# Hyperpolarized <sup>129</sup>Xe MRI and spectroscopy in healthy control subjects reveals agerelated changes in measurements of pulmonary gas exchange

## Introduction

Various metrics derived from hyperpolarized <sup>129</sup>Xe gas exchange MRI and **spectroscopy** have been proposed as potential markers of disease progression and therapy response in diverse pulmonary diseases ranging from asthma and COPD to interstitial lung disease and radiation-induced lung injury. However, the effect of healthy aging on these <sup>129</sup>Xe measurements is poorly understood.

Disease-related findings in <sup>129</sup>Xe studies are often compared with whatever cohort of healthy subjects are convenient at the study site at the time, and who may not be age- or sex-matched with the disease population. However, it is well known that gas exchange function is age- and sex-dependent. Generating "expected" <sup>129</sup>Xe findings for (at minimum) a given sex and age is therefore required to **differentiate disease** processes from the consequences of normal healthy aging.

## Here, we present

- 1. A preliminary analysis of the effects of age and sex on common <sup>129</sup>Xe MRI metrics
- 2. A prototype of a "percent predicted" model for the red blood cell (RBC) to membrane (RBC:M) ratio, one of the most common metrics used in <sup>129</sup>Xe studies.

Methods	
Total	N = 41
Sex	27M, 14F
Age	44±18.3 [min 19, max 87] years
Age Category Breakdown	Under 30: N=14 (34%) 30-50: N=9 (22.0%) Over 50: N=18 (44%)

Table 1. Study population.

## <sup>129</sup>Xe MRI Acquisition:

- Signals from gas phase (airspaces) and dissolved phase (interstitial barrier tissue uptake and red blood cell [RBC] transfer) were acquired during a single breathhold<sup>1</sup>.
- The gas-phase <sup>129</sup>Xe images were rendered into quantitative binning maps with thresholds derived from a healthy reference cohort, as described previously.<sup>2</sup>
- The ratio of RBC to membrane signal (RBC:M) was obtained from <sup>129</sup>Xe spectroscopy.<sup>3</sup>



*Figure 1.* Typical <sup>129</sup>Xe findings in a healthy subject, COPD, and IPF.

**David Mummy, PhD<sup>1</sup>,** Aparna Swaminathan, MD<sup>2</sup>, Elianna Bier, PhD<sup>3</sup>, Aryil Bechtel, BS<sup>4</sup>, Junlan Lu, MS<sup>5</sup>, Suphachart Leewiwatwong, MS<sup>3</sup>, Sakib Kabir, MS<sup>1</sup>, Jennifer Korzekwinski, CRC, RT(N), CNMT<sup>1</sup>, Bastiaan Driehuys, PhD<sup>1,3,5</sup>

<sup>1</sup>Radiology, <sup>2</sup>Medicine, <sup>3</sup>Biomedical Engineering, <sup>4</sup>Physics, and <sup>5</sup>Medical Physics, Duke University, Durham NC, United States



Figure 3. Common <sup>129</sup>Xe gas exchange metrics stratified by age category. Note only significant differences are in the RBC:M and Membrane High % metrics.

## Increasing age was significantly correlated with decreased RBC:M (p < 0.001), as shown in Figure 4 (left panel).

We can further break this down into separate correlations between age and the individual membrane and RBC signals (right panel). This reveals a weak and nonsignificant decrease in membrane signal with age, but a significant decrease in RBC signal with age (p < 0.001), suggesting that decreasing RBC signal is the primary driver of age-related RBC:M decline.

Both age and sex were significant predictors of RBCM (p < 0.0001 for both) in a multivariate linear regression model of RBC:M with both age and sex as predictors, as shown in the figure.



and sex as significant predictors (p < 0.0001 for both)

A ten-year age increase was associated with an RBC:M decrease of 0.039, and male sex was associated with an RBC:M increase of 0.16.

Figure 4. Correlations between and age and RBC:M, and between age and the individual measurements of membrane and gas signal. A multivariate linear model of RBC:M shows both age



- the linear model.
- RBC signal.
- categories

We created a prototype model for generated "percent predicted" values of RBC:M based on age and sex. Establishing reference values for <sup>129</sup>Xe metrics will to be vital to differentiate disease processes from the consequences of normal healthy aging.

Work is ongoing to increase our study sample size, consider additional variables such as height and hemoglobin, and evaluate the model in the context of diseased populations.

# **Duke** University School of Medicine

## Results

## **RBC:M** "Percent Predicted" Prototype

the first steps towards



Figure 5. Distribution of RBC:M "Percent Predicted" values in our study population

**1. Calculate each individual subject's RBCM**pred by plugging age and sex into

2. Divide that subject's actual RBC:M by RBC:M<sub>pred</sub> to get RBCM% 3. The resulting distribution of %pred values in our population is promisingly normal and reasonably tight around 100% (Figure 5).

## Discussion

• **RBC:M decreased steadily with age,** driven primarily by decreasing

## • Imaging-based metrics did not vary significantly across age

• ...other than high membrane signal in multiple outlier subjects in the 30-50 yr category. The significance of this is unclear. It may be a sign of incipient pulmonary disease, an unidentified selection bias, or simply small sample size.

• In a multivariate linear model, both sex and age were significant predictors of RBC:M. This model was then used to generate "percent predicted" RBC:M values in our population.

## Conclusion

Age and sex have measurable affects on common <sup>129</sup>Xe measurements of gas exchange, particularly RBC:M.



**References:** Niedbalski PJ et al. Magn Reson Med 2021 Wang Z, et al. Med Phys 2017;44(6):2415-2428. . Bier EA et al. NMR Biomed 2019;32(1):e4029.

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