8. doi: 10.1016/j.ijcard.2014.12.044. Epub 2014 Dec 23. PMID: 25555284.
- World Society of Pulmonary Hypertension Congress. 6th ed. Nice: Congress Proceedings 2018.
- Tanyeri S, Akbal OY, Keskin B, et al. Impact of the updated hemodynamic definitions on diagnosis rates of pulmonary hypertension. *Pulm Circ*. 2020;10(3):2045894020931299. Published 2020 Aug 28. doi:10.1177/2045894020931299
- Sinan ÜY, Çetinarslan Ö, Arat Özkan A, Ersanlı MK, Küçüköğlü MS. The impact of the new World Symposium on Pulmonary Hypertension definition of pulmonary hypertension on the prevalence of precapillary pulmonary hypertension. *Turk Kardiyol Dern Ars*. 2019 Oct;47(7):594-598. English. doi: 10.5543/tkda.2019.80027. PMID: 31582683.
- Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, Olschewski H. Mild Elevation of Pulmonary Arterial Pressure as a Predictor of Mortality. *Am J Respir Crit Care Med*. 2018 Feb 15;197(4):509-516. doi: 10.1164/rccm.201706-1215OC. PMID: 29099619.
- Maron BA, Hess E, Maddox TM, Opatowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, Swenson ER, Goldstein RH, Leopold JA, Zamanian RT, Elwing JM, Plomondon ME, Grunwald GK, Barón AE, Rumsfeld JS, Choudhary G. Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation*. 2016 Mar 29;133(13):1240-8. doi: 10.1161/CIRCULATIONAHA.115.020207. Epub 2016 Feb 12. PMID: 26873944; PMCID: PMC4811678.