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Seeing Premature Lung Disease: Hyperpolarized Xe Magnetic Resonance Imaging

Preterm birth impacts more than 15 million children annually worldwide and is the leading cause of death in children under 5 years of age (1). Complications related to premature birth, particularly in very preterm infants (less than 32 weeks gestational age), represent 30% of newborn healthcare costs in the United States, nearly $13.4 billion annually (2). Bronchopulmonary dysplasia (BPD), or chronic lung disease of prematurity, is characterized by small- and large-airway obstruction, alveolar simplification, pulmonary fibrosis, and pulmonary vascular abnormalities, which can be precisely quantified using advanced imaging technology (3–6). Pulmonary sequelae of premature birth extend well beyond the neonatal phase and manifest with reduced lung function, progressive lung function decline, and persistent respiratory symptoms (7). In recent years, the limit of viability has decreased to 22 weeks gestational age, and the incidence of lung disease associated with premature birth has increased with improved neonatal survival of the most vulnerable patients. Thus, it is ever more important to precisely define the long-term pulmonary changes that may result from premature birth.

A significant challenge in evaluating pulmonary complications of premature birth is that most existing definitions rely on defining the disease by respiratory support at 28 days of life or 36 weeks postmenstrual age (8). Although these definitions are useful for predicting clinical outcomes, they provide little insight into the underlying pathophysiology of premature lung disease. In this issue of the *Journal*, Chan and colleagues (pp. 89–100) made a leap forward by combining multiple breath washout and hyperpolarized Xe magnetic resonance imaging (MRI) to define ventilation abnormalities and lung microstructure in preterm-born children with different lung function phenotypes (9).

Children born preterm with obstructive lung disease had elevated ventilation defect percentage (VDP) on the basis of hyperpolarized Xe MRI as well as ventilation abnormalities on the basis of multiple breath washout; MRI also revealed a significant increase in ventilation heterogeneity that cannot be defined with other tests of pulmonary function. Furthermore, children with BPD, but not those born prematurely without BPD, had an elevated apparent diffusion coefficient, suggesting that alveolar simplification persists into school age, which differs slightly from a prior study using ^{3}He (10). Surprisingly, children with BPD did not demonstrate an elevation in VDP in this study compared with term control subjects despite a significant reduction in forced expiratory flow. This discordance is different than the relationship of VDP and spirometry seen in other pediatric obstructive lung diseases such as cystic fibrosis and obliterative bronchiolitis and may reflect a novel underlying pathology in BPD or the small sample size in this study, so these findings should be interpreted with caution (11, 12). Furthermore, the children enrolled tended to have a milder neonatal course, with few participants meeting the criteria for severe BPD who are most likely to have long-term respiratory sequelae related to premature birth. Consequently, the findings of Chan and colleagues may underestimate the full spectrum of changes in pulmonary structure and function from prematurity. Nevertheless, these findings provide significant new insight into the pathophysiology of respiratory outcomes in school-age children who were born prematurely.

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In the past decade, chest MRI has emerged as a leading technology to evaluate cardiopulmonary pathology and clinical outcomes in neonates who were born premature (4–6). Although case reports have shown the feasibility of using hyperpolarized Xe MRI to define abnormalities of lung structure and function related to preterm birth in school-age children (13, 14), Chan and colleagues present the first cohort of such patients and highlight how imaging can define different disease phenotypes in this population. MRI can precisely quantify airway obstruction (VDP) and alveolar simplification (apparent diffusion coefficient), as demonstrated in this report. Hyperpolarized Xe can also provide insight into pulmonary hypertension and diffusion impairment via gas-exchange MRI (13). Furthermore, hyperpolarized Xe imaging can be combined with ultrashort echo time proton MRI to evaluate parenchymal scarring, density, and lung volumes (5, 15, 16). Although computed tomography can potentially provide similar information, it exposes children to radiation, which increases risk. Furthermore, chest MRI can evaluate regional changes in lung structure and function, unlike classical tests of pulmonary function, which are limited to an imprecise and nonspecific global measure of respiratory health. As a result, chest MRI has the potential to evaluate lung disease that may not be readily apparent from other tests. Taken together, modern imaging is uniquely poised to evaluate longitudinal changes in lung structure and function throughout childhood in patients who were born prematurely. By precisely quantifying regional changes and multiple pathologies, MRI may also serve as an objective guide for monitoring response to therapies for lung disease related to premature birth, facilitating precision medicine.

Although there are clear advantages and huge potential for chest MRI, this technology is not yet widely available and remains a tool primarily for use in research studies. There are, however, ongoing efforts to obtain U.S. Food and Drug Administration approval for the clinical use of Xe MRI. Moving forward, it will be critical to understand the reliability and reproducibility of Xe MRI for evaluating lung disease related to preterm birth and whether or not this highly sensitive tool can better predict outcomes or be used to better personalize treatments in individual patients. Despite the current challenges, MRI has a strong potential to evaluate lung disease in the high-risk population of children born prematurely. ■

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