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Stewart, N.J., Norquay, G., Griffiths, P.D. orcid.org/0000-0002-2706-5897 et al. (1 more author) (2015) Feasibility of human lung ventilation imaging using highly polarized naturally abundant xenon and optimized three-dimensional steady-state free precession. *Magnetic Resonance in Medicine* , 74 (2). pp. 346-352. ISSN 0740-3194

<https://doi.org/10.1002/mrm.25732>

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**Feasibility of Human Lung Ventilation Imaging using Highly Polarized Naturally-Abundant Xenon
and Optimized 3D SSFP**

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Funding support: MRC, GE Healthcare, EPSRC, NIHR

Manuscript type: Rapid Communication

Word count: **3458** (limit 3500)

Abstract

Purpose: To demonstrate the potential for high quality MRI of pulmonary ventilation using naturally-abundant xenon (NAXe) gas.

Methods: MRI was performed at 1.5 T and 3 T on one healthy smoker and two healthy never-smokers. ^{129}Xe gas was polarized to $\geq 30\%$ using an in-house spin-exchange optical pumping polarizer fitted with a laser diode array with integrated volume holographic grating and optical train system. Volunteers inhaled 1 L of NAXe for an 8-15 second breath-hold whilst MR images were acquired with full-lung coverage using a 3D steady-state free precession sequence, optimized for maximum SNR at a given spatial resolution. For the purpose of image quality comparison, the MR acquisition was repeated at 1.5 T with 400 mL enriched xenon and 200 mL ^3He .

Results: All NAXe lung images were of high quality, with mean SNRs of 25-40 (voxel $4.2 \times 4.2 \times 8/10 \text{ mm}^3$) and $\sim 30\%$ improvement at 3 T versus 1.5 T. The high SNR permitted identification of minor ventilation defects in the healthy smoker's lungs. NAXe images were of comparable SNR to those obtained with enriched xenon and ^3He .

Conclusion: Optimization of MR pulse sequences and advances in polarization technology have facilitated high quality pulmonary ventilation imaging with inexpensive NAXe gas.

Word count: **200** (max 200)

Introduction

Hyperpolarized noble gas lung MRI with ^3He and ^{129}Xe can overcome many of the constraints of existing clinical gold-standard methods for diagnosing pulmonary disease, including: the lack of regional information offered by pulmonary function testing; the ionizing radiation associated with computed tomography; and the low spatial resolution of nuclear scintigraphy. ^3He has made the initial impact in clinical lung imaging research, most likely due to two factors; firstly it has historically been easier to polarize ^3He to higher levels in volumes required for lung MRI, and secondly the higher gyromagnetic ratio of ^3He compared with ^{129}Xe (1). ^3He MRI has been implemented in multi-center studies (2) and has demonstrated clinical utility, with sensitivity to early disease processes, in numerous pulmonary pathologies (3-5). Preliminary studies have shown that hyperpolarized ^{129}Xe is also promising for pulmonary ventilation imaging, with clinical potential similar to ^3He (6-8). Furthermore, ^{129}Xe has additional functional sensitivity (9) as a tracer of gas-exchange and lung perfusion, based on its solubility and NMR chemical shift in tissue and blood.

Although ^3He has intrinsic MR signal advantages over ^{129}Xe , it is generated exclusively as a by-product of tritium decay and is difficult to obtain in quantities needed for widespread clinical dissemination (10). Xenon is naturally-abundant in air (87 ppb), of which 26% comprises spin-1/2 ^{129}Xe . The proportion of ^{129}Xe can be enriched to ~ 80-90% with gas centrifuge techniques, but this requires significant additional investment. Although substantially cheaper than ^3He , inhaled gas doses delivered to patients have typically been ≥ 3 times higher for enriched xenon (EN ^{129}Xe) (up to 1 L (11)) than for ^3He (~ 300-400 mL (7)), in order to obtain lung images of sufficient signal-to-noise-ratio (SNR) for clinical interpretation. The reason is two-fold: the achievable polarization of ^{129}Xe has historically been lower; and the gyromagnetic ratio is only 1/3 that of ^3He . Naturally-abundant xenon gas (26% ^{129}Xe , NAXe) is considerably cheaper than enriched xenon and ^3He , but has not been fully explored for imaging in humans due to SNR limitations imposed by the 3-fold lower proportion of ^{129}Xe (12). However, with recent developments in gas polarization technology, utilizing high power, narrow-linewidth lasers and mid-low cell pressures (13-15), polarization of ^{129}Xe to levels previously achieved with ^3He can now be realized. Furthermore, advances in pulse sequence optimization have shown that improved image SNR can be obtained for hyperpolarized gases using steady-state free precession (SSFP) (16-18) rather than conventional spoiled gradient echo sequences (19,20).

This work assesses the feasibility of lung MR imaging with NAXe at 1.5 T and 3 T. In light of recent high ^{129}Xe nuclear polarizations achieved with our polarizer (15,21), 3D SSFP sequences were optimized for ^{129}Xe ventilation imaging, via in vivo measurements of k-space filters and matrix simulations of the Bloch

equations (18), in order to maximize image SNR. The quality of images produced highlights the potential of NAXe as a cost-effective contrast agent for clinical MR imaging of pulmonary ventilation.

Methods

Study subjects

Three volunteers were recruited for ^{129}Xe imaging: healthy smoker, male, 28 years (HS); healthy never-smoker, female, 32 (HN1); healthy never-smoker, male, 28 (HN2). All subjects showed normal spirometry and > 95% oxygen saturation on room air. Each volunteer provided written informed consent for this UK National Research Ethics Committee approved study.

Hardware requirements

MR ventilation imaging of NAXe, EN129Xe and ^3He was performed on a 1.5 T clinical whole-body MRI scanner – GE Signa HDx (60 cm bore, GE Healthcare, Milwaukee, WI). NAXe MRI was also implemented at 3 T – Philips Ingenia (70 cm bore, Philips, Best, The Netherlands). Custom-built, flexible, transmit-receive quadrature vest coils (CMRS, Brookfield, WI) were used to detect MR signals at the Larmor frequency of ^{129}Xe ; 17.7 MHz (1.5 T) and 35.3 MHz (3 T), and of ^3He ; 48.6 MHz (1.5 T). Xenon gas (The Linde Group, UK) was supplied in pre-mixed cylinders of 3% Xe, 10% N_2 and 87% He, with a ^{129}Xe content of 26% (NAXe) or 86% (EN129Xe). Helium-3 gas (Linde) was supplied in high purity (99.99% ^3He).

^{129}Xe was polarized by Rb- ^{129}Xe collisional spin-exchange optical pumping (22) using a home-built, UK regulatory-approved polarizer constructed from widely available components. In prior work, this polarizer was fitted with an external-cavity diode laser (ECDL), comprising a 30 W, 795 nm laser diode bar externally-tuned by a holographic Bragg grating (2400 lines/mm), and achieved ^{129}Xe polarizations of 10-15% under “continuous-flow” operation (15). This system was recently upgraded by fitting a 795 nm laser diode array with integrated volume holographic grating (BrightLase[®] Ultra-200TM; QPC, Sylmar, CA) providing 50 W incident on the optical cell containing the Rb and Xe. An optical train with solid fiber (see e.g. (14)) was coupled to the diode to minimize light loss and improve beam homogeneity along the optical cell length compared to the ECDL. These factors have facilitated routine attainment of high ^{129}Xe polarizations ($\geq 30\%$ for doses ≤ 1 L) under continuous-flow operation (21). For all ^{129}Xe imaging experiments, the 3% Xe gas mixture was continuously flowed, at 0.4 sL/min, through the optical cell in a direction counter to the incident laser light. Polarized xenon was cryogenically separated from the helium

and nitrogen via a liquid nitrogen trap at the cell output. Accumulation of a 1 L dose of pure xenon required a total flow time of ~ 80 minutes (flow time \approx dosage / (flow rate x Xe fraction)).

^3He was polarized in an optical cell containing 99.99% ^3He by Rb- ^3He collisional spin-exchange under “batch-mode” operation, using a prototype commercial system (MITI, Durham, NC) over a period of 14 hours. Doses of pure polarized ^3He were extracted directly from the cell, with no cryogenic accumulation required.

Sequence Optimization

To maximize the available SNR from a 3D SSFP experiment, the ^{129}Xe magnetization vector was simulated using the matrix form of the Bloch equations for different experimental conditions. The theory underpinning this approach has been detailed previously (16,18,23) and considers the combined effects of: excitation flip angle; off-resonance / B_0 inhomogeneity; and pulse sequence parameters (echo/repetition time, TE/TR). For SSFP with hyperpolarized gases, gas diffusion during the imaging gradients modulates the effective T_2 and the MR signal continuously decays over the course of the image acquisition. This differs from SSFP of thermally-polarized ^1H nuclei, where a true steady-state magnetization is achieved, the transverse relaxation time is much less influenced by diffusion (24) and can be approximated by the Carr-Purcell-Meiboom-Gill (CPMG) T_2 . For a 3D sequence with a hard radiofrequency (RF) pulse, the dominant gradient in terms of diffusional attenuation of MR signal is the read gradient. Therefore, the effective T_2 is modified as follows:

$$T_{2,\text{eff}}(\tau) = \frac{\tau}{b(\tau)D + \frac{\tau}{T_{2,\text{CPMG}}}} \quad (1)$$

where $b(\tau)$ is the b-value of the read gradient, τ is the diffusion time (\equiv TE) and D is the diffusion coefficient, taken to be $D_0 = 0.062 \text{ cm}^2\text{s}^{-1}$ (25), the xenon self-diffusion coefficient. The $T_{2,\text{CPMG}}$ of ^{129}Xe at 1.5 T or 3 T has not been reported, though measurements at low-field (0.2 T) in humans (12), and high-field (4.7 T) in rats (26) have suggested a value of ~ 300 ms in the lungs. However, since the field dependence of $T_{2,\text{CPMG}}$ is not known, and measurement of this parameter is challenging in the lungs with xenon due to the finite inter-echo times attainable and diffusion of the gas causing incomplete refocusing, a range of $T_{2,\text{CPMG}}$ values between 300 ms and 25 ms (the ^{129}Xe T_2^* in partially-inflated human lungs at 1.5 T (27)) was considered in the following simulations. The longitudinal relaxation time of ^{129}Xe in human lungs was taken to be $T_1 = 20 \text{ s}$ (9). It is worth noting that the effect of diffusional dephasing due to applied imaging gradients on the $T_{2,\text{eff}}$ is lesser for ^{129}Xe compared with ^3He (18), due to the ~ 10-fold

lower diffusion coefficient, and the fact that the gradient b-value scales with the square of the gyromagnetic ratio.

Simulations were performed using the matrix product operator approach (16,18,23) to predict the k-space filters imposed by the 3D SSFP ^{129}Xe magnetization evolution, for various receiver bandwidths and flip angles, in order to compare with in vivo experiments. The 3D SSFP image SNR was modeled as a function of bandwidth and flip angle, by normalizing the simulated transverse magnetization, $M_{x,y}$, at the center of k-space (signal) by the square root of the bandwidth (noise). The effect of off-resonance due to inaccurate center frequency estimation or B_0 inhomogeneity was also simulated. Although off-resonance frequencies of tens of Hz can impair SSFP SNR, this effect was minimized for all in vivo experiments by calibrating the ^{129}Xe center frequency as described below. Hence, for all sequence optimization simulations, on-resonance was assumed.

Image Acquisition

Prior to all image acquisitions, the Larmor frequency and flip angle of ^{129}Xe nuclei were calibrated. For center frequency calibration, a high resolution ^{129}Xe spectrum was acquired from the lungs after inhalation of a 3% xenon mixture from a 1 L Tedlar bag (Jensen Inert Products, Coral Springs, FL). Subjects maintained breath-hold for ~ 5 s, and the flip angle was determined by fitting the decay of the hyperpolarized ^{129}Xe signal from a series of pulse-acquire-spoil acquisitions from the whole lungs with an inter-pulse TR of 50 ms. An equivalent procedure was carried out for ^3He using a 5% ^3He :95% N_2 gas mixture.

For comparison with simulations, k-space filters were measured for one subject (HS) in vivo, by nulling the y and z phase-encoding gradients of the 3D SSFP sequence and recording the ^{129}Xe frequency-encoded readout as a function of RF pulse number, for different flip angles and bandwidths. For each flip angle or bandwidth setting, the subject inhaled 200 mL of a 50:50 EN129Xe: N_2 mixture from a 1 L bag and maintained breath-hold for 8-22 seconds, whilst k-space filters were acquired.

The following optimized 3D SSFP sequence parameters were used for ventilation imaging with NAXe at 1.5 T: field-of-view (FOV), 40 cm; phase FOV, 0.8 or 1.0; 20-24 effective coronal slices with no gap; in-plane resolution, 96 x 96 (4.2 mm pixel dimension); effective slice thickness, 10 mm in the anterior-posterior direction; flip angle, 10° ; hard RF pulse; TE/TR = 2.1/6.4 ms (“balanced” SSFP with asymmetric echo); bandwidth, ± 8 kHz; breath-hold, 11-15 sec. Each subject exhaled to functional residual capacity and inhaled 1 L of NAXe gas (30% polarization) from a Tedlar bag prior to image acquisition. In one subject (HN2), same-breath NAXe and ^1H structural MR was performed at 1.5 T,

similar to previous work with ^3He or EN129Xe (8,28). The subject maintained breath-hold for ~ 16 sec after inhalation of 1 L NAXe; a 12 sec NAXe acquisition was followed by a 2 sec ^1H scan, with a small delay due to software limitations. The structural ^1H scan covered the entire thorax (phase FOV, 1): 3D spoiled gradient echo sequence; TE/TR = 0.6/1.9 ms; bandwidth, ± 83.3 kHz; flip angle = 5° ; identical pixel geometry as NAXe.

For comparison with NAXe, the same 3D SSFP imaging was performed on subjects HN1 and HS at 1.5 T using 400 mL EN129Xe mixed with 600 mL nitrogen, and identical imaging parameters. In addition, hyperpolarized ^3He 3D SSFP was performed at 1.5 T with a gas mixture of 200 mL ^3He (25% polarization) and 800 mL nitrogen. The following imaging parameters were modified: TE/TR = 0.6/1.9 ms; bandwidth, ± 83.3 kHz; breath-hold, 5 sec. EN129Xe and ^3He images were acquired subsequent to NAXe images, however, subjects exited the MR scanner for ~ 1 hour between scans to allow for accumulation of hyperpolarized ^{129}Xe and switching of RF hardware, respectively. Subjects were instructed to exhale to the same level prior to inhalation of each gas dose, to ensure comparable lung volumes for each dataset.

Lastly, to evaluate the feasibility of naturally-abundant xenon MRI at 3 T, subject HN2 was scanned using a 3D SSFP pulse sequence with: voxel size, $4.2 \times 4.2 \times 8 \text{ mm}^3$, the latter representing the anterior-posterior direction; flip angle, 12° ; TE/TR = 1.5/4.7 ms; bandwidth, ± 8.5 kHz; breath-hold, 8 sec. As above, the subject inhaled 1 L of NAXe prior to image acquisition.

For comparison of SNR between MR acquisitions with NAXe, EN129Xe and ^3He , regions of interest (ROIs) were placed in the upper right lobe of the lung and at the base of the image (outside the lungs) for each slice. SNR was calculated as the ratio of mean signal in the first ROI to the standard deviation of the signal in the second.

Results

Simulated and in vivo measured ^{129}Xe 3D SSFP k-space filters (for various bandwidths at fixed flip angle of 10°) are presented in Figure 1 (left panel). As expected, the decay in hyperpolarized ^{129}Xe signal over the course of the experiment was steeper for low bandwidths, due to increased dephasing of magnetization in the presence of lengthier readout gradients. The measured in vivo decay of ^{129}Xe longitudinal magnetization was considerably faster than the simulated decay using $T_{2,\text{CPMG}} = 300$ ms; in fact, the best agreement between simulation and experiment was found at a value of $T_{2,\text{CPMG}} = 80$ ms. Simulation results for 3D SSFP SNR (versus bandwidth and flip angle) for a $4.2 \times 4.2 \times 10 \text{ mm}^3$ voxel

and $T_{2,\text{CPMG}} = 80$ ms are shown in Figure 1 (right panel). The available MR signal increases with bandwidth, however, the noise also scales as the square root of the bandwidth, resulting in a simulated optimum SNR at a bandwidth of ± 8 kHz. The simulations highlighted that for 3D SSFP of ^{129}Xe , the SNR is relatively robust and tolerant to variation in flip angle setting; with an optimum flip angle of 9.5° and a predicted SNR penalty of 20-25% for using flip angles of 5° or 15° .

All acquired NAXe images from the three subjects at 1.5 T were of high quality, with mean SNRs of between 25 and 40 (examples shown in Figure 2). The spatial resolution and SNR achieved permitted identification of minor ventilation abnormalities in the healthy smoker's lungs (white arrows, Figure 2). A direct comparison of lung MR imaging with 200 mL ^3He , 400 mL EN129Xe and 1 L NAXe is shown for subject HS in Figure 3. The average SNR values over all acquired slices were 40 ± 8 , 36 ± 4 and 31 ± 5 , respectively for the three doses.

At 3 T, the NAXe image SNR was considerably improved for subject HN2, even with the reduced voxel size (see Figure 4). The average slice SNR at 3 T was 40 ± 10 compared with 26 ± 6 at 1.5 T for this subject. A small abnormality in pulmonary ventilation was identified in the upper right lung of this subject (white oval, Figure 4). This was previously associated with the impingement of a bifid rib. The NAXe image SNR at 1.5 T was also sufficient to identify this defect. The results of same-breath ^1H and NAXe MR, depicted in Figure 5, confirmed that this void in the hyperpolarized gas image was indeed recognizable from the co-registered proton images as a bifid rib.

Discussion and Conclusions

3D SSFP Imaging

With improved ^{129}Xe polarizations and pulse sequence optimization, we have demonstrated full-lung coverage MRI with naturally-abundant hyperpolarized xenon using 3D SSFP, of a similar quality to recent studies with EN129Xe (7,29,30). Scans were completed within a moderate breath-hold (≤ 16 sec), with sufficient resolution ($4.2 \times 4.2 \times 8/10$ mm³) to allow recognition of subtle abnormalities in pulmonary ventilation, comparable to that expected in early-stage lung disease. At 1.5 T, the mean 3D SSFP image SNR for NAXe was moderately variable between subjects, likely due to differences in lung size, completeness of exhalation to functional residual capacity (and residual oxygen content (31)), and fluctuations in ^{129}Xe polarization. Nevertheless, the SNR for any individual slice over all subjects was ≥ 18.5 , sufficient for radiological interpretation and automated segmentation. A minor ventilation defect in the right middle lobe of the healthy smoker's lung was clearly depicted on both EN129Xe and NAXe

scans, although not as noticeable on ^3He images (Figure 3). This is attributable to the different diffusion coefficients of the gases; we note that Kirby et al. observed a higher ventilation defect percentage for ^{129}Xe than ^3He in subjects with chronic obstructive pulmonary disease (6). There is no current literature evidence that ^{129}Xe ventilation defect presentation is altered by the concentration of xenon within the inhaled mixture. Despite accurate calibration of the ^{129}Xe Larmor frequency, slight banding artefacts associated with B_0 inhomogeneity were observed in ≤ 5 slices per subject, typically appearing as dark bands near the diaphragm. These artefacts were easily identified and did not inhibit the recognition of ventilation defects. Although the magnetic susceptibility and hence B_0 inhomogeneity increases with field strength, there was no observation of more prominent banding at 3 T.

NAXe MR is particularly promising at 3 T, wherein the increased SNR compared with 1.5 T – arising from a combination of differences in Larmor frequency, field inhomogeneity, coil sensitivity and the “system” (e.g. transmission line and receiver noise figure) at the two field strengths – reflects previous observations with spoiled gradient echo imaging (27). This SNR benefit, coupled with the possibility of using receiver array coils rather than standard transmit-receive designs as applied here, may facilitate NAXe lung imaging with 3D isotropic resolutions in future. In addition, the feasibility of same-breath ^1H and NAXe MRI is encouraging for obtaining complementary structure-function information from the lungs without necessitating multiple scans crossing different modalities. Same-breath acquisition of the two nuclei provides better-matched ^1H and hyperpolarized gas lung volumes than separate-breath acquisition (32), simplifying image registration. However, the current breath-hold of ~ 16 sec should be shortened for clinical purposes, e.g. via compressed sensing (33).

Perspectives of NAXe MRI

The comparable SNR of lung images acquired with 200 mL ^3He , 400 mL EN129Xe and 1 L NAXe is promising for more widespread viable diagnostic lung MRI with xenon. Taking recent cost estimates provided to our group and others, the relative cost of gas for the scans in Figure 3 could range from approximately 6:2.5:1 to as high as 20:8:1 for ^3He , EN129Xe and NAXe, respectively (assuming that ^3He is purchased under controlled release). For many groups the cost benefits of NAXe could be considerably greater; recently, other institutions have delivered 300-400 mL of ^3He (7) or up to 1 L of EN129Xe (11,30) for lung imaging, compared to the modest doses we have shown to be sufficient for high SNR, though the pulse sequence and gas polarizations used differed from this study.

The implications of economic benefits with naturally-abundant xenon MRI are multi-fold: not only in realization of repeated screening of patients with lung disease, but also longitudinal studies of disease progression and treatment efficacy. Although liter doses of NAXe may not be sufficient for techniques

with a high SNR requirement – such as dissolved ^{129}Xe MR spectroscopy (34) or chemical shift imaging (35) where T_2^* decay is rapid (36,37) – one can envisage the potential of NAXe as the mainstay gas for future routine clinical ventilation imaging applications. Our findings are encouraging for NAXe fulfilling the requirements imposed by reduced availability of ^3He and are timely and relevant to the hyperpolarized gas MRI field as a whole. In particular, NAXe should provide an inexpensive testing platform for development of hyperpolarized gas MR methods and offer additional opportunities for exposure of these techniques to the wider clinical audience.

In addition, further technological developments are permitting the production of hyperpolarized ^{129}Xe in large concentrations for “on-demand” delivery (15,38). Although this polarization technology is currently only in place at a few sites globally, the advent of lower-cost polarizers utilizing high power lasers (14,15) is likely to attract attention from lung clinicians and MR scientists and promote increased application of hyperpolarized ^{129}Xe MRI. Indeed, our group is now undertaking clinical radiology referrals for diagnostic hyperpolarized gas imaging, made feasible in part due to the technical advancements and economic benefits demonstrated in this work.

Conclusions

In conclusion, we have demonstrated the potential of naturally-abundant xenon for clinical imaging of pulmonary ventilation at both of the clinically-relevant MRI field strengths. By exploiting recent advances in polarization technology and optimizing steady-state imaging sequences, high quality lung MR images with liter quantities of inhaled NAXe gas have been acquired using standard transmit-receive RF coil designs, with no loss of functional information compared to hyperpolarized ^3He MR. At a fraction of the cost per scan of ^3He , commercially realistic diagnostic, longitudinal and treatment efficacy studies may now be envisaged.

Acknowledgements

The authors thank Dr. Helen Marshall, Felix Horn and Madhwesha Rao for practical assistance and helpful discussions. We acknowledge funding support from the MRC, EPSRC and GE Healthcare. This article presents independent research funded by the National Institute of Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.

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List of Figure Captions

Figure 1: Left – simulated (solid lines) and in vivo measured (crosses) k-space filters depicting the decay in longitudinal magnetization, M_z , of hyperpolarized ^{129}Xe during a 3D SSFP acquisition. Each cross represents every fiftieth acquired data point. Right – simulated SNR for hyperpolarized ^{129}Xe 3D SSFP, normalized to the maximum predicted value (at ± 8 kHz), as a function of excitation flip angle and imaging bandwidth.

1.5 column figure

Figure 2: Selected coronal 3D SSFP image slices (10 mm thick) acquired from a healthy smoker (HS) and a healthy never-smoker (HN1), after inhalation of 1 L of naturally-abundant hyperpolarized xenon at 1.5 T. White arrows indicate minor ventilation defects (signal voids) identifiable in the lungs of the healthy smoker. The mean SNR (average over all acquired slices) was 31 ± 5 and 33 ± 2 for subject HS and HN1, respectively.

Single column figure

Figure 3: Comparative coronal MR image slices from a healthy smoker (HS) after inhalation of a) 200 mL hyperpolarized ^3He , b) 400 mL enriched xenon (86% hyperpolarized ^{129}Xe) and c) 1 L naturally-abundant xenon (26% hyperpolarized ^{129}Xe), acquired at 1.5 T using an optimized 3D SSFP sequence. The mean SNR of ^3He , EN129Xe and NAXe images acquired from this subject was 41 ± 8 , 36 ± 4 and 31 ± 5 , respectively. Slice locations were not perfectly identical due to the fact that the three scans were not performed in a single session (see Methods).

Single column figure

Figure 4: 3D SSFP data-set from a healthy never-smoker subject (HN2), acquired using 1 L of naturally-abundant xenon at 3 T. The average SNR over all acquired slices was 40 ± 10 . The white oval indicates a small “ventilation abnormality” identified for this subject, present due to a bifid rib, rather than impaired pulmonary function.

1.5 column figure

Figure 5: Example images from same-breath proton and naturally-abundant xenon MR acquisition for a healthy never-smoker (HN2) at 1.5 T. NAXe ventilation images (blue) are overlaid directly on ^1H (greyscale) structural images; no image registration was performed. The mean SNR of the NAXe

ventilation images was 26 ± 6 . The white oval indicates a bifid rib, which is clearly confirmed by the ^1H image as a structural abnormality, external to the lung itself.

1.5 column figure