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Functional Imaging: CT and MRI

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Abstract

Synopsis—Numerous imaging techniques permit evaluation of regional pulmonary function. Contrast-enhanced CT methods now allow assessment of vasculature and lung perfusion. 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 rapid bolus injections of iodinated contrast agent can provide quantitative measure of regional parenchymal perfusion. Advances in magnetic resonance imaging (MRI) of the lung include gadolinium-enhanced perfusion imaging and hyperpolarized helium imaging, which can allow imaging of pulmonary ventilation and measurement of the size of emphysematous spaces.

Keywords

Quantitative CT; Airways; Parenchyma; Ventilation; Perfusion; Xenon CT; Computer Aided Detection; Lung Function; MDCT; MRI; Dual Source CT

INTRODUCTION

The traditional approach to lung imaging, using so-called high-resolution computed tomography (HRCT) consisting of 1 mm slices, is increasingly replaced 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, magnetic resonance imaging (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, both 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

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diseases which tend to be chronic with acute exacerbations, thus requiring 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 towards making access easier and in many centers MRI has already become a main diagnostic tool.

This chapter intends to describe some of the new features involving lung imaging, both from a CT and a MRI perspective. It is our intention that the reader be familiar with the currently available techniques as well as those that are expected to reach clinical applications in the near future.

COMPUTED TOMOGRAPHY

The scanners

Volumetric physiological imaging via x-ray CT had its beginning in the mid 1970's with the Dynamic Spatial Reconstructor, 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 lagged significantly behind this early work. The electron beam CT (EBCT), (3) used parallel X-ray targets to get improved scan speeds up to 50 msec 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 2D detector array, allowing larger scanning range in shorter time with higher image resolution (5,6). Acquiring multiple image slices per rotation with rotation speeds as short as 0.3sec allows 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. We have believed 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 0.5mm isotropic voxel and achieve a full rotation scan aperture of 150 msec and have superior contrast resolution for radiopaque gas and injected contrast detection. The system will be likely coupled with a low Tesla MR scanner which 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 use of the CT component.

With the introduction of dual source MDCT (7,8) into the clinical arena, scan apertures now fall below 150 msec, but z axis coverage with single rotation on these scanners remains at 2.4cm. 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 12cm. By the end of 2007, 128 rows and 4cm z-axis coverage will be the minimum configuration of the high-end MDCT scanners. With the broader coverage, retrospective gating methods have emerged for both cardiac as well as pulmonary imaging whereby, via 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 such that a volumetric image data set is reconstructed for just that location of the respiratory or cardiac cycle. Multiple portions of the physiologic cycle can thus 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 have questioned how many slices is enough. The answer to this question is largely determined by the more advanced functional

applications such as retrospective gating technologies, ventilation, and/or perfusion imaging. As discussed below, perfusion and ventilation imaging requires an axial mode of scanning to dynamically track the first pass of a sharp bolus of contrast agent (approximately 0.5cc/kg over 2–3 seconds injected into the vena cava/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 dynamically evaluate the whole lung then one must have a 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 as well as 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 as well as 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, without the. This simultaneous acquisition avoids the need for acquisition of separate unenhanced and enhanced scans, with associated of added radiation dose, and alignment challenges due to 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, etc.. 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 as well as a virtual unenhanced image(20). The accuracy of the Hounsfield units in the virtual unenhanced image remains untested, and thus it is not clear whether 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 as a “perfused blood volume“ scan, (23–25) so as not to confuse this measure with the quantitative assessment of parenchymal perfusion discussed below. With dual energy imaging, it may be possible to obtain a volumetric image of regional ventilation along with regional lung structure by imaging with dual energy spiral scanning during a single breath of xenon gas . (21,22) This again is an experimental method yet to be validated against the dynamic xenon CT assessment of regional ventilation discussed later in this section. The single breath, dual energy xenon method has been successfully employed in rabbits using a synchrotron source. (26–28)

Quantitative image analysis

Critical to taking full advantage of MDCT (and MRI) is the ability to objectively evaluate the information content of the images. In the case of the lung, the starting point is reliable detection of the lungs (29), lobes (30), airways (31–41) , and blood vessels followed by an analysis of parenchymal attenuation and texture and finally a regional quantification of ventilation and perfusion parameters. We and others have reviewed these capabilities elsewhere (42,43). With the advent of MDCT and isotropic voxels, it is now possible 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 commonly expressed 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 both asthma and COPD. Figure 1 shows a depiction of the airway tree and lobe segmentation from both a normal non-smoker and a patient with COPD. These images can be used to not only quantify the airway and parenchyma characteristics but also to provide a

roadmap linking airway paths to sub-lobar segment. These data were acquired using the VIDA PW+ workstation (Coralville, Iowa).

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 increasingly being used in conjunction with 2D data sets. Methods have ranged from counting the number of voxels below a cut-off (-850, -910, -950HU) (45–56) to those which make use of measures derived from the histogram including skewness, kurtosis, etc. (57). High resolution computed tomography (HRCT), enhances the resolving power of the image (58–62) allowing detection of less severe emphysema. Various computer-assisted texture based methods have successfully been used 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 (i.e.: mean, variance, frequency histogram) or textural measures (autocorrelation, co-occurrence matrices, run-length matrices, etc.) (46,47,55,57,64–74). Lung tissue can be objectively evaluated 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 needs to be taken to assure accurate scanner calibration in the air-water Hounsfield range and lung volumes at which scanning occurs need to be standardized. (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 to access air trapping have been shown to be quite sensitive. (80,81) A density masking approach alone is not sufficient to distinguish normal from diseased lung and Uppaluri et al. have introduced what has been dubbed the Adaptive Multiple Feature Method (AMFM).(82–84) This technique has utilized up to 26 different mathematical formulations to describe the gray scale heterogeneity of parenchymal regions within CT slices and then employed a Bayesian classifier to identify the best, small number of mathematical formulations (“features”) which distinguish one texture (pathologic state) from another.. More recently, Xu et al. (85,86) have shown that using volumetric images with isotropic voxels for 3D texture assessment provides significant improvements in the assessment of regional parenchymal pathology. In one test, Xu et al 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 must be established. Even when the training sets come from CT findings identified by human observers, the computer-based AMFM can be shown to be more consistent than human observers in its assessment of lung regions. Quantitation of lung images has become critical as pharmaceutical and device manufacturers seek to reduce the development time and seek to 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. Figure 2 demonstrates a whole lung classification in which the AMFM simultaneously identified areas of emphysema (red), honeycomb pink), normal (blue), and ground glass (yellow). These data are from the work of Xu et al (204).

Functional imaging—Numerous imaging-based methods have been developed to assess ventilation, perfusion, or their functional outcome - gas exchange. Below we will show

examples of the use of MDCT imaging technology to probe normal and abnormal cardiopulmonary structure and function. We argue that MDCT technology offers a unique and comprehensive approach to evaluating the structural and functional complexity of the respiratory and cardiopulmonary systems.

Ventilation assessed by CT: The measurement of lung ventilation, lung volume, and tidal volume has traditionally been made for the entire lung, despite the fact that lung function in both health and disease is inhomogeneous. Attempts have been made to quantify regional ventilation both 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, and/or complexity. Xenon-enhanced MDCT (Xe-MDCT) is a method for the non-invasive measurement of regional pulmonary ventilation, determined from the wash-in and/or wash-out rates of the radiodense, non-radioactive gas xenon as measured in serially acquired, axial MDCT scans. Little work had been done since the original description of this technique nearly twenty five 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 V/Q (28,102–111) In Figure 3, we 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) as a fixed concentration of Xenon gas was inspired during the wash-in phase and then room air was inspired during wash-out. 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 most effectively applied to research animals breathing via respirators. The transfer of this methodology to humans has required the development of sophisticated feedback devices which monitor respiration via flow meters and displays which provide the subject with information 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 utilizing 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 80 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 et al (21) have demonstrated the feasibility of such an approach, using 80 and 140 kV, during a single breath hold in a sheep. The images are presented in figure 4 showing 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 4D 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, etc. The utility of such measures is only just now being investigated.

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 typically used for evaluating conducting vessels and whole organ analysis. The other data collection regime, referred to as residue detection, is typically used, alone or in conjunction with inlet

detection, for analysis of microvascular regions wherein the individual vessels are below the resolution of the imaging system. Various approaches for determining blood flow and/or mean transit time have been described (114,117–127). There have been a growing number of studies, demonstrating the use of MDCT with infusion of iodinated contrast agent to assess the presence of pulmonary emboli via visualization of flow voids in peripheral lung segments, and the improved ability to detect pulmonary emboli, aortic dissection and coronary atherosclerosis have resulted in the “triple ruleout” method for use in patients with 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 via dynamic axial MDCT, (129,130) we place a catheter in the right ventricular outflow tract in animals and in the superior vena cava in humans. A sharp (0.5 cc per kg over 2 seconds) bolus of iodinated contrast agent is delivered during ECG gated axial scanning. Scanning commences 1–2 heart beats prior to contrast injection with lungs held at functional residual capacity (FRC). By sampling the reconstructed time-attenuation curves within the region of a pulmonary artery and the lung parenchyma as shown in figure 5, we are able to calculate regional mean transit times, blood flow normalized to air or tissue content (131), and we are able to deconvolve the signals such that we can estimate the timing of flow within the microvascular bed (129). In figure 5 we show a color coded image of a non-smoker and a smoker with normal pulmonary function tests but early CT findings of emphysema. Here, color coding provides a regional depiction of mean transit time. Using this approach, Alford et al(132) have demonstrated that heterogeneity of mean transit times is significantly increased in lung regions of smokers who have normal pulmonary function tests but who have very early CT evidence of emphysema. Through a series of publications recently (133–135)) Hoffman and colleagues have used functional CT imaging to demonstrate that hypoxic pulmonary vasoconstriction is normally blocked when hypoxic conditions are accompanied by inflammation. These observations have led to the hypothesis that the failure of inherent mechanisms to block the normal hypoxic pulmonary vasoconstrictor (HPV) response of the pulmonary vasculature in the presence of inflammatory processes may lead to a failure of the normal response mechanisms serving to limit the inflammatory response and thus lead to the emphysema process. Figure 6 provides a demonstration of both an intact hypoxic pulmonary vasoconstrictor response as well as an inflammation-based blocking of the hypoxic pulmonary vasoconstrictor response in the same sheep. This animal had an endobronchial valve placed which allowed air out but not into a regional segment of the lung. At the same time, the animal arrived in the lab with regional pneumonia. The images demonstrate that in the region of the valve, there is a shunting of blood flow away from the hypoxic lung region while in the dependent regions of pneumonia, blood flow shunted away from the valve region is preferentially distributed to the region of inflammation because it presumably represents the path of least resistance. We show these images to demonstrate the power of advanced MDCT imaging to provide a link between structure and function.

MAGNETIC RESONANCE IMAGING

MRI has several advantages over CT, including speed of imaging, lack of ionizing radiation, ability to identify tissue characteristics and potential to obtain information on different nuclei allowing 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, thus allowing 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 as well as the right heart. Within the chest, MR images are almost always obtained during a single breath-hold, although dynamic imaging during a respiratory cycle is feasible (for instance to demonstrate diaphragm excursions). Ultrafast imaging is also 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 due to radiofrequency pulses. The lungs are different from the rest of the body, as there is 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 as pathological 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 increase or decrease in proton signal. For instance, water will lead to increased signal on T2 weighted 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.

In order to achieve faster imaging times, several techniques may be used. The oldest of these uses half-Fourier techniques, which 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 that are also employed in a variety of other body imaging applications, such as MRCP. The newer MRI systems all have the ability to perform parallel imaging techniques, which is somewhat similar to multidetector row CT 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 pathological 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 (Figure 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 diaphragm and chest wall motion assessment and breathing mechanics. (142,143).

Gadolinium-enhanced imaging

The use of Gadolinium contrast has enabled a rapid expansion of chest MR imaging, as it became feasible to assess enhancement of pathological processes as well as visualization of the pulmonary vascular tree (both as static component and 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 (Figure 8) and the assessment of pulmonary hypertension (Figure 9). (145,146) Although CT has maintained a primary role in the diagnosis of pulmonary embolism, the application of MRI for subsets of patients like

pregnant women or those that 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 offers the possibility to assess perfusion of the lung vascular bed by ultra-fast 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 due to signal-noise properties). Several studies have now demonstrated the feasibility of this technique for assessment of normal and pathological 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 whereby 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 a MRI environment, the usual RF frequency 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 so far been widely used in clinical research studies, as 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-Xenon MR imaging 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 than is 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 is non-renewable. In order 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 (more about this below). Several such techniques have been developed for hyperpolarized 3-Helium MRI and these have found a broad range of applications that may be of interest for the future assessment of pathophysiology as well as 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 is usually achieved through the inhalation of the content of a plastic (Tedlar) bag, followed by a breath-hold lasting up to 16 seconds. Several thousands of applications have now taken place world-wide, and no significant adverse events have been observed. (167,168)

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 3D volumetric dataset of the lungs using this technique (169), and several authors have shown the utility of this technique in normal volunteers, patients with asthma, emphysema (including alpha-1-antitrypsin deficiency; Figure 10A), cystic fibrosis (Figure 10B) and lung cancer (Figure 10C). (170–

177) There is homogeneous ventilation distribution in normal volunteers, although small ventilation defects are frequently seen. (170,178–180) In smoking subjects with normal pulmonary function tests, ventilation defects are usually already detectable. (181) In patients with 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, and these are reversible using 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 with lung cancer, suggesting that it may be feasible to use hyperpolarized 3-He MRI as a tool for the planning of radiation fields, offering the possibility of higher tumor dose and sparing of 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 more sensitive than HRCT or spirometry for the detection of bronchiolitis obliterans and ventilation abnormalities. (185,186)

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 significantly further compared to a restricted environment that exists within the lung and airways. Thus, the lung structure actually reduces the effective diffusion distance due to Brownian motion of 3-He atoms, leading to what is known as apparent diffusion coefficient (ADC) measurements, which are a direct representation of small airways size and correlated closely with histology. (187) Discussion has taken place whether these measurements represent terminal bronchioles, and different techniques are under development 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 homogeneously distributed in normal subjects, and becomes progressively more heterogeneous with normal smokers to emphysema (191–194). ADC has been shown to increase under the influence of aging (195, 196), emphysema (194,197,198) and due to gravity dependent compression of the lung (199); Figure 11). A significant issue is the fact that ADC measurements can only take place in areas where 3-He signal is present. In disease states with airway obstruction, such as 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 ms. (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 Figure 12 in a young patient with cystic fibrosis. (202,203) In addition, by 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 airtrapping, 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 ^3He due to loss of polarization. Thus, in areas where oxygen is absorbed rapidly (e.g. ventilation-perfusion matching) the signal of ^3He will remain, whereas areas where oxygen remains in the airways (e.g. ventilation-perfusion mismatch) demonstrate a faster signal loss. (204–206); It is now feasible to obtain 3D maps of oxygen uptake ratios (or ventilation-perfusion maps) using a single breath-hold technique. (207) The method is still under development, but may be able to assist, among many other options, the assessment of pulmonary thromboembolic disease (in particular chronic disease patients in the pre-operative assessment of thromboendarterectomy), the planning of surgical or endobronchial interventions and the pre-operative assessment of patients with borderline respectability of lung cancer. Several groups have demonstrated the feasibility of combining perfusion and ventilation studies in animal model settings .(208,209)

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Glossary

Apparent diffusion coefficient, A measure of the peripheral air space size in the lung as assessed via polarized gas methods

Attenuation, The unit of measure of a CT scan related to regional lung tissue density

Density mask, A measure of the number of voxels in a region of interest (such as the lung field) which fall below or above a given Hounsfield Unit

Dual energy CT, Use of CT images obtained with the x-ray guns set at two different kilo voltage settings (such as 80 and 140kV) to allow for the separation coincident materials such as tissue and iodine or iodine and bone, etc.

Dual source CT, Use of two x-ray guns and associated detector rows on a single rotating gantry to allow for more rapid acquisition of projection images used in the image reconstruction process. This reduces motion blur of rapidly moving structures such as the heart and allows for the use of dual energy imaging for the separation of coincident materials. (see above)

Dynamic scan, Imaging in an axial mode in rapid succession either through timing or gating to a physiological signal. The temporal series of images are used to assess physiological events such as respiration, blood flow, cardiac wall contraction, etc.

Gating, Timing of image acquisition (projection images in the case of CT scanning) such that the projection images are gathered at a fixed point of a physiological cycle such as a particular point in the respiratory or cardiac cycles.

Gray scale, A scaled representation of the x-ray attenuation coefficients within the reconstructed cross sections produced through the process of CT imaging.

Hounsfield units, A scaled representation of the x-ray attenuation coefficient also referred to as the image "gray scale." Air is -1000, water is 0 and dense bone is +1000.

Multi-detector row CT (MDCT), A CT scanner which utilizes a cone beam x-ray source, coupled with more than one row of juxtaposed detectors to allow for the more rapid acquisition of projection data used to reconstruct CT cross sectional images. Currently scanners are available for clinical use with up to 320 rows of detectors.

Pitch, Table travel divided by the total collimation of the x-ray beam.

Scan aperture, Time required to generate the projections used in the reconstruction of a CT slice. This may take the form of an effective scan aperture if a short period of time within multiple physiological cycles are used in the reconstruction process. The period of time within a single cycle would be considered to be the "scan aperture."

Spiral CT, A method whereby projection images are gathered as the patient is moved through the scanning plane.

Tesla, A measure of magnetic flux per square meter

Volumetric, the acquisition of a stack of cross sectional images with near isotropic voxels.

Voxel, An image volume element. The two dimensional equivalent is a pixel. The term voxel recognizes that a cross sectional image has a thickness. A voxel is a three-dimensional point in space for which there is a reconstructed value (in the case of CT this is the x-ray attenuation coefficient or Hounsfield unit, in MRI the value can represent many different units of measure).

Z-axis, The axis running perpendicular to the scanned plane, typically head to foot in a recumbent patient.

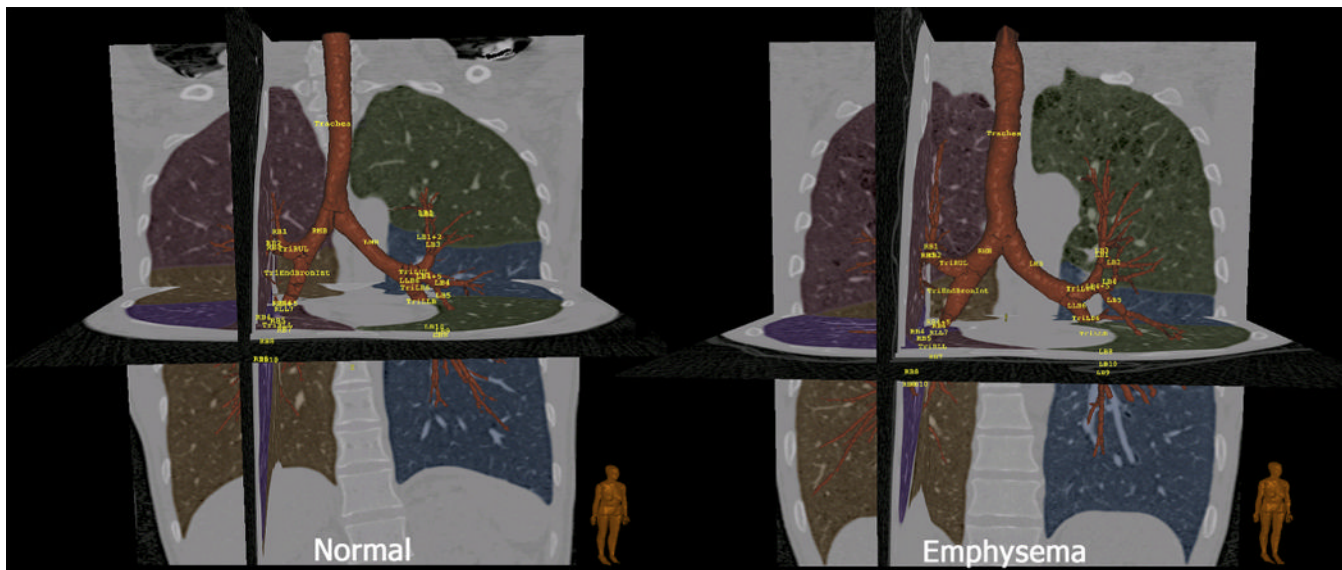


Figure 1. Images derived from MDCT-based imaging of a normal non-smoker (left) and a smoker with emphysema (right). These images demonstrate the automatic segmentation of the lungs, lobes and bronchial tree with automatic bronchial tree labeling. Segmentation and display was via a Pulmonary Workstation Plus (VIDA Diagnostics: Coralville, Iowa)

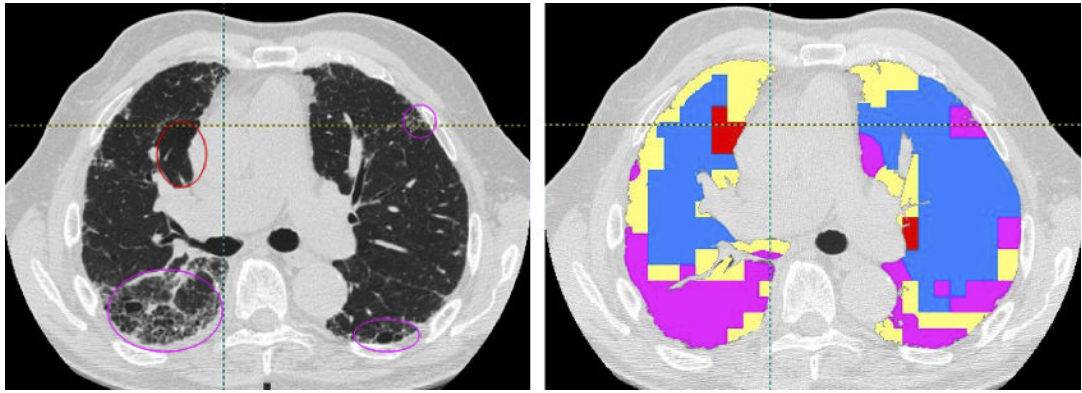


Figure 2. Whole lung classification using the 3D AMFM. Ellipses in the original image slice (left) represent emphysema (red) and honeycomb (purple) patterns. The tissue types are color coded as: Red=emphysema, pink=honeycomb, blue=normal, and yellow=ground glass. (Data are from the thesis work of Ye Xu, University of Iowa, 2007)

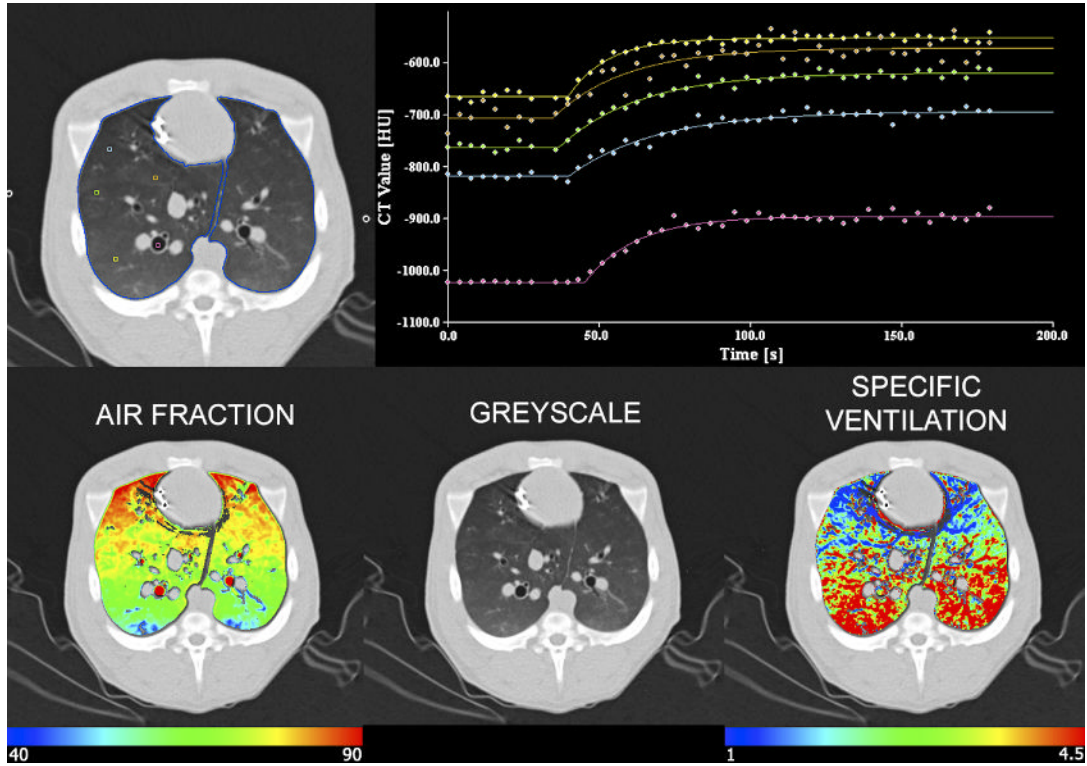


Figure 3. Demonstration of the density changes occurring regionally across time as a result of the re-breathing of a constant concentration of xenon gas. Imaging is in the axial mode and scans are gated to end expiration. Data shown are from a supine anesthetized pig. In the upper panel, regions of interest are sampled including parenchymal regions spaced from the dependent to the non-dependent lung regions, with one region of interest in a right sided bronchus. It can be seen that the exponential rise from baseline is sharper in the dependent (yellow) region vs a much shallower exponential rise in the non-dependent region (blue). The sharp and shallow rise from baseline represent a fast or slow gas turnover rate respectively. Note the gradient in specific ventilation (lower right) where specific ventilation is the gas turn over rate (time constant) normalized by the local amount of air in that region of lung.

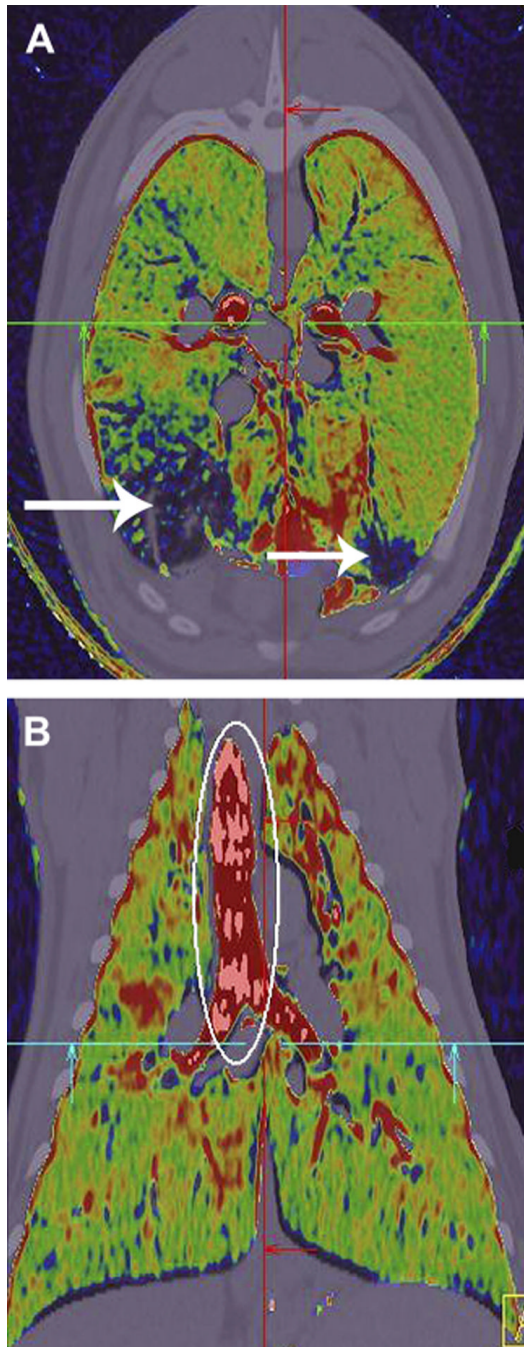


Figure 4. Dual energy color coded images in axial (a) and coronal (b) planes demonstrate the presence of xenon gas following the inhalation of a single breath of 80% xenon. Imaging was accomplished in the prone position at 80 and 140kV, allowing subtraction of the xenon signal while minimally changing 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 the work of Fuld et al. [56] and Saba et al. [145]

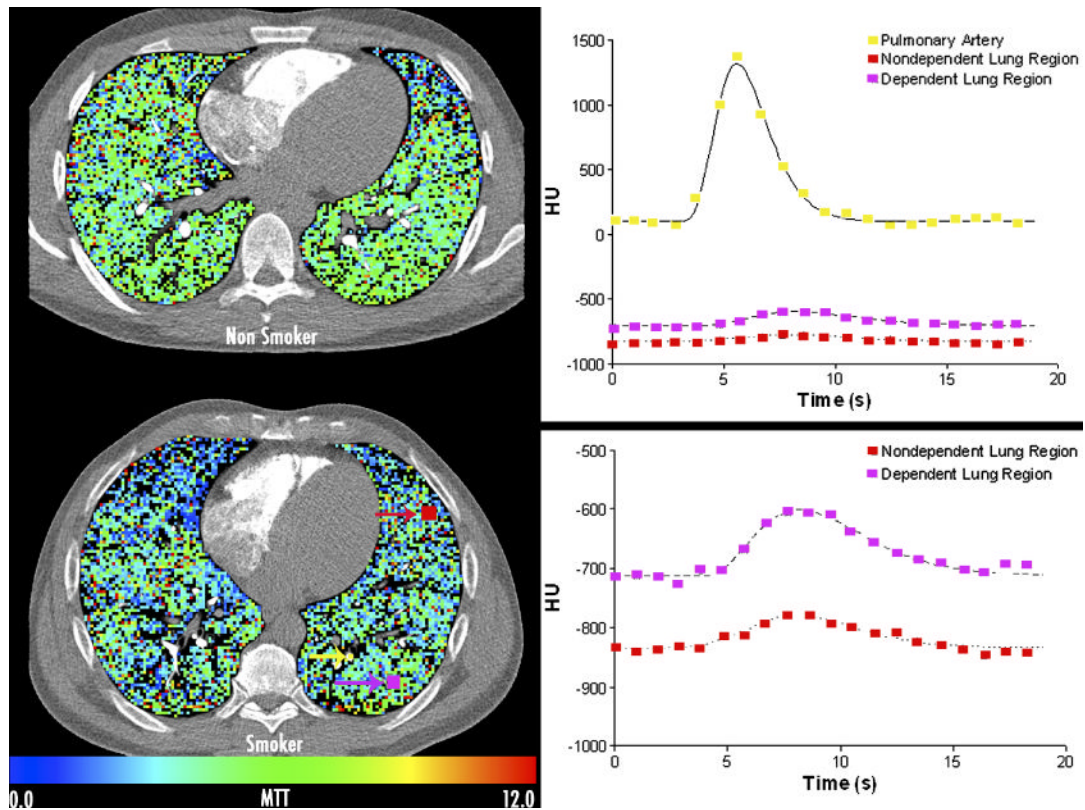


Figure 5.

Regional assessment of pulmonary blood flow mean transit times via use of temporally sequenced axial imaging, gated to the electrocardiogram during a sharp bolus contrast injection (0.5cc/kg iodinated contrast agent) into the superior vena cava / right atrial junction in a normal non-smoking (upper left) and a smoker (lower left) with CT showing only findings of early emphysema. Regions of interest are highlighted in the lower left image showing an ROI placed in the pulmonary artery (yellow); non-dependent (red) and dependent (purple) parenchymal regions. Associated time intensity curves are shown, from which mean transit times and pulmonary blood flow may be calculated, with the parenchymal curves expanded in the lower right graph. Studies have shown that the regional heterogeneity of pulmonary blood flow mean transit times are significantly increased in the smokers with CT findings of emphysema. Data from the work of Alford et al [3]

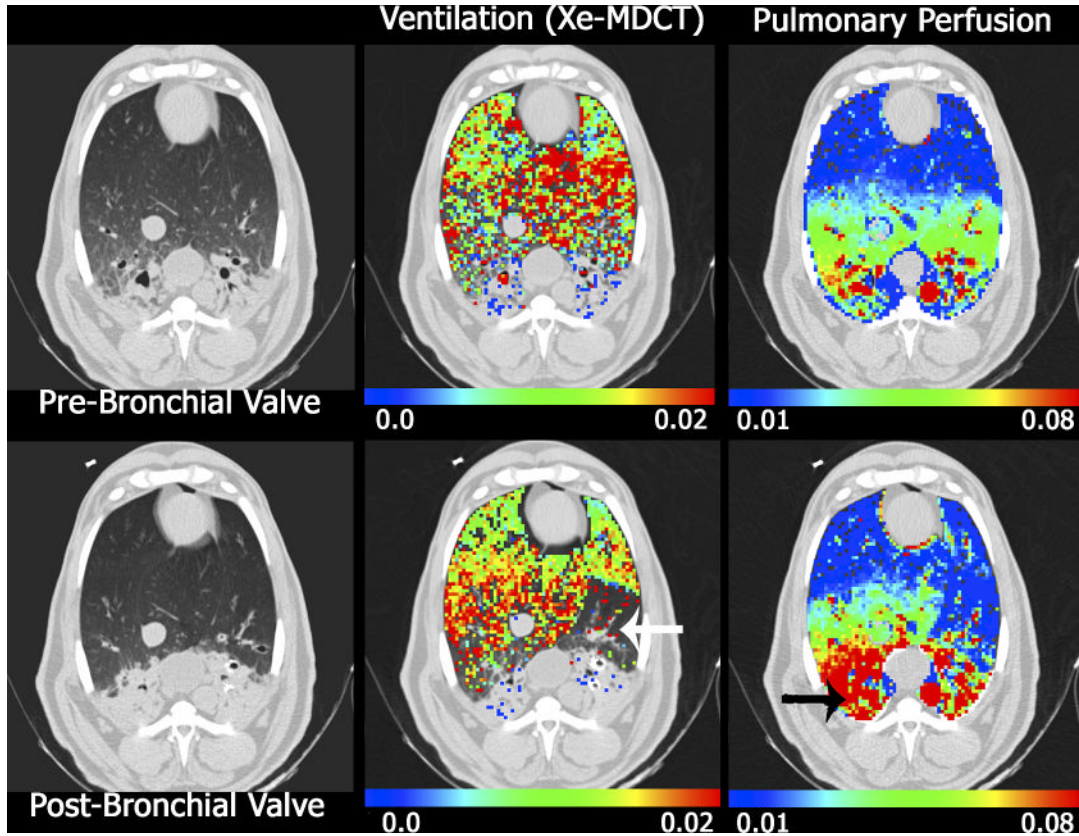


Figure 6. Axial images from a sheep with native pneumonia (dependent lung regions), imaged supine, anesthetized in the MDCT scanner. Ventilation (middle column) and perfusion (left column) data sets were obtained before (upper rows) and after (lower rows) the placement of an endobronchial valve. The white arrow in the lower middle column marks the location of ventilation defect caused by the endobronchial valve. In this same region on the perfusion images (see lower right) there is a regional reduction in perfusion indicating regional, intact hypoxic pulmonary vasoconstriction. The black arrow in the lower right image marks a region that preferentially receives an increase in blood flow following the shunting of perfusion from the regional of the endobronchial valve, presumably because regional HPV is blocked in the presence of inflammation. Reprinted with permission from [74]

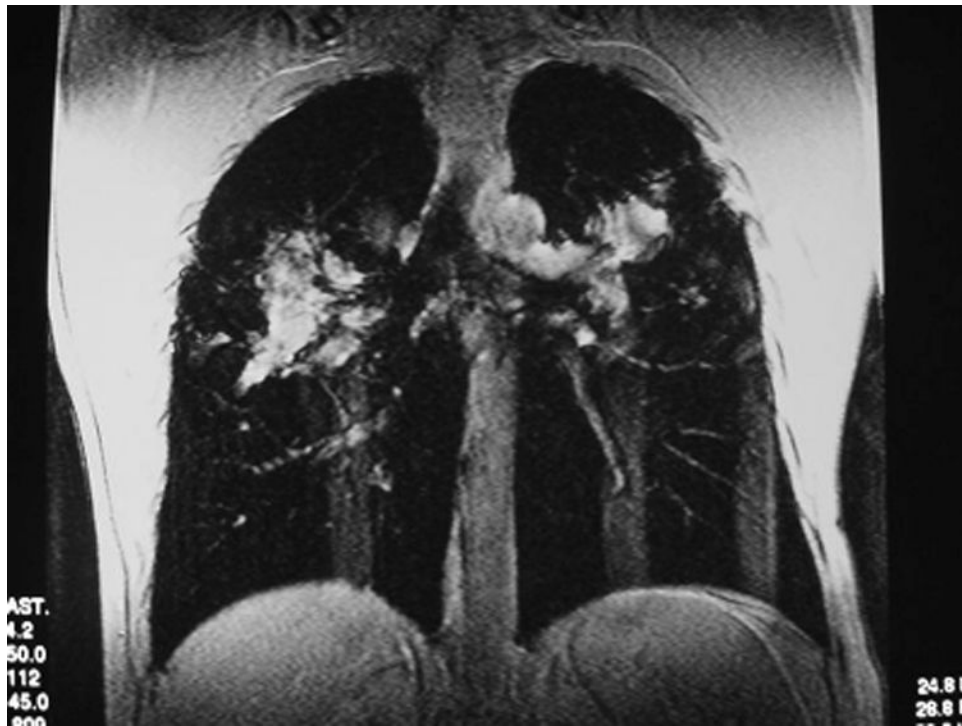


Figure 7. Patient with sarcoidosis. Coronal proton single shot fast spin echo sequence, demonstrating black lungs with some interstitial markings and extensive mediastinal and bilateral hilar lymphadenopathy.



Figure 8. Sagittal 3D-Gadolinium-enhanced MR angiogram, demonstrating direct connection between aorta and pulmonary artery (arrow), consistent with patent ductus arteriosus in a patient with pulmonary hypertension.



Figure 9. Coronal 3D-Gadolinium-enhanced MR angiogram, demonstrating enhancement of an aneurysm of the right pulmonary artery with a black rim of mural organized thrombus (arrow) in a patient with pulmonary hypertension.

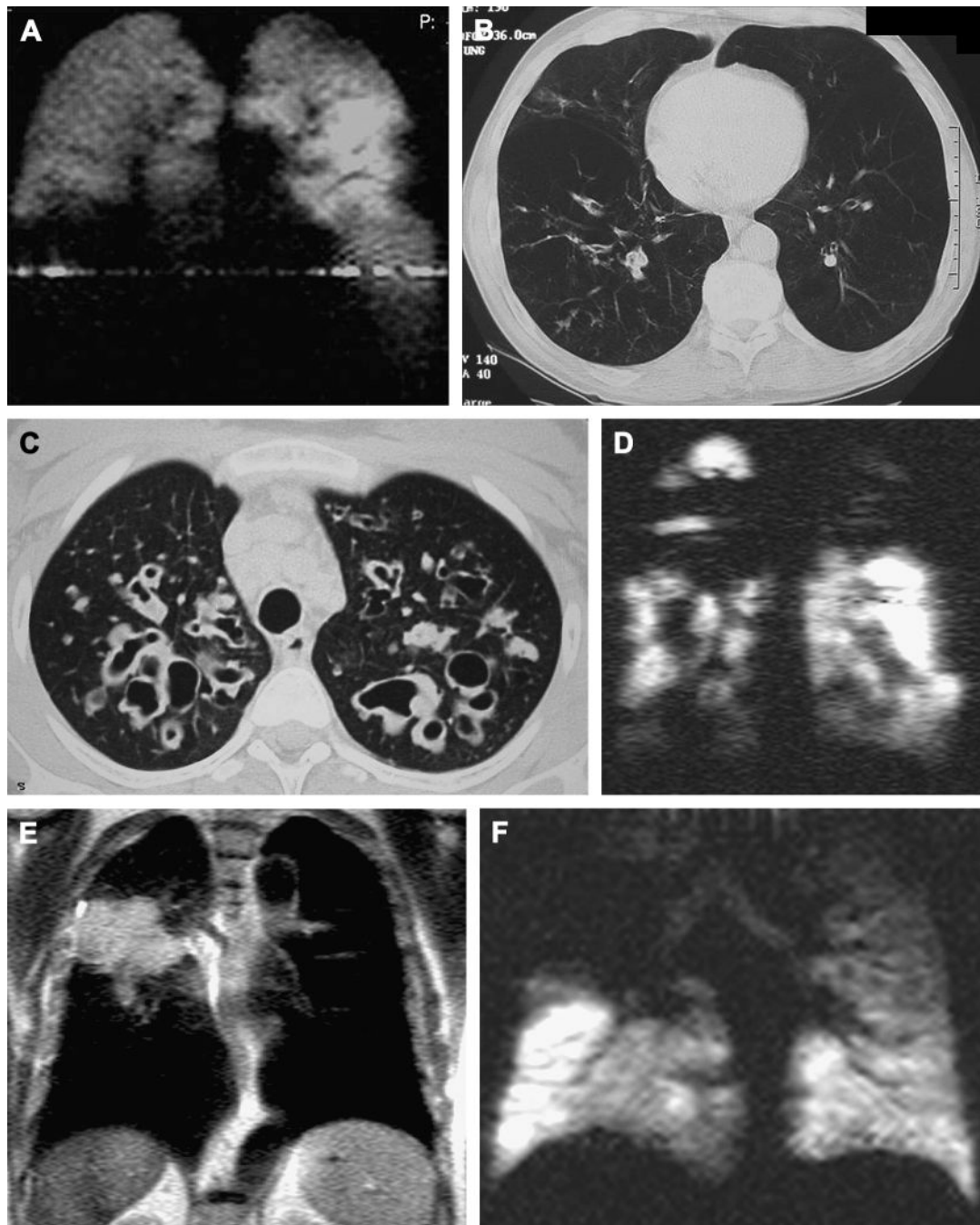


Figure 10.

Examples of hyperpolarized 3-Helium MRI and correlation with HRCT. A, B Patient with alpha-1-antitrypsin deficiency. Notice basal ventilation defects on coronal MRI (a), with corresponding panlobular emphysema on axial CT (b). C, D Patient with 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 with 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).

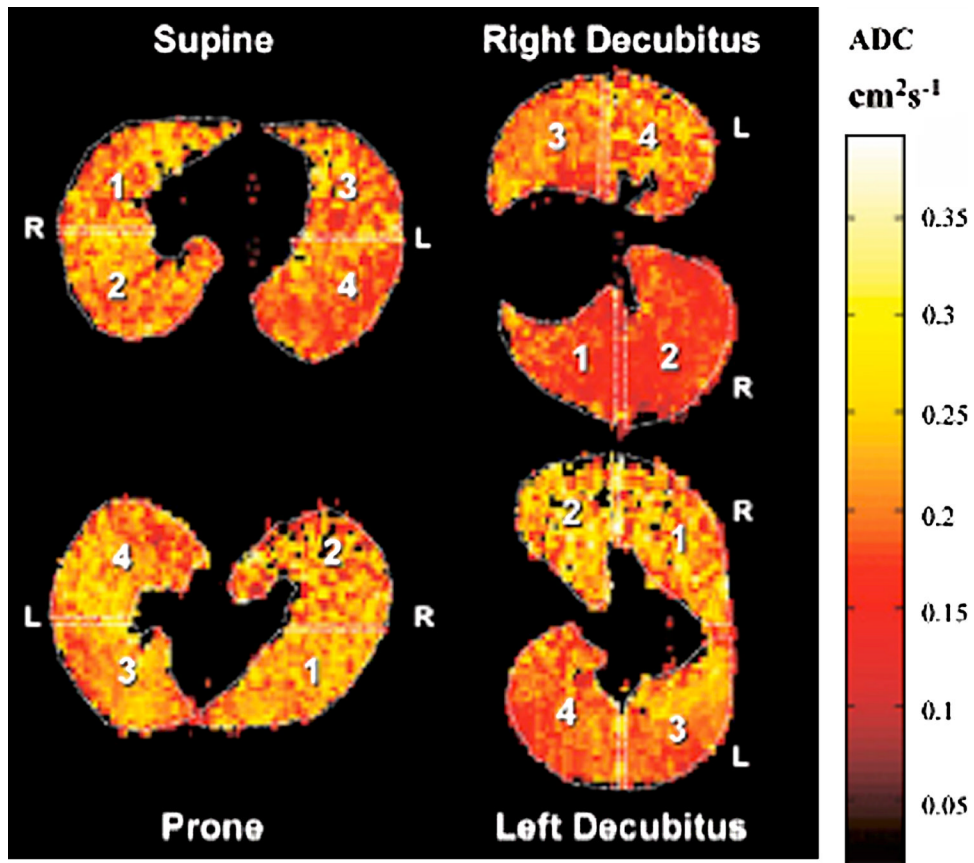


Figure 11. Apparent diffusion coefficient (ADC) imaging in a normal volunteer in different positions, demonstrating gravity dependent changes with decreased ADC values in dependent lung portions (reproduced from Fischele et al. J MRI 2004;20:331–335.)

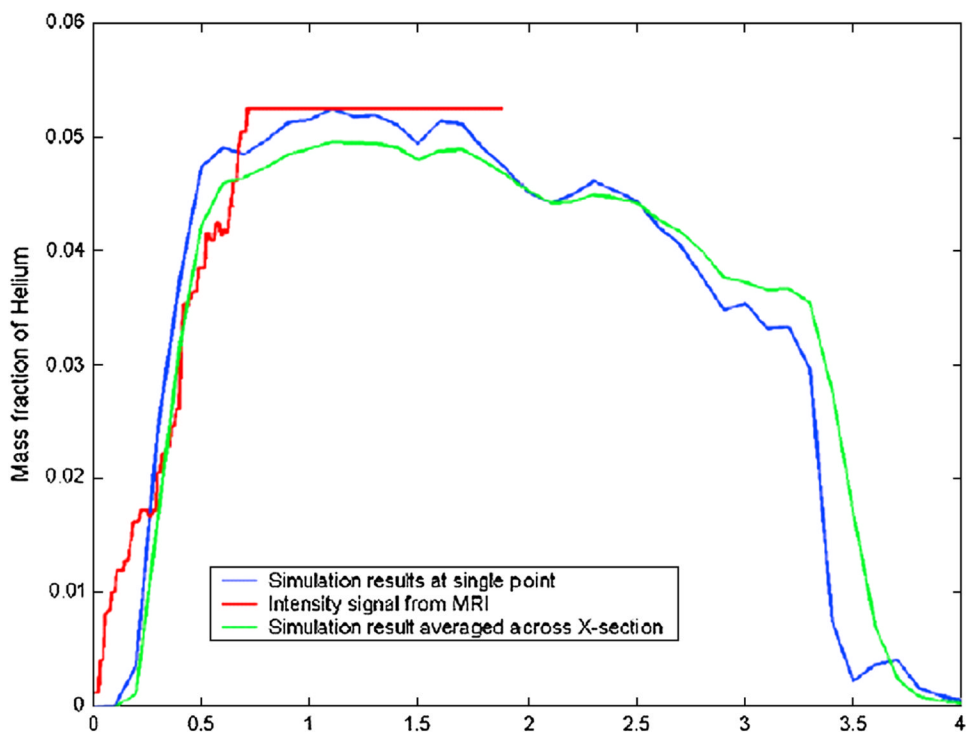


Figure 12. Dynamic 3-He MRI reconstruction of signal change over time during single inspiration demonstrates the slope of the curve, which may be translated to forced inspiratory volume during 1 second (reproduced from Koumellis et al. J MRI 200522:420–426.)