The traditional approach to lung imaging, using so-called high resolution CT (HRCT) consisting of 1 mm slices, is replaced increasingly by novel methods. The introduction of multi-detector row CT (MDCT) has enabled coronal, sagittal, and oblique reformatting at greater spatial resolution than before, while contrast-enhanced CT methods now allow assessment of vasculature and lung perfusion. Developments do not stop there; techniques using spirometric controlled MDCT allow for quantification of presence and distribution of parenchymal and airway pathology; xenon gas can be employed to assess regional ventilation of the lungs, and, although many such applications are currently still driven by research, it is expected that HRCT will become antiquated in the not too distant future as CT evolves from mere static assessment of morphology into a dynamic and quantifiable tool for regional assessment of the lung.

Complementary to CT of the lung, MRI of the lung, which previously was handicapped by field inhomogeneity and the lack of protons in lung tissue, is developing its own arsenal for lung assessment in terms of morphology, pulmonary circulation, ventilation, and right heart assessment. It is clear that the inherent advantage of MRI over CT—its lack of ionizing radiation—makes it of primary interest in the field of lung diseases that tend to be chronic with acute exacerbations and require multiple investigations during the life span of the patient. Unfortunately, availability of some of the tools required (such as gas polarizers) or MRI techniques (such as broadband upgrades) is still somewhat limited. However, there is a significant drive toward making access easier, and in many centers, MRI already has become a main diagnostic tool.

This article describes some of the new features involving lung imaging from a CT and MRI perspective. It is the authors’ intention that the reader should be familiar with the current available techniques and techniques that are expected to reach clinical applications in the near future.

CT

The scanners

Volumetric physiologic imaging by way of x-ray CT had its beginning in the mid 1970s with the dynamic spatial reconstructor (DSR), the prototype of dynamic volumetric x-ray CT designed and installed at the Mayo Clinic [1]. Much of the work establishing the accuracy and precision of volumetric lung imaging was performed on the DSR [1,2]. The primary lesson learned from the DSR was that lungs, in particular, must be studied dynamically and volumetrically. Commercial imaging technology significantly lagged behind this early work. The electron beam CT [3] used parallel x-ray targets to get improved scan speeds up to 50 ms per slice pair, acquiring eight stacked slices in approximately 224 milliseconds. There have been rapid advances in speed and resolution with the advent of MDCT [4]. Its cone-beam spiral CT uses a 2-dimensional detector array, allowing larger scanning range in shorter time with higher image resolution [5,6]. Acquiring multiple image slices per rotation and rotation speeds as short as 0.3 seconds allow for a significant reduction in acquisition time. Faster scan times will significantly impact functional imaging protocols where the rate of
perfusion of a contrast agent is measured over time or gated imaging is needed. It is believed that the future of lung assessment resides with true dynamic low dose volumetric CT scanners that image at least 1/3 of the thorax with at least a 0.5 mm isotropic voxel, achieve a full rotation scan aperture of 150 milliseconds, and have superior contrast resolution for radiopaque gas and injected contrast detection. The system will likely be coupled with a low Tesla MR scanner that will be used to complement the information available from the CT image. Patients will be scanned frequently by low Tesla MR and less frequently over time by the CT component.

With the introduction of dual source MDCT [7,8] into the clinical arena, scan apertures now fall below 150 milliseconds, but z-axis coverage with single rotation on these scanners remains at 2.4 cm. Other single source spiral scanners have advanced to as many as 256 rows of detectors [9,10] with a z-axis coverage of up to 12 cm. By the end of 2007, 128 rows and 4 cm z-axis coverage will be the minimum configuration of the high-end MDCT scanners. With the broader coverage, retrospective gating methods have emerged for cardiac and pulmonary imaging whereby, by way of a very low pitch, images are gathered during the respiratory or cardiac cycles while recording the physiologic signal together with the projection images. Prospectively [11], or retrospectively [10,12–17], the portions of the physiologic cycle of interest can be selected from within the slow pitch spiral data so that a volumetric image data set is reconstructed for just that location of the respiratory or cardiac cycle. Thus, multiple portions of the physiologic cycle can be reconstructed to yield a dynamic image sequence of the organ of interest [10,12–17]. In pulmonary applications, the earliest use of this method has been in oncology, tracking the maximum trajectory throughout a respiratory cycle for the purposes of treatment planning [15,18].

As the scanners become faster with more slices, some people have questioned how many slices is enough. The answer to this question is determined largely by the more advanced functional applications, such as retrospective gating technologies, ventilation, and perfusion imaging. Perfusion and ventilation imaging requires an axial mode of scanning to dynamically track the first pass of a sharp bolus of contrast agent (approximately 0.5 mL/kg over 2–3 seconds injected into the vena cava or right atrial junction). With axial dynamic scanning, the functional parameter under investigation (ventilation or perfusion in the case of the lung) is evaluated only as broadly along the z-axis as the coverage of the multiple rows of detectors will permit (typically 4–12 cm). If it is important to evaluate dynamically the whole lung, then one must have long z-axis coverage; otherwise, the dynamic acquisition will have to be repeated at multiple levels to gain the z-axis coverage. There must be enough rows of detectors to maintain structural detail and apex-to-base coverage.

With the introduction of dual source CT, there is a growing interest in the use of dual energy [19–22] as a means of characterizing tissues regionally and quantitating local amounts of a contrast agent. Dual energy imaging permits mathematical separation of the contrast signal from the background tissue signal on a single scan acquisition. This simultaneous acquisition avoids the need for separate unenhanced and enhanced scans with associated or added radiation dose and alignment challenges caused by variations in breath hold, cardiogenic motion, alterations in chest wall configuration during a breath hold, normal stress relaxation occurring when the lung is held at a fixed inflation pressure, and so forth. In the case of a perfused blood volume scan used to assess pulmonary emboli, it is possible (through the use of dual energy whereby one x-ray source is set to 80kV and the other to 140kV) to generate a virtual contrast-only image and a virtual unenhanced image [20]. The accuracy of the Hounsfield units in the virtual unenhanced image remains untested, and it is not clear if this virtual image data set can be used, for instance, in a density mask analysis seeking to quantify presence and distribution of emphysema in a smoker being imaged with a contrast enhanced scan for the detection and characterization of lung nodules.

With the growing use of prolonged infusions of iodinated x-ray contrast agent to detect pulmonary emboli, the enhancement has been used as an index of regional pulmonary blood flow. This has been and should be dubbed a “perfused blood volume” scan [23–25], so as not to confuse this measure with the quantitative assessment of parenchymal perfusion. With dual energy imaging, it may be possible to obtain a volumetric image of regional ventilation and regional lung structure by imaging with dual energy spiral scanning during a single breath of xenon gas [21,22]. This is an experimental method yet to be validated against the dynamic xenon CT assessment of regional ventilation. The single breath dual energy xenon method has been
Quantitative image analysis

The ability to evaluate objectively the information content of the images is critical to taking full advantage of MDCT (and MRI). In the case of the lungs, the starting point is reliable detection of the lungs [29], lobes [30], Airways [31–41], and blood vessels, which is followed by an analysis of parenchymal attenuation and texture, and is followed finally by a regional quantification of ventilation and perfusion parameters. The authors and colleagues have reviewed these capabilities elsewhere [42,43]. With the advent of MDCT and isotropic voxels, it is possible now to reliably segment the airway tree to approximately the 5th generation (trachea being generation 0), and many of the 6th and 7th generation branches are captured in the segmentation. Airway wall thickness is expressed commonly as wall area percent (percent of the area defined by the outer wall of the airway segment occupied by the airway wall) [44]. These measures are being used to assess airway remodeling in asthma and chronic obstructive pulmonary diseases (COPD). Fig. 1 shows a depiction of the airway tree and lobe segmentation from a normal non-smoker and a patient who has COPD. These images can be used not only to quantify the airway and parenchyma characteristics but also to provide a roadmap linking airway paths to sub-lobar segment.

Evaluation of the lung at its functional interface

Computer-based methods for objective quantitation of MDCT data sets to compare normal and diseased lung are being used increasingly in conjunction with 2-dimensional data sets. Methods have ranged from counting the number of voxels below a cut-off (-850HU, -910HU, -950HU) [45–56] to methods that make use of measures derived from the histogram, including skewness, kurtosis, and so forth [57]. HRCT enhances the resolving power of the image [58–62], allowing detection of less severe emphysema. Various computer-assisted texture based methods have been used successfully for tissue characterization. Traditional methods of texture analysis can be grouped into statistical, structural, and hybrid methods [63]. Methods for tissue classification typically rely on region gray scale statistical measures (ie, mean, variance, and frequency histogram) or textural measures (autocorrelation, co-occurrence matrices, run-length matrices, and so forth) [46,47,55,57,64–74]. Lung tissue can be evaluated objectively by using the attenuation of lung tissue either as mean lung attenuation or by measuring the attenuation of lung falling below a set value (the density mask) [46,47,55,57,73]. It has been demonstrated that lung tissue mean attenuation can be an index of emphysema [46,47,55]. However, a later study showed significant lung attenuation variation in normal individuals that could be misleading [73]. To use attenuation distribution as a quantitative measure, much greater care must be taken to assure accurate scanner calibration in the air-water Hounsfield range and to standardize lung volumes at which scanning occurs [75–79]. Furthermore, one must consider that, in a longitudinal pharmaceutical study, lung attenuation is affected oppositely by changes in emphysema status and inflammation burden. A useful index of peripheral inflammation and airway disease has been a measure of air trapping. Quantitative tools used to access air trapping have been shown to be quite sensitive [80,81]. A density masking approach alone is not sufficient to distinguish normal lung from diseased lung, and Uppaluri and colleagues [82–84] have introduced what has been dubbed the “adaptive multiple feature method” (AMFM). This technique has used up to 26 different mathematical formulations to describe the gray scale heterogeneity of parenchymal regions within CT slices, and then it employed a Bayesian classifier to identify the best small number of mathematical formulations (“features”) that distinguish one texture (pathologic state) from another.. More recently, Xu and colleagues [85,86] have shown that using volumetric images with isotropic voxels for 3-dimensional texture assessment provides significant improvements in the assessment of regional parenchymal pathology. In one test, Xu and colleagues used the AMFM method with appropriate training sets to accurately differentiate the CT scans of normal smokers from those of normal non-smokers. The use of the texture analysis method is only as good as the training sets developed, and if it is desirable to use the method for detection of parenchymal pathology undetectable by the human observer, training paradigms such as the one used by Xu and colleagues must be established. Even when the training sets come from CT findings identified by human observers, the computer-based AMFM is more consistent than human observers in its assessment of lung regions. Quantitation of lung images has become critical, because pharmaceutical and device manufacturers seek to reduce the development time and seek to
Fig. 1. Images derived from MDCT-based imaging of a normal non-smoker (left) and a smoker who has emphysema (right). These images demonstrate the automatic segmentation of the lungs, lobes and bronchial tree with automatic bronchial tree labeling. Segmentation and display was done by way of a Pulmonary Workstation Plus (VIDA Diagnostics, Coralville, Iowa).
use imaging as a tool for the detection of regional lung changes (either a desired effect or an unwanted side effect) not reflected in the traditional pulmonary function tests, which provide a global measure of the pulmonary physiology, but are relatively insensitive to regional changes. Fig. 2 demonstrates a whole lung classification in which the AMFM simultaneously identified areas of emphysema (red), honeycomb (pink), normal (blue), and ground glass (yellow).

Functional imaging

Numerous imaging-based methods have been developed to assess ventilation, perfusion, or their functional outcome (gas exchange). Examples of how MDCT imaging technology is used to probe normal and abnormal cardiopulmonary structure and function are discussed later. The authors argue that MDCT technology offers a unique and comprehensive approach to evaluating the structural and functional complexity of the respiratory systems and cardiopulmonary systems.

Ventilation assessed by CT. The measurement of lung ventilation, lung volume, and tidal volume traditionally has been made for the entire lung, despite the fact that lung function in health and disease is inhomogeneous. Attempts have been made to quantify regional ventilation directly and indirectly with a variety of invasive techniques or radioisotope imaging [87–96], but these methods have been limited by invasiveness, poor spatial and temporal resolution, qualitative nature, or complexity. Xenon-enhanced MDCT (XE-MDCT) is a method for the noninvasive measurement of regional pulmonary ventilation, which is determined from the wash-in or wash-out rates of the radiodense, nonradioactive gas xenon as measured in serially acquired axial MDCT scans. Little work had been done since the original description of this technique nearly 25 years ago [97–100], although the FDA approval of XE-MDCT for measurement of cerebral blood flow has met with moderate clinical acceptance [101]. Recently, however, the application of XE-MDCT for measurement of regional pulmonary ventilation has been updated, validated, and refined, including extension of the technique to estimate regional perfusion and ventilation/perfusion ratio [28,102–111]. In Fig. 3, the authors demonstrate a typical xenon wash-in wash-out attenuation curve in a sheep, along with a color coded image of regional ventilation. Scanning was accomplished through gated imaging (end-expiration), while a fixed concentration of xenon gas was inspired during the wash-in phase, and then room air was inspired during the wash-out phase. A mono-exponential curve is fitted to the wash-in or wash-out phase, providing a time constant as a measure of ventilation. Because the dynamic XE-MDCT method requires the gated acquisition of axial CT images, timed so that the images are gathered at the same point in a series of standardized tidal breaths, the method has been applied most effectively to research animals breathing by way of respirators. The transfer of this methodology to humans has required the development of sophisticated feedback devices that monitor respiration by way of flow meters and displays that provide the subject with information

![Fig. 2. Whole lung classification using the 3-dimensional AMFM. Ellipses in the original image slice (left) represent emphysema (red) and honeycomb (purple) patterns. The tissue types are color coded: red, emphysema; pink, honeycomb; blue; normal; yellow, ground glass. (Data from Ye Xu. Computer aided 3-D texture analysis for lung characterization using MDCT images. PhD dissertation, University of Iowa, 2007.)](image-url)
related to targeted rate and depth of breathing information. Because of the complexity of such a system, there is considerable interest in the application of a single breath method using dual energy CT. With the introduction of dual source CT, it is possible to image a subject during a breath hold following the inhalation of a single breath of a mixture of xenon and oxygen. With the kV of the two x-ray sources set to 80kV and 140kV, it is possible to use material decomposition methods [19] to separate the xenon signal from the inherent x-ray attenuation of the lung [21,22]. Saba and colleagues [21] have demonstrated the feasibility of such an approach, using 80kV and 140 kV, during a single breath hold in a sheep. The images are presented in Fig. 4 and show the color coded xenon distribution superimposed upon the CT sections. In this sheep, a region of ventilation deficit in an area presenting with very subtle ground glass is demonstrated.

With the ability to retrospectively reconstruct 4-dimensional image data sets to represent a complete breathing cycle, it becomes possible to assess regional ventilation through the use of image matching algorithms [12–18,112]. Such image matching provides not only regional volume changes but also regional images of tissue strain, providing potential insights into local tissue properties such as early fibrosis and so forth. The use of such measures is being investigated only now.

Perfusion assessed by CT

Dynamic imaging methods have been used to estimate arterial, venous, and capillary transit times and capillary flow distributions [113–120]. These methods involve two types of image data collection regimes. Inlet-outlet detection is used typically for evaluating conducting vessels and whole organ analysis. The other data collection
regime, referred to as residue detection, typically is used alone or in conjunction with inlet detection, because analysis of microvascular regions wherein the individual vessels are below the resolution of the imaging system. Various approaches for determining blood flow and mean transit time have been described [114,117–127]. A growing number of studies demonstrate the use of MDCT with infusion of iodinated contrast agent to assess the presence of pulmonary emboli by way of visualization of flow voids in peripheral lung segments; the improved ability to detect pulmonary emboli, aortic dissection, and coronary atherosclerosis have resulted in the “triple ruleout” method for use in patients who have chest pain [128]. One must take care not to confuse this method to assess “flowing blood volume” with an assessment of true perfusion parameters. To assess regional parenchymal perfusion by way of dynamic axial MDCT [129,130], the authors place a catheter in the right ventricular outflow tract in animals and place a catheter in the superior vena cava in humans. A sharp (0.5 mL/kg over 2 seconds) bolus of iodinated contrast agent is delivered during ECG gated axial scanning. Scanning commences one to two heart beats before contrast injection, with lungs held at functional residual capacity. By sampling the reconstructed time-attenuation curves within the region of a pulmonary artery and the lung parenchyma as shown in Fig. 5, the authors were able to calculate regional mean transit times, blood flow normalized to air or tissue content [131]; the authors also were able to deconvolve the signals to estimate the timing of flow within the microvascular bed [129]. In Fig. 5 a color coded image of a non-smoker and a smoker who has normal pulmonary function tests but early CT findings of emphysema can be seen. In Fig. 5, color coding provides a regional depiction of mean transit time. Using this approach, Alford and colleagues [132] have demonstrated that heterogeneity of mean transit times is increased significantly in lung regions of smokers who have normal pulmonary function tests but who have very early CT evidence of emphysema. Through a series of recent publications [133–135], Hoffman and colleagues have used functional CT imaging to demonstrate that hypoxic pulmonary vasoconstriction normally is blocked when hypoxic conditions are accompanied by inflammation. These observations have lead to the hypothesis that the failure of inherent mechanisms to block the normal hypoxic pulmonary vasoconstrictor response of the pulmonary vasculature in the presence of inflammatory

Fig. 4. Dual energy color coded images in axial (A) and coronal (B) planes demonstrate the presence of xenon gas following the inhalation of a single breath of 80% xenon. Imaging was accomplished in the prone position at 80kV and 140kV, allowing subtraction of the xenon signal while minimally changing the signal from the natural occurring tissue of the body. Note the region of low or no xenon ventilation (white arrows, upper panel). This region had a ground glass pattern indicative of regional small airway inflammation. (Data from Saba OI, Fuld MK, Krauss B, et al. Dual energy MDC for volumetric assessment of V/Q: initial experiences. American Thoracic Society Annual Meeting 2007;A938; and Fuld M, Saba O, Krauss B, et al. Dual energy Xe-MDCT for automated assessment of the central airway tree: initial Experiences. American Thoracic Society Annual Meeting 2007;A250.)
Processes may lead to a failure of the normal response mechanisms serving to limit the inflammatory response, which will lead to the emphysema process. Fig. 6 provides a demonstration of an intact hypoxic pulmonary vasoconstrictor (HPV) response and an inflammation-based blocking of the HPV response in the same sheep. An endobronchial valve was placed in the animal, which allowed air out but did not allow air into a regional segment of the lung. At the same time, the animal arrived in the lab with regional pneumonia. Fig. 6 demonstrates that in the region of the valve, there is a shunting of blood flow away from the hypoxic lung region, whereas in the dependent regions of pneumonia, blood flow shunted away from the valve region is distributed preferentially to the region of inflammation, because it presumably represents the path of least resistance. These images demonstrate the power of advanced MDCT imaging to provide a link between structure and function.

MRI

MRI has several advantages over CT, including the speed of imaging, the lack of ionizing radiation, the ability to identify tissue characteristics, and the potential to obtain information on different nuclei, which allows for novel approaches to lung function and micro-structure assessment.
Technical requirements

Most modern MR systems will be capable of obtaining excellent quality proton images of the chest. This will lead to relatively black lungs and excellent delineation of the chest wall, mediastinum, and diaphragm. Parallel imaging sequences assist in obtaining images faster, within a single breath-hold, which allows for rapid image acquisition without the issue of motion artifact [136–138] A host of sequences are available, ranging from those focused on the diaphragm and mediastinum to those aimed at obtaining signal from the actual lungs themselves. Using intravenous gadolinium-based contrast agents, it is possible to delineate the pulmonary vascular tree and the right heart. Within the chest, MRIs almost always are obtained during a single breath-hold, although dynamic imaging during a respiratory cycle is feasible (for instance to demonstrate diaphragm excursions). Ultrafast imaging also is capable of obtaining dynamic contrast images, leading to interpretation of pulmonary perfusion.

Proton imaging

As with any MRI technique, proton imaging uses the large magnetic field and the free moving protons to derive signal from changes in proton orientation caused by radiofrequency pulses. The
lungs are different from the rest of the body, because there are a relative low number of protons and most of the lung parenchyma consists of air. Although this is a problem, it can be used to advantage, because pathologic processes tend to increase the number of protons (hemorrhage, edema, inflammation, or tumor) or alternatively lead to relative voids of proton density (as with calcification or fibrosis).

The application of differently weighted sequences will lead to an increase or decrease in proton signal. For instance, water will lead to increased signal on T2-weighted sequences and decreased signal on T1-weighted sequences, whereas fat will have increased signal on both sequences. Moreover, it is possible to produce fat saturation pulses, resulting in complete depression of signal from fat.

To achieve faster imaging times, several techniques may be used. The oldest of these uses half-Fourier techniques that only reconstruct slightly more than half the data space and extrapolate the missing data. This led to the single breath-hold sequences, which tend to be slightly T2-weighted and are employed also in a variety of other body imaging applications, such as MR cholangiopancreatography. The newer MRI systems all have the ability to perform parallel imaging techniques, which is somewhat similar to MDCT in that multiple slices are excited and read out simultaneously, thus increasing temporal resolution by a factor of 2–8 [136–138].

Although MRI has never really played a major role in routine chest imaging, several pathologic processes can be evaluated using proton imaging, including pleural effusions, pneumonia, lung tumors (particularly useful in Pancoast tumors and for determination of tumor invasion in mesothelioma) and the assessment of the mediastinum (Fig. 7) [139–141]. The technique is complementary to CT, although tissue plane definition and characterization is better using MRI.

Assessment of respiratory dynamics has become feasible with the advent of ultrafast proton imaging capabilities. This has resulted in novel approaches for assessment of the diaphragm, chest wall motion assessment, and breathing mechanics [142,143].

Gadolinium-enhanced imaging

The use of gadolinium contrast has enabled a rapid expansion of chest MRI, because it became feasible to assess enhancement of pathologic processes and visualization of the pulmonary vascular tree (as a static component and as dynamics of perfusion) and the other large arteries [144]. This allowed MRI to become competitive with more traditional CT techniques in several aspects of chest imaging, particularly imaging of the large vessels, including congenital anomalies, such as patent ductus arteriosus (Fig. 8) and the assessment of pulmonary hypertension (Fig. 9) [145,146]. Although CT has maintained a primary

---

Fig. 7. Patient who has sarcoidosis. Coronal proton single shot fast spin echo sequence demonstrating black lungs with some interstitial markings and extensive mediastinal and bilateral hilar lymphadenopathy.

Fig. 8. Sagittal 3-dimensional gadolinium-enhanced MR angiogram demonstrates direct connection between aorta and pulmonary artery (arrow), consistent with patent ductus arteriosus in a patient who has pulmonary hypertension.
role in the diagnosis of pulmonary embolism, the application of MRI for subsets of patients (like pregnant women or patients who will require follow-up imaging to assess response to therapy) is now feasible with very high-resolution MR angiographic imaging [147–149].

In addition to the above described imaging techniques, MRI also offers the possibility to assess perfusion of the lung vascular bed by ultrafast imaging during the injection of gadolinium contrast [150,151]. This enables direct visualization of regional perfusion, with the possibility of some form of quantification (though this is notoriously difficult in MRI because of signal-noise properties). Several studies have demonstrated the feasibility of this technique for assessment of normal and pathologic processes [152–155]. This application is now very close to general introduction into clinical practice.

**Hyperpolarized gas imaging**

MR imaging is versatile and has the capability to image other nuclei, including 3-helium and 129-xenon, provided the frequency of the system is adapted accordingly (for instance, for imaging 3-helium at a field strength of 1.5 Tesla, the radiofrequency amplifier and transmit/receive radiofrequency coils are tuned to 48 MHz, compared with 64 MHz for proton imaging) [156]. Researchers discovered the potential of these noble, stable gas isotopes as a side-effect to nuclear physics experiments, which required hyperpolarization of 3-He to produce neutron mirrors. Hyperpolarization is a process in which the atoms are brought to a higher energy level by introduction of laser light at the appropriate bandwidth. When this is achieved within a low magnetic field, the normally random population of spins will change to have a relatively higher population of atoms with spins aligned along the magnetic field. When this gas is introduced in an MRI environment, the usual radio frequency (RF) and response will result in enhanced signal, and this application successfully obtained the first images in the early-mid 1990s [157–159].

Among the noble gases, the application of hyperpolarized 3-He has been used widely so far in clinical research studies, because the gas has better signal-to-noise ratio and remains in the airways without further interaction with the human body (in contrast to 129-Xe, which is lipid soluble and has anesthetic properties at higher concentrations) [156]. However, improvement in hyperpolarization systems has meant that 129-Xe MRI is making rapid strides forward, giving new insight in lung function [160–162]. One of the main features of hyperpolarized gas imaging is that the signal introduced in the system is so high that imaging is less dependent on field strength (which is not the case for proton imaging), and this has advantages as lower field-strength magnets may result in fewer artifacts [163–165]. A main disadvantage to this technique is that the contrast is exogenous and non-renewable. To maximize the use of the contrast, one must design special pulse sequences to minimize loss of polarization by RF pulses and the paramagnetic effects of oxygen.

Several such techniques have been developed for hyperpolarized 3-He MRI, and these techniques have found a broad range of applications that may be of interest for the future assessment of pathophysiology, normal lung function, and structure.

All hyperpolarized gas imaging techniques rely on the delivery of a single breath of gas mixture into the airways, with the hyperpolarization either performed on site or by a central distribution network [166]. This usually is achieved through the inhalation of the content of a plastic bag, followed by a breath-hold lasting up to 16 seconds. Several thousands of applications have now taken place worldwide, and no significant adverse events have been observed [167,168].
Fig. 10. Examples of hyperpolarized 3-He MRI and correlation with HRCT. (A, B) Patient who has alpha-1-antitrypsin deficiency. Notice basal ventilation defects on coronal MRI (A), with corresponding panlobular emphysema on axial CT (B). (C, D) Patient who has cystic fibrosis. Notice upper lobe cystic bronchiectasis on axial HRCT (C) with corresponding ventilation defects on coronal hyperpolarized 3-He MRI (D). (E, F) Patient who has lung cancer. On coronal proton image a large soft tissue mass is visualized in the right upper lung (E), which corresponds to upper lobe ventilation defect on hyperpolarized 3-He MRI (F).
Ventilation distribution is built on the notion that any area with signal is a reflection of the delivery of 3-He gas to this area. It is possible to obtain a 3-dimensional volumetric dataset of the lungs using this technique [169], and several authors have shown the use of this technique in normal volunteers and patients who have asthma, emphysema (including alpha-1-antitrypsin deficiency; Fig. 10A), cystic fibrosis (Fig. 10B), and lung cancer (Fig. 10C) [170–177]. There is homogeneous ventilation distribution in normal volunteers, although small ventilation defects are seen frequently [170,178–180]. In smoking subjects who have normal pulmonary function tests, ventilation defects usually are detectable [181]. In patients who have emphysema, ventilation defects tend to be worse than in normal smokers and correlate with pulmonary function tests [170,180]. In asthmatic subjects, ventilation defects can be provoked using methacholine; these defects are reversible using a bronchodilator and correlate with pulmonary function tests, [171,182] but quantification can be slightly more problematic. One method, using a subtraction of the proton MR mask from the hyperpolarized 3-He images, has shown a very good repeatability with robust measurements and effectively yields “ventilated lung” as a percentage of overall chest cavity volume in a group of normal and smoking subjects [183].

A limited study has been performed in patients who have lung cancer, suggesting that it may be feasible to use hyperpolarized 3-He MRI as a tool for the planning of radiation fields, which offers the possibility of higher tumor dose and of sparing relatively healthy lung, and thereby the reduction of radiation pneumonitis [177]. Finally, limited studies in lung transplant recipients showed that 3-He MRI was capable of detecting abnormal ventilation [184] and was more sensitive than HRCT or spirometry for the detection of bronchiolitis obliterans and ventilation abnormalities [185,186].

Fig. 11. ADC imaging in a normal volunteer in different positions, demonstrating gravity dependent changes with decreased ADC values in dependent lung portions. (Reproduced from Fichele S, Woodhouse N, Swift AJ, et al. MRI of helium-3 gas in healthy lungs: posture related variations of alveolar size. J Magn Reson Imaging 2004;20(2):333; with permission.)
Diffusion imaging is feasible, making use of the very high diffusivity of 3-He. When using several RF pulses separated by a pre-determined time interval, the MR system is capable of obtaining information on the distance traveled by the atoms. In a free open environment, this is compared further with a restricted environment that exists within the lung and airways. Thus, the lung structure actually reduces the effective diffusion distance caused by the Brownian motion of 3-He atoms and leads to what is known as apparent diffusion coefficient (ADC) measurements, which are a direct representation of small airway size and which correlate closely with histology [187]. Discussion has taken place as to whether these measurements represent terminal bronchioles, and different techniques are being developed to assess longer or shorter measurement times, thus allowing for assessment of collateral ventilation (longer time scales) or true alveolar measurements (shorter time scales) [188,189].

ADC works by application of gradient echo pulse sequences at two different intervals, resulting in changes of polarization loss between more or less confined atoms. The ratio of these polarization changes allow the spatial mapping of ADC, with higher values allocated to larger air spaces (such as trachea and large bronchi) [190]. ADC is distributed homogeneously in normal subjects and becomes progressively more heterogeneous in normal smokers who have emphysema [191–194]. ADC has been shown to increase under the influence of aging [195,196] and emphysema [194,197,198] caused by gravity dependent compression of the lung [199]; Fig. 11). A significant issue is that ADC measurements can only take place in areas where 3-He signal is present. In disease states with airway obstruction, such as those seen in mucus plugging, this will affect the overall results.

Dynamic ventilation imaging enables the visualization of the 3-He signal as it flows into the main airways down to the peripheral airspaces and makes use of a combination of ultra-fast imaging sequences and image reconstruction techniques that effectively interpolate the changes that occur during the imaging process, resulting in frame rate in the order of 5–10 milliseconds [200,201]. Ventilation can be quantified by obtaining curves of signal change during the imaging time, and it appears that the resulting curves closely correlate with (overall) lung function tests, as demonstrated in Fig. 12 in a young patient who has cystic fibrosis [202,203]. In addition, by

![Fig. 12. Dynamic 3-He MRI reconstruction of signal change over time during single inspiration demonstrates the slope of the curve, which may be translated to forced inspiratory volume during 1 second. (Data from Koumellis P, van Beek EJ, Woodhouse N, et al. J Magn Reson Imaging 2005;22(3):420–6.)](image-url)
prolonging the duration of the imaging process or by starting the MR data acquisition later in the respiratory cycle, it is possible to assess for regional air trapping, which may be relevant in various types of airway outflow obstruction.

Oxygen sensitive imaging uses the paramagnetic effect of oxygen as a calculable decrease in the signal of 3-He caused by loss of polarization. Thus, in areas where oxygen is absorbed rapidly (eg, ventilation-perfusion matching), the signal of 3-He will remain, whereas in areas where oxygen remains in the airways, (eg, ventilation-perfusion mismatch) the 3-He signal will demonstrate a faster decay [204–206]. It is now feasible to obtain 3-dimensional maps of oxygen uptake ratios (or ventilation-perfusion studies in animal model settings [208,209]. The method is still being developed, but it may be able to assist (among many other options) the assessment of pulmonary thromboembolic disease (in particular, chronic disease patients in the preoperative assessment of thromboendarterectomy), the planning of surgical or endobronchial interventions, and the preoperative assessment of patients who have borderline respectability of lung cancer. Several groups have demonstrated the feasibility of combining perfusion and ventilation studies in animal model settings [208,209].

References

[25] Stillsman AE, Oudkerk M, Ackerman M, et al. Use of multidetector computed tomography for the


[114] Capen RL, Latham LP, Wagner WW Jr. Comparison of direct and indirect measurements of


