In magnetic resonance imaging (MRI), nuclear spins are the source of the image signal. In the lung, low-proton spin density in alveolar gas and abundant gas-tissue interfaces substantially impair conventional native $^1$H-MRI. Spin polarization can be increased in two non-radioactive noble gas isotopes, $^3$He and $^{129}$Xe, by exposure to polarised laser light. When inhaled, such “magnetized” gases provide high-intensity MR images of the pulmonary airspaces. Thus, hyperpolarised gas (HPG) MRI opens up new routes to a) morphologic imaging of airways and alveolar spaces, and b) analysis of the intrapulmonary distribution of inhaled aliquots of these tracer gases; c) diffusion-sensitive MRI-techniques allow mapping of the “apparent diffusion coefficient” (ADC) of $^3$He within lung airspaces, where ADC is physically related to local bronchoalveolar dimensions; d) also, $^3$He magnetisation decays in an oxygen-containing atmosphere at a rate proportional to ambient PO₂. This property allows image-based determination of regional broncho-alveolar PO₂ and its decrease during a breathhold. Currently, these modalities of functional lung imaging are being assessed by several European and American research groups in animal models, human volunteers and patients. First results show good imaging quality with excellent spatial and unprecedented temporal resolution, and attest to the reproducibility, feasibility and safety of the technique. Regionally impaired ventilation of both structural and functional origin is detected with high sensitivity, e.g. in smokers, asthmatics, patients with COPD or after lung transplantation. Studies into regional ADC and PO₂ measurement demonstrate good agreement with reference methods and physiological predictions. The present limitations of HPG-MRI include the HPG production rate and the US and EU health authorities’ still pending final approval for clinical use.

**Key words:** helium; xenon; hyperpolarised gases; magnetic resonance imaging; pulmonary ventilation; gas exchange
the N₂/O₂/CO₂/H₂O atmosphere in airways and alveoli, and second, the vast number of gas-tissue interfaces creates magnetic field inhomogeneities. Native ¹H-MR lung images are thus simply of little practical use. At this juncture, a very fruitful crosstalk between physicists and radiologists from Princeton University and SUNY at Stony Brook, NY, in 1993 led to the development of techniques to artificially enhance spin polarization, and hence MR signal intensity, within the lung airspaces. Since the sixties, nuclear physicists in neutron research have been developing the techniques of so-called hyperpolarisation — or, somewhat more simply, magnetisation — of particular noble gas isotopes by “optical pumping” with circularly polarised laser light [3]. Thus magnetised by a factor of 10³ beyond the normal thermal equilibrium, inhaled ¹²⁹xenon or ³helium became visible in MR images taken with appropriately tuned coils. Albert and Happer were the first to generate ¹²⁹Xe images of an excised mouse lung [4]. First human applications of optically magnetised ³He for lung imaging were published by MacFall, Kauczor, and Ebert [5–7]. Since 1997, numerous patient studies have been performed or are still under way to explore the potential of morphologic and functional ³He MRI [8–11].

Material and methods

Both ¹²⁹xenon and ³helium are chemically inert, non-radioactive, non-toxic noble gas isotopes. Xenon’s diffusibility within the alveolar space is low, its tissue solubility is high and it is quite lipophilic. These properties lead to clinically relevant absorption of inspired Xe into the blood, and to further distribution into well-perfused organs, i.e. brain and myocardium. The atmospheric, naturally abundant mixture of Xe isotopes, which contains ≈ 26 % ¹²⁹Xe, is readily available, whereas enriched (70%) ¹²⁹Xe is more expensive.

Xenon is already in current clinical use, e.g. in nuclear medicine for cerebral blood flow studies and ventilation scintigraphy (¹³¹I), for inhalational anaesthesia and as a gaseous CT contrast agent. Despite its chemical inertness, Xe exerts relevant anaesthetic and analgesic actions, and even subanaesthetic concentrations may already elicit nausea and vomiting. For NMR applications, ¹²⁹Xe has a nuclear magnetic moment (which determines the attainable signal-to-noise ratio) of the order of ½ that of ¹H; the degree of polarisation attainable at present is ~20%. This, however, limits the signal intensity required for MR imaging.

Helium, on the other hand, is a very rare isotope (1.3 ppm of the already rare atmospheric He, or as a byproduct of tritium decay), and more expensive (~150 USD/L at present). It has negligible solubility and absorption, but is highly diffusible. Its physicochemically similar isotope ³He has long been in clinical use (pulmonary function testing, anaesthesia, diving) and has no systemic adverse effects unless used in hypoxic mixtures. Since the magnetic moment of ³He and attainable signal-to-noise ratios exceed those of ¹²⁹Xe, and since ³He can be polarised to up to 50 %, this noble gas is much more suitable for pulmonary MRI studies. The rest of this review, therefore, will chiefly cover research and development in the ³He field and will only briefly discuss the potential, advantages and disadvantages of ¹²⁹Xe MRI.

Hyperpolarisation of ³He and ¹²⁹Xe can be carried out by indirect (for ³He and ¹²⁹Xe) or direct (³He only) optical pumping with circularly polarised laser light. The former, i.e. the indirect polarisation method, involves alkali metals by using spin exchange between, for example, optically pumped Rb vapour and the noble gas to be polarised (spin exchange technique) [3]. This point is of some significance for clinical use, since toxic alkali metal traces must be removed completely from the hyperpolarised noble gas prior to any biological application. The latter method of direct optical pumping is based upon metastability exchange with optically pumped metastable ³He atoms (metastability exchange technique), and so the alkali metal problem does not arise; this is also the preferred method at the Mainz Physics Institute. Hyperpolarisation grades of 25–45% are obtained reproducibly. Magnetisation is preserved during storage and transport within iron-depleted glass cells and magnetic holding fields.

Imaging is performed in a conventional 1.5 T MR scanner (Siemens Magnetom® Vision) equipped with a broad-band amplifier and a transmit-receive coil tuned to the resonance frequency of ³He at 48.4 MHz. Gas dosage and administration are either by inhalation from prefilled collapsible bags (Tedlar®) or using a self-developed PC-controlled applicator device. Connected to a respirator machine (Servo® 900C, Siemens-Elema), the applicator device allows administration of ³He and, if required, supplemental oxygen during spontaneous respiration or assisted or controlled ventilation (figure 1). A typical ³He dose of 200–300 mL is inhaled during a single breath through a nasal continuous positive airway pressure (CPAP) mask, while the patient is monitored (respiratory flows and volumes, respiratory gases, and pulse oximetry). Supplementation of O₂, inspiratory pressure support or CPAP can be provided for. Duration of a typical study is currently 40 min. In the resultant ³He images of the lungs, signal intensity is determined by the following principal factors:

- the amount of inhaled polarisation (³He volume × magnetisation grade);
- loss of magnetisation due to imaging pulses;
- convective distribution and dilution of ³He in the lung airspaces;
- diffusion of ³He within the airspaces;
- loss of magnetisation due to paramagnetic O₂;
- expiration.
In the methodological development of $^3$He MRI our general aim is either to control these variables or utilise them for image-based analysis of regional lung function.

Objectives
The main objectives of our group’s and others’ endeavours are at present:

a. static $^3$He imaging of pulmonary airspace morphology; this is done during one breathhold, using “two-dimensional fast low-angle shot” imaging (2D-FLASH sequences) of adjacent lung slices.

b. dynamic analysis of regional ventilation distribution; this technique uses fast repetitive slice-selective or projection imaging covering several respiratory cycles. Typical imaging intervals are of the order of 130 ms down to 30 ms.

c. analysis of $^3$He diffusivity within the restricted airway geometries. Imaging sequences sensitive to the movement of $^3$He atoms are employed. An “apparent diffusion coefficient” (ADC) of $^3$He can be determined which depends, inter alia, on airway size.

d. measurement of regional alveolar partial pressure of oxygen ($PO_2$). Since molecular $O_2$ is paramagnetic, it reduces the magnetisation of $^3$He at a rate which is proportional to $PO_2$.[12]. The kinetics of signal decay are obtained from serial FLASH images acquired during one or two breathholds. The contribution of the $PO_2$ effect to the total signal decay rate is isolated from that of the imaging process (which in itself destroys magnetisation too) and quantified.

Results
All studies in healthy volunteers and patients were performed in accordance with the principles of the Declaration of Helsinki, with the approval of the Ethics Committee of the Landesärztekammer Rheinland-Pfalz, and after obtaining the subjects’ informed consent. Table 1 summarises volunteer and patient studies performed in Mainz up to 2000.

Initial $^3$He MRI experience in human subjects
In a first series, performed without the dosage/applicator device, Kauczor et al. described findings with the new method in 8 healthy volunteers and 10 patients with lung disease[8]. Generally, the spatial resolution of $^3$He-MRI was judged teeters and 10 patients with lung disease

Table 1

<table>
<thead>
<tr>
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<th>Patients</th>
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<tr>
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<tr>
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<tr>
<td>Total n</td>
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Morphological studies
Morphological comparison of statically acquired $^3$He lung images in clinically healthy smokers vs. healthy non-smoking subjects showed a homogeneous high-intensity distribution of the signal in the lung parenchyma of non-smokers. In contrast, smokers’ lungs showed 1–6 hypointense spots scattered between parenchyma containing high signal intensity (figure 2)[10]. Interestingly, Altes et al. demonstrated, in asthmatic patients, signal defects which were quite similar in location and size to those seen in our smokers; follow-up studies and bronchodilator challenges showed that these areas of regional hypoventilation varied in location over time and disappeared in response to bronchodilators[13]. Preliminary findings in our lung graft recipients demonstrate highly variable signal intensity distribution with multiple large hypointensities[14]. In native lungs these hypointensities may represent fibrosis or emphysema. In grafted lungs they may be non-specific correlates of bronchiolitis obliterans or infiltrates. Not infrequently, however, no structural correlates were detectable in the corresponding lung CT scans of these patients. This again points to the high sensitivity of the $^3$He-MRI method in detecting even small lung regions with ventilation impairment, but also its relatively limited ability to discriminate between structural and functional aetiologies.

Dynamic studies of ventilation distribution
The – compared to conventional $^1$H-MRI – exceedingly strong $^3$He magnetisation (hyperpolarisation) may be utilised for very fast repetitive imaging protocols, i.e. to produce dynamic, movie-like imaging of cyclic respiration. Temporal resolution is currently of the order of 130 ms down to 30 ms/image. This makes it possible to establish
signal-time curves in the trachea and parenchymal regions and to compare lung regions with each other quantitatively, e.g. with regard to inspiratory filling and expiratory emptying (figure 3) [11, 15, 16]. First observations in our cohort show synchronous distribution into healthy volunteers' lungs, whereas in lung graft recipients inflow into fibrotic lungs and rejected grafts was typically delayed, with very heterogeneous signal distribution. Phase II studies are currently under way to explore the feasibility and potential of these techniques in obstructive and restrictive lung disease.

**Diffusion-weighted \(^3\)He imaging**

The unrestricted self-diffusion coefficient of \(^3\)He is \(\sim 2\) cm\(^2\)/s. In the lung, the diffusive movement of \(^3\)He atoms is restricted by bronchial and alveolar walls, to a degree which is dependent on the dimensions of the respective airspaces and the local gas composition. The use of so-called diffusion-sensitive MR imaging sequences allows determination and even mapping of “apparent diffusion coefficients” (ADC) of \(^3\)He (figure 4) [17]. The ADC in lung parenchyma is related to alveolar size, and has consequently been found to increase with age and in emphysema [18]. Consistent with these findings and (patho-)physiological expectations,
Figure 4
Diffusion-weighted 3He MRI: Pulmonary map of the "apparent diffusion coefficient" (ADC) in a patient with IPF on the right, and a well-functioning lung graft on the left (mod. from [17]). Note physiologically high ADC values in the tracheobronchial tree, homogeneity of ADC within the graft, as well as inhomogeneous and sometimes pathologically increased ADC in the native fibrotic lung.

Figure 5
Normal and accelerated decay of 3He signal intensity at normal (FETO2 = 0.16) and increased (FETO2 = 0.35) end-tidal (and hence, alveolar) O2 concentration in a porcine lung (transverse orientation). FETO2, end-tidal fraction of oxygen.

Figure 6
Left, 3He MR projection image of a healthy 25-year-old non-smoker, with regions of interest (ROIs) depicted for image-based PO2 measurement. Right, measured regional PO2 values and their decrease during breathholding. Note homogeneity of both PO2 distribution and rate of PO2 decrease. Image-based PO2 ranged between 94 and 101 mm Hg, measured end-tidal PO2 was 113 mm Hg.
ADC in the trachea was measured at 0.67 cm²/s, in normal lung parenchyma between 0.13 and 0.17 cm²/s, in functional lung grafts between 0.15 and 0.18 cm²/s, and in fibrotic lungs with honeycombing between 0.22 and 0.35 cm²/s [17].

**Image-based regional PO₂-measurement in the lung**

O₂ has paramagnetic properties and therefore, when mixed with hyperpolarised ³He in the alveolar space, destroys magnetisation at a rate proportional to local alveolar PO₂ (PₐO₂) [12]. This opens up a route to non-invasive determination of regional PₐO₂. Its influence can be extracted from ³He signal decay curves generated from appropriately timed image series, which are acquired during breathhold (figure 5) [19, 20]. In healthy subjects very homogeneous PO₂ distribution was found with a mean in agreement with end-tidal PO₂ measured at the mouth (figure 6). Since PₐO₂ is the result of the local ventilation-perfusion ratio, this technique may develop into a quick, non-invasive and easily repeatable method of assessing ventilation-perfusion matching and estimating oxygen uptake from the lung.

**¹²⁹Xenon MRI: advantages and potential**

Although the very first hyperpolarised gas MR images of the pulmonary airspace were produced with ¹²⁹Xe [4], this hyperpolarised gas has since found its chief applications in NMR spectroscopic studies. The nuclear magnetic resonance frequency of ¹²⁹Xe atoms is exquisitely sensitive to their chemical environment. Other characteristics, e.g. the longitudinal relaxation time constant which describes the decay kinetics of ¹²⁹Xe hyperpolarisation, also vary depending on PO₂, haemoglobin and other local physicochemical parameters. Xenon is soluble in blood and tissues; hence, following inhalation, it equilibrates quickly; i.e. almost within one circulation time, with the blood volume and accumulates in highly vasculatized organs (e.g. heart, brain). Consequently, ¹²⁹Xenon’s characteristic chemical shifting of its NMR spectrum from that of gas-phase ¹²⁹Xe to that of ¹²⁹Xe dissolved in plasma, lung tissue, red blood cells or brain allows analyses of ¹²⁹Xe compartmental distribution and the kinetics of its exchange between these compartments. For such studies, e.g. into cerebral perfusion [21] or pulmonary ¹²⁹Xe gas-tissue exchange and perfusion [22, 23], hyperpolarisation of the tracer gas is an elegant way of considerably enhancing the sensitivity of the NMR spectroscopic technique. In addition, the deoxyhaemoglobin and oxygen sensitivity of longitudinal relaxation and NMR spectral peak position suggests that hyperpolarised ¹²⁹Xe may become very useful in non-invasive MR-based measurement of blood and tissue oxygenation [24]. Beyond spectroscopy, both pulmonary gas-phase and dissolved-phase ¹²⁹Xe imaging have also progressed within recent years [25–27], though not as rapidly as lung airspace imaging with ³He.

**Summary and perspectives**

MRI of the lung using hyperpolarised noble gases – in particular ³He – as the signal source opens up new routes to imaging of airways and alveolar spaces with high spatial and yet unmatched temporal resolution. Diffusion-sensitive ³He-MRI-techniques allow indirect assessment of bronchoalveolar dimensions by determining local apparent diffusion coefficients. PO₂ sensitivity of ³He-magnetisation provides an image-based estimation of regional alveolar PO₂ and O₂ uptake into the blood. Hyperpolarised ¹²⁹Xe, on the other hand, opens up a different and unique research field in spectroscopy, perfusion and oxygenation research in view of its lipid solubility and the chemical shifts of its NMR spectrum.

Currently, ³He-MRI is being assessed by several European and American research groups not only in animal models and human volunteers but already in patients (Phase II studies). First results have demonstrated the good imaging quality, reproducibility, feasibility and safety of the technique. Potential clinical applications are early detection and therapeutic monitoring of obstructive lung disease due to the sensitivity of ³He-MRI for small airway obstruction and air trapping. Another useful application may be pre- and postoperative regional lung function analysis in resective pulmonary surgery and lung transplantation. General advantages of ³He-MRI are avoidance of radiation exposure, the biochemical inertness of ³He and the nearly unlimited repeatability of studies, e.g. during follow-up of transplanted patients. Current limitations of the technique include the ³He production rate and the US and EU health authorities’ still pending approval for clinical use.

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