ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

ISMRM 2024 - Singapore

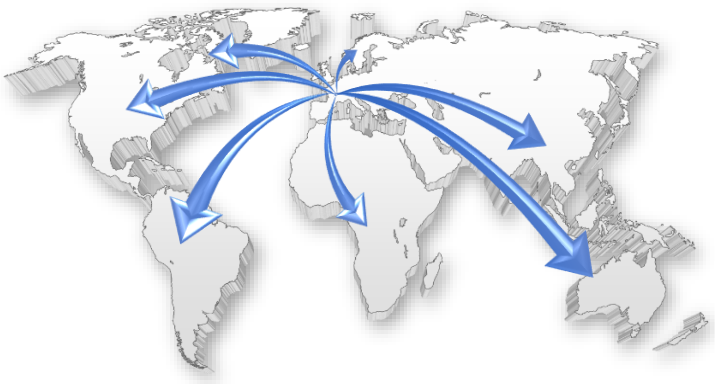
NEWSLETTER & PRODUCT INFORMATION

NUKEM Isotopes GmbH

Vol. # 6

Company Information

NUKEM Isotopes GmbH based in Alzenau, Germany, is a global leader in providing enriched isotopes in the form of ultra-pure substances for industry, agriculture and medical applications. We have been a reliable partner for long term demands of stable isotopes for close to three decades. We maintain our partnership with the major enrichment enterprises in Europe, the People's Republic of China and the Republic of Georgia. With our warehouses at Frankfurt Airport, Hamburg seaport and cooperation partners in the USA, we are able to ship our isotopes within 48 hours to our clients **worldwide**. With our quality management (ISO 9001-2015, 10 CFR50 App. B + 10CFR21) as well as third party analysis of our products, we guarantee our customers reliable services and high-quality isotopes.



In addition, we are proud to work with major research institutes that are leaders in their field (especially in the field of MRI). Among many others, the German Cancer Research Center (DKFZ, Heidelberg), the University Hospital in Freiburg and the University Medical Center Groningen (UMCG) in the Netherlands should be mentioned here.

These cooperations resulted, for example, in the first $^{17}O_2$ study with 10 glioma patients, published in RSNA Radiology Journal (doi: 10.1148/radiol.2020191711) and a O-17 study in which 20 kidneys were examined for vitality using O-17 MRI. Some of the results can be found on page 14 *"Characterizing renal metabolic rate of oxygen during ex vivo machine perfusion using ^{17}O magnetic resonance imaging"*

If you need more information about our company, please do not hesitate to contact us anytime at info@nukemisotopes.de.

Sustainability

Sustainability is a very important aspect for everyone at NUKEM Isotopes. That is why we have used our roof area to install a modern photovoltaic system in 2023. The total size is 635 m² and the peak kilowatt output is 78 kWp. With a distribution of 1/3 self-consumption and 2/3 direct feed-in, we not only cover almost 100% of our own energy requirements (for heating, cooling, lighting, IT, etc.), but also help all companies and households in our area to use sustainable energy. This allows us to feed significant amounts of electricity into the grid on sunny days and provide the additional surplus to our employees (e-bikes, e-cars, etc.). This enables us to get to work using green electricity with zero emissions. Further energy losses are supported by the modern design of our building and we will continue to strive to improve our sustainability in the future.

Insects play an important role in nature. In our garden design, we have placed particular emphasis on ensuring that it provides an oasis of well-being for all insects. We have designed the available space in front of and behind our company building to create a colorful wild meadow that serves as a playground and retreat for all insects with a variety of flowers and shrubs that bloom at different times. A great spectacle in the summer months.

Our main Isotopes

Oxygen-17 enriched gas

The developments with Oxygen-17 in the form of O_2 gas in the recent years could clearly show the big advantages of the Oxygen-17 application. The enhance in quality of information about living tissue can improve the practice of medicine in the fields of cardiology, oncology, neurology and many other fields.

The magnetic properties of O-17 make it a promising "tool" for assessment of in vivo metabolic tissue information and processes at high fields (≥3T).

If you are interested in our ^{17}O-labeled molecules, please do not hesitate to contact us. In cooperation with our synthesis partners, we will be able to provide you with a tailor-made offer.

Oxygen-17 gas specification

Purity	≥ 99.9%	CO	≤ 10 ppm
Enrichment	≥ 70at%	CO_2	≤ 100 ppm
		H_2	≤ 50 ppm
		N_2	≤ 500 ppm

Packing

1 L and 2 L $^{17}O_2$

Seamless stainless-steel cylinder with **50ml water volume** and a **¼" NPT valve**

5 L, 10 L and 20 L $^{17}O_2$

Aluminum cylinder with **400 ml water volume** and a **CGA 540 valve**

Our Oxygen-17 products are manufactured in accordance with cGMP regulations and with the requirements of 21 Code of Federal Regulations: PARTS 210 and 211.

Oxygen-17 enriched water

Oxygen-17 (^{17}O) in the form of water can be used in many fields of research. One example is the use as an MRI contrast agent for analysis of the brain cerebrospinal fluid (CSF). In addition, $H_2{}^{17}O$ is the perfect precursor for the synthesis of NMR active molecules.

Oxygen-17 water specification

Purity	≥ 99.9%	pH	5.5 - 8
Enrichment	≥ 10at%, 20at%, 40at%, 50at%, 60at%, 70at%, 90at%		

Impurities*

Al	≤ 0.05 ppm	Mn	≤ 0.01 ppm
Br	≤ 0.5 ppm	Na	≤ 1 ppm
Ca	≤ 0.1 ppm	Ni	≤ 0.01 ppm
Cl	≤ 0.5 ppm	NO_2, SO_4	≤ 0.1 ppm
Co, Cr, Cu	≤ 0.01 ppm	NO_3, PO_4	≤ 0.05 ppm
F	≤ 0.05 ppm	Si	≤ 1 ppm
Fe	≤ 0.01 ppm	Pb	≤ 0.01 ppm
K	≤ 0.1 ppm	Zn	≤ 0.05 ppm
Mg	≤ 0.05 ppm	** applicable for 10at% enriched and 20at% enriched ^{17}O water only!*	

Packing

1 ml, 2 ml, 5 ml, 10 ml, 20 ml, 50ml (depending on the enrichment)

Our Oxygen-17 products are manufactured in accordance with cGMP regulations and with the requirements of 21 Code of Federal Regulations: PARTS 210 and 211.

Nitrogen-15 enriched salts and gas

Nitrogen-15 (^{15}N) is mainly used for the synthesis of ^{15}N-labelled chemical compounds. These ^{15}N-labelled compounds are used for medical and biomedical applications as well as improving the harvest in agriculture.

In recent years, great progress has also been made in the hyperpolarization of small ^{15}N-labelled molecules, which can open up many new areas of research.

Nitrogen-15 specifications

Gas

Purity	≥ 99%
Enrichment	≥ 99at%

Compounds
Nitrogen gas

Packing
Various cylinders

Salts

Purity	≥ 99%
Enrichment	≥ 99at%

Compounds
Ammonium Chloride,
Ammonium Sulphate,
Potassium Nitrate,
Ammonium Nitrate,
Sodium Nitrate

Packing
400 g or 500 g PE bottles

Oxygen-18 enriched water

Oxygen-18 is used to synthesize radiopharmaceuticals labelled with Fluorine-18 (for example 2-fluoro-2-deoxy glucose [^{18}FDG]), whereby Fluorine-18 is obtained by the irradiating of Oxygen-18 with Hydrogen ions.

The resulting radio-labeled ^{18}FDG can then be detected in Positron Emission Tomography (PET), a nuclear medicine imaging technique, using low radioactive isotopes.

^{18}FDG is still one of the most common cancer diagnostic techniques.

Oxygen-18 specification

Purity	≥ 99.9%
Enrichment	≥ 98.0at%
Pyrogenicity	≤ 0.25 EU/ml
Conductivity	≤ 2 µS/cm
pH	6-8

Packing

Our standard packing size is **50 g per glass vial**, however, upon request we can also fill **25 g** or **10 g** glass vials.

Impurities

Al	≤ 0.05 ppm	Mg	≤ 0.05 ppm
Br	≤ 0.5 ppm	Na	≤ 1 ppm
Ca	≤ 0.1 ppm	NO_2,	≤ 0.1 ppm
Cl	≤ 0.5 ppm	NO_3,	≤ 0.01 ppm
Cu	≤ 0.01 ppm	SO_4	≤ 0.1 ppm
F	≤ 0.05 ppm	PO_4	≤ 0.05 ppm
Fe	≤ 0.01 ppm	Zn	≤ 0.05 ppm
K	≤ 0.1 ppm		

Our Oxygen-18 products are manufactured in accordance with cGMP regulations and with the requirements of 21 Code of Federal Regulations: PARTS 210 and 211.

Xenon-129 enriched gas

Xenon-129 (Xe-129) in the hyperpolarized state is a revolutionary novel MRI contrast agent for diagnostically purposes. Xe-129 facilitates the taking of high-resolution 3D lung images by using a conventional MRI scanner.

Due to the varying solubility of Xenon in different environments, it is additionally possible to illuminate organ functions and tissue characteristics.

Our cooperation partner Polarean designs and manufactures equipment for production of hyperpolarized Xenon-129. Further information about Polarean can be found in this Newsletter on the following pages.

Xenon-129 specifications

Purity	≥ 99.9%
Enrichment	> 80.0at%

Impurities

CO	≤ 10 ppm
CO_2	≤ 10 ppm
H_2O	≤ 10 ppm
O_2	≤ 10 ppm
THC (CH_4)	≤ 1 ppm
THF (CF_4)	≤ 5 ppm

Packing

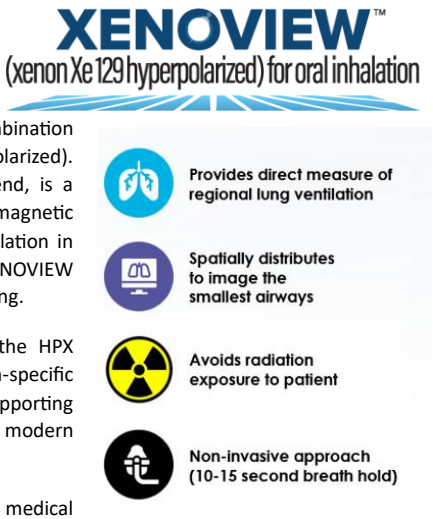
1,000 liter per gas cylinder (with CGA 580 valve).

Other gas volumes can be filled on request, please contact us (info@nukemisotopes.de)

POLAREAN

Polarean Overview

Polarean is a leader in the field of hyperpolarization science and has successfully developed the first and only hyperpolarized MRI contrast agent to be approved in the United States. In December 2022, the FDA granted approval for Polarean's first drug-device combination product, XENOVIEWTM (xenon Xe 129 hyperpolarized). XENOVIEW, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent indicated for use with magnetic resonance imaging ("MRI") for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older. XENOVIEW has not been evaluated for use with lung perfusion imaging.



The company also commercializes systems (such as the HPX hyperpolarization system), accessories (such as xenon-specific chest coils), and FDA-cleared post-processing software (supporting ventilation defect analysis), to support fully integrated modern respiratory imaging operations.

Polarean's vision is to help address the global unmet medical needs of more than 500 million patients worldwide suffering with chronic respiratory disease. This novel imaging modality allows for visualization and longitudinal monitoring of lung ventilation without exposing patients to any ionizing radiation and its associated risks. The dose of XENOVIEW, created through the Polarean HPX Hyperpolarization System, is administered in a single 10-15 second breath hold MRI procedure. Xenon MRI can be used in pulmonary medicine to help characterize disease, evaluate a therapeutic response, educate the patient, or provide image guidance for regional interventions.

First clinical scans

The first clinic scans in the US have occurred at Cincinnati Children's Hospital Medical Center and University of Missouri Health Care for a range of pulmonary diseases. The number of scans at these sites has been steadily increasing.

Important Safety Information
WARNINGS AND PRECAUTIONS

Risk of Decreased Image Quality from Supplemental Oxygen: Supplemental oxygen administered simultaneously with XENOVIEW inhalation can cause degradation of image quality. For patients on supplemental oxygen, withhold oxygen inhalation for two breaths prior to XENOVIEW inhalation, and resume oxygen inhalation immediately following the imaging breath hold.

Please see additional Important Safety Information on the following pages.

Collaboration with Phillips

In June 2023, Polarean announced that it had entered a collaboration with Philips, a global leader in health technology, to advance the field of hyperpolarized Xenon MRI. Philips will showcase its 3T MR 7700 system, featuring fully integrated multi-nuclei imaging, including Polarean's XENOVIEW (xenon Xe 129 hyperpolarized) technology.

This non-exclusive collaboration facilitates the sharing of technical data and marketing materials to jointly advance the field of Xenon MRI into the clinical realm. The collaboration delivers an advanced solution for the evaluation of lung ventilation in patients 12 years of age and older based on Xenon gas MR imaging, providing clinicians with enhanced productivity and image quality improvements.

Additional chest coil clearance

In August 2023, Polarean announced it has received 510(k) clearance from the FDA for a specialized MRI chest coil to now include Philips 3.0T MRI scanners for the visualization of the Xenon-129 (^{129}Xe) nuclei.
The Polarean XENOVIEW™ 3.0T Chest Coil is a flexible, single channel, transmit-receive RF coil tuned to image 129Xe nuclei while a patent is positioned inside a multi nuclei-capable MRI scanner. The XENOVIEW Chest Coil is indicated to be used in conjunction with compatible 3.0T MRI scanners and approved hyperpolarized 129Xe.

XENOVIEW Chest Coil
**not an actual patient*

CMS grants reimbursement code for the Polarean XENOVIEW™ MRI Technology

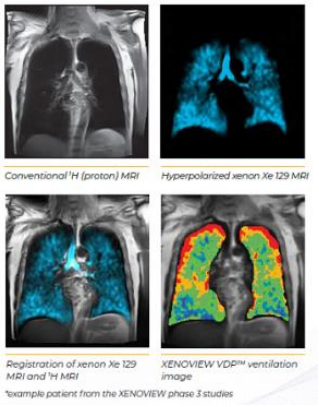
In September 2023, Polarean announced that the Centers for Medicare & Medicaid Services (CMS) had established a new reimbursement code for the Polarean XENOVIEW™ (xenon Xe 129, hyperpolarized) technology, effective October 1, 2023.
The code (C9791) enables healthcare providers a path to bill for "*magnetic resonance imaging with inhaled hyperpolarized xenon-129 contrast agent, chest, including preparation and administration of agent*". This was announced as part of the release of the October 2023 Healthcare Common Procedure Coding System (HCPCS) code set.
In adopting new diagnostic technologies, US-based hospitals look carefully at the return on investment, driven by the reimbursement rates of private and government insurers. Following the Centers for Medicare & Medicaid Services issuance of the reimbursement code for XENOVIEW scans and the associated reimbursement rate of between $1,201 and $1,300 in October 2023, hospitals are steadily recognizing the economic benefits of integrating the XENOVIEW technology into the clinical care pathway for patients with lung disease.

Important Safety Information (continued)
WARNINGS AND PRECAUTIONS (continued)

Risk of Transient Hypoxia: Inhalation of an anoxic gas such as XENOVIEW may cause transient hypoxemia in susceptible patients. Monitor all patients for oxygen saturation and symptoms of hypoxemia and treat as clinically indicated.

Please see additional Important Safety Information on the following pages.

Polarean Partners with VIDA to Streamline Adoption of Advanced MRI of the Lungs



In September 2023, Polarean announced its partnership with VIDA Diagnostics (VIDA), a clinical imaging intelligence company providing medical imaging software solutions which manage the complexities of digital biomarkers. The companies are partnering to develop solutions that further enable Polarean's Xenon MRI platform to accelerate clinical and research use.

VIDA has empowered more than 1,000 clinical and research sites globally with its imaging management platform, a cloud-native AI-enabled solution that drives standardization and efficiencies in clinical trial imaging operations. The platform includes a unique orchestration engine used to integrate and optimize multimodality clinical algorithms and enable new high-quality imaging biomarkers to be more accessible.

The collaboration between Polarean and VIDA aims to integrate Xenon MRI into clinical practices, establish a network for pharma-sponsored trials, and standardize image acquisition and data-sharing. These initiatives will broaden the access to Xenon MRI to investigate new indications and identify biomarkers in broader populations.

2024 Polarean Strategy Update

Polarean continues to make substantial progress toward the implementation of the five-pillar growth strategy.

- Drive utilization: Regularly visiting the initial clinical sites educating pulmonologists and radiologists on the benefits of the XENOVIEW™ technology.
- Grow user base: Actively navigating obstacles to transition multiple research sites to clinical status, alongside engagement of new sites to introduce the Polarean pulmonary functional MRI technology as a solution to their unmet diagnostic needs.
- Broaden reimbursement coverage: With Medicare coverage and private insurer reimbursements secured, Polarean aims to expand coverage further with additional private U.S. health insurers to strengthen the value proposition for the adoption of XENOVIEW.
- Expand total addressable market: FDA approval for younger patients and plans for new indications like gas exchange and cardiopulmonary applications will enhance market accessibility.
- Further develop partnerships: Polarean has been actively engaging multiple pharmaceutical and medical technology companies to increase awareness and adoption of Polarean's Xenon MRI technology. Currently, clinicaltrials.gov lists numerous clinical trials underway that utilize Xenon MRI technology to evaluate the effectiveness of existing and new pharmaceutical treatments.

Important Safety Information (continued)

ADVERSE REACTIONS

Adverse Reactions in Adult Patients: The adverse reactions (> one patient) in efficacy trials were oropharyngeal pain, headache, and dizziness.

Please see additional Important Safety Information on the following pages.

Important Safety Information

Indication

XENOVIEW™, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older.

Limitations of Use

XENOVIEW has not been evaluated for use with lung perfusion imaging.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risk of Decreased Image Quality from Supplemental Oxygen: Supplemental oxygen administered simultaneously with XENOVIEW inhalation can cause degradation of image quality. For patients on supplemental oxygen, withhold oxygen inhalation for two breaths prior to XENOVIEW inhalation, and resume oxygen inhalation immediately following the imaging breath hold.

Risk of Transient Hypoxia: Inhalation of an anoxic gas such as XENOVIEW may cause transient hypoxemia in susceptible patients. Monitor all patients for oxygen saturation and symptoms of hypoxemia and treat as clinically indicated.

ADVERSE REACTIONS

Adverse Reactions in Adult Patients: The adverse reactions (> one patient) in efficacy trials were oropharyngeal pain, headache, and dizziness.

Adverse Reactions in Pediatric Patients: In published literature in pediatric patients aged 6 to 18 years, the following transient adverse reactions were reported: blood oxygen desaturation, heart rate elevation, numbness, tingling, dizziness, and euphoria. In at least one published study of pediatric patients aged 6 to 18 years, transient decrease in SpO2% and transient increase in heart rate were reported following hyperpolarized xenon Xe 129 administration. XENOVIEW is not approved for use in pediatric patients less than 12 years of age.

Please see full prescribing information at Xenoview.net

Information about our booth wall

The illustrations (left tile) were created in close cooperation with UMCG (University Medical Center Groningen, Netherlands). The basis for these information is a joint project to investigate the vitality of organs (kidneys) prior to transplantation.

In addition, the images (right tile) of a Hyperpolarizer and a lung, scanned with hyperpolarized Xe-129 in an MRI scanner was gratefully provided to us by our business partner Polarean.

Oxygen-17 research abstracts

Characterizing renal metabolic rate of oxygen during ex vivo machine perfusion using ^{17}O magnetic resonance imaging

Pamplona CC[1], Castelein J[2],Hamelink TL[1], Lantinga V[1], Ogurlu B[1], Potze JH[2], Bock M[3], Leuvenink HGD[1], Borra RJH[2], Moers C[1]

[1]Department of Surgery – Organ Donation and Transplantation, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [2]Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [3]Department of Radiology, University Medical Center Freiburg, Freiburg, Germany

BACKGROUND Renal normothermic machine perfusion (NMP) is a novel strategy to assess pretransplant renal function and injury, but it remains unclear which markers can provide information about renal viability during NMP. Magnetic resonance imaging (MRI) is commonly used to evaluate tissue morphology, metabolism, and function, and recently it has been applied to study ex vivo renal viability. The oxygen-17 (^{17}O) isotope offers a unique tool for the assessment of metabolic rate. By administering ^{17}O to the organ, $H_2{}^{17}O$ is produced and the occurrence of this immediate end product of oxidative metabolism can be selectively imaged and quantified by functional MRI sequences. This study aimed to evaluate the feasibility of direct and indirect (T1ρ) $H_2{}^{17}O$ MRI imaging during renal NMP to assess real-time organ oxygen metabolism in healthy and partially ischemic porcine kidneys.

METHODS Viable porcine kidneys (n=3) were retrieved at a local slaughterhouse, subjected to 30 minutes of warm ischemia (WI), and preserved by oxygenated hypothermic perfusion. Kidneys were subsequently perfused for 3h at 37°C. Initially, oxygenation was administered with 95% O_2 / 5% CO_2. After 1h of NMP, perfusion to part of each kidney was blocked for 75 minutes using a balloon catheter to induce either 40, 20, or 10 minutes of complete occlusion, and then reperfused for 30 minutes before ^{17}O gas administration. Anatomic and dynamic radial $H_2{}^{17}O$ MR images were acquired before, during, and after ^{17}O administration.

RESULTS Occlusion profiles are shown in Figure 1 by a decrease in tissue perfusion. Partial ischemia was confirmed by a decreased ASL and T2* mapping signal. After reperfusion and ^{17}O gas administration, those fMRI measurements returned to baseline levels, therefore not suggesting ischemic injury to the organs. In contrast, kidney 1 displayed an increase in naturally abundant $H_2{}^{17}O$ during occlusion, followed by a decrease during reperfusion and an increase after ^{17}O gas administration. Kidneys 2 and 3 did not show a clear difference between poles in T1ρ imaging, but their ischemic injury was clearly visible with direct $H_2{}^{17}O$ imaging (Figure 2).

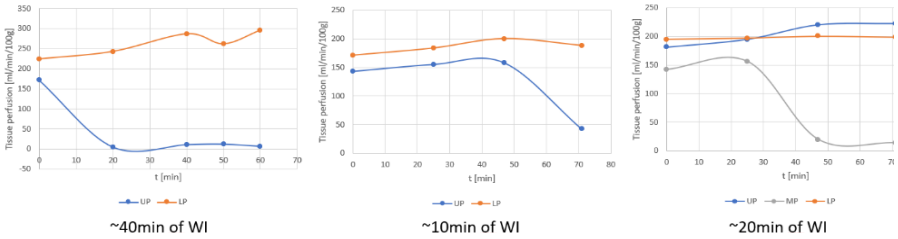


Figure 1. *Graphical representation of occlusion profiles from balloon catheter for all kidneys depicting warm ischemia time (WI). UP= Upper pole, MP = middle pole, LP = lower pole.*

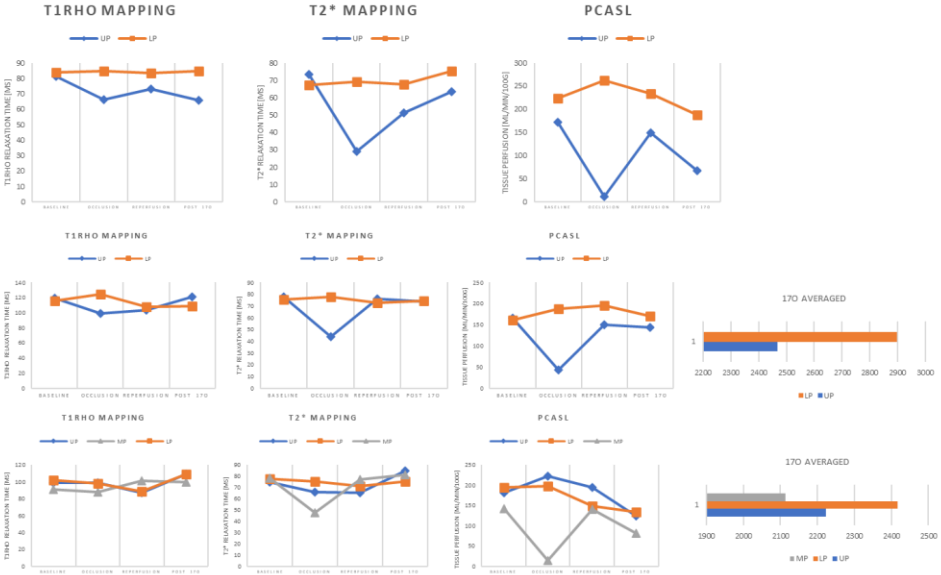


Figure 2. *Quantification of all kidneys during normothermic machine perfusion, measuring MRI markers in each of the poles (MP = middle pole, LP = lower pole, UP = upper pole) during 4 timepoints: baseline, during occlusion, after reperfusion and post ^{17}O gas administration. (A): Kidney 1. (B): Kidney 2. (C): Kidney 3; Displayed sequences are indirect T1ρ mapping, T2* mapping, and ASL. Direct H_2O^{17} imaging was only retrieved for kidneys 2 and 3, as there was a coil malfunction during kidney 1.*

CONCLUSION It can be implied from our study results that both direct and indirect techniques of $H_2{}^{17}O$ imaging are feasible. Direct ^{17}O sequences were sensitive to all degrees of ischemic damage, while indirect signal was only visible after a higher degree of injury. However, direct and indirect measurements showed contradictory results, leading us to hypothesize that T1ρ mapping might not actually measure $H_2{}^{17}O$, but another injury-related process, metabolite or molecule, therefore requiring further investigation to understand the phenomenon being imaged. Nonetheless, both techniques corroborate the presence of kidney injury.

First implementation of dynamic oxygen-17 (^{17}O) magnetic resonance imaging at 7 Tesla during neuronal stimulation in the human brain

Louise Ebersberger, Fabian J. Kratzer, Vanessa L. Franke, Armin M. Nagel, Sebastian C. Niesporek, Andreas Korzowski, Mark E. Ladd, Heinz-Peter Schlemmer, Daniel Paech & Tanja Platt

German Cancer Research Center, Germany; University of Heidelberg, Germany; Bern University Hospital, Switzerland; Heidelberg University Hospital, Germany; Friedrich-Alexander University Erlangen-Nürnberg, Germany; Bonn University Hospital, Germany

Magnetic Resonance Materials in Physics, Biology and Medicine (2023). doi: 10.1007/s10334-023-01119-6

OBJECTIVE First implementation of dynamic oxygen-17 (^{17}O) MRI at 7 Tesla (T) during neuronal stimulation in the human brain.

METHODS Five healthy volunteers underwent a three-phase ^{17}O gas ($^{17}O_2$) inhalation experiment. Combined right-side visual stimulus and right-hand finger tapping were used to achieve neuronal stimulation in the left cerebral hemisphere. Data analysis included the evaluation of the relative partial volume (PV)-corrected time evolution of absolute ^{17}O water ($H_2{}^{17}O$) concentration and of the relative signal evolution without PV correction. Statistical analysis was performed using a one-tailed paired t test. Blood oxygen level-dependent (BOLD) experiments were performed to validate the stimulation paradigm.

RESULTS The BOLD maps showed significant activity in the stimulated left visual and sensorimotor cortex compared to the non-stimulated right side. PV correction of ^{17}O MR data resulted in high signal fluctuations with a noise level of 10% due to small regions of interest (ROI), impeding further quantitative analysis. Statistical evaluation of the relative $H_2{}^{17}O$ signal with PV correction ($p = 0.168$) and without ($p = 0.382$) did not show significant difference between the stimulated left and non-stimulated right sensorimotor ROI.

DISCUSSION The change of cerebral oxygen metabolism induced by sensorimotor and visual stimulation is not large enough to be reliably detected with the current setup and methodology of dynamic ^{17}O MRI at 7 T.

REFERENCE Ebersberger, L., Kratzer, F.J., Franke, V.L. et al. First implementation of dynamic oxygen-17 (^{17}O) magnetic resonance imaging at 7 Tesla during neuronal stimulation in the human brain. Magn Reson Mater Phy (2023). https://doi.org/10.1007/s10334-023-01119-6

First application of dynamic oxygen-17 magnetic resonance imaging at 7 Tesla in a patient with early subacute stroke

Louise Ebersberger, Fabian J. Kratzer, Arne Potreck, Sebastian C. Niesporek, Myriam Keymling, Armin M. Nagel, Martin Bendszus, Wolfgang Wick, Mark E. Ladd, Heinz-Peter Schlemmer, Angelika Hoffmann, Tanja Platt, and Daniel Paech
(German Cancer Research Center, Germany; University of Heidelberg, Germany; Bern University Hospital, Switzerland; Heidelberg University Hospital, Germany; Friedrich-Alexander University Erlangen-Nürnberg, Germany; Bonn University Hospital, Germany)

Frontiers in Neuroscience (2023). doi: 10.3389/fnins.2023.1186558

ABSTRACT Dynamic oxygen-17 (^{17}O) magnetic resonance imaging (MRI) is an imaging method that enables a direct and non-invasive assessment of cerebral oxygen metabolism and thus potentially the distinction between viable and non-viable tissue employing a three-phase inhalation experiment. The purpose of this investigation was the first application of dynamic ^{17}O MRI at 7 Tesla (T) in a patient with stroke. In this proof-of-concept experiment, dynamic ^{17}O MRI was applied during ^{17}O inhalation in a patient with early subacute stroke. The analysis of the relative ^{17}O water ($H_2{}^{17}O$) signal for the affected stroke region compared to the healthy contralateral side revealed no significant difference. However, the technical feasibility of ^{17}O MRI has been demonstrated paving the way for future investigations in neurovascular diseases.

REFERENCE Ebersberger, L., Kratzer, F.J., Potreck, A. et al. (2023). First application of dynamic oxygen-17 magnetic resonance imaging at 7 Tesla in a patient with early subacute stroke. Front Neurosci (2023). https://doi.org/10.3389/fnins.2023.1186558.

Xenon-129 abstract

Combining Hyperpolarized ^{129}Xe MR Imaging and Spectroscopy to Estimate Pulmonary Vascular Resistance

Anna Costelle, David Mummy, Junlan Lu, Suphachart Leewiwatwong, Sudarshan Rajagopal, Bastiaan Driehuys

Funding Sources - R01HL105643 and R01HL153872

RATIONALE Inhaled hyperpolarized ^{129}Xe exhibits distinct resonances in the lung airspaces, membrane tissues, and red blood cells (RBCs), enabling MR imaging and spectroscopy of each gas exchange compartment. ^{129}Xe MR spectra, acquired every 15ms, also reveal cardiogenic oscillations in the RBC resonance[1], which tend to decrease in amplitude in the presence of pre-capillary pulmonary hypertension (PH)[2]. Thus, oscillations may provide a non-invasive alternative to right heart catheterization (RHC), the current gold standard method of measuring pulmonary vascular resistance (PVR) and diagnosing PH. However, many patients also exhibit RBC transfer defects on ^{129}Xe imaging (interpreted as reduced pulmonary capillary blood volume), which tend to *increase* oscillation amplitudes, thereby rendering it difficult to distinguish PH from healthy oscillations[3]. Here, we hypothesize that ^{129}Xe RBC signal oscillations are driven by changes in pulmonary capillary blood volume between systole and diastole, and we implement a windkessel model of pulmonary hemodynamics[4] to estimate the effects of pulmonary capillary and venous impedances on compliance-induced blood storage (Figure 1). We show that as capillary blood volume decreases, capillary impedance increases, thereby increasing the pressure on the microvasculature and the relative oscillation amplitudes. Using this framework, we develop a physiological model to simultaneously account for the competing effects of RBC transfer defects and PH on oscillations, thus enabling combined ^{129}Xe MRI/MRS to non-invasively estimate PVR.

CONCLUSION ^{129}Xe RBC oscillations increase when capillary blood volume is reduced, consistent with the hypothesized model of blood-flow, pulmonary capillary compliance and impedance. This permits estimation of the contribution of pulmonary capillary impedance and venous impedance to overall PVR. Notably, this also permits oscillations to be corrected for reduced capillary blood volume, thereby yielding a non-invasive means of estimating PVR. Given that this PVR estimate depends on two of the weaker signals in ^{129}Xe MRI/MRS (RBC transfer images and RBC oscillations), it is imperative to optimize the SNR of both acquisitions. Furthermore, given the hypothesized physiological model, future work will distinguish changes in the ratio of pulmonary capillary compliance to mean healthy capillary blood volume from changes in systolic and diastolic blood-flow, as a function of PVR, in order to determine which physiological parameters are driving the

negative linear correlation between corrected oscillations and PVR. Nonetheless, these results suggest the potential for improved utility of ^{129}Xe MRI/MRS in assessing PH, thus limiting the need for RHC.

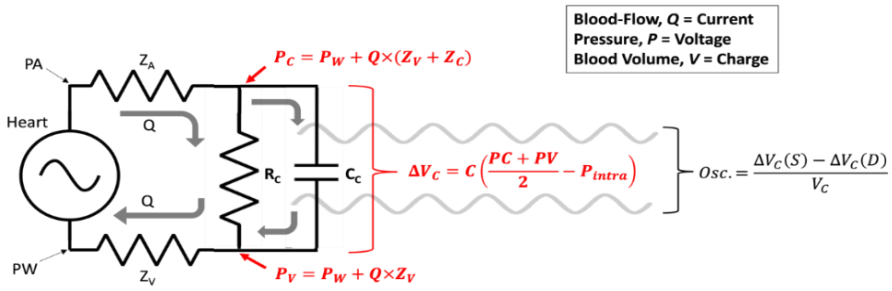


Figure 1. *Illustration of pulmonary loop using windkessel circuit analogy. PVR is the sum of arterial, capillary, and venous impedances, where each impedance consists of a parallel resistance and compliance. The pressure gradient across the pulmonary compliance determines the associated volume change in the pulmonary capillaries. While the heart is a "constant current" source when averaged over many cycles, instantaneous flow is higher at systole than diastole. We can calculate PC and PV and, accounting for differences in flow, obtain a model of ^{129}Xe RBC signal oscillations in terms of capillary and venous impedances.*

SUMMARY Motivation: Pulmonary hypertension (PH) and reduced capillary blood volume, V_C', have competing effects on oscillations in the hyperpolarized ^{129}Xe red blood cell (RBC) resonance, rendering it difficult to distinguish PH.

Goal: Our goal was to correct RBC oscillations for reduced capillary blood volume, then use corrected oscillations to estimate pulmonary vascular resistance (PVR).

Approach: We developed a model of RBC oscillations as a function of VC' in a cohort without known PH and used this model to derive a correction factor. Corrected oscillations were regressed against known PVR in a cohort with suspected PH.

Results: Corrected oscillations improved PH sensitivity and were significantly correlated to PVR.

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Senior physician Emma I.
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Contact us

Company Video

NUKEM Isotopes GmbH

Rodenbacher Straße 47
63755 Alzenau, Germany

T +49 (0) 6023 9474 800
F +49 (0) 6023 9474 813
E info@nukemisotopes.de

www.nukemisotopes.de