Limited imaging of lung function is possible with methods that use ionizing radiation, such as computed tomography (CT) and lung scintigraphy. Methods using magnetic resonance (MR) are preferable because they do not involve ionizing radiation. At first, MR methods were difficult because of the lack of protons and artefacts caused by inhomogeneity in the lungs. Recently, new techniques have allowed static and dynamic lung imaging with MR. We discuss the methods that allow functional imaging of the lung and describe new developments in functional MR imaging (MRI). From being almost invisible to MRI, lung images with MR may soon radically affect the way we assess the function of the lung and the pulmonary circulation.

Techniques available to functionally image the lung
The first attempts to obtain functional information of the lungs date back to the early days of x-ray fluoroscopy. However, these concentrated on the tissues and structures surrounding the lung. Fluoroscopy could show diaphragm motion during spontaneous breathing and sniffing, but gave variable results in detecting pathology. Ultrasonography allows useful imaging of structures around the lung, such as pleural effusions, diaphragm movement during sniffing or phrenic nerve stimulation, or even diaphragm thickness, but lung tissue itself is not readily penetrated by ultrasound.

Nuclear medicine and scintigraphy
Lung scintigraphy was developed in the 1960s, and has become the key test for assessment of lung perfusion and ventilation. This method uses inhaled radioactive substances and monitors the wash-in and wash-out of the isotopes with scintigraphic detection; however, the images do not have high temporal or spatial resolution. The inhaled radioactive gases include $^{133}$Xe, $^{127}$Xe and $^{81}$Kr. Radioactive aerosols including technetium 99m diethylene-triamine pentacetic acid (DTPA) suffer from problems of deposition in the larger airways. Technetium 99m Technegas uses carbon particles as a carrier as an ultrafine aerosol to allow deeper deposition. However, anatomical detail of the air passages remains poor. These techniques have been refined by combination with rotating gamma cameras to form single-photon emission CT (SPECT), which allows cross-sectional imaging with a slice thickness of 15 mm.

Positron emission tomography allows resolution down to 10 mm. However, temporal resolution is limited compared with the duration of the respiratory cycle, requiring about 30 s per image. Furthermore, a proximal cyclotron is needed for isotope production because the tracers have short half-lives.

Electrical impedance tomography (EIT)
EIT detects the impedance of the chest to very small electrical currents applied via skin surface electrodes. This allows virtually non-invasive imaging of axial slices of the lung throughout the respiratory cycle, by differentiating between regions where electrical resistance is high (inflated lung) and regions where current can flow more easily (collapsed lung). Although the spatial resolution is poor, EIT can give a real-time measure of lung tissue properties such as airway collapse, expansion or over-
inflation. This ability may be enhanced by using multiple electrical frequencies. A significant advantage of the technique is that it can be used at the bedside even in intensive-care patients.

**Computerized tomography**

Lung tissue can be imaged rapidly and volumetric data obtained by using slip-ring technology (spiral CT), multiple rows of detectors (multislice CT) and high-speed reconstruction algorithms, which speed image acquisition and increase resolution. High-resolution CT (HRCT) uses a narrow-beam collimation (1 mm), a narrow field of view and high spatial frequency reconstruction algorithms. Functional information can be gained in detection of air trapping, lung volume measurement (total and regional) and direct imaging of regional ventilation with the aid of inhaled xenon or aerosols.

Dynamic CT imaging can be applied to a single slice during a respiratory cycle, but even when using the latest multidetector technology, CT is not fast enough to image the whole lung during the respiratory cycle. Paired inspiratory and expiratory HRCT scans allow detection of air trapping. Assessment of lung volume is usually done by spirometry, with body plethysmography or helium-dilution methods in addition. However, volume information for specific lung regions or individual lungs is not available without imaging. CT scanning gives this information, although inspiratory helical CT consistently underestimated total lung capacity by 15%, and expiratory helical CT overestimated residual volume by almost 1 litre. Further refinements using three-dimensional reconstructions have reduced errors to about 3%.

Dynamic lung CT requires very rapid imaging and potentially high radiation exposure if continuous imaging is used. To increase speed, the initial method was to fire electron beams at tungsten targets, generating X-rays that could be directed very rapidly by controlling the direction of the electron beams, so avoiding moving mechanical parts. Electron-beam CT scans are usually performed at three levels (aortic arch, lung base and carina), to reduce interference from lung motion.

Dynamic upper-airway imaging can assess changes in the trachea during inspiration and expiration in normal subjects (35% decrease in area), tracheomalacia (82% decrease) and sleep apnoea (75%). Inspiratory and expiratory images can be obtained with a temporal resolution of 100 ms. This has allowed the assessment of conditions such as emphysema, where in addition to increased air space size and loss of interstitial tissue reducing attenuation, lung tissue remains hyperinflated during expiration and so does not undergo the expected increase in density seen in normal lungs. The technique has also allowed identification of patients with normal, restricted or obstructive lung conditions. Bronchial reactivity in asthmatics has also been assessed before and after methacholine and salbutamol administration. Diagnostically, the technique can show a variety of causes of main bronchus obstruction in children, such as dynamic changes in airway calibre, intraluminal polyps, tracheal atresia, compression resulting from mediastinal masses, and foreign bodies in the airway, and is improved when combined with HRCT. In pigs, continuous dynamic multiscan CT can show lung recruitment effects in experimental models of actue respiratory distress syndrome and assess ventilatory strategies during cardiopulmonary resuscitation.

CT images show the lung parenchyma and from this, information can be inferred about the air spaces. However, to image the air spaces directly some form of inhaled contrast is needed. Xenon is a noble gas. It is denser than air and will appear denser on CT scan depending on concentration. It is also non-radioactive and possesses anaesthetic properties, related to its lipid solubility, which become evident in inspired concentrations above 21% (MAC 71%). Equilibration of xenon within the air passages is not instantaneous and therefore wash-in and wash-out can be assessed. The greater the density of xenon in a particular area, the greater the ventilation in that region. Unfortunately, the anaesthetic effects and technical difficulties with imaging have limited the use of xenon. Early studies involved animals, normal subjects, or sedated and ventilated intensive-care patients. The technique was standardized by Simon and colleagues, and single-breath techniques using rapid electron-beam dynamic CT with subtraction techniques to compare images with and without xenon have reduced the problems of the anaesthetic effect. 

Gravity can affect the distribution of perfusion and ventilation and cause areas of lung collapse. Image interpretation is complex, but microvascular regional blood flow and the effects of gravity and posture have recently been seen with xenon CT in animals. Xenon also passes in the circulation to the brain, where it is taken up because of its lipid solubility. Inhaled xenon may therefore have a role in assessing cerebral perfusion. Oxygen and sulphur hexafluoride (SF6) mixtures, and oxygen and helium mixtures, have been used during continuous-breathing CT studies of patients with chronic obstructive pulmonary disease (COPD). Images at end-inspiration showed changes with time, by comparing images taken during breath number two and number 60. Abnormal areas of lung with slow time constants were seen, with...
marked changes in attenuation between the two images. Early gas flow was poor compared with the late images.\textsuperscript{123} 

CT is versatile, and is being increasingly used to study pulmonary embolism, where it is gradually replacing the use of ventilation–perfusion scintigraphy. CT pulmonary angiography requires injection of 100–130 ml iodinated contrast agent into a peripheral vein, followed by imaging when opacification of the pulmonary arterial tree is optimal. Using state-of-the-art CT systems, a resolution of 1 mm is possible, with visualization of sub-sub-segmental pulmonary arteries.\textsuperscript{47 91 112}

MRI of the lungs

Basic theory of MRI

To be sensitive to nuclear magnetic resonance (NMR), a material needs to contain atoms with odd numbers of nucleons (protons and neutrons). All nucleons possess a spin, which is an intrinsic property of atomic particles, as are mass and charge. Therefore, molecules containing hydrogen (\textsuperscript{1}H) protons, such as water and numerous organic molecules, are sensitive to NMR and are candidates for MRI. Other nuclei are also sensitive, providing they possess unpaired nucleons in their nucleus, examples being \textsuperscript{13}C, \textsuperscript{3}He, \textsuperscript{15}O and \textsuperscript{129}Xe. In a strong static magnetic field (\(B_0\)), these uncoupled spins can exist in one of two energy states aligned either parallel to or anti-parallel to \(B_0\). Conventional proton MRI uses the fact that in thermal equilibrium, a spin divided by the static field strength extremely high. This is why conventional clinical MRI scanners that image protons in the body typically operate at field strengths of 1 T and above. By imaging with long repetition times, all spins with a range of T1 relaxation times have a chance to relax back to thermal equilibrium before they are subsequently tipped by the next RF discharge used to scan the next line of data, which is used to build up the image in reciprocal space. Such an image would represent a spatial map of absolute proton spin density and as such tends to show little contrast between adjacent tissue types of approximately the same spin density. Contrast can be introduced into the image by weighting the MRI pulse sequence towards specific ranges of T1 and T2 by careful timing of the repetition time and the echo time of the sequence. For example, water has a long T1 because water molecules are relatively free to tumble, having relatively few spin–lattice interactions and so they return to the ground state more slowly than, say, larger fat molecules. Thus, in clinical MRI it is possible to weight the image contrast so that T1 weighted images (with a short T1) are too short to record the water signal and so show water as dark, and fat as bright. The interested reader is referred to a recent overview of basic principles of MRI for further reading.\textsuperscript{90}

Use of proton MRI in the lung

The density of the lungs is low compared with other tissues. They have a low proton spin density and therefore offer less MRI signal than other tissues such as brain parenchyma. Furthermore, the static magnetic fields within the thorax vary because of the magnetic susceptibility difference between paramagnetic oxygen in air and diamagnetic tissue, and this effect is compounded by the complicated geometry of the lungs. These field inhomogeneities rapidly dephase any transverse signal, and cause very short transverse relaxation times – short T2. Further problems arise from cardiac and respiratory motion and the lung is a technically challenging organ for \textsuperscript{1}H MR imaging. The very short T2 of lung tissue means that to provide anatomical detail of the fine structure in the parenchyma, \textsuperscript{1}H MRI needs to be done at extremely short echo times. The image has to be recorded before the signal produced by decay can become incoherent (i.e. dephased or damped). Therefore, radial projection gradient echo sequences\textsuperscript{14 100} or short-echo-time fast-spin...
Echo sequences \(65\) have given the best results to date at high field strengths of 1.5 T and above (Fig. 1).

Recent developments with ultrafast steady-state free precession sequences show promise for parenchymal imaging at low field strengths (0.2 T). This is because the T2 of lung tissue is longer at low magnetic field strengths, the signal suffers less disruption of phase and more signal is available in the transverse plane for a longer period of time, with more opportunity to construct an image. \(86\) \(115\) To reduce motion artefacts, these images are best acquired either during a breath-hold with cardiac gating or with both cardiac and respiratory gating if the image sequence is not a single-shot acquisition.

Information on the fine structure of the parenchyma is gradually increasing with proton MRI as technical advances in pulse sequences are made. However, if the lung walls and pulmonary blood vessels are of primary interest then these limitations are less restrictive. For example, the fast acquisition times obtained with gradient and single-shot spin echo sequences lend themselves to dynamic imaging where bulk motion of the chest wall and diaphragm is of primary interest. The fat and bone in and around these structures have a short T1, which can therefore be imaged well with fast sequences (Fig. 2). The movements of these structures and their behaviour during spontaneous breathing have been assessed using proton MRI of the thorax with three-dimensional image reconstruction. \(29\) Similar work has allowed the construction of a two-compartment mathematical model of the ‘inspiratory pump’, \(10\) which could help predict the impact of diseases or therapeutic interventions on the respiratory system. Fetal lung volumes have been measured using proton MRI and an equation to predict normal lung size produced. Comparison with MR scans of fetuses with pulmonary hypoplasia in isolated congenital diaphragmatic hernia \(74\) could predict post-natal pulmonary hypoplasia and poor outcome. Proton MRI has also been used to investigate the role of lung liquid in the presence of respiratory distress syndrome in human neonates. Increased lung liquid was detected in those requiring ventilatory support. At the same time, a reduction in the gravity-dependent gradient in the prone position was detected, suggesting a reduction in atelectasis. \(1,3\) Dependent atelec-

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**Fig 1** The image on the left is an axial high-resolution CT image of the lungs of a patient with emphysema, acquired during breath-hold. It shows the chest wall anatomy and the fine structure in the parenchyma. On the right is an axial single-shot spin echo MRI scan obtained during a breath-hold on a 1.5 T clinical MRI system. The image delineates soft tissue and thorax, but demonstration of fine structure in the parenchyma is limited.

**Fig 2** A series of ultra-fast proton gradient echo MR images (four images s\(^{-1}\)), acquired from a single coronal slice during a respiratory cycle, clearly showing chest wall and diaphragm movement.
Assessment during anaesthesia in the supine position, its volume and its resolution by a specific recruitment manoeuvre, but not by simple application of continuous positive airway pressure (CPAP), has been shown in children using proton MRI. MR has been used to detect lung water in animals. Comparison of dehydrated and hydrated porcine lung parenchyma showed differences in components of the spin relaxation T2 curves that were related to water content.

**Oxygen-enhanced ^1H MRI**

Difficulties in imaging the lung with proton MRI led to a search for alternatives. Oxygen-enhanced proton MRI has been studied as a means of measuring ventilation. The technique uses fast imaging sequences (such as single-shot fast-spin echo, with an inversion recovery pre-pulse) to introduce some T1 contrast. Molecular oxygen is paramagnetic and passes into the water in the lungs. The T1 of water in the lungs when breathing pure oxygen should be lower than when breathing air. Differences in contrast can be assessed by subtracting the signal intensities measured whilst breathing oxygen and air. The technique requires less equipment compared with hyperpolarized-gas MRI (see below), and can be performed with a standard proton MRI scanner. However, it is uncertain whether the oxygen enhancement truly represents ventilation, because the images are built up as a statistical average from multiple images. Furthermore, it is not clear whether solution of oxygen in interstitial lung water and the vessels, causing a T1 reduction, truly represents regional ventilation.

**Contrast agents**

The use of contrast agents is typically associated with MR angiography. Solutions of gadolinium-chelated contrast agents (e.g. Gd-DTPA) are injected into the bloodstream, causing a shortening of the T1 of the blood and vessel enhancement when imaging with fast sequences at short repetition times. Much work has been published on MR pulmonary angiography and it is routinely used for diagnosis of pulmonary embolism and vessel disease. More recently, gadolinium-chelated contrast agents have been given through the respiratory tract to enhance the intrinsically weak signal from native protons. The mechanism of contrast enhancement is fundamentally the same as with molecular oxygen, causing a shortening of the parenchymal and interstitial T1 of water. These agents have been given by inhalation with and without i.v. contrast to look for matched defects in perfusion and ventilation in experimental models of pulmonary emboli, to examine pulmonary veins and to assess perfusion in transplanted lungs. Initial results in animals were poor because of failure to reach peripheral air spaces. More recent efforts to aerosolize Gd-DTPA demonstrate signal strength increased by more than 100%.

The above is an overview of the advances in lung imaging using native protons in the lung and some of the functional information such as ventilation and perfusion that can be inferred from these images. The problems of intrinsic low spin density and field inhomogeneity will always limit ^1H MRI, especially in accurate quantitative estimates of function, and alternatives to proton imaging have been sought, including MRI with noble gases.

**MRI with noble gases**

Isotopes of certain non-radioactive noble gases with an odd number of nucleons, such as ^3He or ^129Xe, can be imaged within the air passages using MR. However, the signal is extremely weak because of the low spin density, unless the population of spin states adopted by the nuclear spins can be...
enhanced by a process of ‘hyperpolarization’, 12 yielding ‘magnetized’ noble gas (Fig. 3). This increases the potential MR signal by a factor of 100 000 beyond that achieved normally by thermal equilibrium in the presence of a strong static B0 field, 6 as described above for 1H MRI.

3He can be polarized by two techniques: (i) spin exchange (SE) with an optically pumped rubidium (Rb) vapour, 16 or (ii) by metastability exchange (ME) scattering with optically pumped metastable 3He atoms. 31 These techniques became feasible with the development of powerful pumping lasers for the necessary wavelengths: 795 nm for Rb and 1083 nm for 3He. The photons emitted by the laser are circularly polarized by filtering with a quarter wave plate that allows a net transfer of angular momentum from the light to the electron and nuclear spins of Rb or 3He. 58

**SE optical pumping**

This technique uses the Rb vapour as an intermediary for transfer of spin to the 3He. 83 The laser light excites the valence electron of Rb within a homogenous magnetic field, which collides with 3He, transferring polarization to the helium nuclear spin. This process occurs at a temperature of 80–160 °C under a pressure of 3 bar and the helium is mixed with a small amount of nitrogen. The apparatus can give polarizations of up to 40% and can be adapted to produce hyperpolarized 129Xe.

**ME optical pumping**

The intermediary Rb is not required. Instead, an RF discharge is used to excite electrons of 3He from their ground state to a metastable state. The laser light can then optically pump these electrons until they are polarized. This polarization is then passed on to the spin of the 3He nucleus of a ground-state atom. However, because this process takes place at low pressure (1 mbar) the gas has to be compressed without losing its polarization and then stored. This process can potentially produce gas that is more than 60% polarized.

Both SE and ME techniques are complex and require skilled maintenance and operation. ME is more difficult to maintain in less sophisticated environments. Although a local production facility is effective, the associated costs (housing, machine, personnel) are considerable. Central on-demand production could be an alternative to avoid start-up costs. Once produced, the polarization decays with time and is disrupted by stray magnetic fields. The helium is therefore transported in glass containers with low iron content and shielded within a stable magnetic field. This concept was successfully tested on a European scale, with delivery of hyperpolarized-3He gas from Mainz via air courier to Sheffield. 119 Polarization decreased from 50% to 25–30% in transit, but this is acceptable for imaging.

Although hyperpolarized-xenon MR was applied first to lung air space imaging, 5 hyperpolarized helium MR followed soon after. 81 The handling of 3He was simpler and the signal change more pronounced. Thus, most subsequent clinical developments have used 3He gas.

Several 3He MRI methods have been developed, each providing specific information. This ‘four-step’ protocol can allow information in ventilation distribution, small airway size and its distribution pattern, gas in-flow and out-flow dynamics, and regional oxygen partial pressure within the ventilated lung spaces. Many of the data are new, since no other techniques give similar (often detailed) information in vivo.

**Technical aspects of hyperpolarized-gas MRI**

An external source of polarization by optical pumping makes the signal-to-noise ratio less dependent on field strength. Thus, hyperpolarized-3He imaging lends itself to low-field-strength MR applications. 37 113 Although this would reduce artefacts during imaging, most of the developments of hyperpolarized-3He MRI have used 1.5 T systems. This is largely because this is the standard field strength in the clinic and the scanner manufacturers concentrate their MR technology developments at this field strength. There are two key constraints in imaging with inhaled hyperpolarized-3He gas. The first is the loss of hyperpolarization of the spin population once magnetization has been tipped into the transverse plane by the RF excitation pulse used in the imaging process. This limits both the size of flip angle and the number of applicable RF pulses (phase encode views) in the sampling of the reciprocal image space. The fact that thermal recovery of polarization is negligible in comparison with the size of the hyperpolarization allows ultra short repetition times. Furthermore, the introduction of oxygen will reduce the T1 relaxation time from several hours to a few seconds, which, combined with the finite time of a patient’s breath-hold, means that fast imaging sequences are required. The second constraint results from the high diffusion coefficient of 3He at atmospheric pressure (D=0.8×10⁻⁴ m² s⁻¹ for 3He in air at standard temperature and pressure). This could potentially lead to significant signal dephasing as a function of the view-dependent MRI gradients. 118 In conclusion, the pulse sequences used for standard proton MRI need to be adapted and optimized for efficient use of a hyperpolarized-gas signal.

**Administering hyperpolarized 3He**

Administration of hyperpolarized 3He can be either by self-inhalation from metered bags or by delivery of a preset volume from an ‘applicator’. Inhalation from metered bags involves a 330/670 mixture of 3He in nitrogen, giving a 1-litre anoxic breath. The nitrogen is used to prolong the lifetime of the 3He signal, since ambient molecular oxygen rapidly ‘relaxes’ hyperpolarization of 3He towards its normal thermal equilibrium. Alternatively, administration can be by a 50–500 ml bolus of 3He within a breath of air via
nasal CPAP mask or mouthpiece, using a pneumatically driven, microprocessor-controlled dosing and delivery device (applicator). Self-inhalation from bags is simple, but the volumes and rate of delivery are not well known and it involves inhaling a hypoxic mixture without additional fresh gas. The use of an applicator is a little more complex but allows the administration of a measured $^3$He dose at an arbitrarily set point during inspiration. Pressures, flows and volumes of the $^3$He bolus and the carrier breath, as well as gas concentrations, are monitored. Supplemental oxygen, inspiratory pressure support or CPAP can be provided by an attached respirator machine for patients with impaired lung function. Additionally, the applicator device allows recovery of the exhaled $^3$He, allowing recycling of up to 95% of the inhaled dose of this rare isotope.\(^{50}\)

**Single-breath static distribution of ventilation in normal subjects, smokers and patients with asthma, cystic fibrosis and COPD**

During a breath-hold immediately after inhalation of 300 ml hyperpolarized $^3$He, normal subjects always show a homogeneous distribution of polarization within the air spaces (Fig. 4). This consistency is important, as it allows the confident identification of abnormalities. Loss of signal implies absent inspiratory gas inflow and hence functional or structural pathology. This reduces inter-observer variation when assessing hyperpolarized $^3$He images.\(^{36}\)

Typical patterns of abnormalities include oval defects, which may be predominantly alveolar, and wedge-shaped defects, which may relate to bronchial obstruction. A mixture of oval and wedge-shaped defects are seen in smokers, but may be found even in those with apparently normal lung function (Fig. 4).\(^{51}\) Transient, flitting, peripheral defects are also seen in otherwise healthy subjects with mild ‘hay fever symptoms’.\(^{52}\) $^3$He imaging in asthma shows similar defects (Fig. 4), which resolve with bronchodilator therapy. Larger defects are present in asthmatics with more symptoms and abnormal lung function.\(^{7}\)

Early studies comparing proton MR images with $^3$He images in patients with cystic fibrosis showed disproportionately severe ventilation defects compared with the morphological changes.\(^{36}\) This was particularly the case in upper lung zones. The $^3$He MR images appeared more sensitive than the Brasfield chest radiography score, and were related to abnormalities in pulmonary function tests.\(^{60}\) Multiple wedge-shaped defects are seen in the bronchiolitis obliterans of chronic rejection following lung transplantation.\(^{52}\)

COPD produces defects in the spread of $^3$He\(^{59,60,64}\) because of restricted entry of a single breath of $^3$He into already overinflated areas, with long time constants for gas wash-in (Fig. 4). The diffusion characteristics of $^3$He and the

**Fig 4** Hyperpolarized helium images: from a normal subject (top left), a smoker with normal lung function tests (bottom right), an asthmatic (top right) and a patient with emphysema (bottom left).
rate of spread of $^3$He through the lungs add valuable information to the diagnosis and the assessment of severity of the condition.

Regional volumetric imaging with hyperpolarized $^3$He

Three-dimensional reconstruction of static $^3$He lung images allows split-lung and even regional volumetry of ventilated lung tissue. $^3$He volumetry and conventional global spirometry were well correlated, both in healthy subjects and in patients with pulmonary fibrosis and unilateral lung transplants. Only the image-based method, however, quantified the relative contributions of native and grafted lung to total aerated volume.77

Figure 5 shows a surface-rendered three-dimensional reconstruction of aerated lung tissue of a patient with idiopathic pulmonary fibrosis (native right lung) and a single left-lung graft, imaged with $^3$He 300 ml. The ventilated lung volume of the grafted lung is about 66% and of the native lung is about 34% of the total lung volume. A change in calibre can be seen in the left main bronchus of the transplanted side.77

$^3$He atoms will move about 0.4 mm in 1 ms if they are free to do so. However, in normal lungs the alveolar, acinar and bronchiolar walls restrict this movement, leading to an ADC in healthy human lungs of 0.2 cm$^2$ s$^{-1}$ and less. Emphysema results in abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls.102 This extra space in the acinar airways allows room for greater longitudinal and transverse diffusion paths. Destruction of some of the obstacles to diffusion in emphysema means that this value increases to 0.55 cm$^2$ s$^{-1}$ in severe emphysema.94 Alveoli and the related air passages are not spherical; indeed, if a molecule moves along the axis of an airway it can travel much further without reaching an obstacle compared with when it moves at right angles to the axis. Therefore, diffusion in the airway is anisotropic and it may be possible to model the diffusion behaviour to provide information on the anatomy at the acinar level.

Investigations in guinea-pig lungs confirmed that diffusion constants in the trachea were similar to values in free space; as expected, however, values were much less in distal pulmonary air passages (0.16 cm$^2$ s$^{-1}$).24 25 27 28 In rats, diffusion was less restricted during inspiration compared with expiration in the normal control rats. The greater inspiratory lung volumes allowed larger diffusion paths compared with expiration. However, in rats with elastase-induced emphysema, ADC was increased and the inspiratory-expiratory difference was reduced, suggesting that the walls of the small air spaces had been partially broken down.26 Studies in humans have suggested an increase in ADC with increasing age, which may be related to decreasing elastic recoil.19 In human emphysema, mean ADC may be 2.5 times that in healthy lungs.94 Diffusion MRI with $^3$He has shown that in normal and emphysematous subjects, $^3$He diffusivity is anisotropic. The mean longitudinal ADC is three times greater than the mean transverse ADC. However, in normal subjects, transverse diffusion is almost eight times less than the free-$^3$He diffusion coefficient in air (0.1–0.2 cm$^2$ s$^{-1}$, compared with 0.88 cm$^2$ s$^{-1}$). In emphysema, both the longitudinal and transverse diffusion coefficients are increased, allowing greater movement in all directions and actually reducing anisotropy.121 An example of an ADC map in a normal volunteer is given in Figure 6; that in Figure 7 is from a patient with smoking-related centri-acinar emphysema.

Dynamic ventilation MRI with $^3$He

Initial $^3$He imaging used ‘static’ breath-holding images. However, imaging during free-breathing ‘dynamic’ imaging can provide information on the dispersion of $^3$He gas through the lungs and allows visualization of the full respiratory cycle (Fig. 8). This is particularly important in emphysema (to demonstrate flow abnormalities such as air trapping), but can also provide information concerning the trachea and upper airways. In normal subjects, the timing of
The appearance of peak levels of $^3$He during MRI after application of a 300 ml bolus was 260 ms in the trachea and 910 ms in the parenchyma. In emphysema, dynamic analysis using transaxial slices at three different lung levels showed sequential filling of non-segmental lung regions of variable size. There were even areas where no filling occurred. The signal became more uniform during re-breathing and wash-out phases. Wash-out was relatively slow, with signals persisting in some poorly ventilated areas. This may have been compounded by low levels of oxygen in these lung zones, so reducing the rate of loss of $^3$He MR signal that occurs in the presence of oxygen. The areas of slow uptake and slow wash-out corresponded with severe defects seen on CT. This information, combined with ADC assessments, may be important for early diagnosis and assessment of patients with COPD, particularly those who may warrant bullectomy or even lung volume reduction surgery.

More recently, novel imaging sequences have made it possible to obtain images at very short intervals (between...
120 ms and 5.4 ms per frame), allowing the analysis of a single breath in slow motion, which led to the first work to determine regional spirometry.

**Intrapulmonary measurement of $P_{O_2}$ with $^3$He MR**

Measurement of partial pressure of oxygen ($P_{O_2}$) in inspired and expired gas, as well as oximetry of arterial and mixed venous blood, allows the study of oxygen uptake in the lung and the estimation of venous admixture (‘shunt’). A much more precise description of the equilibrium between ventilation and perfusion in the lung is possible using the multiple inert gas elimination technique (MIGET). However, none of the techniques that rely on global respiratory and blood gas analysis provides topographical allocation of their information. Split-lung gas analysis and particularly regional alveolar gas sampling and analysis are difficult. Therefore, alveolar and corresponding end-capillary $P_{O_2}$ are usually derived indirectly – from inspired $P_{O_2}$, arterial carbon dioxide partial pressure and the gas exchange ratio.

Researchers soon noticed in the development of $^3$He MRI that during repetitive MRI of inhaled $^3$He, signal intensity disappeared rapidly, even if the breath is held and no $^3$He is exhaled. Two major reasons apply: first, the non-equilibrium (hyper-) polarization of $^3$He decays (depolarizes) during MRI because of the effect of the RF pulses required for image acquisition (the magnetic gas is ‘shaken’), and secondly, the interaction with paramagnetic oxygen molecules (dipoles) in the alveolar gas destroys $^3$He hyperpolarization progressively within about the time of a breath-hold (‘relaxation’). The rate of this signal decay $R(t)$ depends on the ambient $P_{O_2}$, according to the proportional relationship $R(t)=P_{O_2}/\zeta$, with a so-called oxygen-induced longitudinal relaxation time constant $\zeta=2.61$ s.bar, known from in vitro experiments. During early attempts at lung imaging, signal loss resulting from alveolar oxygen was regarded as a nuisance, and self-experimenting physicist researchers breathed pure nitrogen before the $^3$He in order to get ‘nicer’ images of the lung. Soon, however, the potential to use this oxygen sensitivity of hyperpolarized $^3$He for instantaneous, non-invasive and regional intrapulmonary $P_{O_2}$ measurement was realized. An estimate of local alveolar partial pressure of oxygen ($P_{A_O_2}$) is of physiological interest since the latter is uniquely dependent on the ventilation/perfusion ratio prevailing in the imaged region. Technically, the contribution of the $P_{O_2}$ effect to the total signal decay rate can be isolated quite simply from that of the imaging process, and can be quantified. For instance, the kinetics of signal decay may be obtained from a series of fast low angle shot (FLASH) images. During image acquisition, one of the two major determinants of relaxation (i.e. flip angle [RF voltage] or exposure time to oxygen [interval between consecutive images]) is varied methodically and its relative contribution to relaxation assessed.

To improve accuracy, other minor determinants of $^3$He signal attenuation must be taken into account or minimized, such as the relaxation properties of the surfaces that come into contact with the $^3$He and the convective and diffusive movement of $^3$He out of the imaged field. Meanwhile, several techniques have been described to determine regional $P_{O_2}$ at the very beginning of a breath-hold manoeuvre as well as the rate of its decrease during breath-holding. This rate of decrease is the net result of both alveolocapillary oxygen transfer and non-ventilatory mass movement of fresh gas to replace it. This has been developed in lung phantoms, pigs and human volunteers breathing various fractional inspired oxygen concentrations. In healthy subjects’ lungs, $P_{O_2}$ distribution determined by $^3$He MRI appears very homogeneous, with its mean close to end-tidal $P_{O_2}$ (Fig. 9). Patients with
idiopathic pulmonary fibrosis and a single-lung transplantation, serving as a model of disparate split-lung function, showed greater MRI-determined \( PAO_2 \) in functioning grafts than in the remaining native lungs. This was compatible with the restrictive abnormalities and reduced ventilation/perfusion ratio in the native lung. Mean image-based \( PAO_2 \) of these patients ranged between \( PO_2 \) levels determined in end-tidal gas and arterial blood. The measurement of intrapulmonary \( PO_2 \) may thus have further important clinical implications. If an area of lung is poorly perfused, then the rate of uptake of oxygen by the blood passing through vessels in that area will be low. Therefore, \( PO_2 \) will be relatively high in such an area and would fall relatively slowly on breath-holding. This raises the possibility that this technique could detect areas of ventilation/perfusion mismatch, such as could be caused by pulmonary embolism. Indeed, in an animal model of pulmonary embolism, alveolar deadspace generated by pulmonary arterial obstruction is depicted topographically correctly by image-based \( PAO_2 \) determination. Other researchers have also derived \( PO_2 \) from intrapulmonary \(^3\)He relaxation in small animals in vivo and post mortem, and have estimated pulmonary oxygen uptake and cardiac output from their data. Meanwhile, intrapulmonary \( PO_2 \) measurements have also been performed successfully in small animals using low-field MRI.

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**Fig 9** Maps of intrapulmonary \( PO_2 \) distribution are illustrated at the very start of breath-holding. Each breath-hold was preceded by wash-in of fresh gas with different fractional inspired oxygen concentrations, resulting in stable end-expiratory \( PO_2 \) levels before the imaged breath-hold. End-expiratory \( PO_2 \) is measured immediately before the imaged breath-hold. A 250 ml bolus of \(^3\)He has then been inhaled at the front of a tidal inspiration containing the respective fresh gas mixture. Image data are derived from serial \(^3\)He projection imaging using a single acquisition technique in a healthy subject.
Thus, in the future oxygen-sensitive $^3$He MRI may become a quick, non-invasive and easily repeatable method to assess ventilation/perfusion matching, and to estimate oxygen uptake from the lung.

**Low/ultra-low field imaging with $^3$He**

MR, and in particular MR at high field strength like that used in the clinical 1.5 T scanners, is complex and expensive. However, because of the artificially increased spin density, hyperpolarized gas imaging does not require strong $B_0$ fields, and hence smaller and cheaper systems can be used, with permanent magnets less than 0.3 T field strength. It is therefore possible to image the lung using low-strength magnetic fields of around 0.1 T, with advantages in cost, size of equipment and patient comfort, with no worsening of signal-to-noise ratio. Work in this area is part of an ongoing EU sponsored project (www.phil.ens.fr).

**$^3$He microbubbles and vascular imaging**

Hyperpolarized $^3$He provides a strong signal in the lung air spaces, but is not soluble in blood so other techniques or contrast media are used to image the vasculature. However, because the signal from $^3$He is very strong, attempts have been made to create suspensions of $^3$He microbubbles to enable vascular imaging. The rapid deterioration in polarization would remove the problem of recirculation of signal leading to a second pass. Initial animal studies suggest possible high quality vascular imaging.

**Hyperpolarized xenon**

$^{129}$Xe is another inert noble gas that can be hyperpolarized and used for lung imaging. It behaves in a similar way to $^3$He in the presence of oxygen. It is hyperpolarized using a Rb SE process similar to that described with $^3$He. However, $^3$He is easier to polarize and it yields a stronger signal than xenon, although xenon is more abundant. Following initial studies in mice, xenon has been used in humans.

An interesting feature of xenon is its solubility in blood, which allows it to pass around the body. Some will enter the nervous system because of its lipid solubility. A drawback is that the polarization decreases rapidly, thus allowing only 15 s of effective use. Models of the compartmental distribution of xenon have been developed, and could allow study of the brain and its behaviour. Intriguingly, because of the anaesthetic properties of xenon, there may be the possibility of gaining further insight into the mechanisms of anaesthesia.

**Lung imaging with $^{19}$F**

With the use of appropriately resonant MR coils and amplifier equipment, $^{19}$F atoms bound within highly fluorine-substituted molecules (perfluorocarbons [PFC], SF6 gas, and in principle, fluorine-containing volatile anaesthetics) can be imaged. Oxygen-carrying blood substitutes have been developed from PFC. In addition, since dissolved oxygen has paramagnetic properties and also affects the T1 of fluorine nuclei, this could allow MRI of $P_O$ effects. This opens up the possibility of using $^{19}$F as means of ventilation imaging of the lung, and of tracking oxygen levels in the lung through to other tissues such as liver and spleen. Inhaled SF6 has recently been used for morphological and ventilation imaging in pigs. Also, a PFC solution employed in partial liquid ventilation has been imaged and used for regional measurement of $P_O$ within the alveolar PFC phase.

**Conclusion**

Functional imaging of the lung is now possible without the use of radioactive agents or ionizing radiation. These techniques give information on a macro scale, demonstrating areas of poor ventilation in the lung, and also show changes at the microscopic level. $P_O$ can be imaged at sites within the lung and this allows ventilation and perfusion information to be gathered using hyperpolarized gases. In the future, xenon could also allow investigation of other organs, in particular the brain, while MRI of $^{19}$F-substituted compounds may allow tissue oxygenation to be studied within a wide range of organs. Detailed information of previously inaccessible sites and non-invasive detection of pathology in the lungs before conventional lung function tests become abnormal is now almost with us. In contrast to previous years, the future of lung MRI is bright (see Fig. 1).

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