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COMMENTARY

Using the full power of multiple hyperpolarized ^{129}Xe contrasts to interrogate aging, smoking, and COPD

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Chronic obstructive pulmonary disease (COPD) remains one of the top causes of death worldwide. With an aim toward precision medicine, pulmonary imaging is increasingly used to phenotype at-risk populations and COPD patients. Historically, the most broadly available imaging modality for such efforts has been CT imaging, but lung MRI is gaining popularity as a radiation-free technique for measuring lung structure and function. Among lung MRI techniques, hyperpolarized ^{129}Xe MRI (Xe-MRI) is uniquely sensitive to the three main structural and functional impairments associated with COPD: ventilation imaging from Xe-MRI can identify obstructive pathophysiology; diffusion-weighted (or alveolar airspace size) imaging can identify emphysema; and gas exchange imaging and spectroscopy can identify impaired transport of gas from the airspaces to membrane tissues and red blood cells [1]. Xe-MRI thus enables a complete structural and functional regional assessment of the lungs, which may ultimately help to lead to precision medicine for patients with COPD and other lung diseases.

While Xe-MRI shows great promise for supporting precision medicine interventions in the context of COPD, its high sensitivity to regional lung structure and function can be a double-edged sword. The detection of subtle abnormalities or small changes to regional lung function over time provides it with great power to detect or monitor lung disease. However, this same high sensitivity leads to strong age-dependence of many Xe-MRI quantitative measures [2], and thus care must be taken to ensure that observed differences over time or between groups are rooted in pathophysiology rather than as a part of normal healthy aging. Recently, this question of age-related decline in Xe-MRI features has been an emphasis within the field, and multiple groups have published their findings [2–4]. However, our understanding of the age-dependence of Xe-MRI remains incomplete because of the limitations of these studies to date, including: (1) small sample sizes; (2) sparse sampling across the age range; (3) incomplete inclusion of Xe-MRI contrasts; and (4) incomplete characterization of participants.

These limitations are understandable based on the technical complexity and cost of Xe-MRI. However, these are limitations that must be overcome to make Xe-MRI the powerhouse for early disease detection, disease phenotyping, clinically meaningful outcomes, and therapy monitoring that many of us within the community hope it will become.

In this issue of European Radiology, Rao et al begin to address these limitations through a comprehensive assessment of Xe-MRI structural and functional measures in healthy volunteers over a large age range [5]. Notably, all three dominant Xe-MRI contrasts (ventilation, diffusion-weighted, and gas exchange) were implemented in participants across the lifespan, from ages 20 to 80. These age-related data are augmented by the inclusion of asymptomatic smokers and COPD patients, which enable the contextualization of Xe-MRI features.

As other groups have shown, Rao et al demonstrate that most Xe-MRI features are age-dependent, with the strongest age-dependence observed in VDP, alveolar sleeve depth, and pulmonary gas exchange parameters [5]. Other measures, such as apparent diffusion coefficient, mean linear intercept, and septal wall thickness, showed weaker age dependence but strongly differentiated between healthy volunteers, asymptomatic smokers, and COPD patients. As

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the authors note, this argues that these parameters may be strong candidates as outcome measures in clinical trials, as changes to Xe-MRI measures are more likely to be disease-related as opposed to age-related.

One of the more thought-provoking results of this work was that the septal wall thickness modeled based on gas exchange spectroscopy appears to show particular promise for differentiating between health and early disease. This finding is in agreement with a previous report that similarly suggested that this parameter may uniquely be sensitive to changes between healthy volunteers and smokers [4]. This could suggest sensitivity to inflammation within the lungs that could be the preamble to clinically significant lung disease. This may be particularly relevant given that sensitive and non-invasive methods of detecting inflammation are a pressing need in several disease contexts, including autoimmune disease, cystic fibrosis, and the development of early COPD.

At the same time, the only way to measure septal wall thickness with Xe-MRI is by using chemical shift saturation recovery (CSSR) [6] combined with a model of gas transport in the lungs [7, 8]. These experiments are generally performed without spatial encoding. In contrast, the Xe-MRI field has moved toward imaging methods, at least in the context of multi-site trials [1]. Results such as those proposed by Rao et al should motivate careful consideration of the types of Xe-MRI protocols that we conduct [5]. CSSR has commonly been relegated to the domain of basic science interrogation of pulmonary physiology, but this interesting study adds to the existing evidence that we should consider translating CSSR to more common usage as a potential outcome measure in clinical trials.

Particular strengths of this study are the relatively large participant numbers (at least 20 in each of the four groups studied) and the excellent age distribution over the range of 20–80-year-olds for the healthy volunteers. The biggest limitation of this study was relatively poor sex matching between healthy volunteers and smokers/COPD patients. Recent work in the Xe-MRI field has begun to highlight that Xe-MRI features, particularly those of gas exchange, are different between male and female participants [9]. The healthy volunteers imaged by Rao et al are dominantly female, compared to dominantly male patients [5]. Their results thus could be underestimating the true impact of smoking on Xe-MRI markers.

Ultimately, this study has provided a significant step forward toward understanding the age dependence of Xe-MRI markers. In addition, they have provided important food for thought for the Xe-MRI community as we work to define optimal Xe-MRI protocols for evaluating pulmonary pathophysiology and performing multi-site trials. Within the Xe-MRI field, we need to continue to work toward the performance of larger imaging studies that use the full range of Xe-MRI contrasts to evaluate participants across a wide range of age, sex, and racial/ethnic groups. In doing so, we will continue to support the translation of Xe-MRI from a niche research technology to an essential tool for clinical research.

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Compliance with ethical standards

Guarantor
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Conflict of interest
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Methodology

- Commentary

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