Hyperpolarized ^{129}Xe MRI and spectroscopy in healthy control subjects reveals age-related changes in measurements of pulmonary gas exchange

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Introduction

Various metrics derived from **hyperpolarized ^{129}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 ^{129}Xe measurements is poorly understood.**

Disease-related findings in ^{129}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" ^{129}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 ^{129}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 ^{129}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.*

^{129}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 breath-hold[1].
- The gas-phase ^{129}Xe images were rendered into quantitative binning maps with thresholds derived from a healthy reference cohort, as described previously.[2]
- The ratio of RBC to membrane signal (RBC:M) was obtained from ^{129}Xe spectroscopy.[3]

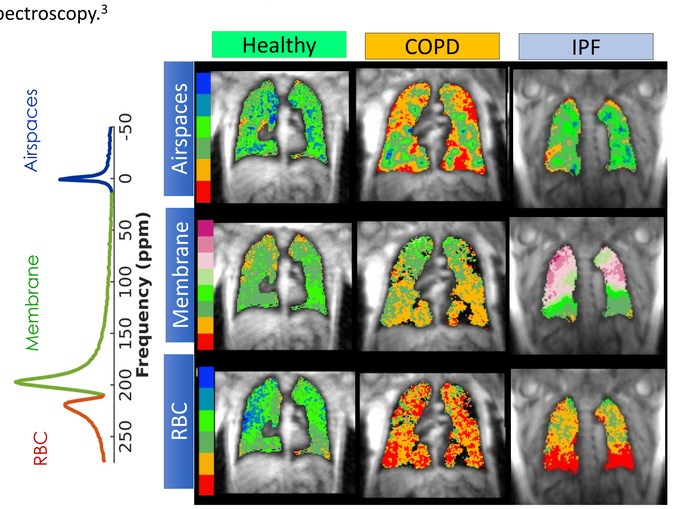

Figure 1. *Typical ^{129}Xe findings in a healthy subject, COPD, and IPF.*

Representative images from each of the age groups in our study population are shown in Figure 1 (right). The subject in the 50+ group exhibits a decreased RBC:M, ventilation defects, and a modest reduction in RBC transfer. **However, membrane signal is appears preserved across all age groups.**

Figure 2 (below) shows patterns of gas exchange stratified by age group across the whole study population. While there were trends towards increased ventilation defect percent (VDP) and RBC defect % with age, we only observed significant differences in two metrics:

(1) RBC:M. The < 30 group was significantly higher than in the 30-50 and 50+ groups.

(2) Membrane High %. The 30-50 group was significantly higher than the 50+ group.

The first result is largely expected, but interpretation of the second is unclear (see Discussion).

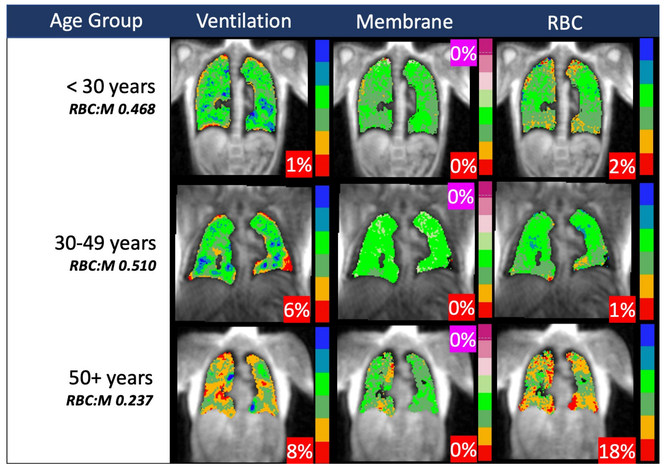

Figure 2. *Representative images from subjects in each of the three age groups. Note the presence of reduced RBC:M, ventilation, and RBC transfer in the 50+ subject, whereas the membrane signal appears preserved.*

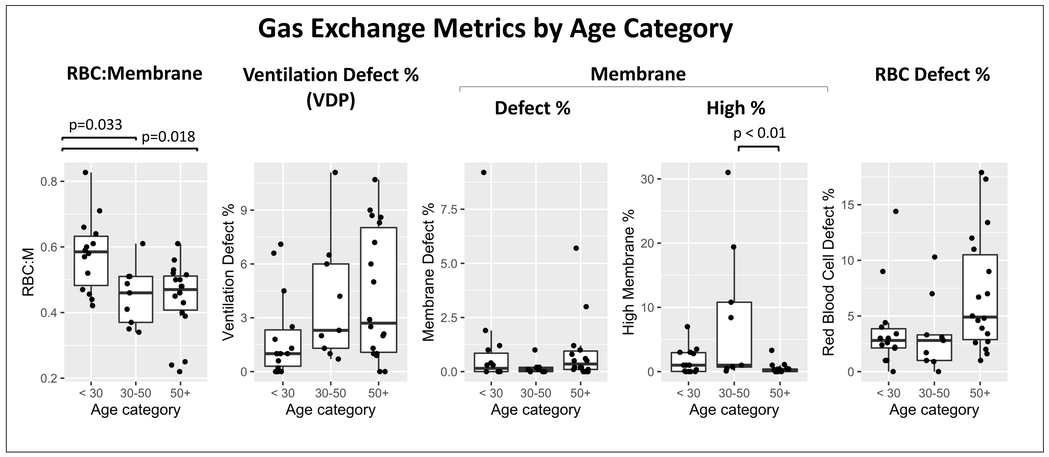

Figure 3. *Common ^{129}Xe gas exchange metrics stratified by age category. Note only significant differences are in the RBC:M and Membrane High % metrics.*

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 non-significant 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.

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.

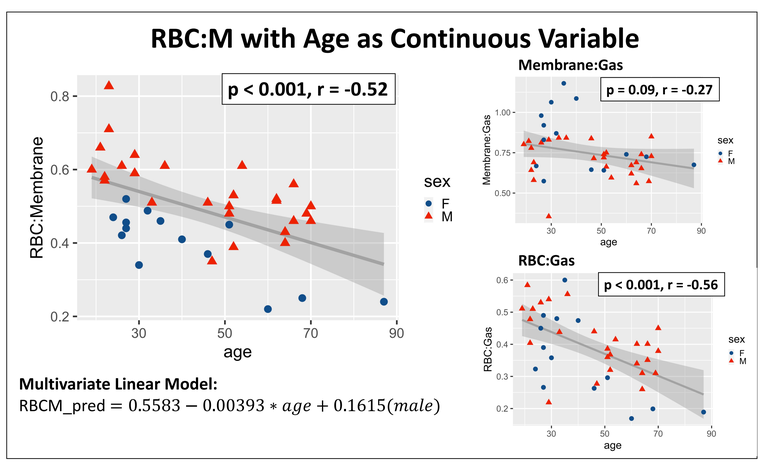

Figure 4. *Correlations between and age and RBC:M, and between age and the individual measurements of membrane and gas signal. A multivariate linear model of RBC:M shows both age and sex as significant predictors (p < 0.0001 for both)*

Results

RBC:M "Percent Predicted" Prototype

From this multivariate model, **we can take the first steps towards generating reference values for RBC:M akin to conventional pulmonary function tests.**

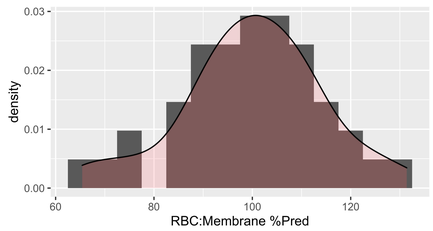

Figure 5. *Distribution of RBC:M "Percent Predicted" values in our study population.*

1. **Calculate each individual subject's RBCM$_{pred}$** by plugging age and sex into the linear model.
2. **Divide that subject's actual RBC:M by RBC:M$_{pred}$ 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 RBC signal.
- **Imaging-based metrics did not vary significantly across age categories**
  - …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 ^{129}Xe measurements of gas exchange, particularly RBC:M.

We created a prototype model for generated "percent predicted" values of RBC:M based on age and sex. **Establishing reference values for ^{129}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.

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References:

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2. Wang Z, et al. *Med Phys* 2017;44(6):2415–2428.
3. Bier EA et al. *NMR Biomed* 2019;32(1):e4029.

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