in the CF piglet. Because the timing of fetal CFTR expression in the mammalian lung is synchronous with the branch development of the large airways, the authors submit that the findings observed in the CF piglet are a direct correlate of CFTR dysfunction and not reduced fetal lung liquid or impaired chloride secretion. They also suggest that absent CFTR function affects a host of cells, including chondrocytes, smooth muscle, and neural cells.

The findings of Adams and colleagues (10), if they indeed occur in young children with CF, support a growing concept that ventilation heterogeneity *per se* is fundamental to the pathobiology of lung disease. In study participants with asthma, the magnitude of ventilation heterogeneity measured by lung clearance highly informs the degree of bronchial hyperresponsiveness, better than biomarkers of inflammation, and predicts asthma control after up- and down-titration of inhaled corticosteroid treatment (13, 14). Repeated exposure of individuals with stable asthma to methacholine-induced bronchospasm induced early structural changes of airway wall thickening (15). The results of this study suggest that the compressive mechanical forces attendant to bronchospasm support regional airway remodeling independent of inflammation. These provocative findings highlight the fact that the relationship between regional lung inflammation and lung function is not well understood. The mandate is clear for innovative studies examining such relationships (16). Exciting new imaging methods, including positron emission tomography, hyperpolarized noble gas MRI, and single-photon emission computed tomography, coupled to image-guided bronchoalveolar lavage and biopsy, will foster new understanding of the pathobiology of lung disease. The result will be a paradigm shift away from the conception of diseases like CF and asthma as involving the entire lung to an informed understanding of regional pathology linked to significant ventilation heterogeneity.

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Idiopathic Pulmonary Fibrosis: Time to Get Personal?

Despite significant progress in understanding the mechanisms underlying pulmonary fibrosis in general, our understanding of how these mechanisms contribute to individual and patient-specific manifestations of idiopathic pulmonary fibrosis (IPF) remains poor. Within interstitial lung diseases, IPF remains the deadliest of the pneumonitides (1), with a course that is highly variable (2, 3). The iterative nature of diagnosis (4) and the unpredictable course of the disease have made treatment planning extremely difficult. This has complicated the design of drug

studies and raised a noticeable debate regarding patient-relevant outcomes.

Until recently, other than lung physiology in such scoring systems as the GAP (gender, age, and physiology) score (5), we did not have replicated molecular and genetic markers that would allow better prediction of outcome and classification of disease. However in the last 2 years, several studies that incorporated derivation and replication cohorts in their design suggested that peripheral blood proteins (6), changes in gene expression (7), or

gene variants (8, 9) may be used to better classify patients with IPF as belonging to groups with high risk for early mortality compared with those with significantly more stable disease. Although these studies strongly suggest the notion that molecular and genetic information could be used to personalize management in IPF, they still lack a direct link to such a therapeutic option.

In this issue of the *Journal*, O'Dwyer and colleagues (pp. 1442–1450) go a step further toward implementing personalized medicine approaches in IPF by identifying a gene variant that is indicative of distinct outcomes in patients with IPF, is mechanistically relevant, and at the same time, may have some very practical therapeutic implications (10). The authors chose to explore a candidate polymorphism in the Toll-like receptor 3 (TLR3) gene, which is known to be important in pathogen recognition and activation of the innate immune response to viruses through recognition of molecular patterns such as the double-stranded RNA. The L412F polymorphism of TLR3 has been previously noted to be functionally important in epithelial cell lines (11). The authors started their investigation by looking at the function of TLR3 in primary human lung fibroblasts from the lungs of patients with IPF with and without the L412F polymorphism. They divided these samples on the basis of presence or absence of the polymorphism and demonstrated that fibroblasts homozygous for the polymorphic allele produce less IL-8 as a readout of nuclear factor- κ B activity, and RANTES (regulated upon activation, normal T-cell expressed and secreted) as a readout of interferon regulatory factor 3. IPF fibroblasts that were homozygous or heterozygous for the polymorphic allele also exhibited an impaired IFN- β response and as a consequence exhibited enhanced fibroproliferation after TLR3 stimulation. Impressively, this effect was ameliorated in the presence of recombinant IFN- β .

They also provided a circumstantial evidence that TLR3-mediated signaling was potentially important in fibrosis by comparing the response to bleomycin between TLR3 knockout mice and wild-type control mice. Compared with wild-type mice, TLR3 knockouts exhibited significantly increased mortality, with increased levels of transforming growth factor- β 1, IL-13, IL-4, and hydroxyproline.

Finally they proceeded to determine the clinical implications of the polymorphism in two independent cohorts of patients with IPF. The first consisted of a United Kingdom population of 170 subjects, and the second consisted of 138 subjects from the placebo arm of the INSPIRE clinical trial of IFN- γ , where patients were followed for 24 months. They assessed mortality within 12 months in these two groups. The analysis demonstrated a hazard ratio of 4.98 (95% confidence interval, 1.25–20.00; $P = 0.023$ corrected for age, FVC, and diffusing capacity of carbon monoxide) for patients that carried the minor allele. There seemed to be an additive effect for each allele in that the homozygous minor (TT for CC) carried a hazard ratio of 9.71 (95% confidence interval, 2.70–34.93; $P = 0.001$) in the United Kingdom cohort. Furthermore, they also demonstrated an association with decline in FVC from baseline over time in the INSPIRE cohort that again seemed to have a dose-response relationship to the polymorphism.

One of the strongest attributes of this manuscript beyond the use of two cohorts is the significant effort to provide a strong mechanistic link between a hypothesis-driven candidate polymorphism and altered fibrosis, the immune response, and survival in patients. It must be mentioned here that the bleomycin results in this case cannot be really considered more than circumstantial evidence for a role of TLR3 in fibrosis, because the mechanisms and downstream effects of bleomycin in TLR3-deficient mice are very, very different than those active in patient carrying a variant in the sequence of TLR3 and exposed to mild environmental injury.

Another strong attribute of this study is that it may and should revive an interest in a therapy previously tried unsuccessfully in IPF. At the International Conference of the American Thoracic Society in 2000, Raghu and colleagues (12) presented the results of a multicenter, randomized double-blind placebo-controlled study and reported no therapeutic benefit, though the study itself was never fully published. The results of the current study, which demonstrate an impaired IFN- β response in cells from patients carrying the rare allele and that IFN- β supplementation blunted aberrant fibroblast activation seen in these patients, suggest potentially revisiting Raghu and colleagues' results and maybe even retrying IFN- β in patients that carry the polymorphic allele, especially because they are such a high-risk group.

Given the significance, reproducibility, and ease of measurement of the proteins, genes, or genetic variants recently demonstrated to be predictive of outcome in IPF, one must wonder why there is not stronger adoption of the use of molecular and genetic markers in IPF, as it seems only logical to follow the evidence and implement personalized medicine approaches in our referral for lung transplant or decision about drug studies based on molecular and genetic markers. Not only does the article by O'Dwyer and colleagues move us a significant step closer to this goal, it also provides a clue about a potential approach to personalizing therapy in IPF, in which a drug (IFN- β) will only be tried in those patients in whom a positive disease-modifying effect on their fibroblasts exists. Adoption of such approaches has the potential to shorten the duration of drug studies, make them cheaper to execute and most importantly more likely to benefit our patients, a benefit they at last deserve.

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Sleep Apnea and Subclinical Myocardial Injury: Where Do We Stand?

Obstructive sleep apnea (OSA) is independently associated with coronary heart disease (CHD), heart failure (HF), and adverse cardiovascular outcomes (1, 2). Although the mechanism for the relationship between OSA and myocardial injury is complex and not well established, there are suggestions that many of the pathophysiologic changes induced by OSA interact to promote the development and/or progression of manifestations of CHD, ranging from subclinical atherosclerosis to acute myocardial infarction (MI) and ischemic HF (3). For example, intermittent airway obstruction in OSA causes high negative intrathoracic pressure swings that increase transmural gradients across the heart ventricles and thus increase myocardial afterload. Additionally, intermittent hypoxia and hypercapnia lead to heightened sympathetic activity (4), resulting in elevated blood pressure and heart rate and subsequent increase in myocardial oxygen demand. The combination of these events with diminished oxygen supply during apneic episodes may cause myocardial ischemia/injury in patients with OSA (5).

Clinical evidence of myocardial ischemia induced by OSA has been reported in several studies (6–8). Furthermore, treatment of OSA may decrease cardiovascular risk. Garcia-Rio and colleagues (6) reported that mild to severe OSA was an independent predictor of MI and the risk of recurrent MI and coronary artery revascularization was lower in patients with OSA with MI who tolerated continuous positive airway pressure (CPAP) treatment compared with those who did not (6). In other studies, nocturnal ST-segment depression, a marker of myocardial ischemia, was observed among patients with known CHD and OSA (7) and in patients with OSA without known CHD (8). Contrary to the usual diurnal pattern, acute coronary syndromes (9) and sudden cardiac death (10) are more frequent during the nighttime in patients with OSA, suggesting that OSA may trigger acute ischemic events. Given that both OSA and CHD share common risk factors, such as obesity, male sex, age, and smoking (11), proving that OSA is an independent cause of myocardial injury has been a great challenge.

The study by Querejeta Roca and colleagues (pp. 1460–1465) in this issue of the *Journal* addresses this challenge (12). They performed a cross-sectional analysis of data from the prospective epidemiologic cohorts of the Atherosclerosis Risk in Communities and the Sleep Heart Health Study. Among 1,645 community-dwelling participants without prevalent CHD or HF, more severe OSA was found to be significantly associated with subclinical myocardial injury determined by serologic measurements of high-sensitivity troponin T (hs-TnT), after adjusting for 17 potential confounders. Of note, this relationship

was stronger among women compared with men. Furthermore, they found that hs-TnT levels were associated with incident cardiovascular disease events or death in each category of OSA severity, largely driven by higher hs-TnT in participants with severe OSA compared with those without OSA. After 12.4 years of follow-up, higher hs-TnT levels were associated with a higher hazard ratio for death or incident HF, death or incident CHD, and the composite of death, incident HF, or incident CHD. These data are especially relevant and timely, given the increasing evidence linking OSA to adverse cardiovascular outcomes. On the contrary, they did not observe a significant association between OSA and ventricular wall stress determined by serologic measurements of N-terminal pro-B type natriuretic peptide after adjustment for potential confounders.

Limitations to the generalization of Querejeta Roca and colleagues' results are more related to unmeasured confounders and differences between their findings and those in the existing literature than to the study design itself. Gami and colleagues reported a conflicting result in a small series of patients with known CHD and moderate to severe OSA (apnea/hypopnea index > 30) (13). Using a sophisticated protocol, these authors reported no evidence of myocardial injury assessed by a third-generation troponin T assay during sleep. One could argue that the differences in results may be related to the fact that the newer hs-TnT assay is more sensitive than traditional TnT assays for identifying myocardial injury. However, in a recent study by Randby and colleagues (14) in which hs-TnT was measured in a community-based sample of middle-aged patients (30–65 yr) without known CHD, the association of OSA with hs-TnT did not remain significant after adjusting for potential confounders.

Other investigators have suggested that the chronic intermittent hypoxia that occurs in patients with OSA may actually cause ischemic preconditioning in the myocardium and as a result be protective against myocardial ischemic injury (15). In a recent observational study involving 136 patients with nonfatal MI who were screened for OSA, Shah and colleagues reported significantly lower hs-TnT in patients with more severe OSA compared with those without OSA. This relationship remained significant even after adjusting for potential confounders (15). These authors suggested that their findings may be related to a cardioprotective role of ischemic preconditioning due to sleep apnea. Further systematic studies are warranted to clarify the potential cardioprotective role of OSA.