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 include improving hemodynamics and right ventricular function. Additional therapies to improve exercise tolerance and relieve dyspnea in PAH include improving hemodynamics and right ventricular function. Additional therapies to improve exercise tolerance and relieve dyspnea in PAH include improving hemodynamics and right ventricular function.

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 FEV1/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 uncertain. 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...
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 FEV1 and/or FVC, and six had an FEV1/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 FEV1 and FVC over the duration of follow-up. For example, the annual rate of FEV1 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 FEV1/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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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).
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