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Commentary

Imaging how and where we breathe oxygen: another Big Short?

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The Big Short (1) tells the story of a small group of skeptics who profited from the financial crisis in 2007 by betting against collateralized (mortgage) debt obligations (CDO). Importantly, the novel paints a clear picture of the eccentric nature of contrarians who think divergently and against the grain or bet against an accepted truth or "sure" thing. In a similar manner, Ishii and co-workers' recent work (2) describes their team's development of a pulmonary imaging technology that provides divergent and disruptive *in vivo* lung measurements of oxygen partial pressure in the context of the prevailing and longstanding consensus around FEV_1 as the definitive diagnostic of chronic lung disease.

It is well-understood and universally-accepted that the efficiency of pulmonary gas exchange is highly dependent on the symbiotic relationship between ventilation (oxygen delivery via the airways) and perfusion (oxygen uptake by the blood) that occur in the functional units of the lung, the alveoli. Accordingly, heterogeneity or mismatch between pulmonary ventilation and perfusion is a hallmark finding in respiratory diseases, such as chronic obstructive pulmonary disease (COPD). Indirect measurements of the alveolar partial pressure of oxygen (P_AO_2), such as arterial blood oxygen concentrations ($[O_2]$) (3) and the measurement of the partial pressure of expired carbon dioxide-oxygen mixtures using helium washout (4), provide clinically-acceptable measurements of gas exchange. Unfortunately, while these approaches provide physiologically relevant measures to support patient phenotyping and perhaps treatment decisions, these cannot provide regional information about ventilation, perfusion or its mismatch. This is important because in the last decade, lung imaging research has demonstrated that in obstructive lung diseases like asthma and COPD, lung functional abnormalities are regionally persistent and not randomly distributed throughout the lung. Accordingly, imaging methods, such as single photon emission computed tomography (SPECT) (5) and positron emission tomography (PET) (6), have been exploited to provide regional estimates of regional gas exchange and local partial pressures of oxygen. While also very useful, these imaging methods have limited spatial resolution and in addition, there is a small but clinically-relevant risk to patients that stems from the ionizing radiation of the SPECT and PET contrast agents. An alternative imaging approach that does not pose such risks may also provide some helpful information and utilizes inhaled hyperpolarized noble gases and magnetic resonance imaging (MRI) (7).

Since its first description (8,9), hyperpolarized noble gas MRI, using either ^{3}He or ^{129}Xe gas, both of which are stable, non-ionizing isotopes that can be magnetized so they are MRI visible, has provided non-invasive measurements of lung ventilation and parenchymal morphology. Inhaled gas MRI has provided new insights into pulmonary physiology and biomechanics of COPD (10), asthma (11), cystic fibrosis (12), radiation-induced lung injury (13) and lung transplantation (14). This previous research has led to the development of oxygen-sensitive or oxygen-weighted noble gas MRI, first described by Saam and colleagues (15) in 1995. This pioneering study suggested the potential for MRI to spatial and temporal ventilation-perfusion and oxygen distribution/uptake in the lung via alveolar oxygen partial pressure maps (7,16). This method exploits a unique property of the hyperpolarized noble gas polarization decay rate that is directly related to the presence of molecular oxygen and linearly related with the local oxygen concentration. The oxygen-induced

relaxation measurements can then be used to estimate the regional P_AO_2 by measuring local differences in gas signal intensity (7). Although the method allows for rapid image acquisition to measure ventilation-perfusion match and oxygen uptake, a number of limitations including coil inhomogeneity, lung motion, delayed ventilation and/or diffusion have all significantly slowed clinical uptake and translation (17). Importantly, measurement variability has never yet been reported and this is absolutely required before such measurements can be used in clinical trials and for individual patient investigations.

In an extension of these previous studies, Ishii and colleagues (2) endeavored to evaluate the test-retest reproducibility of alveolar oxygen tension measurements using ^{3}He MRI in 25 subjects including 10 non-smokers and 15 asymptomatic smokers. Reproducibility was measured using intra-class correlation coefficients and a mixed-effect model of P_AO_2. They showed there was no spatial or temporal difference in reproducibility in the non-smokers and the case-matched current smokers. Importantly, they also observed that although the cross-cohort repeatability was not significantly different, the spatial and temporal variability of P_AO_2 in smokers was greater than in non-smokers. Furthermore, a loss of gravity-dependent gradients in P_AO_2 was observed in asymptomatic smokers-similar to previous work in mild-to-moderate COPD using ^{13}N PET (18). In healthy, normal never-smokers, it is well-established that the lung deforms due to gravity and Ishii *et al.* showed clearly that such effects are regionally quantifiable using P_AO_2 mapping. Because the P_AO_2 maps clearly showed abnormalities in otherwise normal smokers, this suggests that such maps can be interrogated to detect early lung structure-function changes in asymptomatic smokers and ex-smokers.

This work showed for the first time that P_AO_2 measurements and maps provide the necessary and sufficient test-retest repeatability in non-smokers and asymptomatic smokers for novel biomarkers of COPD. Given this new information, it is now clear that P_AO_2 map and measurement variability beyond these thresholds may be ascribed, at least at this centre, to physiological changes that have occurred (alterations in gas exchange) as opposed to measurement error due to patient and technological factors. These reliability results should accelerate the more wide-spread use of MRI to develop novel lung disease imaging biomarkers based on P_AO_2.

What is needed next to translate this method beyond imaging centres to respiratory care? Similar to other novel pulmonary imaging methods, patient motion/movement during image acquisition represents a predominant source of error that compounds subsequent image analyses especially when comparing images at multiple time-points. Image processing, including image registration provides a way to compensate for motion, although this may lead to other sources of error. The complex imaging protocol, pulse sequence, multinuclear hardware, and corrections needed to generate estimates of P_AO_2 may also slow or impede clinical translation. The system used to deliver the mixture of hyperpolarized ^{3}He and oxygen requires simultaneous administration in a controlled fashion to eliminate depolarization of the gas prior to inhalation. This may reduce uptake in pediatric studies. Reproducibility of these measurements is also strongly dependent on image quality measured using the signal-to-noise ratio (SNR) which is dependent on many factors including polarization levels, the gas dispensing/delivery system for the patient and inhomogeneous signal acquisition via the thoracic coils used to capture the MRI signal. Finally and perhaps most importantly, there has been little opportunity to validate the regional P_AO_2 measurements generated using MRI. Once validated, widespread translation in clinical research and clinical care trials may help uncover the structural foundations of ventilation/perfusion mismatch.

It is important to note that two decades after its first demonstration, hyperpolarized inhaled gas MRI is still limited to a handful of research centers worldwide. Some of the delay in clinical translation and uptake likely stems from the depleted global supply of ^{3}He gas that has also resulted in significantly increased cost. What is clear is that moving forward, hyperpolarized ^{129}Xe will be the translational target because the gas is naturally abundant and relatively less expensive with complexity and speed of image acquisition similar to ^{3}He MRI. It is also clear that some of the physical properties of ^{129}Xe gas including the gyromagnetic ratio and enrichment result in lower polarization and signal intensity making it more challenging (19) to acquire and measure complex quantitative phenotypes. The solubility of ^{129}Xe in both blood and tissue adds another degree of freedom in the model used to estimate P_AO_2. Not to be confused with the current reproducibility demonstration of inhaled hyperpolarized ^{3}He MRI, oxygen-enhanced measurements that stem from more conventional ^{1}H MRI and inhaled O_2 also provides estimates of the partial pressure of oxygen dissolved in lung tissues (20). This is achieved by comparing T_1-weighted ^{1}H images acquired whilst breathing room air (~21% [O_2]) and pure oxygen (100% [O_2]). This method

could potentially be used to validate or provide additional information that is complementary to oxygen-weighted hyperpolarized inhaled noble gas MRI. For all of these approaches however, what is yet required are streamlined and clinically-acceptable pipelines for both image acquisition and data analysis. Once integrated and accepted into clinical workflows, more widespread translation and use in clinical trials may be undertaken.

Like the small group of contrarians who predicted the credit collapse and betted against the "mortgage" market (1), Ishii and co-workers (2) understand the risks inherent in the assumption that FEV_1 will remain the dominant diagnostic for obstructive lung disease. They have bet on a different approach and invested in the development of oxygen-weighted noble gas MRI to generate P_AO_2 measurements. While this is yet to be translated more widely, the biomarkers provided by MRI have the potential to generate new insights into mechanisms of pulmonary disease pathogenesis as well as the development and delivery of novel treatments. All of this is now urgently required if we are to stem the tidal wave of asthma and COPD costs—both human and financial burdens that are being driven by an evolving demographic, environmental and other factors in the developed and developing world.

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Footnote

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