Inert fluorinated gas MRI: a new pulmonary imaging modality

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INTRODUCTION

A number of gaps have been identified in the care of asthma and chronic obstructive pulmonary disease (COPD), which can lead to an inadequate assessment of diagnosis and treatment progression (1). Asthma is associated with airway wall inflammation and reversible bronchial obstruction, and it affects between 5 and 16% of the world’s population (2). COPD is characterized by progressive and irreversible airflow limitation, and it globally affects 9–10% of adults aged 40 and over (3). Non-invasive imaging techniques may be able to help bridge this gap, by providing structural and functional information to assist with the management of chronic respiratory diseases (4). Furthermore, imaging can provide regional information that is not available from spirometry and plethysmography. Imaging modalities such as chest X-rays and computed tomography (CT) can provide high resolution structural information, but they yield very minimal functional information and use ionizing radiation.

Conventional proton (1H) MRI is both non-invasive and non-ionizing, but it is challenging to make high quality 1H MR images of the lungs, due to low tissue density, magnetic susceptibility, and respiratory/cardiac motion. Due to very short transverse relaxation times in the lungs, the use of optimized ultra-short echo time (UTE) techniques can substantially improve the structural quality of conventional 1H MR lung images (5). Functional lung information can be obtained using 1H-based techniques such as O2-enhanced MRI (6,7) and Fourier-decomposition MRI (8); however, many MRI researchers have focused on hyperpolarized (HP) noble gas MRI, using helium-3 (3He) or xenon-129 (129Xe), which is a technique that can offer high resolution images of the lung air spaces, and can also directly measure regional ventilation, gas exchange, and lung microstructure (9). Fluorine-19 (19F) MRI of the lungs using inhaled inert fluorinated gases can potentially provide high quality images of the lungs that are similar in quality to those from hyperpolarized (HP) noble gas MRI. Inert fluorinated gases have the advantages of being nontoxic, abundant, and inexpensive compared with HP gases. Due to the high gyromagnetic ratio of 19F, there is sufficient thermally polarized signal for imaging, and averaging within a single breath-hold is possible due to short longitudinal relaxation times. Therefore, the gases do not need to be hyperpolarized prior to their use in MRI. This eliminates the need for an expensive polarizer and expensive isotopes. Inert fluorinated gas MRI of the lungs has been previously demonstrated in animals, and more recently in healthy volunteers and patients with lung diseases. The ongoing improvements in image quality demonstrate the potential of 19F MRI for visualizing the distribution of ventilation in human lungs and detecting functional biomarkers. In this brief review, the development of inert fluorinated gas MRI, current progress, and future prospects are discussed. The current state of HP noble gas MRI is also briefly discussed in order to provide context to the development of this new imaging modality. Overall, this may be a viable clinical imaging modality that can provide useful information for the diagnosis and management of chronic respiratory diseases. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: apparent diffusion coefficient; UTE; functional lung imaging; inert fluorinated gas MRI; ventilation gradients; hyperpolarized gas MRI

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flourinated gas MRI of humans and animals will be discussed, along with the future prospects of this new pulmonary imaging modality.

**Hyperpolarized noble gas MRI**

HP noble gas imaging was first demonstrated in 1994 by Albert et al., with $^{129}$Xe MR images of excised mouse lungs (Figure 1) (12). Born out of the desire to understand the mechanism of general anesthesia in the brain, $^{129}$Xe was chosen due to its anesthetic ability, NMR sensitivity, and ability to dissolve into blood and be carried to tissues and organs of interest (13). Naturally, imaging the lungs seemed like a practical starting point, since inhalation is the simplest route of administration and the signal in the gas phase would be much higher than in the dissolved phase. Although some pre-clinical work has continued to explore functional MRI of $^{129}$Xe in the brain (14,15), the majority of the HP noble gas literature published in the past 20 years has focused on imaging the lungs (16). Figure 2 shows current examples of HP $^3$He MR images acquired in a healthy individual and three patients with pulmonary diseases: asthma, moderate COPD, and severe COPD. Although each image in itself bears a striking structural distinctiveness, many functional imaging techniques have been developed to provide additional information, such as airway tree measurements (17), apparent diffusion coefficients (ADCs) (18), and mapping the alveolar partial pressure of O$_2$ ($P_{a}O_2$) (19).

Historically, the use of $^3$He has been more common in the literature, due to the available polarizer technology and its gyromagnetic ratio being 2.7 times greater than that of $^{129}$Xe, leading to a greater signal strength. Unfortunately, $^3$He is well known to be an extremely rare and expensive isotope, and its only means of production is through the radioactive decay of tritium (20,21). For this reason, $^{129}$Xe MRI has been receiving increasing attention recently as it is cheaper and more widely available, and improvements in polarizer technology are ongoing (22,23). Recent work has focused on validating HP $^{129}$Xe MRI against HP $^3$He MRI (24), measuring $^{129}$Xe ADC (25), diffusion anisotropy (26), and probing gas exchange (27). It should also be noted that the anesthetic properties of xenon have necessitated some careful studies with respect to safety and tolerability (28). Other current perspectives on HP noble gas MRI have been reviewed recently by Lilburn et al. (16).

Properties of $^{19}$F MRI

Due to the high cost of noble gas isotopes and the limited availability of polarizer technology, $^{19}$F MRI of the lungs using inhaled inert fluorinated gases is emerging as a potential alternative to HP $^3$He and $^{129}$Xe MRI of the lungs (10,11). $^{19}$F MRI can be performed with inert gases such as tetrafluoromethane (CF$_4$), sulfur hexafluoride (SF$_6$), hexafluoroethane (CF$_3$F), and perfluoropropane (CF$_3$F or PFP), all of which contain multiple $^{19}$F nuclei per molecule. Fluorinated gases are non-toxic and safe for human inhalation, as they are commonly used in pulmonary function tests, such as SF$_6$ (in small concentrations) in the multiple inert gas elimination technique (29). Inert fluorinated gas MRI can potentially provide high quality images of the distribution of lung ventilation and measure functional biomarkers in a similar fashion to HP noble gas MRI. This technique has the advantage of using gases that are abundant and inexpensive compared with HP gases. Most importantly, inert fluorinated gases do not need to be hyperpolarized prior to their use in MRI, which eliminates the need for polarizer technology that is currently very expensive. It is interesting to note, however, that HP fluorinated compounds have been explored for $^{19}$F molecular imaging applications, using parahydrogen-induced polarization (30).

A comparison of the physical properties of $^{129}$Xe, $^3$He, SF$_6$, and PFP is shown in Table 1 (10,20,31–36). It can immediately be seen that $^{19}$F has a very high gyromagnetic ratio, SF$_6$ and PFP have a negligible solubility (32), and the $T_1$ relaxation times of fluorinated gases in the lungs are substantially shorter than those of HP gases (10,34–36). In terms of HP gas MRI, a long $T_1$ can be beneficial for imaging, and changes in $T_1$ allow for $P_{a}O_2$ mapping (19). In the context of inert fluorinated gas MRI, a short $T_1$ is advantageous, since averaging is necessary to overcome a thermal polarization that has much less available magnetization than HP gases. Therefore, it is possible to acquire an inert fluorinated gas MR image with a reasonable signal-to-noise ratio (SNR), *in vivo*, within a single breath-hold. Since the presence of O$_2$ has a much less dramatic effect on the $T_1$ of fluorinated gases than it does for HP gases, the fluorinated gases can be mixed with O$_2$ to improve patient safety with little impact on image quality. The presence of O$_2$ in inert fluorinated gas mixtures can potentially allow for longer breath-holds than anoxic HP gas inhalations. Where HP gas inhalations have historically used a bolus on the order of 1 L, a mixture of inert fluorinated gas and O$_2$ can be breathed continuously to wash out residual air from the lungs and to reach a steady-state concentration of the inert fluorinated gas mixture, thereby maximizing the available magnetization for imaging. Continuous breathing of inert fluorinated gases allows for dynamic imaging measurements, such as wash-in and wash-out time constants, and can potentially allow for the acquisition of more physiologically meaningful information. Likewise, multiple breath HP $^3$He MRI techniques are being developed for the measurement of fractional ventilation, ADC, and $P_{a}O_2$ mapping (37,38).

**Static breath-hold imaging**

Edwin Heidelberger and Paul Lauterbur were the first to demonstrate gas phase MRI in the 1980s, by acquiring $^{19}$F images using CF$_4$. These initial images were acquired in phantoms, excised rabbit lungs (39), and healthy dog lungs (40,41) at a field strength of 0.1 T. Little progress was made for many years, due to the development of HP gas MRI and the ability to produce high quality $^3$He MR images of the lungs. In 1998, Kuehle et al. demonstrated high resolution 3D imaging of rat lungs with continuous breathing of a mixture of CF$_3$F and O$_2$ (42). It is interesting to note that...

Figure 1. First biological HP $^{129}$Xe MR image acquired in excised mouse lungs. Image reproduced with permission from Albert et al. (1994) Nature 370: 199–201.
Kuethe et al. used an image acquisition approach that was essentially the same as Paul Lauterbur’s original demonstration of MRI in 1973, except that a 3D inverse Fourier transform was used to reconstruct the data (43). Figure 3 shows current examples of $^{19}$F MR images of SF$_6$ in rat lungs that were acquired by our research group. Each image in Figure 3 was a 2D projection in the axial or coronal plane, acquired with two separate 10 s breath-holds using the 2D x-centric pulse sequence (44).

In 1998, Kuethe et al. hypothesized that it would be possible to acquire inert fluorinated gas MR images in human lungs with a similar SNR efficiency as $^1$H MRI. This hypothesis was based on the assumption that the short $T_1$ relaxation of fluorinated gases allows for more averaging, and a relatively coarse matrix size (64 x 64) would increase the number of $^{19}$F nuclei per voxel (42). Inert fluorinated gas MRI of human lungs was first demonstrated by Wolf et al. in 2008 using a mixture of SF$_6$ and O$_2$ (45). 2D whole lung projection images were reported in a healthy volunteer, and the SNR did not exceed 9. Although these initial images were very poor in quality, this work was an important benchmark as not only did safety need to be taken into consideration, but there were likely significant regulatory obstacles that needed to be overcome before human studies could begin with this new imaging modality.

More recently, inert fluorinated gas MRI has been reported in healthy volunteers by Couch et al. (10). Figure 4 shows 12 slices from a $^{19}$F 3D UTE MR image that was obtained in a healthy volunteer during a 15 s breath-hold, following continuous breathing of a mixture of 79% PFP and 21% O$_2$. Figure 5 shows similar $^{19}$F 3D UTE MR images that were acquired in the axial plane using the same settings as Figure 4. These images were acquired at 3 T using a flexible wrap-around quadrature transmit–receive coil (Clinical MR Solutions). A 5 L Tedlar bag was used to give five to seven wash-out breaths of the PFP/O$_2$ mixture, which effectively washed out most of the residual air from the lungs, allowing the inert fluorinated gas concentration to reach an approximate steady state. In order to acquire $^{19}$F MR images...
at a lung inflation of approximately functional residual capacity +1 L, the 5 L bag was replaced with a full 1 L bag of the PFP/O2 mixture, which was completely inhaled before the volunteers held their breath for 15 s. For 19F 3D UTE MR images using this continuous breathing protocol, Couch et al. reported a mean SNR (±standard deviation) of 32 ± 6 (10). Due to the short $T_2^*$ of inert fluorinated gases (as short as 2.2 ms for PFP in the lungs at 3 T), the SNR was expected to benefit from a short echo time. It should be noted however, that the 19F UTE lung images in Figure 4 show substantial $T_2^*$ blurring and phase artifacts around the edges of the lungs.

Halaweish et al. recently demonstrated gradient echo 19F MRI using the same mixture of PFP and O2 in both healthy volunteers and in patients with COPD, asthma, and lung transplants (11). Figure 6(a) shows an example of a 19F 3D gradient echo MR image that was acquired in the coronal plane from a COPD patient with emphysema. This image contains signal voids that appear to be qualitatively similar to ventilation defects in HP 3He and 129Xe MRI. Similar to the work of Couch et al., these images were acquired at 3 T using a flexible vest coil, and imaging occurred after several breaths of the PFP/O2 mixture were taken and the inert fluorinated gas concentration reached a steady state. The PFP/O2 mixture was delivered to subjects using a custom-built MR-safe gas delivery system and breathing mask (46). The computer-controlled delivery system was able to switch between air, O2, and the fluorinated gas mixture, as well as providing additional information in real time, such as heart rate, O2 saturation, O2 and CO2 concentration, and flow rate. Ideally, a robust gas delivery system can potentially improve patient compliance, as well as providing additional information to aid in the interpretation of inert fluorinated gas images. The 19F gradient echo MR images from Halaweish et al. had a mean SNR (±standard deviation) of

Figure 4. Coronal pulmonary 19F 3D UTE MR images obtained in a healthy volunteer during a 15 s breath-hold after continuous breathing of a mixture of 79% PFP and 21% O2. Images are reproduced with permission from Couch et al. (2013) Radiology 269: 903–909.

Figure 5. Axial pulmonary 19F 3D UTE MR images obtained in a healthy volunteer during a 15 s breath-hold after continuous breathing of a mixture of 79% PFP and 21% O2. Images are reproduced with permission from Couch et al. (2013) Radiology 269: 903–909.
16 ± 6 for healthy volunteers and 12 ± 5 for patients with respiratory diseases including COPD, asthma, and lung transplants (11). The SNR of these gradient echo images was, on average, approximately half of the UTE SNR reported by Couch et al. (10).

Halaweish et al. showed that inert fluorinated gas MRI has the ability to detect ventilation defects in patients with COPD, in a manner similar to HP noble gas MRI. Future work in our laboratory will focus on quantifying these ventilation defects, and validating these measurements with a direct comparison to HP ³He and ¹²⁹Xe MRI. For example, the total ventilation volume (VV) and ventilation defect volume (VDV) can be obtained from Figure 6(b), which shows the ¹⁹F gradient echo image from a COPD patient with emphysema overlaid on a ¹H localizer image (11,47). The density and diffusivity of PFP will be important in interpreting the size of ventilation defects, as a recent comparison of VDV measurements using HP ³He and ¹²⁹Xe MRI in COPD patients demonstrated a significantly greater VDV as measured from HP ¹²⁹Xe MRI. It was suggested that the higher density and lower diffusivity of ¹²⁹Xe may be contributing factors that lead to slower filling in the terminal airways, and larger disease-related defects (24). On the other hand, the use of continuous breathing to reach a steady-state concentration of the inert fluorinated gas before imaging may compensate for the slow filling and make ventilation defects appear smaller. It should also be noted that an accurate measurement of VV and VDV may require corrections for B₁ inhomogeneities (48).

Overall, Couch et al. (10) and Halaweish et al. (11) have demonstrated that inert fluorinated gas MRI is a safe and well-tolerated technique, and that it can be performed in volunteers and patients with severe pulmonary diseases. Interestingly, the resolution of the recently reported ¹⁹F MR images in humans is not

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Figure 6. (a) Coronal ¹⁹F 3D MR images obtained in a COPD patient with emphysema using a mixture of 79% PFP and 21% O₂. (b) ¹⁹F MR lung images were segmented from the surrounding background, registered to ¹H MR images, and overlaid in greyscale. Images are reproduced with permission from Halaweish et al. (2013) Chest 144: 1300–1310.
unlike the initial images reported by Heidelberger and Lauterbur in 1982 (which was 7.5 mm) (39); however, significant improvements have been made in SNR and image quality since that time. PFP was the gas of choice used in the recent work of both Couch et al. and Halaweish et al.; however, using SF₆ may provide some additional advantages, especially due to its shorter T₁ relaxation and single resonance. On the other hand, the desire to use shorter repetition times with SF₆ may lead to issues with specific absorption rate limits. Regardless of the choice of fluorinated gas, substantial improvements have clearly been made since the early work of Wolf et al., and improvements in image quality are ongoing.

**Dynamic imaging**

Since inert fluorinated gases are generally mixed with at least 21% O₂, it is possible to perform dynamic MRI during long periods of continuous breathing of the inert fluorinated gas mixture, without sacrificing the safety of the animal or human subject. The majority of the dynamic ¹⁹F MRI literature has been performed in animals. In one study of rats continuously breathing a mixture of SF₆ and O₂, lung volumes were measured throughout the respiratory cycle by analyzing the periodic changes in whole-lung spectroscopy signals (49). This technique could easily be translated to humans, as an SNR benefit would be expected from the differences in lung size alone. Naturally, this raises possibilities of using ¹⁹F MRI to obtain information that is similar to pulmonary function tests, while using the imaging component to provide regional information that is complementary to the dynamic lung volume measurements.

A number of animal studies have used dynamic ¹⁹F MRI to investigate the kinetics of pulmonary ventilation by measuring the wash-in and/or wash-out of inert fluorinated gases (50–52). For example, one study in pigs measured both the wash-in and wash-out kinetics of SF₆ using a breathing scheme as follows: the animal was first ventilated with pure O₂ for 10 min (baseline); the animal was then ventilated with ten breaths of pure SF₆ (wash-in phase), and then the animal was ventilated with seven breaths of pure O₂ (wash-out phase). One single slice 2D ¹⁹F MR image was acquired following each breath, and the signal was fitted to mono-exponential decays in order to extract the whole-lung wash-in and wash-out time constants. These results agree with literature expectations from xenon-enhanced CT (Xe-CT), which have shown that wash-out time constants are longer than wash-in time constants, and that this difference may be related to the density and viscosity of heavy gases (53). Dynamic ¹⁹F MRI of SF₆ wash-in measurements in pigs have been validated with a comparison to respiratory gas analysis (54).

Halaweish et al. recently investigated the wash-in and wash-out characteristics of PFP in healthy volunteers and patients with respiratory diseases, such as asthma and COPD (55). In this study, a total of eight ¹⁹F 3D gradient echo images were acquired during ~15 s breath-holds in order to capture the wash-in and wash-out of a mixture of 79% PFP and 21% O₂. Imaging was interleaved with three breaths of the PFP/O₂ mixture during the wash-in phase or with three breaths of room air during the wash-out phase. For healthy volunteers, the ¹⁹F signal distribution was homogeneous, and the wash-in/wash-out curves were qualitatively similar to Xe-CT results (53). As expected, the images from patients with respiratory diseases showed increased heterogeneity and ventilation defects; however, there was significant variability in appearance of the wash-in/wash-out curves, which can be indicative of gas trapping. Future work in our laboratory will focus on quantifying the fractional ventilation parameter, r, which is defined as the fractional refreshment of gas per breath (56). Ventilation maps can be determined through a pixel-by-pixel analysis of the wash-in/wash-out curves, and this will allow for a quantitative comparison with other ventilation mapping methods that have been demonstrated in animals, such as Xe-CT (57) and HP noble gas MRI (37,58,59). There has been a recent focus on ventilation mapping in humans using HP ³He MRI, as it may provide complementary information to ADC and Peto₂ mapping (38).

A heterogeneous distribution of fractional ventilation has been observed in COPD patients, along with areas of high r near ventilation defects, which may be due to gas transport between well-ventilated and poorly-ventilated regions of the lung (59).

**Diffusion imaging**

HP noble gas ADC measurements are well known to be sensitive to the lung microstructure, and these measurements can distinguish between healthy and emphysematous tissue (18,25). Preliminary inert fluorinated gas ADC measurements are currently underway, and this technique may be able to provide similar information to HP noble gas MRI. The first demonstration of inert fluorinated gas ADC measurements was performed in healthy rats using SF₆, and the measured ADC was slightly less than the self-diffusion coefficient of SF₆ (33,60). An elastase-induced model of emphysema in rats was employed to help determine whether this technique had a potential to detect pulmonary disease, and elevated C₂F₆ ADC values were detected in emphysematous regions of rat lungs (61). This result was expected, based on previous measurements in the literature performed using HP noble gas MRI. Significant differences in C₂F₆ ADC values were also detected in a study of healthy and emphysematous excised human lungs (62,63), which was an important first step towards translating this technique to human imaging.

Despite the challenges of imaging gases with very short T₂* values, it is possible to probe ADCs in humans using a UTE approach in combination with bi-polar diffusion-sensitizing gradients. As an example, Figure 7(a) shows three slices from a ¹⁹F 3D UTE image without diffusion weighting acquired in a healthy volunteer using a mixture of 79% PFP and 21% O₂ (images with diffusion weighting not shown). The images shown in Figure 7(a) were acquired in our laboratory using methods similar to those for the UTE images shown in the static breath-hold imaging section. In order to achieve a b value of 9.59 s · cm⁻² and diffusion time of 1 ms, a Tₑ of 3.8 ms was required. In this case, these settings yielded an SNR in the center slice image (without diffusion weighting) of approximately 15. Figure 7(b) shows the corresponding ADC maps with mean ADC values of 0.034 ± 0.021 cm² · s⁻¹, 0.025 ± 0.016 cm² · s⁻¹, and 0.023 ± 0.011 cm² · s⁻¹, where the error represents the heterogeneity in each respective ADC map.

The ADC values for the healthy volunteer shown in Figure 7 were similar to previously published values for the diffusion of PFP mixed with O₂ (31). This was to be expected for a diffusion time of 1 ms and the slightly restricted diffusion length scale that was probed. A longer diffusion time would be required to reach the restricted diffusion regime that is normally used for HP noble gas measurements of ADC. Some of these HP noble gas measurements employ a geometrical model in order to determine morphological parameters, and this method has been successfully validated against lung histology (64). Since this method
requires long diffusion times that necessitate long $T_1$ values, lung morphometry measurements will not be possible with inert fluorinated gases (26). However, by probing multiple diffusion times, it may be possible to measure the surface to volume ratio ($S/V$) with inert fluorinated gases, which is an important biomarker of lung microstructure. Measuring $S/V$ will require at least two diffusion times that are less than or of the order of $T_2^*$. It is also possible to mix inert fluorinated gases with other inert gases, such as $^3$He, to increase the free diffusivity, and hence the diffusion length scale that will be probed. Although there are a number of potential difficulties, inert fluorinated gas diffusion measurements have been demonstrated in humans, and there is a possibility for probing the lung microstructure in humans with pulmonary diseases.

**V/Q Measurement**

The ventilation/perfusion ratio ($V/Q$) is known to be directly related to gas exchange, and measurements of $V/Q$ can be a sensitive indicator of pulmonary disease (65). $V/Q$ measurements have been made using HP $^3$He MRI, and this method uses regional $P_O_2$ measurements to determine $V/Q$ (66). Kuether et al. explored $V/Q$ measurements with rats continuously breathing a mixture of SF6 and O2 (35). This measurement requires the acquisition of two images in order to isolate the $^{19}$F signal changes that are due to a variation in $V/Q$ only. A reference image was acquired using a low O2 concentration (20%), and the resulting SF6 signal was fairly homogeneous. A second image was acquired with a high O2 concentration (75%), where the resulting SF6 signal was higher in regions of the lung where $V/Q$ was low. By taking the quotient image and numerically computing the dependency of $V/Q$ on the fluorinated gas partial pressures, a map of $V/Q$ was generated. In a model of obstructed ventilation, differences in $V/Q$ distributions were detected for the left and right lungs. The same group developed another approach to $V/Q$ mapping, which involved mapping $T_1$ with a modified Look-Locker technique (67). A map of $V/Q$ was generated by computing the dependency of $T_1$ on the fluorinated gas partial pressure, which in turn is related to $V/Q$. The $T_1$ method for $V/Q$ mapping yielded similar results to the quotient method in the model of obstructed ventilation in rats (67).

Since $V/Q$ is a meaningful biomarker for disease, it would naturally be of great interest to extend these $V/Q$ mapping techniques to human imaging; however, it should be noted that this technique has some potential limitations. In particular, $V/Q$ mapping using inert fluorinated gas MRI is weakly sensitive to high and low $V/Q$ values. Although Adolphi et al. reported $V/Q$ values ranging from about 0.01 to 10, $V/Q$ is weakly dependent on the fluorinated gas $T_1$ at both high and low $V/Q$ values (67). Therefore, a robust method for $T_1$ mapping is required, as any small errors in determining $T_1$ will lead to large errors in $V/Q$. The ongoing development and optimization of efficient image acquisition techniques will determine if there is sufficient SNR to measure $T_1$ and generate $V/Q$ maps in humans within reasonable safety limits.

**Gravitational distribution**

It is well known that pulmonary ventilation exhibits a gravitational gradient due to a gradient in regional compliance. This relationship has been previously demonstrated with a variety of imaging techniques, such as Xe-CT (68), O2-enhanced 1H MRI (6), and HP noble gas MRI (58,69), where ventilation is always greater in more dependent regions of the lung. These techniques typically use a wash-in/wash-out approach to quantify regional fractional ventilation, and then gradients in ventilation are calculated in the vertical direction. The dynamic imaging section discussed in detail the potential for wash-in/wash-out imaging with inert fluorinated gases, and efforts to perform ventilation mapping are currently underway. It would be natural to expect that inert fluorinated gas MRI should exhibit a similar gravitational distribution of ventilation; however, the literature currently lacks quantitative data.

Figure 8(a) shows an example of how wash-in/wash-out imaging with inert fluorinated gases can be used to generate $V/Q$ maps. The image shown in Figure 8(a) was acquired using methods similar to the UTE images shown in the static breath-hold imaging section. Figure 8(b) shows the normalized mean signal intensity from the axial projection image in Figure 8(a) plotted as a function of vertical distance from the dorsal surface of the lung. The solid line represents the calculated gradient, which has a slope of $-0.033 \text{ cm}^{-1}$, representing an 84% change in signal intensity from the anterior to posterior edges of the lung. Although this preliminary data appears to demonstrate...
the expected gradient in the $^{19}$F signal, it is difficult to compare these results to literature values, which generally quantify ventilation rather than analyzing static breath-hold images. In the future, quantitative ventilation mapping in humans will determine if the ventilation gradients obtained from $^{19}$F MRI can provide meaningful information regarding lung physiology and the distribution of ventilation in the lungs.

CONCLUSIONS

Although the first inert fluorinated gas images reported by Heidelberger and Lauterbur were extremely primitive, it was recognized in their 1982 abstract that gas phase MRI could potentially become an important component of pulmonary imaging technology (39). That statement still rings true today, as HP noble gas and inert fluorinated gas technology continues to evolve. The same group that originally co-pioneered HP noble gas MRI is now helping to develop the next pulmonary imaging modality: inert fluorinated gas MRI. Once fully optimized, this technique may have a significant advantage over HP noble gas MRI, since it is inexpensive, the gases are abundant, there is a sufficient thermal polarization for imaging, and the technique can be performed on any MRI scanner with broadband capability. All of these developments and advantages may help lead to FDA and Health Canada regulatory approval for clinical imaging using inert fluorinated gas MRI. The ongoing improvements in image quality will allow for the continued investigation of dynamic imaging and the detection of functional biomarkers, such as ADC and regional ventilation. Overall, inert fluorinated gas MRI has the potential to become a viable clinical imaging modality for non-invasively imaging the lung and aiding in the management of respiratory diseases.

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REFERENCES


32. Scenes of the 21st Annual Meeting ISMRM, Salt Lake City, UT, 2013; 4111.


