BRIEF OBSERVATION

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Lung MRI as a Potential Complementary Diagnostic Tool for Early COPD

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ABSTRACT

INTRODUCTION: Many knowledge gaps in the nature of early chronic obstructive pulmonary disease (COPD) still exist, mainly because COPD has always been considered a disease of the elderly. Little attention has been paid to the pathologic changes in the lungs of young adults with risk factors for COPD, such as bronchopulmonary dysplasia. One major limitation is the current lack of noninvasive ways to sensitively measure or image functional declines from subjects who are at risk for COPD but haven't yet developed more significant clinical symptoms of the disease.

METHODS: We report the use of lung magnetic resonance imaging with hyperpolarized gas in the diagnostic workup for bronchopulmonary dysplasia with underlying chronic airflow limitation in presence of spirometry criteria that meet the diagnosis of early-onset COPD.

CONCLUSIONS: In the postsurfactant era, where more young adults will be spirometrically diagnosed with COPD, patients should be classified not only on the basis of their airflow limitation, but also on lung abnormalities identified with safe, comprehensive imaging technologies that allow regular, longitudinal follow-up.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent disorder with heterogeneous onset and progression. COPD caused by inhaled smoke represents the vast majority of the patients; however, 20%–25% of all COPD patients worldwide have never smoked.[1] In addition, genetic, environmental, and developmental factors that are associated with diverse biologic mechanisms and that exert their effects during childhood and adolescence can determine low lung function in young adults.[2,3] Thus, the term "early COPD" was recently introduced to define ever-smokers younger than 50 years with a low or fast-declining forced expiratory volume in the first second (FEV_1).[4] However, this definition comes with several caveats. First, the terms "early" vs "late" take as reference point the time when COPD is diagnosed or studied for the first time, and do not necessarily mirror the real time course of the disease. Second, in historical COPD cohorts and often in current COPD patients, serial lung

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function measurements or imaging are often unavailable, and thus, the pathobiological processes occurring in the earlier years and leading to clinically manifest airflow limitation in adulthood are unknown.

Bronchopulmonary dysplasia is a chronic respiratory disease of prematurity that has increased prevalence[5] in the post-surfactant era due to the increased resuscitation and survival of extremely premature infants. Infants with bronchopulmonary dysplasia begin their childhood with low lung function and often have airways obstruction and alveolar simplification[6]—both of which can contribute to spirometrically-diagnosed COPD early in adulthood, especially if there is a second injury such as cigarette smoking. Infants with bronchopulmonary dysplasia have been shown to have long-term diminished FEV_1, yet the characterization of the transition toward adulthood, and potential COPD diagnosis, has yet to be elucidated.[7] One of the major reasons for the lack of early diagnosis of COPD is the paucity of sensitive techniques that can longitudinally measure early abnormalities in the lungs of individuals with minimal signs and symptoms of disease.[2] MRI with hyperpolarized gases demonstrated exquisite sensitivity to early emphysema and airway obstruction in COPD[8,9] by providing sensitive measures of airway obstruction, emphysema, and/or gas-exchange abnormalities in obstructive lung diseases without ionizing radiation exposure.[10] We hereby report the use of MRI in the identification of specific lung abnormalities associated with bronchopulmonary dysplasia and accompanied by spirometric chronic airflow limitation consistent with diagnoses of early-onset COPD.

CLINICAL SIGNIFICANCE

- Perinatal genetic, environmental, and developmental factors can determine low lung function in young adults, defined as "early [chronic obstructive pulmonary disorder] COPD."
- There is a lack of noninvasive ways to measure or image functional declines from subjects who are at risk for COPD but haven't yet developed significant clinical symptoms of the disease.
- Lung magnetic resonance imaging with hyperpolarized gas can identify lung abnormalities in patients with bronchopulmonary dysplasia and chronic airflow limitation, who meet the spirometry criteria for early-onset COPD.

METHODS

A 20-year-old never-smoker male, born prematurely at 30 weeks of gestation with a clinical diagnosis of bronchopulmonary dysplasia, underwent MRI at Cincinnati Children's Hospital Medical Center after providing informed consent. Past medical history included an episode of respiratory syncytial virus-induced severe bronchiolitis at 2 years of age. Current symptoms include gradually progressive dyspnea on exertion. For at least 8 years preceding the study, the subject had consistent severe airflow obstruction by spirometry, poor postbronchodilator reversibility, and a markedly reduced forced expiratory flow at 25%-75% of the pulmonary volume. Lung volumes measured by body plethysmography demonstrated air trapping and hyperinflation. The diffusing capacity for carbon monoxide was toward the lower limits of normal. His echocardiogram showed no evidence for pulmonary hypertension at rest. Six-minute walk test revealed moderate−severe exertional O_2 desaturation. Current pharmacological treatment included inhaled corticosteroids and a combination of beta agonists and muscarinic antagonists.

Hyperpolarized ^{129}Xe MRI was performed in 3 separate, 15-second breath holds to image and quantify gas distribution at tidal inspiration, apparent diffusion coefficient, and dissolved-phase peaks, which correspond, respectively, to regional ventilation, alveolar-airspace size, and gas exchange.[8,9,11,12] Proton MRI via ultrashort echo time stack-of-stars (TE = 0.2 ms) provided images of structure and gross parenchymal density.[13]

RESULTS

Chest x-ray study showed hyperinflation but otherwise no remarkable signs of lung pathologies, and the ultrashort echo time MRI was largely unremarkable, with the exception of one focal area of more severe emphysema in the right upper lobe (Figure 1). In contrast, the ventilation MRI revealed a pattern of small ventilation defects throughout the lungs, 4-5 cm^3 in size, which would correspond to obstruction in the smaller airways consistent with the severely reduced forced expiratory flow 25%-75% seen on pulmonary function tests. Apparent diffusion coefficient maps (Figure 1) revealed homogenous, elevated values, consistent with moderately increased alveolar-airspace size (0.053 cm^2/s, compared with 0.035 cm^2/s for a normal young adult and 0.056 cm^2/s for a 65-year-old with GOLD-II COPD[9]). Gas-exchange maps (Figure 2) indicated significantly reduced ^{129}Xe in the interstitium/plasma and concomitantly reduced gas transfer to red blood cells. When combined with apparent diffusion coefficient maps indicating enlarged alveolar spaces, this pattern is consistent with mild diffuse emphysema, likely implying early arrest of alveolar septation and alveolar simplification.

DISCUSSION

We demonstrate in this subject the value of modern MRI in detecting early defects of the airways and lung parenchyma in young adults with underlying chronic airflow limitation. In addition, while this patient meets the spirometry criteria for early-onset COPD, the MRI maps show a more spatially homogeneous pattern than what is typically observed in COPD.[14] While there is evidence of continued alveolarization in adolescents born prematurely,[15] this case illustrates grossly incomplete "catch-up" growth.

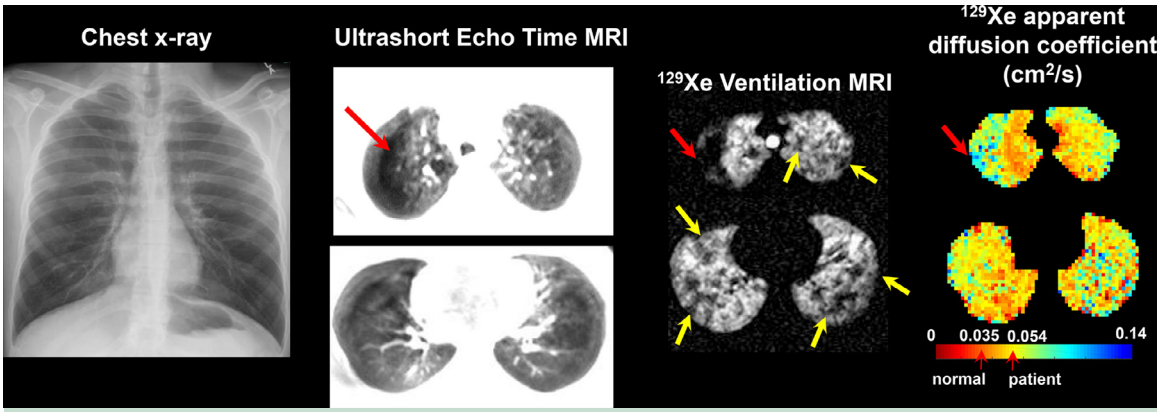

Figure 1 Patient's chest X-ray study showing hyperinflation but otherwise no remarkable signs of lung pathologies. Axial slices of proton ultrashort echo time, ^{129}Xe ventilation, and ^{129}Xe apparent diffusion coefficient images, from left to right, demonstrating a small bullous area in the apex (red arrow), widespread focal ventilation defects (yellow arrows), and near-uniformly elevated apparent diffusion coefficient (0.054 cm^2/s) indicative of enlarged alveolar airspaces.

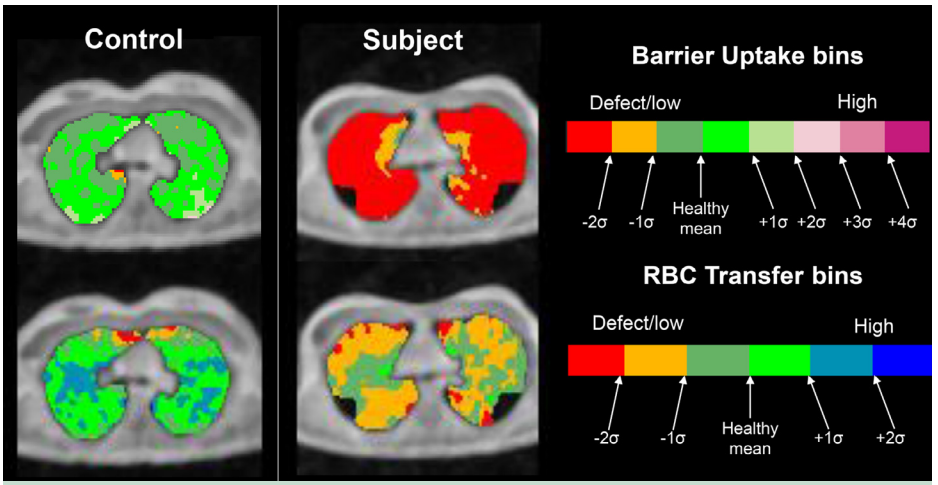

Figure 2 Axial ^{129}Xe magnetic resonance imaging gas-exchange maps show very low interstitial signal (top), compared with young-adult controls (ages 26 and 29 years) leading to a lower transfer to red blood cells (bottom); low values for Xe gas exchange are consistent with increased airspace size indicated by elevated apparent diffusion coefficient in Figure 1.

Chronic lung conditions in young adults may have begun as a result of insults in utero, in the neonatal period, or in early childhood, and can cause persistent airflow limitation. In addition, childhood infections can exacerbate the lung function limitation and decline caused by the underlying chronic pulmonary condition.[16] Thus, there is a critical need for improved distinction between the various pathophysiological mechanisms that begin early in life and often lead to chronic airflow limitation as adults. In clinical practice, physicians rely heavily on pulmonary function tests, even though these measures are not sensitive enough to detect early minor changes over time. Computed tomography scan has been used extensively to better define and quantify both the distribution and extent of emphysema and airway disease.[17] However, there are concerns over the use of ionizing radiation, particularly in younger individuals when there is not a clear functional decline, or where longitudinal follow-up studies are required. The combination of proton MRI with hyperpolarized-gas MRI provides a nonionizing imaging modality with structural and functional information, maps of gross parenchymal abnormalities, regional ventilation, alveolar-airspace size, and gas-exchange abnormalities. These techniques could be a useful and safe tool to longitudinally follow patients with pulmonary childhood diseases that may transition into fixed airflow limitation. Future studies are needed to better classify young adults on the basis of their underlying airway, emphysematous, and gas-exchange abnormalities identified with sensitive technologies similar to those employed here. As we prepare for an increasing number of young adults with airflow limitation (who may be inaccurately clustered together under the umbrella terminology of early

COPD), our ability to characterize early-onset airflow obstruction phenotypes and subtypes is key to establishing earlier and patient-tailored therapies that could prevent progression and help alleviate burden of COPD.

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