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Functional Imaging of the Lungs with Gas Agents

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Abstract

This review focuses on the state-of-the-art of the three major classes of gas contrast agents used in magnetic resonance imaging (MRI) – hyperpolarized (HP) gas, molecular oxygen, and fluorinated gas – and their application to clinical pulmonary research. During the past several years there has been accelerated development of pulmonary MRI. This has been driven in part by concerns regarding ionizing radiation using multi-detector computed tomography (CT). However, MRI also offers capabilities for fast multi-spectral and functional imaging using gas agents that are not technically feasible with CT. Recent improvements in gradient performance and radial acquisition methods using ultra-short echo time (UTE) have contributed to advances in these functional pulmonary MRI techniques. Relative strengths and weaknesses of the main functional imaging methods and gas agents are compared and applications to measures of ventilation, diffusion, and gas exchange are presented. Functional lung MRI methods using these gas agents are improving our understanding of a wide range of chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis (CF) in both adults and children.

Keywords

pulmonary MRI; hyperpolarized noble gas; ^{3}He MRI; ^{129}Xe MRI; Fluorinated gas MRI; Oxygen-Enhanced MRI; COPD; Cystic fibrosis; Asthma

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Introduction

Pulmonary MRI has conventionally been limited by low signal to noise in the lung parenchyma. This limitation stems from the combined effects of low proton density and high local susceptibility induced by the numerous air tissue interfaces intrinsic to the lung parenchyma that facilitate gas exchange. For conventional proton MRI, the former limits the available number of spins per unit volume while the latter creates local field inhomogeneity that contributes to very short T2* decay times on the order of 1–2 ms.(1) In part because of these challenges, significant research focus has been dedicated to developing methods to enhance contrast in the lungs, particularly in the lung parenchyma. Oxygen-enhanced (OE) and fluorinated gas MRI were introduced in the early 1990's(2,3) for imaging lung function, principally ventilation weighted imaging, but were not widely disseminated. Hyperpolarized (HP) gas MRI, particularly ^{3}He and more recently ^{129}Xe, gases are comparatively more mature having been demonstrated to provide a wider array of functional contrasts inclusive of spin density, diffusion-weighted imaging, and gas exchange each with demonstrated applications to different obstructive and restrictive lung diseases in clinical research (4,5), and yet despite these established roles for HP gas imaging clinical dissemination and impact in the clinic has been limited.

More recently the outlook for pulmonary MRI is improving due largely to the increased performance of gradient systems and constrained reconstruction methods (6–9) that have enabled 3D high spatial resolution (~1 mm) MRI of lung structures with improved contrast and coverage (10–12). The recently developed pre-clinical (13,14) and clinical (15–17) ultra-short echo time (UTE) methods and short repetition time (TR) methods (18,19) are largely robust to motion and demonstrate improved lung signal for both structural and functional lung MR imaging (FLI) applications by mitigating the effects of T2* decay. For HP gases, there has been a resolution in the commercial uncertainty in the availability of polarizer systems (5) improving the outlook for wider dissemination of hyperpolarized ^{129}Xe technologies.

The structure of this review focuses on technical tradeoffs and principal applications of the most common functional lung imaging (FLI) methods using HP gas, fluorinated gas, and OE MRI. First, a rationale for FLI is discussed in the context of current clinical measures of whole lung function. Second, the physical properties of the gas agents are discussed and how these properties influence imaging strategy and types of imaging contrast. Third, specific tradeoffs in terms of cost, availability, and capability are discussed. The final sections review the major clinical research applications explored thus far using each of HP, fluorinated and OE methods respectively.

Lung Function and Imaging

An important potential role for FLI is to provide regional information regarding diseases affecting ventilation and gas exchange. Inexpensive whole lung spirometry and plethesmography measures, commonly referred to as "pulmonary function tests" or PFTs, are derived from respiratory maneuvers designed to measure fixed lung volumes and dynamic air flow curves. However, PFT's have well known limitations in that they measure

average obstruction over the whole lung and reveal only limited information about regional distribution or spatial heterogeneity of obstructive disease. Most common among spirometry measures are forced expiratory volume at 1 second (FEV1) and FEV1 normalized to forced vital capacity (FEV1/FVC) (20). Both FEV1 and FEV1/FVC are reduced in obstructive disease because the large and small airways in the lungs have increased resistance to air flow, limiting both the total volume of air exhaled and the rate of exhaled air flow (20). Plethesmography, using Boyle's Law and a "body box" (20), is used to measure absolute lung volumes include the total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) that are typically increased in obstructive disease due to hyperventilation and air trapping respectively (21). However, PFT's are standardized with commonly agreed upon reference values for different populations, gender, and body size (22,23). This standardization to normative values is an important strength that makes it possible to make general comparisons of disease severity across different populations – this and the low cost of conventional PFTs make them attractive as a means to screen for and monitor disease progression.

Several more refined measures of whole lung function are important but less commonly used. These include the carbon monoxide diffusing capacity (DLCO) method that exploits the high chemical affinity of carbon monoxide (CO) for blood hemoglobin. Specifically DLCO measures the difference between trace amounts of a known inhaled and exhaled concentration of CO. DLCO is affected by reduced alveolar surface area to volume ratio (e.g. emphysema) or by diffusion-block (e.g. fibrotic lung disease) (24) and therefore can be a useful measure for quantifying lung function and severity of chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) respectively. Lung clearance index (LCI) is another whole lung measure that is an emerging standard for improving quantitative assessment of ventilation heterogeneity in obstructive lung diseases such as asthma and the pulmonary complications of cystic fibrosis (CF) (25). The method uses the multiple breath nitrogen wash out method (20) and is considered sensitive to ventilation heterogeneity because the delay in oxygen wash-in reaching non-ventilated units of the lungs prolongs the nitrogen washout time (normally ~7 minutes).

However, the insensitivity of these conventional PFT's to early disease has driven pulmonary clinicians and radiologists to seek measures that are more sensitive to regional and early disease processes. The role for FLI using MRI has therefore continued to grow especially in clinical research of regional disease processes in asthma, CF, and COPD with an eye towards improving treatments. According to the World Health Organization, over 65 million people have moderate to severe COPD world-wide. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally (http://www.who.int/respiratory/copd/burden/en/). Over 235 million people suffer from asthma, and asthma is the most common chronic disease among children (http://www.who.int/respiratory/asthma/en/). CF, while a comparatively rare obstructive lung disease, is also an important pediatric lung disease. There is a prominent role for MRI to reduce ionizing radiation during surveillance and to guide more precise drug therapy in CF especially (http://www.cff.org/research/DrugDevelopmentPipeline). In all 3 major obstructive lung diseases, there is a growing clinical need to improve the precision of therapies tailored to specific airways (26,27), lung regions(28), and/or phenotypes of lung disease.

Multiple methods of FLI using MRI exist with tradeoffs and imaging strategies that are dependent on the properties of the gas used. The most mature of these are the HP gases, ^{3}He and ^{129}Xe, but the new implementations of OE and fluorinated gas methods are reemerging as competitive alternatives thanks to technical advances in scanner hardware and software that enable dynamic imaging of gas wash-in and wash-out. These advances have further improved the traditional advantages of MRI over nuclear medicine such as higher 3D spatial and temporal resolution and non-ionizing radiation.(29) Improved 3D temporal-spatial resolution of pulmonary UTE MRI is now approaching that of computed tomography (CT) (15) while the myriad of tools for assessing lung function exceed those available with CT. (30) These factors coupled with concerns over X-ray radiation dose for longitudinal studies using CT have made MRI especially attractive for pediatric and young adult populations. (31–33)

Gas Properties and Imaging Strategies

The physical properties of the gases, their natural abundance, and method of manufacture require different imaging strategies and cost models. The signal to noise ratio (SNR) and spatial resolution are governed largely by physical parameters such as the degree of polarization, gyromagnetic ratio, free diffusion coefficient, T1, and T2 (Table 1 & Table 2). For HP ^{3}He and ^{129}Xe, the non-recoverable longitudinal polarization of the gas nuclei is approximately 100,000 times greater than thermal equilibrium. This HP state is achieved typically using the spin exchange optical pumping (SEOP) method.(34–36) The effective T1 time for imaging in the lungs is approximately 30 s (Table 2), allowing sufficient time for acquisition within a breath-hold.

Inert ^{19}F gases on the other hand, are not hyperpolarized but are still used for ventilation imaging. Fluorinated gases are an attractive choice because the ^{19}F isotope is 100% naturally abundant, with a high gyromagnetic ratio (Table 1) on the order of that of ^{1}H (37) The T1 relaxation is dominated by spin-rotation interactions (38), T1 ~ T2 (Table 2). Both magnetic resonance decay parameters depend upon the concentration of the gas itself and are generally on the order of a few milliseconds for the ^{19}F nucleus. The most commonly used fluorinated gases are sulfur hexafluoride (SF_6) and hexaflourethane (C_2F_6), but tetraflouromethane (CF_4) and octofluoropropane (C_3F_8) are also under investigation. T1 and T2 values at or near the 1.5 T field strength are less than 6 ms for C_2F_6, and as low as 2 ms for SF_6. C_3F_8 is of particular interest because it possesses two additional fluorine atoms, providing greater spin density(39) and similarly short T1 and T2 (38).

Both HP and fluorinated gases are imaged directly and their T1 properties lend themselves to fast imaging with low flip angle gradient-recalled-echo (GRE), also known as fast-low-angle-shot (FLASH), pulse sequences for 2D multi-slice (40,41) or 3D volumetric (42,43) imaging with Cartesian or radial acquisition trajectories (44). For HP gases, the non-recoverable longitudinal polarization can be excited frequently with low flip angle acquisitions with the consequence that signal decay due to the RF-consumption of the magnetization is known to contribute to signal modulation and filtering of both slice profile and within-slice blurring.(41) RF signal modulation due to a constant flip angle can be offset by precise flip angle modulation (45,46) but is infrequently used in favor of simply using

low flip angles (~2–7°) and centric view ordering (47,48). For fluorinated gases, T1 is short enough (~1–20 ms – Table 1) that fast GRE or FLASH sequences are also signal to noise and time efficient.(49–52) For dynamic imaging applications using both HP and fluorinated gases, fast low flip angle GRE sequences with non-Cartesian readout trajectories that frequently sample the central region of k-space are used. Time-resolved 2D radial (44), spiral (53) or 3D radial spoiled GRE sequences with isotropic resolution (49,54) and constrained reconstruction (54–56) have been used.

The comparatively longer T2 of HP gases vs. the short T1 and T2 of fluorinated gases, make them favorable for SNR efficient balanced steady-state free precession (SSFP) imaging, although optimizing flip angle and T2 raise additional challenges (46). Recent advances combining SSFP imaging with cheaper natural abundance (~26%) HP ^{129}Xe gas has recently shown promise for ventilation-weighted imaging (57). Parallel imaging with HP gases has also been explored (58–61) but widespread implementation has been slowed by hardware costs for multi-channel RF-coils and compatibility with multi-nuclear clinical MRI systems. This is a ripe area for future advances in FLI using both HP and fluorinated gases.

Diffusion weighted imaging (DWI) has been one of the most promising FLI tools to investigate lung microstructure in normal and diseased lungs. The physical diffusion coefficients differ markedly for HP ^{3}He, ^{129}Xe and for fluorinated gases (Table 1), which strongly impacts utility. The greater free diffusion coefficients and polarization of HP ^{3}He and ^{129}Xe gases enable rapid measurement of multiple b-values using existing clinical gradient systems (62,63) using fast GRE pulse sequences with bi-polar diffusion weighting gradients. The separation, Δ, between these short bipolar gradient pulses determines the diffusion weighting as well as the dependence of the diffusion measures on the scale of restricted diffusion displacement. For helium the average displacement of helium atoms using Δ=1–2 ms is the same order of magnitude as alveolar diameters (a few hundred micrometers). This so-called “short range ADC” measure is the one most widely used in patient studies (64). Additional b-value weightings can be acquired using HP ^{3}He to enable more precise modeling of restricted diffusion either using q-space (55,65) or model-based techniques (66).

DWI for denser HP ^{129}Xe (5), and fluorinated gases (67–69) is possible, but their lower free diffusivity and short T2* make high gradient performance to increase b-value, reduce TE, and preserve sufficient SNR particularly important making multi-b-value DWI challenging. Advances in radial FID acquisitions may help meet these challenges and are typically used in DWI of fluorinated gases, as the short TE and TR help to exploit the short T1 recovery times while mitigating T2* decay.

Another important physical distinction is gas solubility in tissues and blood. Both HP ^{129}Xe and molecular O_2 are relatively soluble in blood and tissues compared to HP ^{3}He and fluorinated gases (Table 1). Therefore, ^{129}Xe and O_2 diffuse from the gas phase into the tissues and blood where they reflect useful properties of the local spin environment. Image contrast for both of these gases represents a combination of ventilation, tissue density, blood volume, and perfusion. In the specific case of HP ^{129}Xe, the 200 ppm chemical shift

associated with the dissolved phase (Fig. 1) can be imaged directly (10,70,71) or indirectly (72,73) to enable quantitative modeling of gas exchange.

Unlike HP ^{129}Xe, the OE effect is based on the concentration-dependent paramagnetic effect of dissolved molecular oxygen on the rate of T1 recovery of protons (2,74). Note that this is not the diamagnetic effect of hemoglobin-bound oxygen that results in the T2*-effect commonly associated with BOLD MRI (75,76). FLASH or GRE sequences can be used to perform rapid T1 mapping at multiple O_2 concentrations to derive the Oxygen Transfer Function (OTF) measure (77–79). More typically, OE-MRI methods have favored inversion-recovery (IR) pulse sequences in combination with single-shot fast spin-echo (SSFSE), to exploit the ~30 ms T2 of protons in the lungs (Table 2) compared to the much lower T2*. For IR-SSFSE in this application, the TI is typically set to the null point of the lungs in the air-breathing image (2,80,81) or to maximize the contrast between the T1 recovery curves (82–86). Centric view ordering reduces the effects of T2 decay and provides better contrast in the OE image. Using this approach, the image of a single 2D slice can be acquired in a fraction of a second, but the low contrast of OE MRI requires signal averaging on the order of 10+ minutes for a complete OE scan. Prospective respiratory gating to end-expiration and retrospective deformable image registration combined with interleaved 2D slices, parallel imaging and half-Fourier reconstruction have enabled multi-slice 2D OE-MRI using IR-SSFSE in 8–13 minute total scan times (85).

The emergence of UTE MRI with clinical hardware systems has advanced both structural and functional imaging of the lungs with varied impact thus far on FLI using all three gas agents. For OE-MRI, T1 weighting can now be achieved without IR using 3D radial UTE (11,14,15). Radial acquisitions in FLI more generally are inherently robust against cardiac motion artifact due to the large number of signal averages at the center of k-space per unit time. UTE combined with radial trajectories has recently contributed to important advances in fluorinated gas MRI by improving image quality, coverage and reducing scan time (3,87,88), and to HP gas MRI for spectroscopic imaging of the dissolved phases of HP ^{129}Xe in the tissue and blood compartments (10,70,71).

Tradeoffs in Cost and Access

A well-known disadvantage of HP ^{129}Xe and ^{3}He is their dependence on polarizer and multinuclear technology that is not widely available (4). The global quantities of ^{3}He are also very limited, leading to high cost (89) (Table 3). This fact has necessitated migration to the more widely available ^{129}Xe nucleus (90). The technical challenges of this migration have been made easier by advances in ^{129}Xe SEOP polarization (91,92). Most typically, HP ^{129}Xe MRI uses enriched ^{129}Xe isotope from the natural abundance of 26% to ~85% to compensate for lower gyromagnetic ratio and achievable polarization compared to ^{3}He gas. All the major types of contrast-weighting demonstrated for ^{3}He MRI have now been replicated robustly with enriched HP ^{129}Xe (5,93).

High SNR, the availability of different functional contrasts, and ease of use in terms of gas delivery and image acquisition are important advantages of HP gas MRI (Table 3). The HP gases are most commonly delivered as an anoxic gas mixture to the subject followed by a 6–

15 s breath-hold, although it is possible to mix with O_2 at the mouth to make a normoxic dose (94). The repeatability and utility of quantitative measures of ventilation defect percentage (VDP) is high (Fig. 2), but depend on normalization of the ventilation-weighted images by the total lung volume (TLV) typically acquired from a proton image of the lungs during a second breath-hold. Misregistration can occur between breath-holds adding systematic error to the ventilation defect measurement. Recently, acquiring both HP gas and proton images of the TLV in spatial registration within the same breath-hold was demonstrated (95). Extensive experience with HP ^{3}He MRI and now ^{129}Xe has shown that repeated inhalation of these gases is safe. (93,96–98) The anesthetic effects of xenon are not a concern in adult subjects (98) but remain to be studied in pediatric lung disease. Since ^{3}He gas has been safely used in a wide range of pediatric studies (99–101), it will likely remain an important gas during the translation of ^{129}Xe to pediatric lung disease. (100) Additionally, improved polarization methods for ^{129}Xe (92,102) may eventually make the use of natural abundance HP ^{129}Xe MRI feasible (57), significantly reducing cost (Table 3). There are now two companies developing commercial HP ^{129}Xe polarizers and technology for lung imaging applications – Xemed LLC (http://www.xemed.com/) and Polarean (http://www.polarean.com/). In addition, an open source ^{129}Xe polarizer system that can be manufactured locally using 3D printing technology was introduced recently (102,103).

Despite the advantages and more positive outlook for HP ^{129}Xe gas, fluorinated and oxygen gases are inexpensive by comparison. Oxygen is already widely available in the clinical environment, including most MRI suites, requiring no specialized hardware modifications to clinical scanners. Both low cost and accessibility support the high potential of OE-MRI for widespread dissemination (Table 3). Fluorinated gases fall somewhere between HP gases and oxygen on the scale of cost and technical complexity. The gases themselves are relatively inexpensive, but dedicated multi-nuclear transmit and receive RF coils are required. Fluorinated gases compare favorably to HP gases in that scan times can be relatively short (12–15s), but the method requires respiratory-controlled breathing to enable multiple breath wash-in to reach a normoxic steady-state breath-hold with sufficient SNR (104).

OE-MRI would likely be the clear winner if limitations of lower SNR could be robustly overcome within a clinically feasible workflow. However, the advantages of cost and accessibility are offset by the more complex gas delivery and longer acquisition time. Proton spins in the vicinity of dissolved oxygen have a modest T1 difference of 8–15% (2,77,82,86) and as for fluorinated gases, the OE effect is not instantaneous, requiring a physiological wash-in and wash-out with time constant ranging from as long as 45–50 s (79,105) to as low as 17–30 s. (74,106,107). It is therefore necessary to signal average over multiple breaths. Respiratory and cardiac motion must be addressed either prospectively or retrospectively. Usually, a dual acquisition is performed: one during inhalation of 21% O_2 (normal atmospheric oxygen concentration) and the other during inhalation of 100% O_2 (Fig. 3). Most researchers allow 1–2 minutes between changes in fractions of inhaled O_2 to avoid transient effects. Well-ventilated regions of the lung show an oxygen-dependent signal enhancement; typically, a map of this signal enhancement is provided in units of percent signal enhancement. Both respiratory (108) and cardiac triggering have been implemented successfully for 2D OE-MRI (85,109). Typically non-rebreather facemasks are used with a

constant flow of oxygen at 15 L/min (110,111). Even with the use of respiratory gating or triggering, lung volume can vary with changes in the fraction of inhaled O_2 (112). Since most complete OE-MRI datasets take ten or more minutes to acquire, this fact combined with bulk patient motion can cause misregistration between the two sets of images. Initially, many researchers performed signal averaging by taking advantage of the large number of acquired images to blur the misregistration, particularly near the diaphragm.(77,80,113) Since then, Mai et al. demonstrated an improved correlation between the fraction of inhaled O_2 input function and the OE-MRI signal by using only the images with minimal divergence in diaphragm position.(84) The majority of researchers have implemented this approach prior to signal averaging – in effect implementing a combination of both prospective and retrospective respiratory gating (2,82,106,109,114,115). More recently, diffeomorphic registration (116,117) has been applied to 3D isotropic OE MRI (11).

Applications

Hyperpolarized Gases

The MR physics of imaging with polarized gases have been extensively treated elsewhere (5,34–36,41,92,100,118–126), so we here focus on contrast mechanisms and their applications in clinical research.

Images of Ventilation—Spin density images during breath-hold represent a snapshot of gas distribution. The resulting “ventilation defects” (Fig. 2) are influenced by regional airway obstruction and air trapping. (127,128) The ventilation defect volume (127,129,130), ventilated volume (129,131), and coefficient of variation (132,133) derived from these images have all proven useful for demonstrating regional heterogeneity of ventilation in a wide range of obstructive lung diseases. Measures of ventilation defects are also sensitive to subclinical decline in function due to aging in healthy never-smokers (128,133) as well as smokers. (134–136) One semi-automated measure that is emerging as a biomarker is the ventilation defect percentage (VDP), defined as the defected lung volume normalized by the TLV. (137–140) Multiple groups have demonstrated repeatability (130,139,141,142) and validity of this measure compared to pulmonary function testing (130,133,143–145) and severity of disease. (133,143,145) It should be noted that larger values for VDP are observed with ^{129}Xe MRI than with ^{3}He MRI in the same individual. (146) This bias is likely attributable to the difference in gas densities (Table 1) although this remains a matter for speculation and further research. (147)

Diffusion Weighted Imaging (DWI)—DWI exploits the high free diffusion of ^{3}He and ^{129}Xe gases. In the context of restriction by the lung micro-structure, this allows indirect measurement of the average dimensions of the lung airspaces. When ^{3}He or ^{129}Xe gas is restricted by tissue boundaries, the diffusivity is referred to as the apparent diffusion coefficient (ADC). A semi-quantitative ADC map (Fig. 4) – a surrogate for airspace size – is easily derived. Regional ADC changes have been observed in response to increases in lung volume (148,149), gravity dependence (148,150,151), age (152), and etiology of emphysema, i.e. COPD or alph1-antitrypsin.(122,131,150,153) Values for ^{3}He ADC in the lungs range from 0.66 cm^2/s for an elderly COPD patient (FEV_1 26% predicted) to as low as

0.16 cm^2/s for a young nonsmoker. For reference, the free diffusion coefficient of pure ^3He is 2.05 cm^2/s and ~0.8 cm^2/s in air mixture.(154) Values for ^{129}Xe ADC, by comparison, are lower than ^3He ADC by an order of magnitude, due to the higher density of ^{129}Xe gas (Table 1). For example, the ^{129}Xe ADC is 0.021 cm^2/s for a young non-smoker, compared with 0.16 cm^2/s for ^3He ADC. Despite the differences in the magnitude of the measured ADC using ^3He and ^{129}Xe, the ^{129}Xe ADC in human subjects is strongly associated with increased COPD severity and correlates well with ^3He ADC reported in previous studies. (93,147,151)

An important limitation of ADC is that it represents a *relative* measure of structural dimension that is *proportional* to the average alveolar and acinar dimensions. Its absolute value depends on specific scan parameters, such as the time delay and degree of diffusion weighting. A more quantitative measure of acinar dimensions would be very useful in answering several important physiologic questions regarding lung development (65,99), alveolarization (155) and alveolar recruitment (156). Lung models of restricted diffusion that allow calculation of measureable histological features such as mean length and surface area to volume are in development (55,65,157–159) and have been reviewed previously (66). More refined models that account for terminal airway branching (159,160) have stimulated healthy debate (161,162) and have challenged the field to develop more rigorous quantitative methods. (163,164)

pO_2 Mapping—The paramagnetic effects of oxygen reduce the T1 and T2 of HP gases (as well as proton signals) (2) and can therefore be exploited to provide a quantitative estimate of regional pO_2.(47,165,166) Typically, the same slice is imaged repeatedly at different delay times following gas inhalation to separate radio frequency (RF) saturation of signal from signal loss due to local O_2 concentration.(167) The measurement is performed within a single breath-hold.(47,168) Modified centric and reverse-centric view orders mitigate effects due to locally variable flip angle (B1-field variation).(168) Gas flow effects within the lungs during a breath-hold using ^3He have recently been described, underscoring that pO_2 is a mixture of regional pO_2 and local collateral ventilation effects.(169) Regional pO_2 measures can potentially be used to calculate the ratio of ventilation to perfusion (V/Q).(167) In fact, pO2 measurements have recently been used as a marker of disease severity in a study of V/Q heterogeneity in smokers.(170,171)

^{129}Xe MRI of Gas Exchange—The soluble “dissolved phase” fraction of ^{129}Xe in blood and tissues is approximately 2% of the total signal after accounting for the lower density of lung tissue and blood. The dissolved phase of ^{129}Xe has a different chemical shift frequency than the gas phase. This fact can be exploited to quantify gas exchange. Polarized gas nuclei diffuse rapidly between gas, blood cells, and plasma/tissue compartments, with different chemical shifts in each compartment – 0 parts per million (ppm), 222 ppm, and 198 ppm, respectively (Fig. 1).(172) Compartmental modeling of these components has advanced relatively rapidly.(173) Simple and robust single voxel MR spectroscopy readily resolves tissue and blood fractions and enables the calculation of blood/tissue ratio as a possible biomarker of “diffusion block.”(174,175) More quantitative measures such as “saturation transfer time” allow the kinetics of ^{129}Xe recovery to be modeled. These more advanced

methods can provide direct (10,70,71,176) or indirect (72,73) estimates of average septal wall thickness and alveolar surface area to volume ratio (72,173,177). Both single-voxel (177,178) and spectroscopic imaging methods (10,71) are feasible.

Clinical Research—The vast majority of clinical research studies using HP gas MRI have been performed in asthma (127,132,139,143,144,179,180) and COPD (133,153,181), with a growing number of recent studies focusing on CF in children and adults.(142,182,183) Perhaps the greatest advantage of pulmonary MRI is for characterizing, or "phenotyping," disease progression and severity. The ADC has found particular utility in studies of COPD that have shown that ADC correlates with pulmonary function (153,184,185), is highly reproducible (148), and is sensitive to subclinical disease (134–136,186) and disease progression.(150,181) A multi-institutional prospective study of COPD in 122 subjects found that ADC was more predictive of COPD severity and more highly correlated to DLCO than quantitative CT.(131) In a separate 2-year longitudinal study of subjects with mild to moderate COPD, both ADC and VDP increased in the absence of significant change in FEV1, suggesting progression detected by imaging but not conventional methods. (181) In mild to moderate COPD, the VDP in particular is associated with severe outcomes such as hospitalizations for exacerbations – an association that is not observed using conventional measures, including CT.(145) This work suggests the potential use of HP gas MRI to identify patients most likely to have severe outcomes at an earlier stage of disease progression. This, in turn, could allow more aggressive treatment to be targeted at these higher-risk individuals – an example of HP gas MRI providing the means to personalized medicine.(187)

In asthma, regional ventilation heterogeneity revealed by HP ^{3}He MRI has changed the way in which clinicians and researchers view this disease. Relatively large cross-sectional and longitudinal studies (141,143,188) have revealed that up to half of ventilation defects persist in the same locations over time intervals of several days to a year.(188) The persistence of ventilation defects in these studies was independent of asthma severity and medication use, suggesting that persistent defects were refractory to therapy. Because defects are observed even in asymptomatic patients and involve both the central and peripheral airways, conventional assumptions that asthma is a predominantly small airways disease have been challenged.(189–191) VDP and ADC-related measures are also associated with both differences in lung microstructure in asthma compared with controls (192) and also with asthma risk factors in adults (193,194) and children.(101,190)

Other important emerging applications using HP gas MRI include image-guided therapy, characterization of gas exchange, and combined structure-function MRI. Image guided interventions using HP ^{3}He MRI show promise for evaluating the effects of stent placement in COPD (28,195,196), smooth muscle ablation treatments in asthma (27,197) and radiation treatment planning in lung cancer.(198–203) There will be a growing role for HP gas MRI in assessing the response to therapy and progression of disease in CF.(100,142,182,183) Moreover, gas exchange imaging with ^{129}Xe MRI shows promise for detection of gas diffusion block in idiopathic pulmonary fibrosis (IPF), a disease that is presently untreatable and for which conventional diagnostic imaging methods such as CT are insensitive.(175)

However, with promising drug trials currently in progress early detection and prognosis may be sensitively detected with HP ^{129}Xe MRI.

Fluorinated Gases

Images of Ventilation—The first use of fluorinated gas for lung ventilation MRI in vivo was in 1984 by Rinck et al. (204) in a dog study. However, the technique was not widely adopted in research settings until the late 1990s. In 1998, Kuethe et al. (3) demonstrated an early proof of principle experiment in a rat model using a 3D radial acquisition with C_2F_6. Image acquisition times were in excess of 4 h to achieve SNR of 8, but the 3D images were of good quality. In a reproducibility and validation pig study, Scholz et al. (50) compared ventilation imaging with SF_6 with respiratory gas analysis by measuring the fluorine content of exhaled gas simultaneously. The reproducibility of both techniques was strong, with a standard error across 24 breaths of 8% for imaging and 5% for respiratory gas analysis. In addition, the expected correlation between the two techniques was very high ($R = 0.99$).

In the late 1990s and early 2000s, several groups (39,205,206) demonstrated that the paramagnetic effect of oxygen on the T1 relaxation time of fluorinated gas made it possible to extrapolate the regional pO_2 using ^{19}F MRI. This work demonstrated the potential of regional assessment of lung physiology; a gravitational dependence of pO_2 opposite to that expected was observed (39,207), with the ventral regions of the supine anaesthetized pig exhibiting higher pO_2 compared to the dorsal regions.

In 2013 Carrero-Gonzalez et al. (67) compared ADC values between 5 healthy normal rats and 6 rats that had undergone elastase treatment in one lung as a model of emphysema. ADC values in the control rats did not differ between right and left lungs. However, in the treated rats, ADC values were significantly higher in the elastase-treated lung compared to the normal lung. The ADC of the untreated lung did not differ from the control rats. In addition, elastase-treated lungs were more heterogeneous than normal lungs.

More recently, advanced MR acquisition schemes have enabled full 3D ventilation imaging in healthy human subjects. By implementing a 3D radial UTE FID sequence, Couch et al. (87) were able to perform full 3D volumetric ventilation imaging in a 15 second breath-hold of C_3F_8. Image quality was quite good (Fig. 5), and a relatively homogeneous distribution of ventilation was observed. Importantly, SNR increased by nearly a factor of 2 when ^{19}F gas was allowed to wash into the lungs prior to imaging by breathing a mixture of O_2 and C_3F_8. This observation opened up the possibility of using the technique to assess fractional ventilation (defined as the ratio of fresh gas entering a volume “region” of the lung to the total end-inspiratory volume of the region (208)) by imaging dynamically.

The short T1 recovery time of fluorinated gases combined with the use of equilibrium phase polarization allows repeated acquisitions over short temporal windows. Therefore, fluorinated gases are well suited for dynamic imaging of ventilation. The first feasibility study of dynamic fluorinated gas MRI was done in a pig model by Schreiber et al.(51) They measured SF_6 wash-out time constants and demonstrated an inverse correlation between wash-out time and tidal volume. In a follow-up study, Wolf et al. (52) demonstrated the feasibility of dynamic C_2F_6 MRI, also in a pig model. Though a direct comparison to SF_6

was beyond the scope of the work, high quality dynamic images were demonstrated with a 2s temporal resolution. In a rat study comparing SF_6 and C_3F_8 for the purpose of mapping regional fractional ventilation, Ouriadov et al. (209) showed that while SF_6 baseline images had superior SNR, both gases yielded similar values for fractional ventilation. Moreover, a gravitational dependence of fractional ventilation was observed, in good agreement with previous results using nuclear imaging, HP gas MRI, and oxygen-enhanced (OE) MRI. (115,144,210,211)

Diffusion Weighted Imaging (DWI)—To mitigate the rapid T2 and T2* decay, radial FID sequences with short TE are most commonly employed for DWI with ^{19}F. The first example of this was a 2005 study, in which Perez-Sanchez et al. (69) measured an average ADC of SF_6 in a pool of five rats as $2.22 * 10^{-6}$ m/s^2. In another study (68) the same group measured the impact of the relative concentration, or partial pressure, of SF_6 mixed with respiratory gases and demonstrated variations in the free diffusivity of the gas mixture. The expected anisotropy of diffusion was in agreement with previous studies.(154,212) Interestingly, ADC measured at FRC was not significantly different from the ADC measured at TLC. This result differed from previous ^3He results that showed that ADC increased with lung inflation volume.(213)

Carrero-Gonzalez et al. (67) suggest that C_2F_6 is superior to SF_6 for DWI because the longer relaxation times of C_2F_6 (Table 2) allow the estimation of ADC using lower b-values and thus shorter TE and higher SNR. In addition, limitations on the measureable diffusion time imposed by the finite diffusion gradients and the shorter T2 of SF_6 approach the unrestricted diffusion regime in the lungs, and may not fully probe the lung microstructure. Despite these challenges, Chang (38) and Couch (214) have recently published findings that suggest that DWI with ^{19}F may be feasible in healthy human subjects.

V/Q Mapping—Since fluorinated gases do not cross the alveolar wall to enter the blood, they cannot be used directly to measure gas exchange. For spin density imaging an approximately normoxic mixture of 80% flourinated gas / 20% O_2 is typically used to maximize the number of fluorine spins per unit volume, albeit with an overall higher density than air. However, in pre-clinical studies Kuethe et al. (88) presented an indirect method of estimating gas exchange with fluorinated gases. Regional pO_2 variations indirectly affect partial pressure of SF_6 because O_2 is taken up differentially in lung tissues and blood due to regional variations in ventilation (V) and perfusion (Q). Thus, steady-state images of fluorinated gas will show higher spin density in regions of high perfusion where oxygen is being rapidly removed and lower spin density in regions of reduced perfusion where higher pO_2 exists. Kuethe et al recognized that this effect is enhanced while breathing a hyperoxic gas mixture of fluorinated gas, e.g. 30% SF_6 / 70% O_2, compared to a normoxic mixture, e.g. 80% SF_6 / 20% O_2. Since the normoxic mixture is comparatively insensitive to V/Q, it can be used to normalize the hyperoxic image to remove physical variations related to the image acquisition, like B_1-field and coil sensitivity differences. Therefore, a ratio of the hyperoxic image, that is V/Q sensitive, to the normoxic image is proportional to regional V/Q (Fig. 6). This approach was refined by Adolphi et al (215) to obtain the V/Q estimate using the positive linear relationship between SF_6 partial pressure and local T1 with a Look-

Locker sequence. T1 images were acquired with the hyperoxic mixture, 30% SF_6 / 70% O_2, alone. This method combines the tendency of SF_6 to gather in regions of poor V/Q matching with quantitative T1 mapping that varies directly with SF_6 partial pressure and does not require a normoxic reference scan. Good agreement was shown between this T1-mapping method and the original Kuethe technique.(88)

Clinical Research—Overall ^{19}F MRI is less well developed than HP gas MRI, likely due to the challenges with respect to development of gas delivery systems and SNR. Nonetheless, as the costs and access to HP gases have become increasingly challenging, there has been a revitalization of clinical research in this area. Compared to DWI using HP gas MRI methods that have been used successfully to demonstrate microstructural differences in subclinical and clinical obstructive lung disease, studies of DWI with fluorinated gases have been limited thusfar to ex vivo studies. In a study comparing ^{3}He MRI and ^{19}F MRI techniques, Conradi et al. (38) demonstrated an increased mean ADC of C_3F_8 in 8 excised emphysematous human lungs compared to 2 excised normal donor lungs. In another study comparing healthy and emphysematous explanted lungs, Jacob et al. (216) also demonstrate a higher ADC of C_2F_6 in the emphysematous lungs (0.018 cm/s^2 vs 0.031 cm/s^2).

Preliminary studies of ventilation in human subjects by Halaweish et al. (49) were performed in a range of patients with obstructive lung diseases. 28 subjects were imaged (11 normal, 2 asthma, 7 COPD, 3 transplant, 1 COPD/transplant, 4 emphysema) using 2D FLASH MRI with C_3F_8 to evaluate the suitability of ^{19}F breath-hold MRI for characterization of disease. Normal subjects demonstrated the expected homogeneous distribution of ^{19}F gas, while diseased subjects showed heterogeneity patterns that varied based on disease. As expected from previous studies with HP gas MRI, COPD subjects demonstrated ventilation defects that worsened with increasing disease severity. Asthmatic subjects did not present with ventilation defects, but the distribution of ^{19}F signal was significantly more heterogeneous than in healthy normal subjects. In a bronchiolitis obliterans subject with sibling donor transplant, it was possible to clearly differentiate the well-ventilated and homogeneous distribution of the healthy transplanted lung from the diseased lung, which demonstrated marked heterogeneity and ^{19}F ventilation defects (Fig. 7).

Ultimately, the promise of fluorinated gases are related to their relatively low cost, the avoidance of complex hyperpolarization hardware, the ability to image during steady state breathing, a resonance frequency very close to proton resonant frequency, and a relatively high SNR (albeit lower than with HP gases). The very short T1 of ^{19}F compounds allows dynamic imaging that can be used to provide more quantitative ventilation measures including estimates of V/Q. The confirmation of heterogeneity and ventilation defects in disease, DWI anisotropy, and gravitational dependences previously seen with HP gas MRI makes ^{19}F MRI a promising approach with potential for clinical translation. The image quality of ^{19}F approaches is lower than HP gas MRI, although it continues to improve and may prove an attractive alternative to HP gas MRI.

Oxygen Enhanced

Steady-State Imaging—The first breath-held OE-MRI images were described by Edelman et al (2), acquired with an IR-SSFSE sequence. Oxygen-enhanced signal is observable in the regions corresponding to healthy lung (Fig. 8), while regions corresponding to bullous emphysema have a markedly lower signal enhancement. In an animal model, Chen et al (114) demonstrated ventilation-perfusion matching of abnormalities comparing OE-MRI to contrast-enhanced perfusion MRI by occluding a secondary bronchus using a balloon catheter. Dietrich et al (85) demonstrated an effective multi-slice OE-MRI acquisition in healthy human subjects through the use of interleaved slices, dual respiratory and cardiac gating, and parallel imaging. In 2014, Kruger et al (11) demonstrated the feasibility of 3D isotropic OE-MRI using a 3D radial UTE sequence in healthy human subjects (Fig. 9).

Dynamic Imaging—The first publication that reported wash-in and wash-out decay constants by using dynamic OE MRI was by Hatabu et al.(81) Subjects were scanned using an IR-SSFSE sequence. Acquisition was respiratory gated to end-expiration and an image was acquired every 3 seconds as the FiO_2 was varied. Dynamic 2D OE MRI images were acquired by averaging of SSFSE images over a moving temporal averaging window and calculating PSE relative to baseline. Dynamic signal in an ROI was fit to an exponential curve to calculate decay constants of ~20–25 s for O_2 wash-in and wash-out. Successive works by Ohno et al. (107,217) with dynamic OE MRI found a correlation of PSE with diffusing capacity $\%DL_{CO}$. In addition, the oxygen wash-in time was shown to correlate inversely with $\%DL_{CO}$ and FEV_1. Sa et al (115) and Tedjasaputra et al (218) used a similar technique for a voxelwise computation of specific ventilation (SV) (219) using OE MRI, and showed the well known gravitational dependence (207,220) in SV using this method. Dynamic acquisition of T1 maps during oxygen wash-in and wash-out to obtain regional time constants of R1 (=1/T1) has also been explored as a quantitative marker of lung function (79).

Clinical Research—Ohno et al. (81) showed in a 2001 study that mean PSE in 10 cancer subjects was lower than that in 7 healthy normal subjects, while the combination of cancer and emphysema in 8 subjects resulted in an even lower PSE. In an effort to segment localized ventilation defects, Nakagawa et al. (221) in 2001 compared OE MRI and contrast-enhanced perfusion MRI in 9 cancer and 6 pulmonary embolism (PE) subjects. The typical ventilation-perfusion mismatch expected in PE was observed. No ventilation defects were found in either case, even in the regions of clear perfusion defect shown on perfusion MRI. In a 2005 study of 30 cancer subjects, Ohno et al. (222) demonstrated that OE-MRI was equal or superior to CT and nuclear scintigraphy in predicting post-surgical lung function as measured by FEV1.

In 2004, Jakob et al. (78) measured the OTF directly in a pool of 5 normal and 5 CF subjects by repeating T1 measurements at various FiO_2 using an IR-FLASH sequence. In normal subjects they found a homogeneous distribution of T1 under normoxic conditions, and a homogeneous decrease in T1 under hyperoxic conditions. However, CF subjects showed an inhomogeneous distribution of T1 under normoxic conditions. Under hyperoxic conditions

the diseased lung regions (as measured with perfusion MRI) had a smaller OE-related decrease in T1 than the more normal lung regions. In 2014, Kruger et al. (223) demonstrated significant correlation between ventilation defects in CF as measured with 3D radial UTE OE MRI and HP ^{3}He MRI (Fig. 10).

Ohno et al. have found that PSE on OE MRI is lower and more heterogeneous in emphysema subjects compared to healthy normal subjects. (217,224) In addition, a later trial comparing PSE as measured with OE MRI to functional lung volume (FLV) as measured with CT (225) in a pool of 160 smokers showed that OE MRI yielded a superior correlation coefficient to pulmonary function tests. Furthermore, PSE as measured with OE MRI correlated with disease severity classifications for emphysema.

Using dynamic OE MRI, the oxygen wash-in slope was found to inversely correlate with $\%DL_{CO}$ in smoking-related COPD (107) and IPF.(83) In a small study of mild/moderate and severe asthma, reduced oxygen wash-in time constant and mean peak enhancement were associated with greater severity.(32) In addition, in studies of lung volume reduction surgery candidates (226) and asthma patients (227,228), OE MRI showed equal or superior performance in detecting treatment effect and disease severity compared with PFT, CT, and/or nuclear medicine study. More recently the OTF was shown to decrease in asthmatics after allergen challenge and correlated with the percentage of eosinophils in bronchoalveolar lavage at the site of challenge.(229)

The ready availability of oxygen and the freedom from dedicated multinuclear imaging hardware make OE MRI a promising research tool with high potential for clinical translation. The technique has shown strong correlations with other reference standards for pulmonary function such as PFT, CT, DLCO, scintigraphy, and HP ^{3}He MRI. Before OE MRI will be able to move into routine clinical use, however, further work with respect to quantitative analysis and reproducibility of the various OE MRI metrics is needed.

Discussion

As shown in Table 3, the current and emerging pulmonary functional MRI methods each have significant strengths and challenges. Of the functional imaging techniques reviewed here, HP gases are more mature in their development, and therefore are better positioned for short-term clinical success. However, limited cost and access to HP gases has led directly to the recent efforts to advance fluorinated and oxygen-enhanced MRI, which could change the cost-benefit tradeoffs currently slowing dissemination of FLI methods to the clinic.

Pulmonary MRI approaches have important advantages over established clinical methods such as pulmonary function testing and scintigraphy that could change the current cost-benefit calculus. Pulmonary function testing cannot easily characterize different phenotypes of disease. Furthermore, pulmonary function testing is a global assessment of the lungs and is generally insensitive to clinically important changes in disease severity that might impact patient management, especially as more therapy options become available and more mild disease is targeted. The spatial resolution of scintigraphy is generally poorer than that achievable with MRI and scintigraphy requires ionizing radiation. The use of X-ray based

methods, including CT, diminish the numbers and types of imaging sessions that are practical for longitudinal assessment of lung disease due to the potentially harmful effects of accumulated ionizing radiation exposure in patients with chronic lung disease. The continued development of ultra-low dose CT (230) may impact this assessment, but it should also be noted that newer FLI methods using x-ray CT – for example, perfusion (231) and dual energy xenon CT (232) – require more radiation than standard chest CT. Furthermore, recent advances in gradient performance and image reconstruction have significantly improved image quality for structural MRI of the lungs. This has led to advances in combined structure-function assessment of disease severity and therapy response in CF only possible with pulmonary MRI (233).

There remain significant challenges to translating FLI methods to the clinic. Unlike many organ systems where early or sensitive diagnosis has led to earlier and efficacious treatments, this virtuous cycle is only now emerging for many respiratory diseases. Nonetheless, respiratory diseases still have significant unmet needs in terms of pharmaceutical development, minimally invasive interventions, longitudinal follow-up, and prognosis. Disorders such as asthma and COPD are widespread and will continue to be a leading cause of death and disease as the world becomes more industrialized and polluted. The gas agents reviewed here underscore the unique ability of pulmonary MRI to measure the functional consequences of obstructive lung diseases. Moreover, continued dissemination and advances in UTE MRI further support an emerging clinical role for combined structure-function imaging. Complementary approaches that use the gas and technique best suited to the available hardware capabilities of a given site may become feasible as the field and clinical research community matures.

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Glossary

ADC	Apparent Diffusion Coefficient
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease

DWI	Diffusion Weighted Imaging
DLCO	Carbon Monoxide Diffusivity in the Lungs
FEV1	Forced Expiratory Volume in 1 Second
FLI	Functional Lung Imaging
FVC	Forced Vital Capacity
FRC	Functional Residual Capacity
HP	Hyperpolarized
LCI	Lung Clearance Index
RV	Residual Volume
TLC	Total Lung Capacity
TLV	Total Lung Volume

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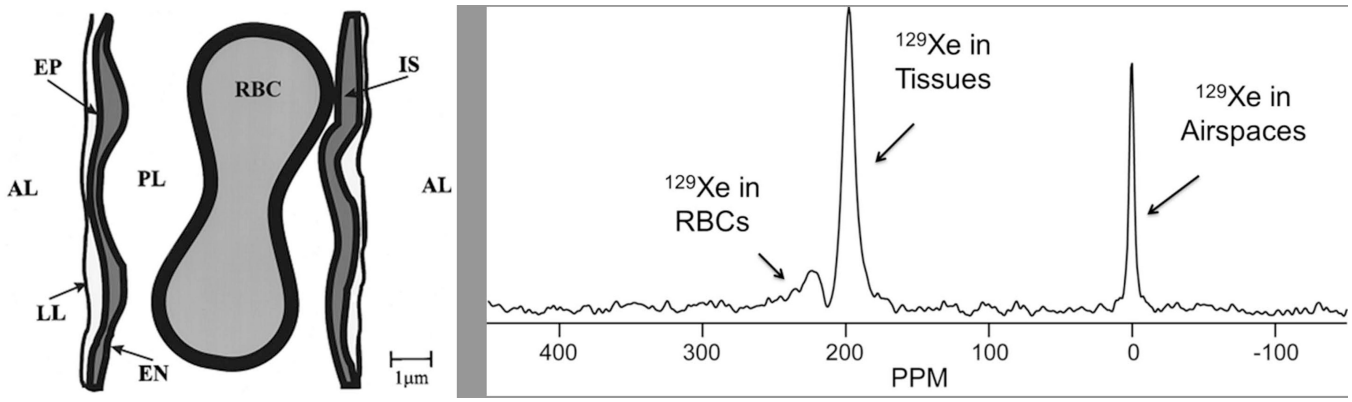

Figure 1.

(a) Schematic of the tissue-capillary boundary. Gas phase is contained within the alveoli (AL). Septal wall comprises the liquid lining (LL), tissue epithelium (EP), interstitial space (IS), and tissue endothelium (EN). Blood volume comprises the PL = blood plasma, and RBC = red blood cells (Adapted from (72)). (b) ^{129}Xe MR spectrum from the human lung with peaks corresponding to the gas, plasma-tissue, and red blood cell (RBC) compartments. Note that the spectral peak for the ^{129}Xe gas in the airspaces is attenuated by a factor of ~100 by using a lower flip angle relative to the dissolved phases.

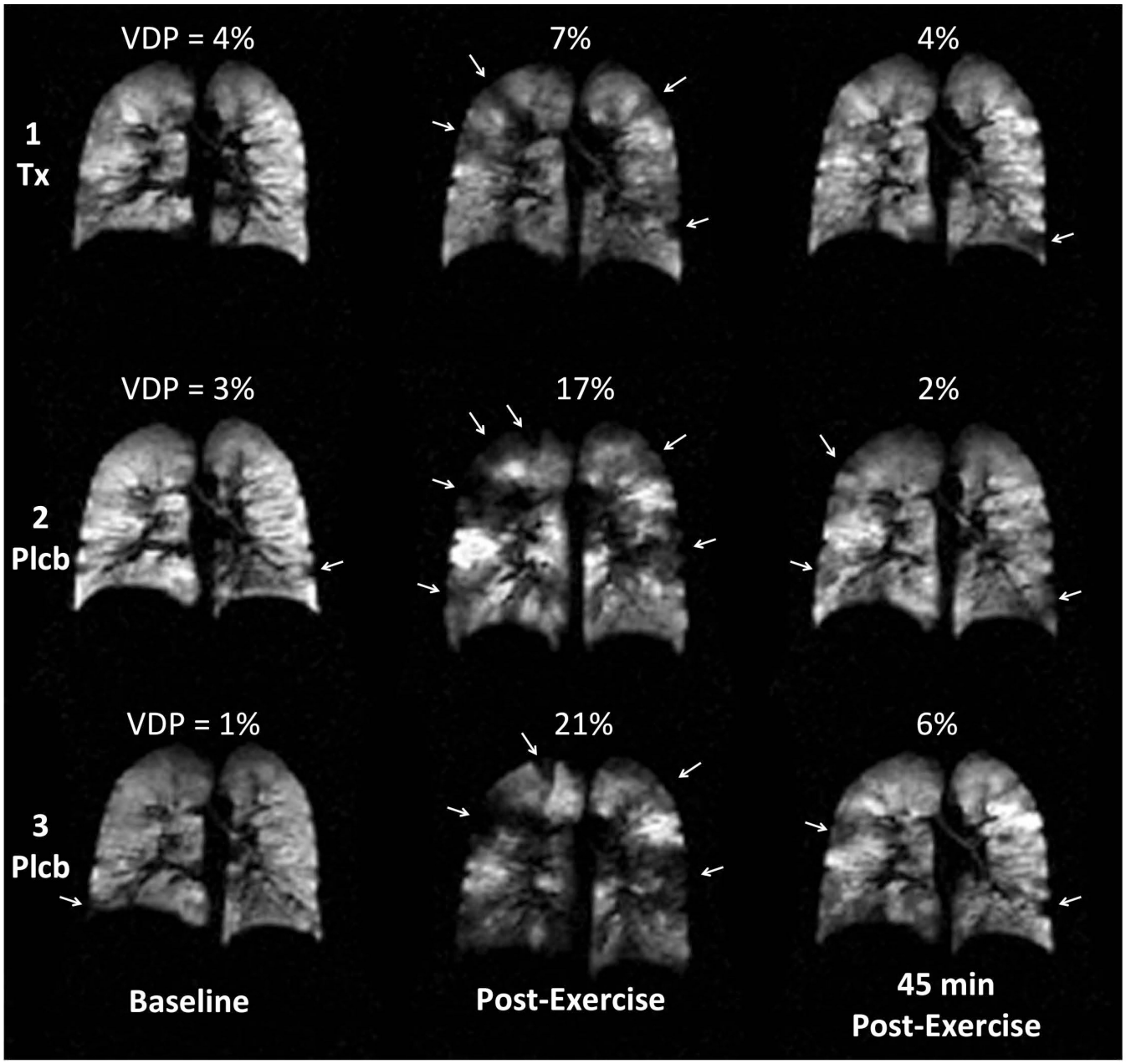

Figure 2.

^{3}He MRI lung images showing a strong VDP response to challenge pre (baseline) and post-exercise challenge in a subject with exercise-induced bronchoconstriction and treatment with Montelukast (visit 1 vs. visits 2 and 3). Defects (arrows) occur most prominently after exercise challenge and post-challenge decreases in FEV1 for this subject coincide with decreases in VDP as indicated. Recovery 45 minutes post-exercise shows residual VDP for visit 3. Overall, residual VDP after recovery was significantly higher on ^{3}He MRI but not on FEV1. Plcb = “placebo visit”; Tx = “treatment visit.” Adapted from Ref. (144) with permission.

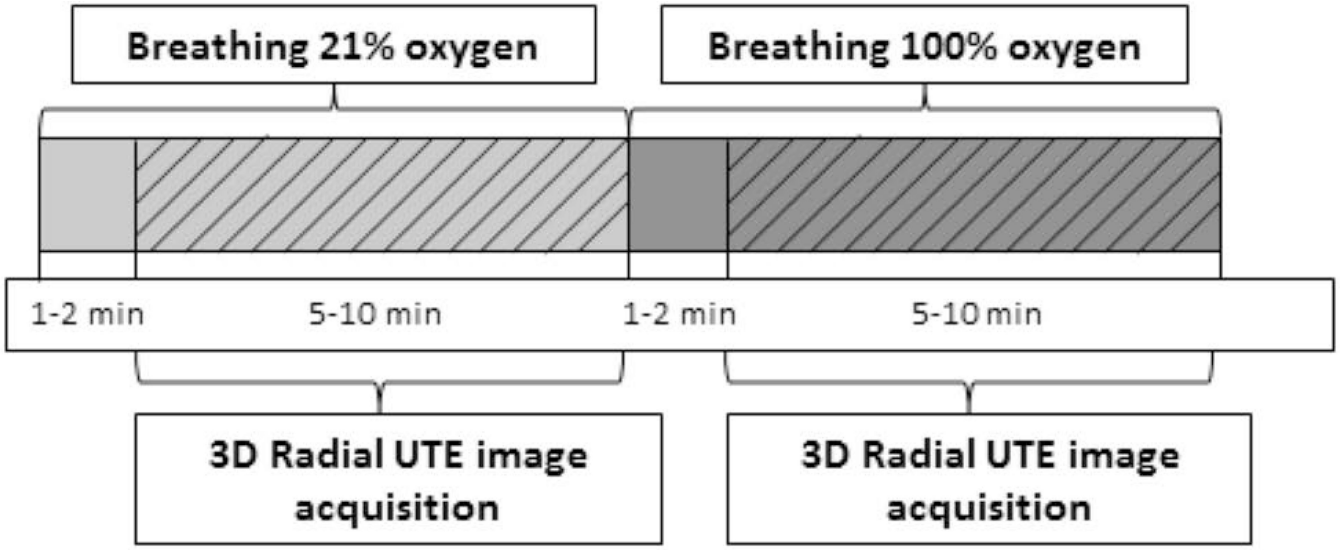

Figure 3.

Timing and general protocol for oxygen-enhanced MRI as performed in (11). Typically, images are acquired at different concentrations of inhaled oxygen (usually 21% and 100%), with a 1–2 minute wash-out period to avoid transient effects. Similar approaches are used for other OE-MRI acquisition techniques.

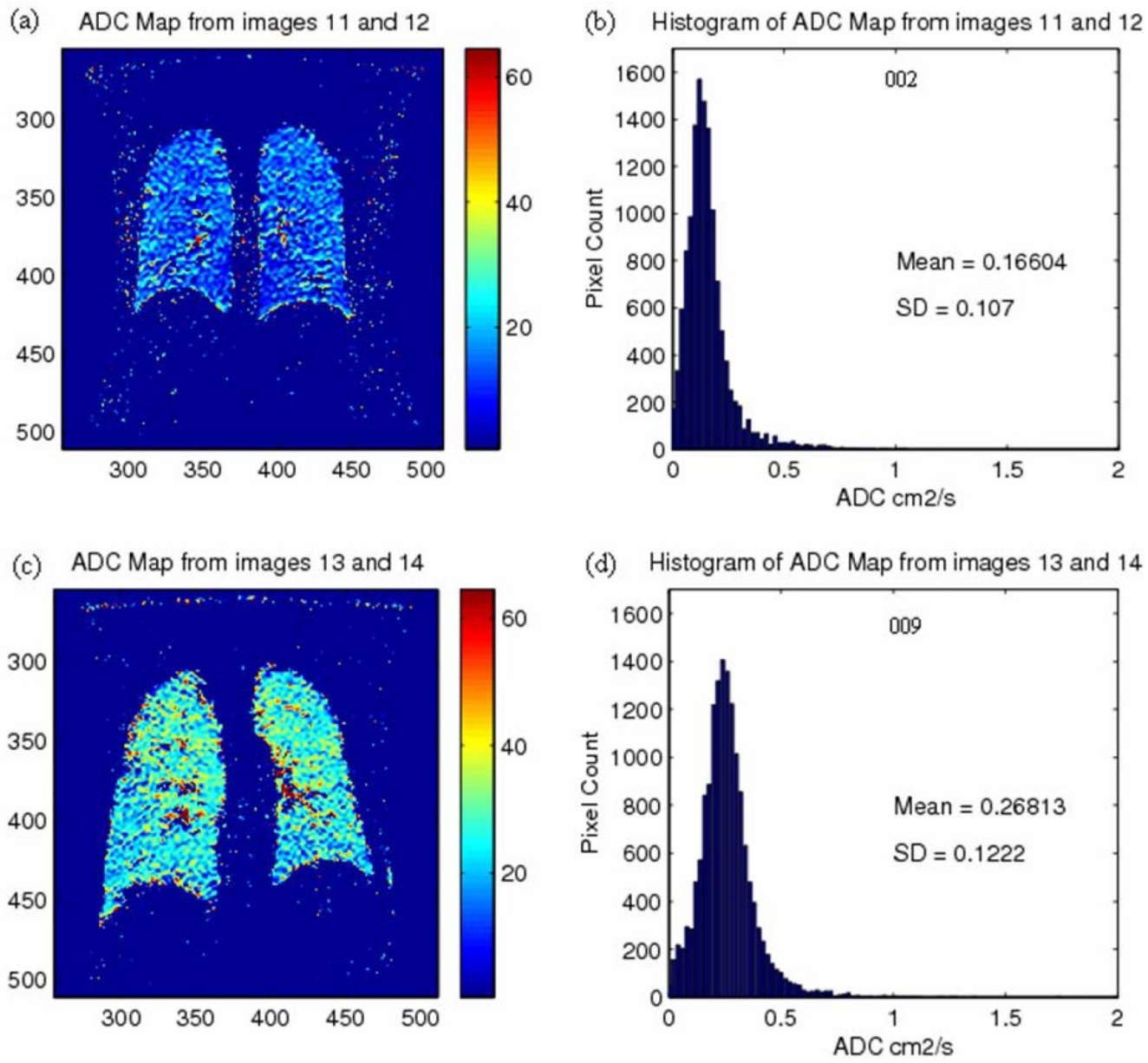

Figure 4.

ADC maps derived from coronal slices acquired using diffusion-weighted ^{3}He MRI for (a) non smoker with (b) histogram for the typical slice shown, mean ADC = 0.166 cm^2/s and (c) smoker with (d) histogram mean ADC = 0.268 cm^2/s. Color bar units: mm^2/s. Adapted from Ref. (134) with permission.

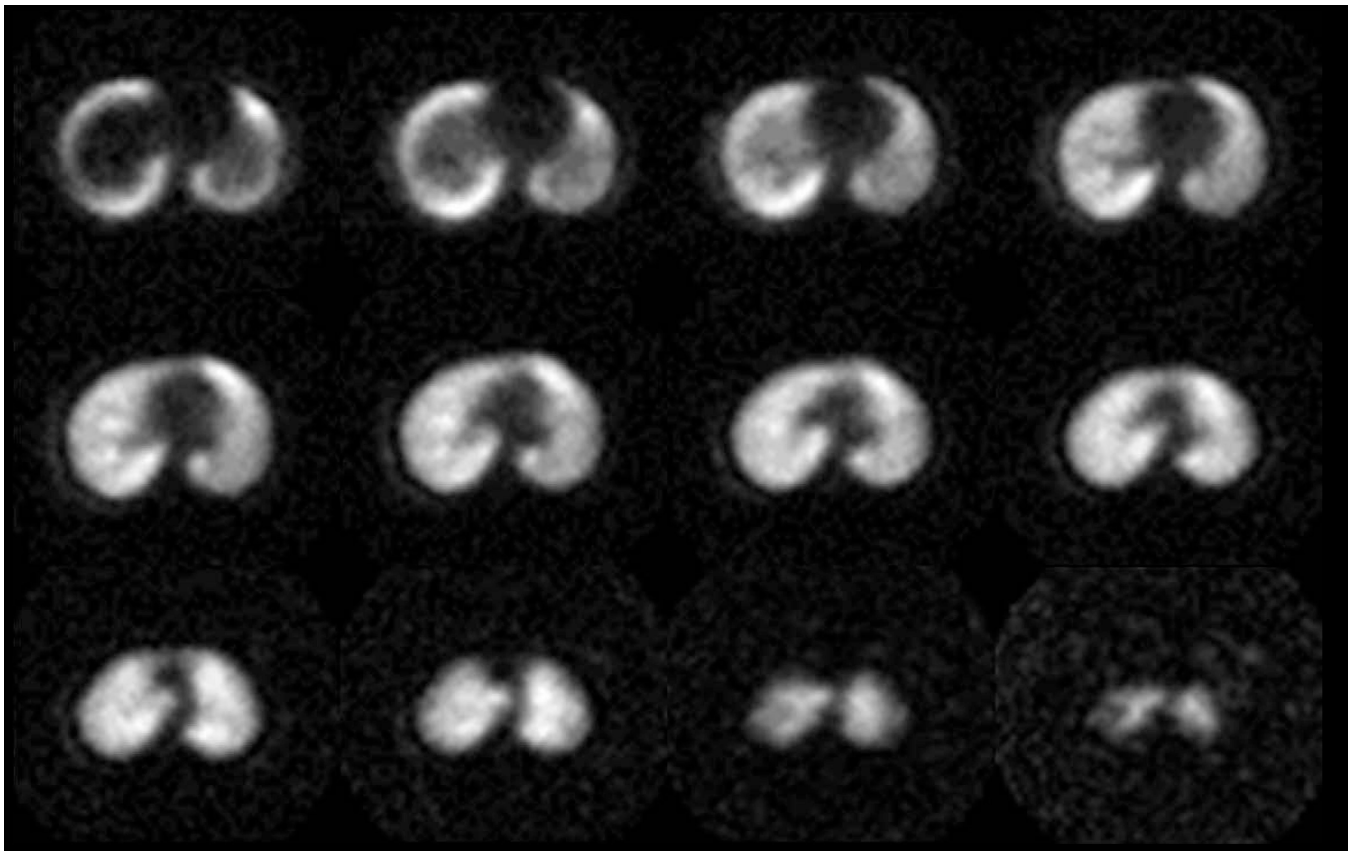

Figure 5.

Axial reformation of 3D radial UTE FID MRI ventilation imaging with C_3F_8. This dataset was acquired in a 15-second breath hold. Good image quality and the expected homogeneity of gas distribution are observable in this healthy normal human subject.

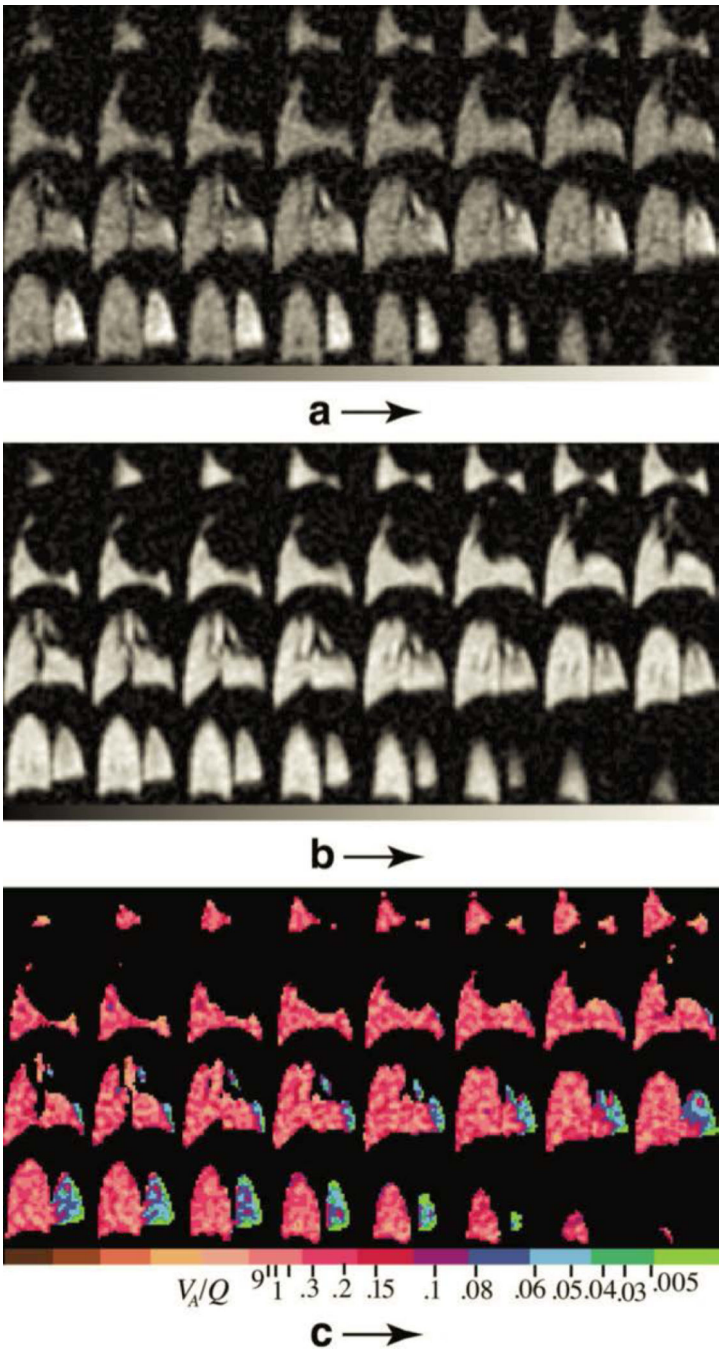

Figure 6.

SF_6 MRI as a surrogate for V/Q measurement in a rat model of ventilation obstruction (left upper lobe). Multiple slices of a 3D volume acquired with the hyperoxic 30% SF_6 / 70% O_2 mixture (numerator) (**a**), and normoxic 80% SF_6/20% O_2 mixture (denominator) (**b**), and resulting ratio images (**c**). The color bars of the corresponding V/Q scale are the width of the SD of the ratio values. This figure is republished from (215) with permission of the Journal of Magnetic Resonance in Medicine.

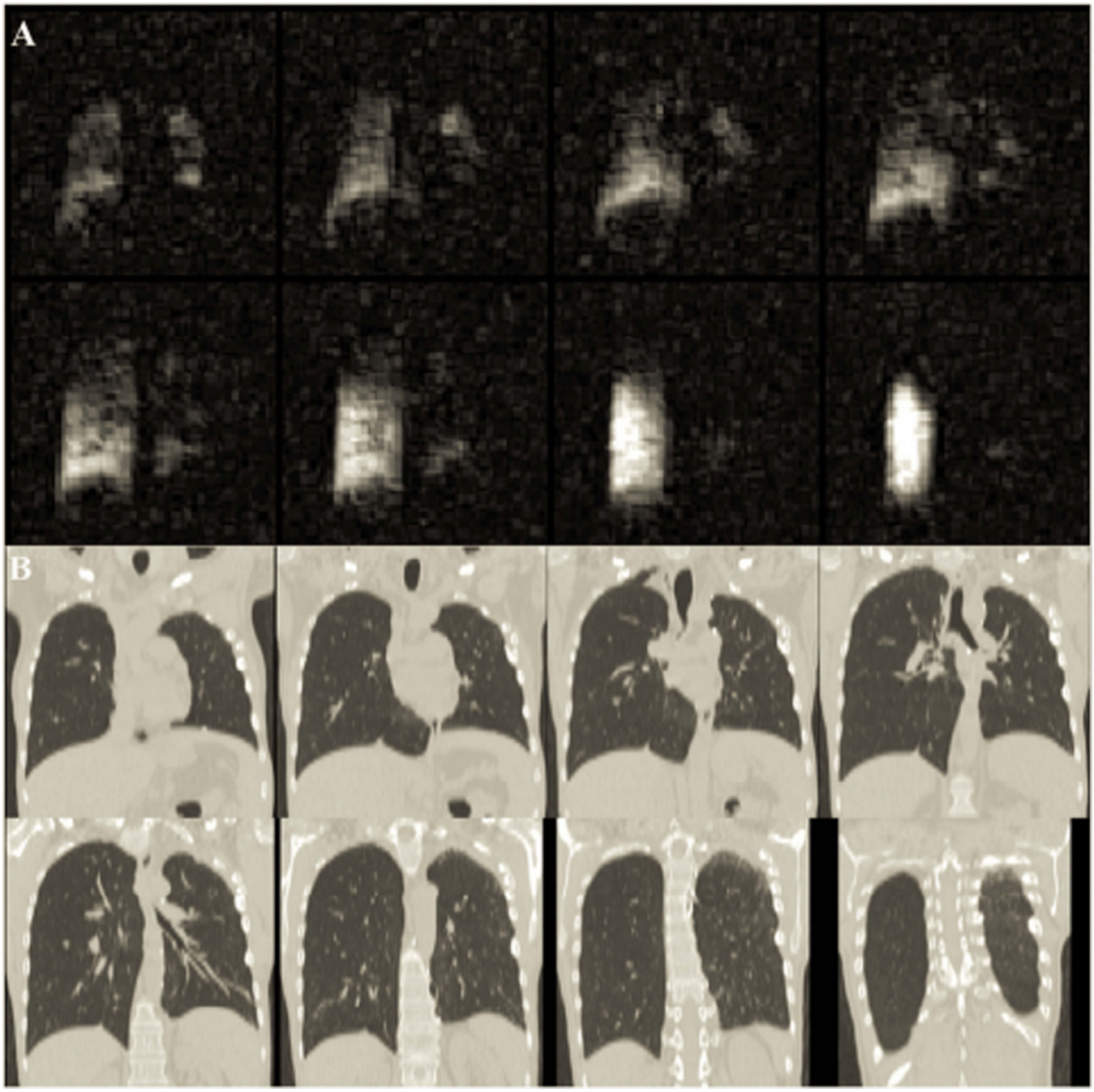

Figure 7.

(a) ventilation image of a lung transplant recipient (coronal field of view 40 cm). Prior to this study, both lungs had developed BOS after transplant from a non-sibling donor. The right lung was then transplanted from a sibling donor. The high ^{19}F signal intensity in the healthy right lung is clearly differentiable from the BOS left lung. **(b)** Matching CT slices (coronal field of view ~34 cm) to provide structural reference. This figure is republished from (49) with permission.

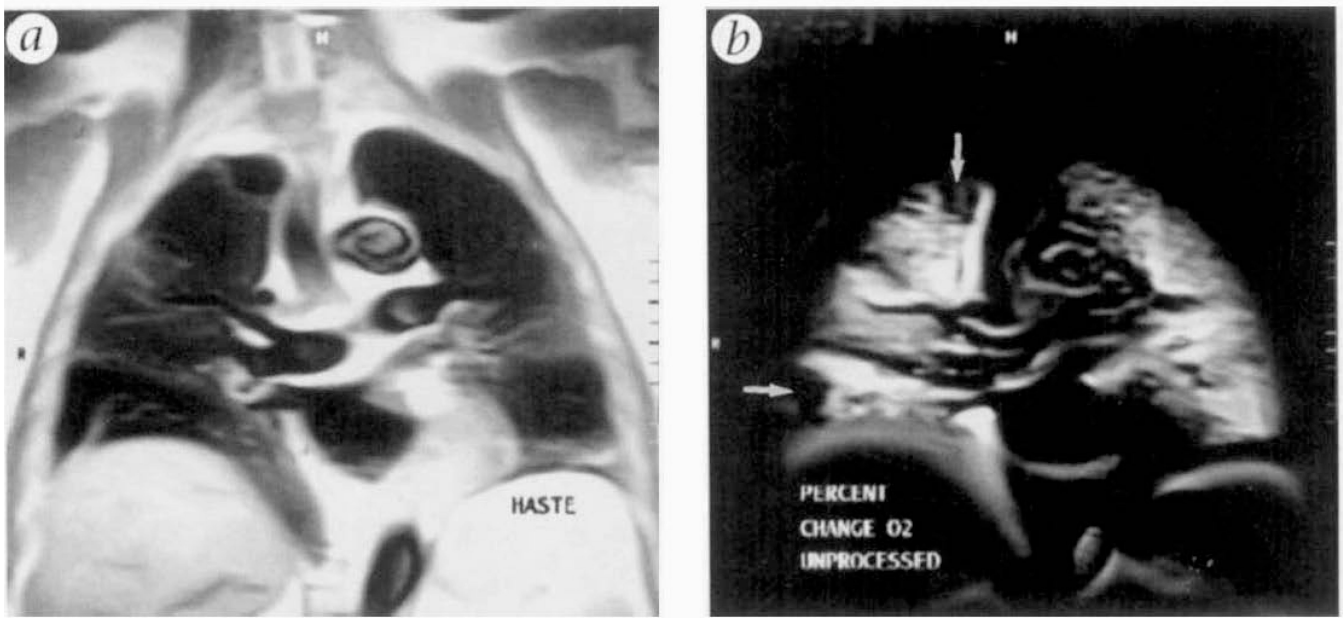

Figure 8.

(a) Coronal IR-SSFSE image showing low-signal regions in the right lung corresponding to bullae. **(b)** OE MRI showing ventilation defects (arrows) in the bullous regions. This figure was originally published in (2), and is reprinted here with the permission of Nature Medicine.

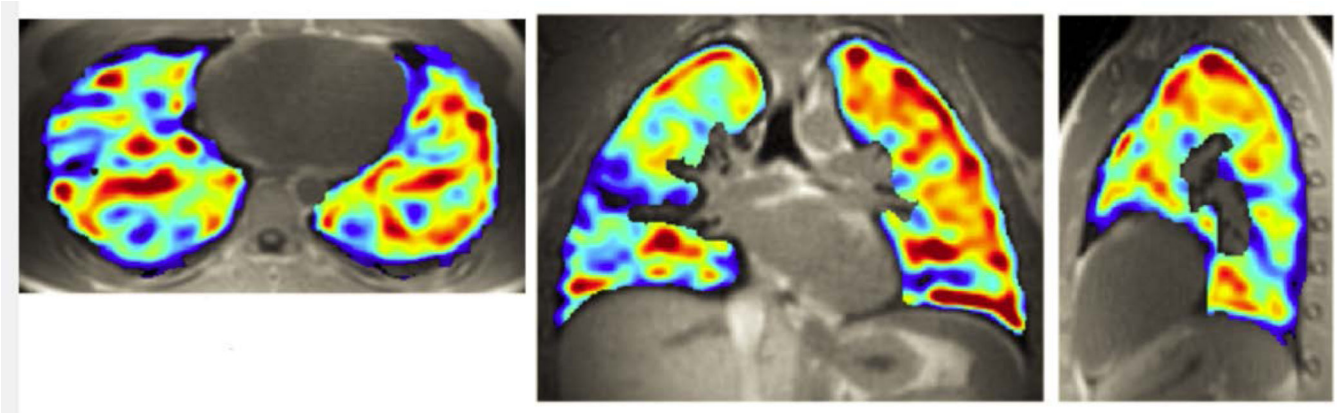

Figure 9.

Example from (11) showing a healthy normal subject with parametric color map. The isotropic 3D resolution is apparent in the axial, coronal, and sagittal reformations of the same dataset. The color bar is in units of percent signal enhancement (PSE).

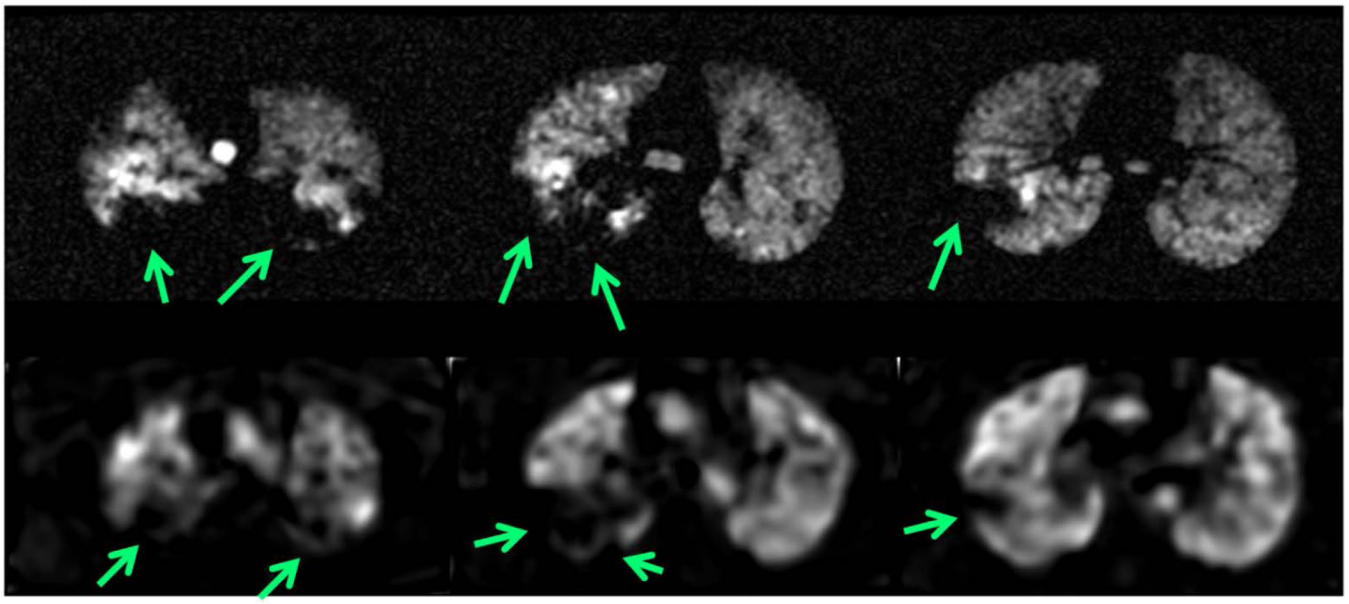

Figure 10.

Comparison of hyperpolarized (HP) ^{3}He MRI images (top row) with OE-MRI images (bottom row) originally presented in (223). Arrows indicated regions of agreement in ventilation defect extent and location. The in-plane spatial resolution of the HP ^{3}He images is greater than in the OE MRI images by a factor of 3.2. However, the resolution in the OE MRI images in this study was isotropic in all 3 dimensions, while the HP ^{3}He images were thick axial images.

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Table 1

Physical parameters for the most common gas contrast agents used for pulmonary MRI. Abbreviations: HP: hyperpolarized; SF_6: sulfer hexafluoride gas; C_2F_6: hexafluoroethane gas; ppm – part per million nuclei.

	HP ^{3}He	HP ^{129}Xe	^{1}H / O_2 Enhanced	SF_6	C_2F_6
Nuclear Gyromagnetic Ratio (MHz/T)	33.434	11.777	42.576*	40.052	40.052
Polarization	30–40%	8–25%	~1 ppm♯	~1 ppm♯	~1 ppm♯
diffusion coefficient - free (cm^2/s)	2.05 (154)	0.062 (154)	0.176 (234)	0.033 (214)	0.033 (216)
Apparent Diffusion Coefficient - ADC (cm^2/s)	0.16 (154)	0.021 (154)	**	0.0222§ (69)	0.018§ (216)
density of the gas (g/cm^3)	1.34 × 10−4	5.75 × 10−3	1.43 × 10−3	6.51 × 10−3	6.16 × 10−3
normoxic or anoxic dose	Anoxic	Anoxic	Norm/hyperoxic	Normoxic	Normoxic
Cost	$800 / L	$120 / L	~$0.01 / L	$20 / L	$20 / L
Volume required for typical study	1 L	1 L	300 L	5 L	5 L
Partition coefficient in blood (Ostwald - unitless)	0.0085 (235)	0.17 (235)	0.0261 (235)	0.0075 (235)	0.001273 (236)

*Via paramagnetic effect on proton signal

**No value in the literature

§Derived from pre-clinical rat studies.

♯Field strength-dependent - value is approximate for B_0 = 1.5 T.

Table 2

MRI longitudinal and transverse decay constants in the lungs and at the field strength indicated for the most common gas contrast agents. Abbreviations: HP: hyperpolarized; SF_6: sulfer hexafluoride gas; C_2F_6: hexafluoroethane gas

	Value						
	HP ^{3}He	**HP ^{129}Xe**	**Normoxic ^{1}H (21%)**	**Hyperoxic ^{1}H (100%)**	**SF_6**	**C_2F_6**	**C_3F_8**
Field Strength (T)	1.5	1.5	1.5	1.5	1.5	1.9	1.5
T1 (ms)	32,000 (237)	20,000 (214)	1,237 (77)	1,129 (77)	1.2 (214)	5.9 (3)	18 ms (38)
T2 (ms)	2,000 (238)	310 (239)	30 (240)	**	**	5.9	16 ms (38)
T2* (ms)	20 (241)	18.5 (63)	1.8 (75)	1.6 (75)	1.0 (209)	**	**

** No value in the literature

Table 3

Strengths and challenges of different gas contrast agents for pulmonary functional imaging. Abbreviations: HP: Hyperpolarized; OE: Oxygen-enhanced; SNR: Signal to noise ratio; IND: Investigational New Drug (FDA) application; ADC: Apparent diffusion coefficient; VDP: Ventilation defect Percentage; pO2: oxygen partial pressure; MRSER: Mean relative signal enhancement ratio; PSE: Percent signal enhancement; OTF: oxygen transfer function; V/Q: ventilation-to-perfusion ratio

	HP He-3 MRI	HP Xe-129 MRI	OE MRI	F-19 MRI
SNR	High	Med-High	Low	Low
Breath-hold Imaging	Yes	Yes	No	Both
Cost	~$800–1200/L	$170/L (enriched) $15/L (natural abundance)	<$1/L	$15–20/L
Hardware Requirements	MNS T/R Polarizer	MNS T/R Polarizer	Conventional Clinical MRI	MNS T/R
IND Required	Yes	Yes	No	Yes
Scan Length	5–10 s	5–10 s	5–30 min	12–15 s
Typical Spatial Resolution	3 mm×3 mm×10 mm	3 mm×3 mm×10 mm	2 mm×2 mm×10 mm	6 mm×6 mm×15 mm
Most Common Quantitative Measures	ADC, VDP, pO_2	ADC, VDP, pO2	MRSER, PSE, OTF	VDP
Repeatability Established	Yes	Yes	No	No
Signal Weightings	Ventilation, Diffusion, Oxygen Mapping	Ventilation, Diffusion, Oxygen Mapping, Gas Exchange	Ventilation and Perfusion	Ventilation and Oxygen Mapping
Clinical Research Strengths	High spatial-temporal resolution regional measures of emphysema and gas trapping and airflow obstruction.	Regional measures of emphysema and gas trapping and airflow obstruction. Dissolved phases in tissue and blood are a measure of gas exchange.	Inexpensive, widely accessible method for ventilation weighted imaging. Potential for quantitative ventilation.	Less expensive method for ventilation weighted imaging. Potential for quantitative ventilation.