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### References

1. World Health Organization. The End TB Strategy [accessed 2021 Sept 17]. Available from: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy.
2. Abubakar I, Drobniewski F, Southern J, Sitch AJ, Jackson C, Lipman M, *et al.*; PREDICT Study Team. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis* 2018;18:1077–1087.
3. Mahomed H, Hawkridge T, Verver S, Abrahams D, Geiter L, Hatherill M, *et al.* The tuberculin skin test versus QuantiFERON TB Gold® in predicting tuberculosis disease in an adolescent cohort study in South Africa. *PLoS One* 2011;6:e17984.
4. Gupta RK, Calderwood CJ, Yavlinsky A, Krutikov M, Quartagno M, Aichelburg MC, *et al.* Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings. *Nat Med* 2020;26:1941–1949
5. Haas CT, Roe JK, Pollara G, Mehta M, Noursadeghi M. Diagnostic 'omics' for active tuberculosis. *BMC Med* 2016;14:37.
6. Södersten E, Ongarello S, Mantsoki A, Wyss R, Persing DH, Banderby S, *et al.* Diagnostic accuracy study of a novel blood-based assay for identification of tuberculosis in people living with HIV. *J Clin Microbiol* 2021;59:e01643–e20.
7. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM, *et al.*; ACS and GC6-74 cohort study groups. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet* 2016;387:2312–2322.
8. Gupta RK, Turner CT, Venturini C, Esmail H, Rangaka MX, Copas A, *et al.* Concise whole blood transcriptional signatures for incipient tuberculosis: a systematic review and patient-level pooled meta-analysis. *Lancet Respir Med* 2020;8:395–406.
9. Scriba TJ, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Kimbung Mbandi S, Borate B, *et al.*; CORTIS-01 Study Team. Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. *Lancet Infect Dis* 2021;21:354–365.
10. Mendelsohn SC, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Mbandi SK, Borate B, *et al.*; CORTIS-HR Study Team. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study. *Lancet Glob Health* 2021;9: e841–e853.
11. Mulenga H, Musvosvi M, Mendelsohn SC, Penn-Nicholson A, Kimbung Mbandi S, Fiore-Gartland A, *et al.*; CORTIS Study Team. Longitudinal dynamics of a blood transcriptomic signature of tuberculosis. *Am J Respir Crit Care Med* 2021;204:1463–1472.
12. Turner CT, Brown J, Shaw E, Uddin I, Tsaliki E, Roe JK, *et al.* Persistent T cell repertoire perturbation and T cell activation in HIV after long term treatment. *Front Immunol* 2021;12:634489.
13. Turner CT, Gupta RK, Tsaliki E, Roe JK, Mondal P, Nwayo G, *et al.* Blood transcriptional biomarkers for active pulmonary tuberculosis in a high-burden setting: a prospective, observational, diagnostic accuracy study. *Lancet Respir Med* 2020;8:407–419.
14. Gupta RK, Rosenheim J, Bell LC, Chandran A, Guerra-Assuncao JA, Pollara G, *et al.*; COVIDsortium Investigators. Blood transcriptional biomarkers of acute viral infection for detection of pre-symptomatic SARS-CoV-2 infection: a nested, case-control diagnostic accuracy study. *Lancet Microbe* 2021;2: e508–e517.





# Double Trouble: Airflow and Pulmonary Vascular Obstruction

Pulmonary arterial hypertension (PAH) is an incurable disease with progressive symptoms despite the dynamic and increasingly rapid changes in PAH-specific therapies over the past three decades. All currently available medications target increased pressure and resistance within the pulmonary vascular bed with the goal of improving hemodynamics and right ventricular function. Additional approaches to improve exercise tolerance and relieve dyspnea in PAH is a topic of considerable interest. In addition to the historically recognized reduced gas exchange and right ventricular dysfunction, concurrent airflow obstruction may also contribute to PAH pathobiology and symptomatology.

The presence of airway disease has been documented in animal models of experimental pulmonary hypertension (1), and it has also been described in humans with PAH for some time (2, 3). Although overt airflow obstruction with reduced ratio of $FEV_1$/FVC at rest is not commonly observed in PAH, studies have suggested the probable involvement of small, peripheral airways in the disease (2, 4). Prior studies have shown reduced airflow through the small airways in some patients with PAH whose inspiratory capacity progressively declined during standardized exercise (5, 6). A more recent study demonstrated this dynamic reduction in inspiratory capacity is indicative of air trapping (i.e., airflow obstruction) (7), and not solely a result of PAH-associated respiratory muscle weakness (8, 9). Notably, there also appears to be an association between obstructive lung physiology and quality of dyspnea, underscoring the importance of further defining the mechanism of small airways obstruction in PAH and potential therapeutic approaches (10).

How PAH might affect the airways remains unclear. Although it has been postulated that dilated pulmonary arteries can mechanically compress adjacent airways, this phenomenon has been only rarely described, typically involving very proximal large bronchi (11, 12). Whether the same mechanism can occur in smaller bronchovascular bundles is unknown. Others (4) have speculated that vasoactive



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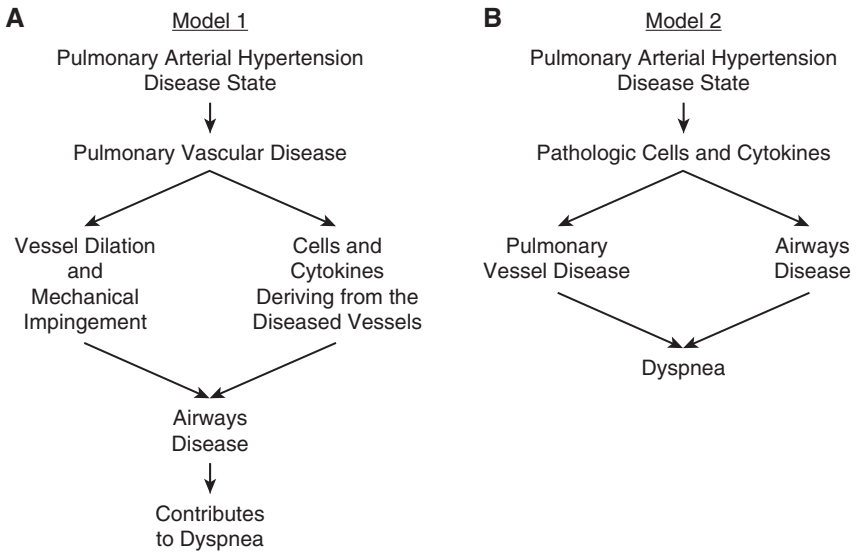


**Figure 1.** Two putative mechanistic links between pulmonary vascular and airways obstruction in pulmonary arterial hypertension. (*A* and *B*) Pulmonary vascular disease might secondarily contribute to airway disease (*A*), or, alternatively, common pathogenetic signal(s) might affect both the pulmonary vasculature and the airways in parallel (*B*).

substances, such as endothelin-1, simultaneously affect smooth muscles of the airways and the pulmonary arteries. Supporting this hypothesis is the potential association between vasodilatory response to calcium channel blockade and bronchodilation to albuterol (3). However, the possibility of superimposed reactive airway disease such as mild asthma represents a potential confounder (2, 3).

In this context of uncertainty, the study in the current issue of the *Journal* by Rahaghi and colleagues (pp. 1479–1482) provides key new insights (13). The authors investigated the longitudinal trajectory of respiratory physiology over the course of PAH. They made use of a unique, retrospective cohort of patients at the University of California Los Angeles: 15 individuals who were diagnosed with PAH and who ultimately underwent lung transplantation, with a median time of 8. 7 years from diagnosis to transplant.

Based on pulmonary function tests (PFTs) at the time of transplant, almost all had reductions in $FEV_1$ and/or FVC, and six had an $FEV_1$ to FVC ratio less than the fifth percentile predicted. Looking back at the change from baseline PFTs obtained at the time of initial PAH diagnosis, there were relatively rapid declines in both $FEV_1$ and FVC over the duration of follow-up. For example, the annual rate of $FEV_1$ decline in this cohort was 140 ml/yr, as compared with a predicted 22 ml/yr in healthy individuals (14). Six of the patients had computed tomographic (CT) imaging both at diagnosis and again at time of transplant—in these individuals, the three with the most rapid decrease in $FEV_1$/FVC over time also had the greatest increase in mean pulmonary artery diameter, as well as a decrease in airway size measured on CT imaging.

Histopathologic examination of the explanted lung tissue did not reveal any evidence of airway disease, emphysema, or interstitial fibrosis, and there was no or minimal evidence of either air trapping or emphysema on the CT scans performed before transplant.

The major strengths of the study are the lengthy duration between the initial and final pretransplant PFTs, and the extensive multimodal analysis including physiology by PFT (and right heart catheterization), CT imaging, and histopathology of the explanted lungs. The major limitation is the relatively small sample size. One other limitation is that even in patients initially presenting PAH, disease is relatively well established—there remains a 2.5-year mean duration from disease onset to diagnosis (15), and even at the time of earliest symptom onset there is likely to be substantial vascular disease burden.

Although obstructive lung disease has been described in patients with PAH (2, 4, 7), its evolution over the course of the disease is characterized for the first time in this study. The authors were also able to correlate the decrement in airflow with the enlargement of the pulmonary vasculature, providing additional evidence that pulmonary arterial dilation may induce obstruction of the small airways through either mechanical compression or cell receptor signaling. It is possible there may be signaling mechanisms emanating from the diseased vasculature, which consequently affects the airways, or that shared proximate signaling may underlie the development of both vascular and airway disease.

Overall, these data suggest airway obstruction can play a role in severe PAH that may contribute to dyspnea (Figure 1). Although the results of this study are certainly interesting from a physiologic standpoint and build on previous observations, its clinical relevance remains unclear. However, in patients with end-stage right ventricular failure and decreased gas exchange, it is quite possible and perhaps likely that worsening airway obstruction would further worsen exercise capacity, quality of life, and mortality. It will remain to be seen if this aspect of PAH could be targeted for therapy. ■

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## References

1. Inscore SC, Stenmark KR, Orton C, Irvin CG. Neonatal calves develop airflow limitation due to chronic hypobaric hypoxia. *J Appl Physiol (1985)* 1991;70:384–390.
2. Fernandez-Bonetti P, Lupi-Herrera E, Martinez-Guerra ML, Barrios R, Seoane M, Sandoval J. Peripheral airways obstruction in idiopathic pulmonary artery hypertension (primary). *Chest* 1983;83:732–738.
3. O'Hagan AR, Stillwell PC, Arroliga A. Airway responsiveness to inhaled albuterol in patients with pulmonary hypertension. *Clin Pediatr (Phila)* 1999;38:27–33.
4. Meyer FJ, Ewert R, Hoeper MM, Olschewski H, Behr J, Winkler J, *et al.*; German PPH Study Group. Peripheral airway obstruction in primary pulmonary hypertension. *Thorax* 2002;57:473–476.
5. Richter MJ, Voswinckel R, Tiede H, Schulz R, Tanislav C, Feustel A, *et al.* Dynamic hyperinflation during exercise in patients with precapillary pulmonary hypertension. *Respir Med* 2012;106:308–313.
6. Laveneziana P, Garcia G, Joureau B, Nicolas-Jilwan F, Brahimi T, Laviolette L, *et al.* Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2013;41:578–587.
7. Laveneziana P, Humbert M, Godinas L, Joureau B, Malrin R, Straus C, *et al.* Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2015;45: 1495–1498.
8. Meyer FJ, Lossnitzer D, Kristen AV, Schoene AM, Kübler W, Katus HA, *et al.* Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2005;25:125–130.
9. de Man FS, van Hees HW, Handoko ML, Niessen HW, Schalij I, Humbert M, *et al.* Diaphragm muscle fiber weakness in pulmonary hypertension. *Am J Respir Crit Care Med* 2011;183:1411–1418.
10. Boucly A, Morélot-Panzini C, Garcia G, Weatherald J, Jaïs X, Savale L, *et al.* Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur Respir J* 2020;55:1802108.
11. Saha BK, Beegle S. Central airway compression by massively dilated pulmonary artery in a patient with pulmonary arterial hypertension: a rare entity. *BMJ Case Rep* 2019;12:e232468.
12. Sandhu G, Sharma D, Rajdev K, Habib S, El-Sayegh D. Bronchial obstruction caused by a dilated pulmonary artery. *Cureus* 2019;11:e5354.
13. Rahaghi FN, Trieu M, Shaikh F, Abtin F, Diaz AA, Liang LL, *et al.* Evolution of obstructive lung function in advanced pulmonary arterial hypertension [letter]. *Am J Respir Crit Care Med* 2021;204:1478–1481.
14. Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open* 2019;9:e028150.
15. Khou V, Anderson JJ, Strange G, Corrigan C, Collins N, Celermajer DS, *et al.* Diagnostic delay in pulmonary arterial hypertension: Insights from the Australian and New Zealand pulmonary hypertension registry. *Respirology* 2020;25:863–871.