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The role of hyperpolarized ^{129}xenon in MR imaging of pulmonary function

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ABSTRACT

In the last two decades, functional imaging of the lungs using hyperpolarized noble gases has entered the clinical stage. Both helium (^{3}He) and xenon (^{129}Xe) gas have been thoroughly investigated for their ability to assess both the global and regional patterns of lung ventilation. With advances in polarizer technology and the current transition towards the widely available ^{129}Xe gas, this method is ready for translation to the clinic. Currently, hyperpolarized (HP) noble gas lung MRI is limited to selected academic institutions; yet, the promising results from initial clinical trials have drawn the attention of the pulmonary medicine community. HP ^{129}Xe MRI provides not only 3-dimensional ventilation imaging, but also unique capabilities for probing regional lung physiology. In this review article, we aim to (1) provide a brief overview of current ventilation MR imaging techniques, (2) emphasize the role of HP ^{129}Xe MRI within the array of different imaging strategies, (3) discuss the unique imaging possibilities with HP ^{129}Xe MRI, and (4) propose clinical applications.

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1. Introduction

For more than a century, the assessment of lung function has relied on global measurements derived from spirometry and body plethysmography [1–3]. Despite its limitations, forced expiratory volume in one second (FEV_1) continues to serve as the main intermediate endpoint in numerous longitudinal studies. As a global measure FEV_1 is not sensitive to disease heterogeneity and is non-specific for the underlying cause of airway obstruction. More generally, traditional pulmonary function tests (PFTs) insufficiently characterize regional lung function in the early stages of disease. Subtle alterations of the lung parenchyma are generally poorly detected by conventional PFTs; for example, a local loss of ventilation in a given pulmonary segment is missed by these global methods of assessment. Hence, there is a strong demand for more local measures of lung function capable of depicting regional ventilation patterns that are characteristic of different obstructive and restrictive lung diseases in their early stages [4–6].

Imaging technologies have improved the sensitivity and specificity for the detection of lung diseases but without quantification of these processes there has been limited impact outside of the Radiology Department [7]. Chest computed tomography (CT) is considered the reference standard for lung imaging due to its superior spatial and temporal resolution compared to magnetic resonance imaging and nuclear imaging techniques. However, CT excels primarily for lung morphology but relies on indirect signs in cases of obstructive or restrictive pulmonary disease. Interstitial alterations of the lung parenchyma are less conspicuous on CT and are consequently under-diagnosed. However, these very

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subtle, interstitial alterations are critical to the early diagnosis of potentially reversible changes in the lungs [6]. Consequently, there is a pressing need to move beyond form to function in pulmonary imaging.

Thus far, only nuclear imaging methods such as scintigraphy and single positron emission computed tomography (SPECT) are clinically well-established methods to visualize regional ventilation in the setting of the diagnosis of acute and chronic pulmonary embolism [8] and pre-surgical planning of lung volume reduction surgery (LVRS) in COPD [9]. Although several sites have employed SPECT and positron emission tomography (PET) for research applications [10,11], nuclear imaging methods are limited by low resolution, long exam times, and the use of ionizing radiation.

In the attempt to combine the advantages offered by chest CT with ventilation and perfusion assessment, numerous groups have investigated the use of CT with iodinated contrast [12] or with inhaled xenon gas [13] serving as luminal contrast agents. Of note, xenon gas is radiopaque, providing contrast for CT techniques in ventilation and perfusion imaging. Despite the promising results for lung ventilation and brain perfusion yielded by xenon CT, the radiation dose remains an inherent limitation. The risks of medical radiation induced malignancy increase with the accumulated radiation dose [14], imposing practical limits on the role of CT for time-resolved and longitudinal applications unless major dose reductions are realized. As a result, dose reducing CT reconstruction methods are currently an area of intense research [15]. For the foreseeable future patients requiring longitudinal imaging assessment of chronic conditions (i.e. cystic fibrosis, asthma, COPD and lung transplant patients) with a heterogeneous course of disease would benefit the most from radiation free imaging methods.

In light of the aforementioned considerations, MRI has many favorable attributes. Nonetheless, anatomical and physiological properties of the lung parenchyma and the conducting airways represent extreme challenges for MR imaging [16–18]. First, the proton density of normal lung parenchyma is roughly one fifth that of muscle tissue [17]. Second, the air-tissue interface causes a large magnetic susceptibility difference which leads to short T2* relaxation times on the order of 2 milliseconds making diagnostic MR image acquisition of lung parenchyma particularly challenging [17,18]. A third important limitation is sensitivity to motion during the respiratory and cardiac cycles (the heart and the aorta within the field of view) due to the overall longer acquisition time of pulmonary MRI methods [16]. For these reasons lung parenchymal imaging is the “final frontier” of MRI.

An alternative approach is to exploit the many sources of contrast available in MRI to image lung function. Currently available MR scanners paired with state-of-the-art technologies can minimize the impact of the major confounding factors described above. In particular, the introduction of inhaled hyperpolarized (HP) noble gases – specifically xenon-129 (^{129}Xe) and helium-3 (^{3}He) – enhances the signal in the lung air spaces sufficiently to enable breath-held images of ventilation with MRI. The hyperpolarization process increases the net nuclear magnetization (and therefore the T_1 signal intensity of the gas) by five orders of magnitude above the thermal equilibrium. Additionally, by inflating the lungs with an MR-visible contrast agent the short T2* of the parenchyma is offset by the increased T2* of the gases inside the alveoli, approximately 20 ms [19], thus improving acquisition efficiency and flexibility for HP gas MRI.

Improvements in MRI acquisition speed stemming from fast parallel imaging and constrained image reconstruction methods has enabled shorter breath-hold times [20,21] and even imaging during dynamic breathing maneuvers [22]. These advances have increasingly improved the feasibility of HP gas MRI methods to explore lung function beyond the morphologic picture derived from CT and the limited global lung assessment of PFTs.

The high cost of HP gas technologies has been a challenge for dissemination of this methodology. One major impediment to the rise of this technology has been the limited availability and high cost of ^{3}He [23]. The isotope is produced as a by-product of the decay of tritium that was used in the production of nuclear warheads in the 1960s and ‘70s. Moreover, because ^{3}He is an efficient neutron detector, much of its supply has been directed towards this application since 2001 [16,24]. As supply is scarce, ^{3}He faces sharply rising costs. Driven by these drastic economic factors, the transition towards ^{129}Xe gas (distilled from the atmosphere) has accelerated.

Concurrent to the ^{3}He-^{129}Xe transition, other MRI approaches to lung imaging, such as oxygen enhanced (OE) MRI and perfluorinated (PF) gas MRI have emerged as competitive means to assess for ventilation [25–27]. Each technique has fundamental advantages and inherent limitations [28] with the additional value of OE and PF gases to be determined in larger scale studies. For context, we introduce these techniques, but our primary focus remains on HP ^{129}Xe gas MRI. This focus is further motivated by the timely transition of the field from the comparatively rich history of ^{3}He MRI of ventilation to the emerging body of work using ^{129}Xe MRI that has been enabled by recent technical advances improving polarization levels and rates [29,30].

There are two purposes to this review. In Section 1, we introduce the most common gas agents that are used for MR imaging of lung ventilation and discuss the advantages and limitations of each method. In Section 2, we review several unique clinical research applications of HP ^{129}Xe MRI; we especially emphasize the capability of HP ^{129}Xe for spectroscopic imaging of gas exchange.

2. Gas agents for MRI of lung function

The predominant MRI approaches that have been developed to characterize regional ventilation include oxygen-enhanced, PF gases, and the hyperpolarized noble gases ^{3}He and ^{129}Xe. This list of HP gases continues to expand as MRI with both hyperpolarized ^{83}Kr [31] and propane-d6 [32] were recently demonstrated. Methodology for imaging of lung function using each gas is treated below with some context to provide a basic understanding of relative strengths and weaknesses of the techniques (Table 1).

2.1. Oxygen-enhanced MRI (OE-MRI) [28]

First reports on oxygen as a contrast agent in pulmonary imaging were published in 1996 [33]. Fundamentally, the inhalation of pure oxygen (100% O_2) simultaneously increases the partial pressure of O_2 in the alveoli, the barrier tissues and the pulmonary capillaries. Due to the paramagnetic properties of oxygen, it decreases T1 relaxation times of protons in the barrier and capillaries. Therefore, using T1 weighted imaging can increase the parenchymal signal to a sufficient degree (on the order of 8–10%) to provide contrast in proportion to the concentration of oxygen in these tissues. Of note, the images resulting from oxygen-enhanced MRI do not directly visualize ventilation itself; images represent oxygen dissolved in both tissues and blood, which reflects the physiology of both ventilation and perfusion [28,34]; For example, the OE effect is seen in the pulmonary venous blood as well as the parenchymal tissues due to oxygen dissolved in the blood returning to the heart (See arrow in Fig. 1).

The advantages of OE MRI are the unlimited supply, the low cost of oxygen gas, and its ready implementation on clinical MR scanners without further modifications. Unlike with hyperpolarized gases, no additional hardware is required.

However, the main disadvantage is substantially longer acquisition times. First, the oxygen effect is not instantaneous. After

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