heavily on IPF; however, targeted studies analyzing rheumatoid arthritis–associated ILD and chronic hypersensitivity pneumonitis suggest that the prevalence of both *MUC5B* promoter polymorphism (16, 17) and rare variants in telomere-related genes is similar to that observed in IPF (18, 19). The most powerful insights that could come from future genetic studies in ILD would be links between genetic risk factors and specific ILD features or phenotypes. Such studies will require large and diverse cohorts, high-resolution phenotyping, and high-quality longitudinal data. This study by Allen and colleagues gives us reason to be optimistic that the large-scale collaborative efforts required for such investigations may be possible in the near future. ■

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Positive Airway Pressure in Obesity Hypoventilation: Getting to the Heart of the Matter

The past decade has seen an increasing interest in the early identification and treatment of obesity hypoventilation syndrome (OHS). This has largely arisen from a greater recognition that untreated OHS is associated with significantly higher levels of morbidity and mortality compared with obstructive sleep apnea (OSA) alone (1). Individuals with OHS experience poorer quality of life, increased health resource use, and greater adverse socioeconomic impacts than equally obese eucapnic individuals (2, 3). In addition, more than 50% of those with OHS have echocardiographic evidence of pulmonary hypertension and left ventricular hypertrophy (4, 5). Positive airway pressure (PAP) remains the mainstay of therapy for OHS, aiming to correct sleep disordered breathing, reverse awake

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respiratory failure, and improve clinical outcomes. Both continuous (CPAP) and bilevel (BPAP) therapy have been used for this condition, with several randomized comparative trials finding no difference between therapies in terms of resolution of awake respiratory failure, quality of life, or treatment adherence (6–8). However, few studies have specifically examined the effect of PAP therapy on the resolution of cardiac dysfunction and pulmonary hypertension (5, 9, 10).

The Pickwick project is a large, multicenter study undertaken by the Spanish Sleep Network evaluating the comparative effectiveness of PAP therapy in patients with stable ambulatory OHS.

During the initial phase of the study, 221 patients with OHS and severe OSA were randomly assigned to CPAP, BPAP, or a control group for 2 months (11). Two-dimensional and Doppler echocardiograms were used to evaluate medium-term changes in cardiac structure and function with these interventions (5). Only those allocated to BPAP showed an improvement in systolic pulmonary artery pressure (−3.4 mm Hg) and a reduction in left ventricular hypertrophy. Whether these differences between therapies would be sustained longer term remained unanswered. In this issue of the *Journal*, Masa and colleagues (pp. 586–597) provide data to address this question (12). After 2 months of intervention, those who had been initially allocated to the control group were rerandomized to either the CPAP or BPAP treatment groups, with all patients followed for 3 years with annual echocardiograms. Both PAP groups experienced significant improvements in systolic pulmonary artery pressure and left ventricle diastolic dysfunction, with no between-group differences. Awake blood gases, blood pressure, and dyspnea also improved significantly and similarly in both groups. No significant longitudinal changes in left ventricular hypertrophy or ejection fraction were seen with either mode of PAP.

Although these are important and clinically relevant findings, a few issues need to be considered in interpreting the results. Right heart catheterization (the gold standard for evaluation of pulmonary hemodynamics) would have provided a more accurate assessment of pulmonary hypertension (13), but would have been unrealistic in such a large study population during a prolonged follow-up period. However, without right heart catheterization, the exact mechanism or mechanisms responsible for pulmonary hypertension remains unclear. Nevertheless, the cause of pulmonary hypertension in an OHS population is likely to be multifactorial, resulting from increased pulmonary vascular resistance caused by hypoxia-induced vasoconstriction and/or elevated left atrial pressure resulting from left heart dysfunction (10, 14). Another limitation of the study was that echocardiographic assessment of both right ventricular and left ventricular functions were rather limited; for example, common parameters for right ventricular systolic function (such as fractional area change, S-wave, and tricuspid annular plane systolic excursion) were not assessed. The precision of echocardiographic measurements can also be challenging in morbidly obese patients. Other interventions such as changes in medications during the study period may have confounded the improvements seen in pulmonary hypertension. Because pulmonary hypertension is often a result of left ventricular diastolic dysfunction, alterations in the use of diuretics over the study period could have produced some of the changes in systolic pulmonary artery pressure reported.

So what are the major clinical insights this study provides? First, less than 10% of the patients were diagnosed with pulmonary hypertension before enrolment in this study, rising to more than 50% once a more thorough assessment was performed. This suggests that pulmonary hypertension, albeit generally mild to moderate, is both common and underrecognized in this population. Second, although the mean fall in systolic pulmonary artery pressure was around 6 mm Hg for both PAP groups, those with baseline pulmonary hypertension experienced a much greater mean fall of around 11 mm Hg, irrespective of the mode of PAP used. Furthermore, an improvement in 6-minute-walk distance was observed only in subjects with baseline pulmonary hypertension. This provides indirect evidence that mild to moderate pulmonary hypertension contributes to an exercise limitation in OHS. Third, improvements in pulmonary hypertension, similar to those of blood gases, may occur more slowly with CPAP therapy (6), necessitating close monitoring during the first months of treatment with CPAP to ensure the patient is responding favorably to the intervention. Fourth, around a quarter of patients experienced residual pulmonary hypertension irrespective of the type of PAP used, which may adversely affect quality of life (14). For those with significant residual pulmonary hypertension after optimized PAP, referral to an expert pulmonary hypertension center should be considered.

The findings from this study are important and should provide the clinician with greater assurance that long-term management of patients with stable OHS and coexistent OSA with CPAP therapy is safe, effective and not inferior to BPAP in the majority of cases (15). Nevertheless, those individuals presenting with more severe respiratory failure, who are older or who have less severe OSA may still respond better to BPAP, highlighting the need for careful follow-up and considered clinical judgement. However, weight loss and reductions in sedentary behaviors should remain at the heart of our intervention strategies in this population. ■

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The Risk of Falsely Declaring Noninferiority of Novel Latent Tuberculosis Treatment in Large Trials

Addressing the global burden of latent tuberculosis infection (LTBI) is critical to eliminate TB and will require a much-improved diagnostic test, a much shorter treatment, or both. It is an exciting time for research to shorten LTBI treatment, with ongoing and recently completed studies holding promise of ultrashort, safer, more sterilizing regimens that would be easier to deliver to large populations (1–3). As in trials involving other diseases for which there is an existing effective treatment, developers of LTBI trials often opt for a noninferiority design to minimize sample sizes and costs. A particular challenge for investigators in these trials is deciding which subjects to enroll in the absence of a robust "gold-standard" diagnostic test for LTBI. In a modeling analysis presented in this issue of the *Journal*, Stout and colleagues (pp. 598–605) examined the factors that would lead to a false-positive outcome in a noninferiority trial comparing new versus established treatments for LTBI in the absence of a perfect test (4). After performing sensitivity analyses of key assumptions, the authors concluded that their model findings were valid under certain alternate scenarios.

The authors examined the impact of LTBI prevalence, the sensitivity and specificity of currently available proxy tests for LTBI, and the choice of noninferiority margins and other parameters on the design and interpretation of noninferiority trials. There is much debate about what constitutes "true" latent infection. A particular concern in noninferiority trials relates to the specificity of a test for LTBI and the prevalence of true LTBI in the study population.

A low prevalence of LTBI would mean that many individuals in the trial are not infected, which increases the risk of falsely declaring noninferiority. This modeling analysis suggests that without testing for LTBI, that risk is substantial when the LTBI prevalence is below 45%. When LTBI prevalence is less than 45%, it is still better to "enrich" the trial population for LTBI by enrollment based on LTBI tests. However, as the low specificity of the LTBI test would again result in low prevalence, more specific tests, such as IFN-γ release assays (IGRAs), should be used. Indeed, more broadly, the authors conclude that noninferiority trials evaluating regimens for treating LTBI should enroll participants based on IGRAs rather than on the PPD tuberculin skin test (TST), to decrease the risk of misclassifying ineffective regimens as noninferior. The conclusion

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