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Development of equipment and techniques for magnetic resonance imaging of the lungs of laboratory animals with the use of hyperpolarized ^{129}Xe

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Received May 29, 2025
Revised August 11, 2025
Accepted August 21, 2025

A method for NMR imaging of the lungs of laboratory animals with the use of hyperpolarized (HP) ^{129}Xe was validated. A setup for producing HP ^{129}Xe was designed. A magnetic resonance imaging system was modified for operation with xenon nuclei, and an apparatus for controlling the breathing of laboratory animals was designed and manufactured. A tracheostomy procedure needed to maintain the breathing of laboratory animals in the course of lung imaging was validated. An experiment on imaging of the lungs of laboratory animals with the use of HP ^{129}Xe was carried out.

Keywords: magnetic resonance imaging, hyperpolarized ^{129}Xe, artificial lung ventilation, laboratory animals.

DOI: 10.61011/TPL.2025.11.62218.20392

The development of methods for imaging the lung tissue of patients has become particularly important in light of the COVID epidemic. Magnetic resonance imaging (MRI) has been used in medical practice for quite some time. The level of polarization of most types of stable nuclei used in biomedicine (^{1}H, ^{13}C, ^{15}N, etc.) is $10^{-6}-10^{-5}$. With these parameters, MRI becomes a relatively low-sensitivity technique even in strong magnetic fields. Hyperpolarization provides an opportunity to raise the level of polarization of nuclear spins up to the theoretical limit of 100 %, increasing the sensitivity of MRI by several orders of magnitude. In addition to providing imaging data on processes at the molecular level, hyperpolarized compounds reduce significantly the time required for MRI scanning. Moreover, the sensitivity of scanning does not depend on the magnetic field strength of an MRI scanner. This offers the potential to use inexpensive low-field MRI scanners, which would make the MRI procedure significantly cheaper.

Most importantly, this approach makes it possible to perform non-invasive examination of the lungs with a high resolution that is impossible to obtain in conventional MRI and computed tomography. The high solubility of ^{129}Xe and its large chemical shifts (over 200 ppm) make it a unique tool for visualizing pulmonary gas exchange, which is the fundamental function of the lungs. Hyperpolarized (HP) ^{129}Xe exhibits distinct resonance frequencies in various media of the respiratory system: in air, the interstitial barrier, and red blood cells (erythrocytes) [1]. Xenon MRI methods allow for a fundamental improvement in quality of functional diagnostics of the lungs, making it possible to track the path of gas from the lungs into blood vessels within a short time and identify quickly the lung structure defects that hinder effective gas exchange in tissues [1–6].

This method is rapidly gaining ground abroad. In Russia, efforts to produce MRI equipment for obtaining of HP gases [7] (HP ^{129}Xe included) and introduce xenon tomography into medical practice [8] are also underway.

In this regard, the development of protocols and methodological approaches and the modification of equipment for operation with HP ^{129}Xe become particularly relevant. The present study is aimed at expanding the capabilities of magnetic resonance imaging in terms of operation with HP ^{129}Xe nuclei for lung imaging.

The first stage of experiments involved MRI of the lungs of laboratory animals.

The most efficient method for polarizing noble gases is optical pumping of alkali metal atoms with subsequent spin exchange with nuclei of noble gas atoms (spin-exchange optical pumping, SEOP) [6,8]. This method of ^{129}Xe nuclei polarization was the basis for the first Russian full-scale experimental prototype of a ^{129}Xe polarizer designed at JSC NIIEFA. In a single operating cycle within no more than 40 min, it produces up to five medical doses of HP ^{129}Xe with an approximate degree of polarization of 50 %.

At the start of this study, we had a prototype magnetic resonance (MR) imager with a permanent magnet, a magnetic field strength of 0.41 T, and a gap of 206 mm [9] at our disposal. It was designed by the Zavoisky Physical-Technical Institute (FRC „Kazan Scientific Center of the Russian Academy of Sciences“) and LLC Gradient MRT for

operation with protons, which have a resonance frequency ~ 17.5 MHz in the indicated field. Therefore, operation with ^{129}Xe nuclei, which have a resonance frequency of approximately 4.84 MHz, required significant modifications to the radio frequency unit of the MR imager: first and foremost, the transceiver system, the preamplifier, the NMR signal receiver, the radio pulse transmitter, and the radio frequency synthesizer.

Preliminary measurements and adjustment of the MR imager for operation with xenon were carried out with the use of nuclei identical in their NMR spectral characteristics to HP ^{129}Xe. The best suited for these purposes are ^{23}Na nuclei, since they have a close gyromagnetic ratio: in our field, the resonance frequency for ^{23}Na is around 4.63 MHz. Sodium chloride (NaCl) is a readily available reagent containing ^{23}Na nuclei. All preliminary measurements and equipment adjustments were performed using aqueous NaCl solutions. The high solubility of NaCl in water (35.9 at $+21\,^{\circ}$C) makes it possible to achieve a high concentration of ^{23}Na nuclei and obtain a high signal-to-noise ratio for the MRI signal.

To test the MR imager operation at frequencies close to the resonance frequency of HP ^{129}Xe nuclei, the transceiver system was tuned to the resonance frequency of ^{23}Na nuclei. Images of phantoms containing an aqueous solution of NaCl were obtained in these experiments. One such image is shown in Fig. 1. In addition, a concentration dependence of the free induction decay signal amplitude was obtained in order to determine the ultimate sensitivity of the receiving channel of the MR imager in operation with ^{23}Na nuclei. Operation with HP ^{129}Xe nuclei requires readjustment of the transceiver system and the radio frequency unit from a frequency of 4.63 MHz to 4.84 MHz. The coils are tuned to the resonance frequency using a decoupling and matching device.

Laboratory animals must be kept sedated and anesthetized in the process of MR imaging of the lungs. The respiratory function should be maintained with the use of an artificial lung ventilation (ALV) unit [10]. This unit is to provide periodic switching of supply of a breathing mixture and HP xenon and ensure breath holding during the MRI examination.

Xenon remains in a hyperpolarized state for up to several hours. Its relaxation time depends strongly on the gases and materials with which it comes into contact. These materials should not contain ferromagnetic impurities [11]. This precludes the use of common non-magnetic materials, such as brass and stainless steel, in the ALV unit design. HP xenon is also depolarized easily by paramagnetic oxygen [12]. This gives rise to specific requirements as to the HP xenon transport and supply equipment and the sequence of gas supply to the respiratory tract of laboratory animals.

1. Medical bags with valves made of Tedlar®, which are approved for medical practice and exert a minimal influence on relaxation processes, must be used to transport HP ^{129}Xe. It is best to keep transport bags in an external uniform magnetic field in order to slow down the relaxation. Vessels for temporary storage of HP xenon must be impermeable to oxygen.

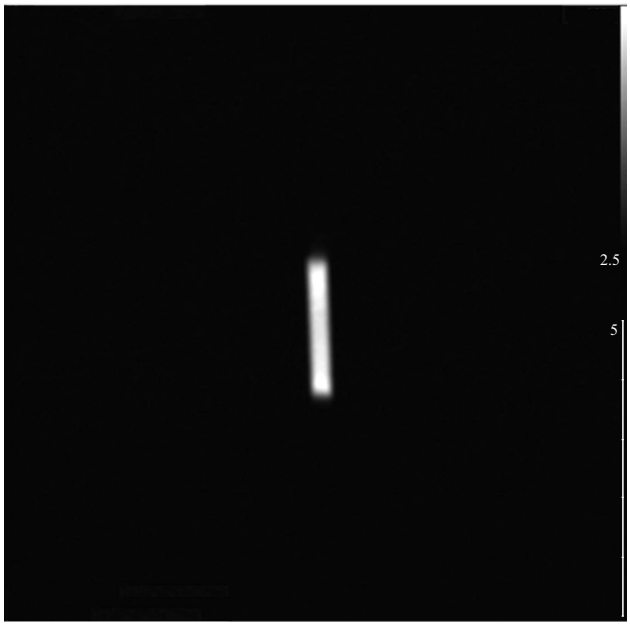

Figure 1. Image of the phantom containing an aqueous NaCl solution obtained using a small-diameter (21 mm) coil. Pulse sequence: spin–echo. Imaging parameters: repetition time, 500 ms; echo time, 20 ms; number of acquisitions, 2; number of lines per image, 128; MRI acquisition time, 2 min 10 s.

2. Prior to the introduction of HP ^{129}Xe into the respiratory tract, oxygen must be removed from it by flushing with a gas neutral to HP xenon (e.g., nitrogen) or with HP ^{129}Xe.

3. Materials with minimal depolarizing properties should be used to fabricate all equipment components involved in supply, switching, and adjustment of HP xenon flow.

A „Fast Gradient Echo“ pulse sequence, which includes excitation pulses with small angles of magnetization vector rotation (in the present case, $\sim 9^{\circ}$) that allow one to perform a complete image scanning cycle with a single portion of gas, was configured for imaging of samples with hyperpolarized gas. It was tested on objects containing common liquid substances: with proton nuclei and ^{23}Na.

The diagram of this pulse sequence is shown in Fig. 2. To test the operation of all systems, a phantom filled with HP ^{129}Xe was subjected to MRI scanning. The resulting image is shown in Fig. 3. The scanning parameters were as follows: repetition time, 60 ms; echo time, 5.97 ms; number of lines per image, 32; pulse angle, $\sim 9^{\circ}$.

The conditions of imaging of samples with ^{23}Na and HP ^{129}Xe nuclei differed significantly. The standard method for obtaining T1-weighted images (T1WI) was used in scanning of samples with ^{23}Na nuclei. The image matrix was then 128×256 points in size: 128 phase-encoding gradient values; 256 points of echo signal digitization. Two

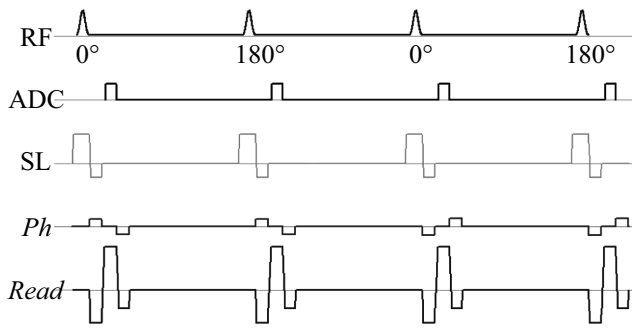

Figure 2. Fragment of the „Fast Gradient Echo“ pulse sequence diagram. RF — radio frequency pulses (0°/180° — phase), SL — selective gradient, *Read* — readout gradient, *Ph* — phase-encoding gradient, and ADC — signal digitization region.

acquisitions were performed. Therefore, both the signal-to-noise ratio and the spatial resolution were fairly high. This approach is inapplicable to samples with HP ^{129}Xe nuclei, since each radio frequency pulse induces their partial depolarization. Therefore, the method of gradient echo with a small excitation angle (fGRE) was used instead of spin echo. The image matrix was 32×32 points in size. The T1WI and fGRE scanning times were more than 2 min and 5–6 s, respectively.

To achieve the planned objectives, further MRI experiments were conducted on laboratory animals (rats). The experimental procedure was as follows: following surgical tracheostomy, which was performed under anesthesia, ALV was maintained and the lungs were examined with the MR imager using HP ^{129}Xe.

Surgical procedures on laboratory animals were performed under aseptic and antiseptic conditions and under general anesthesia induced by intraperitoneal administration of drugs. Surgical access was gained through a longitudinal incision along the midline of the neck extending from the middle and upper thirds to the jugular notch. Access to the trachea was then established layer-by-layer in a blunt manner with mosquito forceps. Next, a longitudinal incision was made with a scalpel through tracheal rings II-IV from bottom to top in order to avoid damaging the parathyroid gland. The wound edges were separated with microsurgical forceps, and a catheter was inserted into the trachea. After that, the wound was sutured above and below the catheter to which the ALV unit was connected, and the animal was introduced into the MR imager for lung examination with ^{129}Xe.

A typical breathing cycle consists of three stages: inhalation, breath holding, and exhalation. At the inhalation stage, air is supplied to the respiratory tract through a controlled inhalation valve. At the holding stage, all controlled valves are closed and the flow of gases into the lungs ceases. At the exhalation stage, the respiratory tract is connected to the atmosphere via the corresponding controlled valve. Natural exhalation occurs at this stage due to the elasticity of the lungs of a laboratory animal.

For MR imaging experiments, the animal's lungs are filled with HP ^{129}Xe. This is preceded by preliminary flushing and measurement breathing cycles. The flushing respiratory cycle is needed to replace the respiratory gas mixture (air) containing paramagnetic oxygen in the lungs with neutral nitrogen or HP ^{129}Xe. At the flushing inhalation stage, HP ^{129}Xe is supplied briefly to the respiratory tract via the corresponding controlled valve of the ALV unit. This is immediately followed by the exhalation stage. To expel the entire volume of air from the lungs, the flushing breathing cycle is repeated several times. The duration and number of repetitions of the flushing cycle are determined experimentally.

As its name suggests, the respiratory measurement cycle is performed during the MRI examination. The purpose of this cycle is to fill the lungs of the test animal with HP ^{129}Xe for the time needed to conduct the study. At this stage, HP ^{129}Xe is supplied to the respiratory tract via the corresponding controlled valve of the ALV unit for the entire time needed for MR imaging (several seconds). When the lungs are filled, the ALV unit generates a synchronization pulse to trigger MRI scanning. The configuration and volume of the test animal's lungs remain unchanged throughout the entire length of the scanning procedure. The measurement cycle concludes with the exhalation stage.

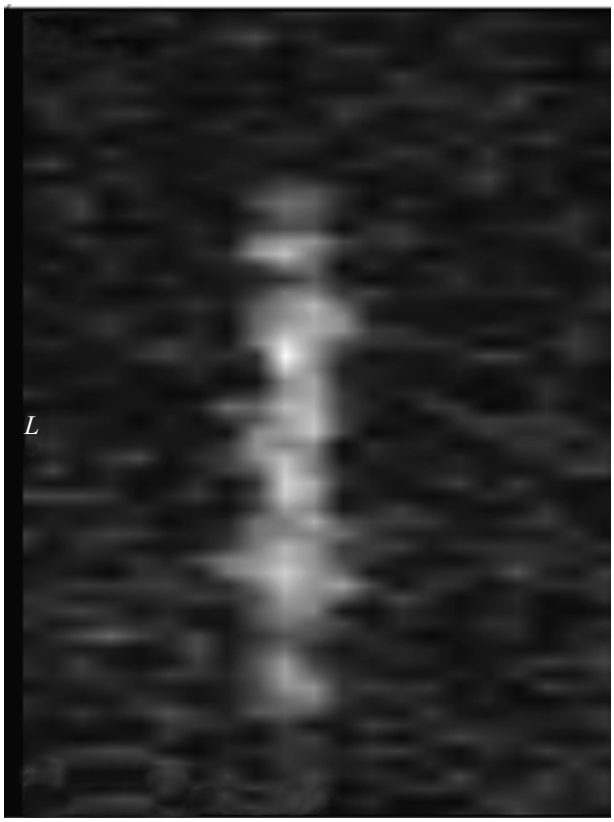

Figure 3. Tomographic image of a phantom filled with HP ^{129}Xe obtained using a small-diameter (21 mm) coil.

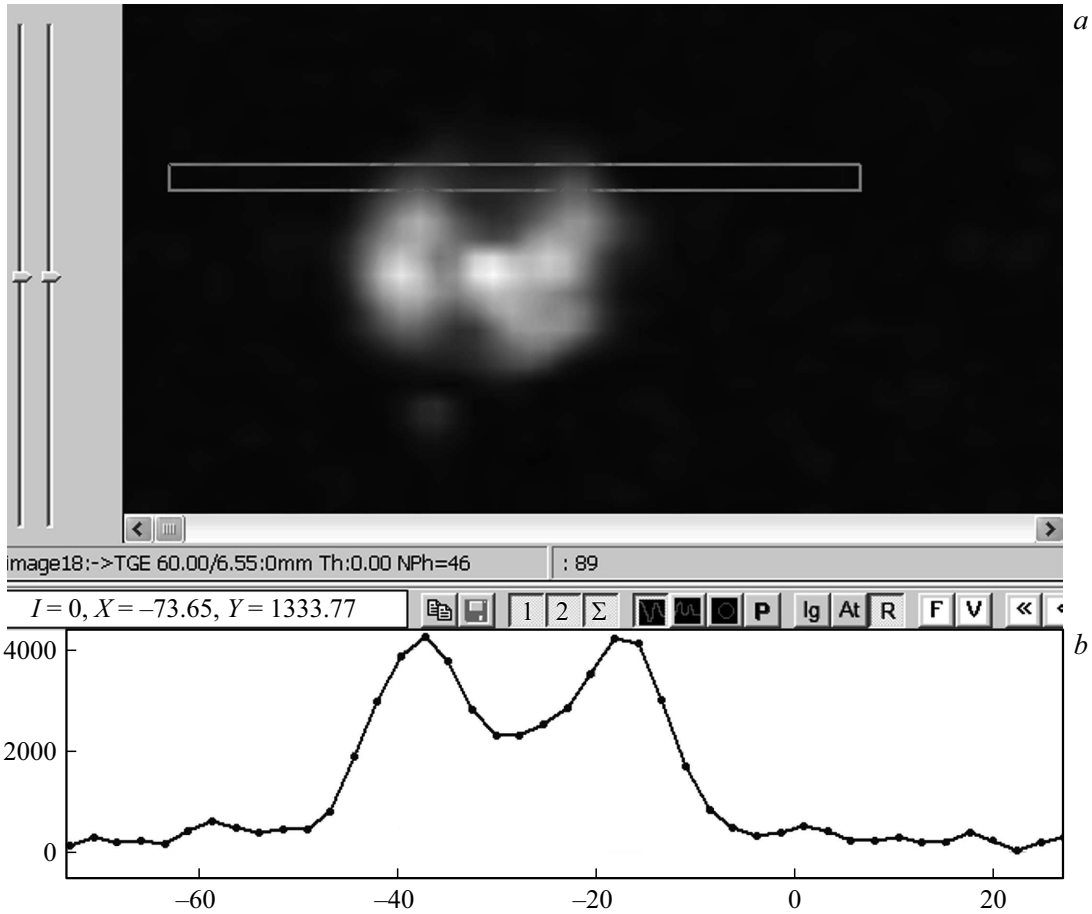

Figure 4. Fragment of the working window of the MR imager control application. *a* — Magnetic resonance image of the lungs of a laboratory animal filled with HP ^{129}Xe by the ALV unit; transaxial (cross-sectional) view. *b* — Plot characterizing the distribution of brightness of the lung image along the long side of the rectangle shown above.

Figure 4 shows the working window of the MRI scanner control application with an MR image of the lungs of the laboratory animal. The section is transaxial (transverse; i. e., orthogonal to the longitudinal axis of the animal's body). Both lungs are visible in the image. The scanning parameters are as follows: repetition time, 60 ms; echo time, 6.55 ms; number of lines per image, 46. This MR image was obtained in less than 3 s.

The distribution of brightness along the side of the rectangle superimposed on the image [13] is shown below the image window (Fig. 4). The number of points here corresponds to the number of image matrix points positioned lengthwise within the highlighted rectangular image area. Averaging was performed over the points positioned along the shorter side.

We note in conclusion that the first full-scale Russian experimental ^{129}Xe polarizer prototype was constructed. The proton MR imager was modified to work with HP ^{129}Xe nuclei: coils for experiments with laboratory animals and phantoms were designed and manufactured, the preamplifier mixer circuit was upgraded, new low-frequency filters with the needed characteristics were designed for the frequency synthesizer, an FPGA control device for the NMR signal receiver was constructed, and the output power of the transmitter and gradient current amplifier was increased. The tracheostomy and anesthesia procedure for laboratory animals was tested. An artificial lung ventilation unit for experiments on laboratory animals, which provides MCU control of the supply of gases and monitoring of respiratory parameters, was designed.

Thus, the performance efficiency of all techniques used for visualizing the lungs of laboratory animals with HP ^{129}Xe was demonstrated. This should allow us to develop a method for diagnosing lung conditions in patients without radiation exposure.

Funding

The work on polarizer design was funded by Private Enterprise for Nuclear Industry Scientific Development „Science and Innovations“ (ROSATOM State Atomic Energy Corporation) under contract No. 774/302-D dated September 20, 2021 („Laser Polarization of Noble Gases by Nuclear Spin“). Experiments on NMR imaging of the lungs of laboratory animals with ^{129}Xe were carried out under contract No. 20588/251 dated August 29, 2023,

between FRC „Kazan Scientific Center of the Russian Academy of Sciences“ and JSC NIIEFA. The work on the experimental NMR imaging setup was funded in part under the state assignment of FRC „Kazan Scientific Center of the Russian Academy of Sciences“ (state registration number 122011800133-2).

Compliance with ethical standards

All applicable international, national, and/or institutional guidelines for laboratory animal care and management were observed.

Conflict of interest

The authors declare that they have no conflict of interest.

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Translated by D.Safin