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ISMRRM 2025 - Honolulu

NEWSLETTER & PRODUCT INFORMATION

NUKEM Isotopes GmbH

Vol. # 7



Contact us



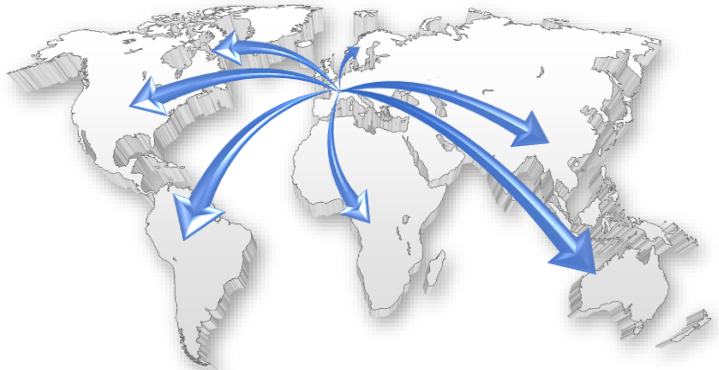
Company Video



Company Information	1
Sustainability	2
Our main Isotopes	3
Oxygen-17 enriched gas	3
Oxygen-17 enriched water	4
Nitrogen-15 enriched salts and gas	5
Oxygen-18 enriched water	6
Xenon-129 enriched gas	7
Information about our booth wall	12
Oxygen-17 research abstracts	13
Characterizing renal metabolic rate of oxygen during ex vivo machine perfusion using ¹⁷ O magnetic resonance imaging	13
Xenon-129 abstract	15
Mapping the Chemical Shift of ¹²⁹ Xe in Red Blood Cells as a Biomarker for Pulmonary Hypertension	15
Our ISMRM rubber duck family	20

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 $^{17}\text{O}_2$ study with 10 glioma patients, published in RSNA Radiology Journal (doi: [10.1148/radiol.2020191711](https://doi.org/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 13 "*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 O₂ 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 ¹⁷O-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 ¹⁷O₂



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

5 L, 10 L and 20 L ¹⁷O₂



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	$\geq 99.9\%$	pH	5.5 - 8
Enrichment	$\geq 10\text{at}\%, 20\text{at}\%, 40\text{at}\%, 50\text{at}\%, 60\text{at}\%, 70\text{at}\%, 90\text{at}\%$		

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 $\geq 99\%$
Enrichment $\geq 99\text{at}\%$

Compounds

Nitrogen gas

Packing

Various cylinders



Salts

Purity $\geq 99\%$
Enrichment $\geq 99\text{at}\%$

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}F FDG]), whereby Fluorine-18 is obtained by irradiating of Oxygen-18 with Hydrogen ions.

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

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

Oxygen-18 specification

Purity	$\geq 99.9\%$
Enrichment	$\geq 98.0\text{at}\%$
Pyrogenicity	$\leq 0.25 \text{ EU/ml}$
Conductivity	$\leq 2 \mu\text{S/cm}$
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	$\leq 0.05 \text{ ppm}$	Mg	$\leq 0.05 \text{ ppm}$
Br	$\leq 0.5 \text{ ppm}$	Na	$\leq 1 \text{ ppm}$
Ca	$\leq 0.1 \text{ ppm}$	NO_2 ,	$\leq 0.1 \text{ ppm}$
Cl	$\leq 0.5 \text{ ppm}$	NO_3 ,	$\leq 0.01 \text{ ppm}$
Cu	$\leq 0.01 \text{ ppm}$	SO_4	$\leq 0.1 \text{ ppm}$
F	$\leq 0.05 \text{ ppm}$	PO_4	$\leq 0.05 \text{ ppm}$
Fe	$\leq 0.01 \text{ ppm}$	Zn	$\leq 0.05 \text{ ppm}$
K	$\leq 0.1 \text{ ppm}$		

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.

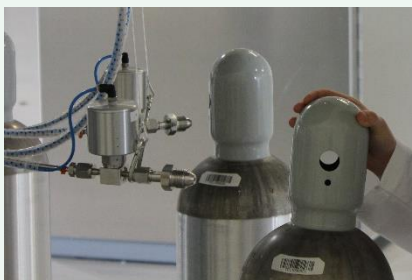
Our cooperation partner Polarean designs and manufactures equipment for production of hyperpolarized Xenon-129. Further information about Polarean can be found in this Newsletter on the following pages.

Xenon-129 specifications

Purity	≥ 99.9%
Enrichment	> 80.0at%

Impurities

CO	≤ 10 ppm
CO ₂	≤ 10 ppm
H ₂ O	≤ 10 ppm
O ₂	≤ 10 ppm
THC (CH ₄)	≤ 1 ppm
THF (CF ₄)	≤ 5 ppm



Packing

50 liter or 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 medical imaging technology leader in functional Magnetic Resonance Imaging (MRI) of the lungs 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, XENOVIEW® (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 distribution 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.

XENOVIEW® (xenon Xe 129 hyperpolarized) for oral inhalation



Evaluates regional lung ventilation



Spatially distributes to image the smallest airways



No radiation exposure to the patient



Single breath hold scan



Effort-independent procedure

Important Safety Information

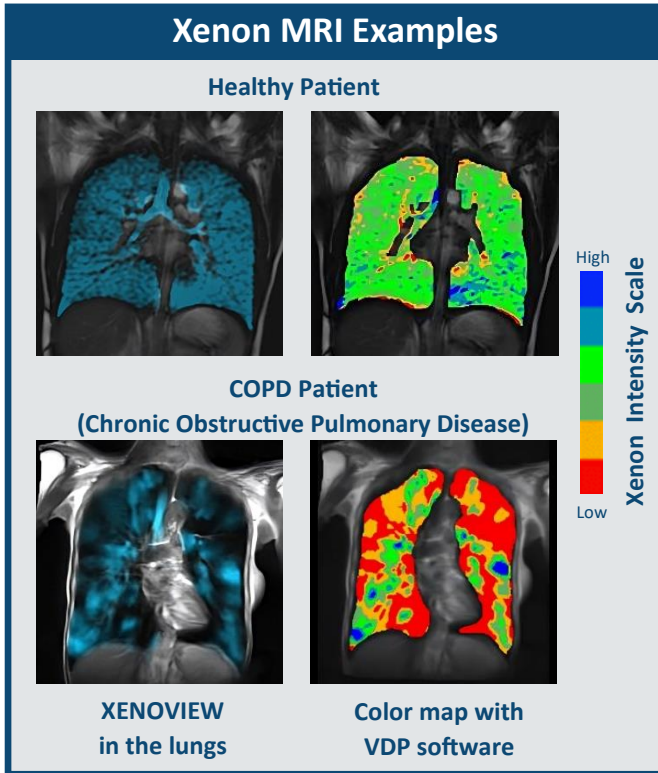
WARNINGS AND PRECAUTIONS

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.

Xenon MRI is a platform to gain deep insights when navigating complex treatment decisions, including:

- **Detecting Early and Mild Ventilation Problems:** Xenon MRI is a sensitive and repeatable measure, enabling appropriately timed intervention
- **Connecting Structural Anatomy with Function:** Xenon MRI is a functional measure that can evaluate lung ventilation when CT or clinical findings don't fully explain symptoms



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.

Additional Chest Coil Clearance

In November 2024, Polarean announced it has received 510(k) clearance from the FDA for its specialized MRI chest coil to now include GE Healthcare 3 Tesla (3T) 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 ^{129}Xe nuclei while a patient 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 ^{129}Xe .

This advancement means Polarean now supports Xenon MRI scanning of both clinical and research patients on all three major MRI scanner vendors—GE HealthCare, Philips, and Siemens Healthineers.



XENOVIEW Chest Coil

Collaboration with SimonMed

In January 2025, Polarean announced a strategic collaboration with SimonMed Imaging, one of the largest outpatient medical imaging providers in the United States, to expand access to Polarean's cutting-edge Xenon MRI platform.

SimonMed Imaging operates in over 170 facilities across 11 states, offering comprehensive medical imaging with cutting-edge technology and artificial intelligence, all with an emphasis on affordability and accessibility. This collaboration will integrate Polarean's innovative Xenon MRI platform within SimonMed's network, enhancing diagnostic capabilities and advancing the standard of care for patients with pulmonary diseases.

The first SimonMed site to adopt Polarean's Xenon MRI platform will be in Scottsdale, Arizona, which is expected to be installed later this year, with scope to increase the number of sites installing systems as the collaboration matures.



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

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

Your global supplier for stable isotopes



The booth wall display features a central white MRI scanner. Overlaid on the scanner are several teal hexagonal tiles containing text and images. A central tile reads "Stable Isotopes for medical application". To the left, a tile for ^{17}O Oxygen describes its use in MRI for measuring oxygen consumption. To the right, a tile for ^{129}Xe Xenon describes its use as a contrast agent in MRI. Below these are two tiles: one for ^{18}O in the form of water and gas, and another for ^{13}C in the form of pure gas. A small tile on the far left is titled "In vivo perfused kidney (^{13}C -MRI)". At the bottom of the display is a dark teal banner with the text "Realizing ideas with isotopes" and the website "nukem-isotopes.com".

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 CC¹, Castelein J², Hamelink TL¹, Lantinga V¹, Ogurlu B¹, Potze JH², Bock M³, Leuvenink HGD¹, Borra RJH², Moers C¹

¹Department of Surgery – Organ Donation and Transplantation, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ²Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands;

³Department 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 (T1 ρ) 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 T1 ρ imaging, but their ischemic injury was clearly visible with direct H_2^{17}O imaging (Figure 2).

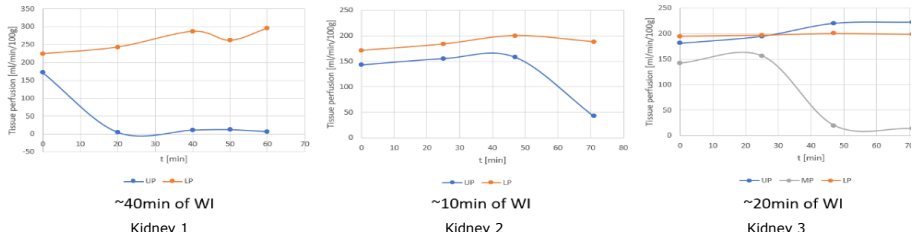


Figure 1. Graphical representation of occlusion profiles from balloon catheter for all kidneys depicting warm ischemia time (WI). UP= Upper pole, MP = middle pole, LP = lower pole.

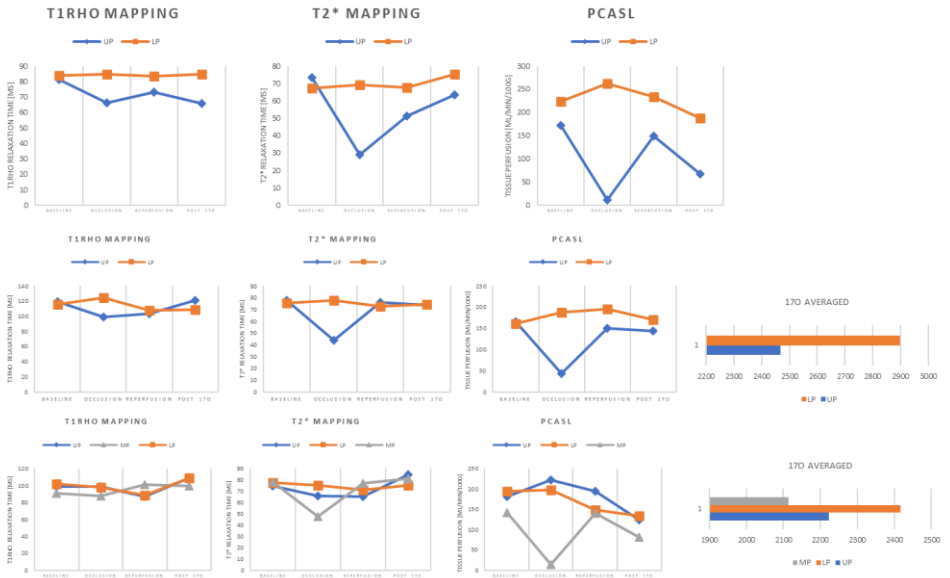


Figure 2. Quantification of all kidneys during normothermic machine perfusion, measuring MRI markers in each of the poles (MP = middle pole, LP = lower pole, UP = upper pole) during 4 timepoints: baseline, during occlusion, after reperfusion and post ^{17}O gas administration. (A): Kidney 1. (B): Kidney 2. (C): Kidney 3; Displayed sequences are indirect T1 ρ mapping, T2* mapping, and ASL. Direct H_2^{17}O 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 T1 ρ 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.

Xenon-129 abstract

Mapping the Chemical Shift of ^{129}Xe in Red Blood Cells as a Biomarker for Pulmonary Hypertension

Anna Costelle, Suphachart Leewiwatwong, John Mugler, Sudarshan Rajagopal, David Mummy, and Bastiaan Driehuys

SYNOPSIS

MOTIVATION Prior work suggests that pre-capillary vascular occlusion in pulmonary hypertension (PH) may lead to paradoxical regions of enhanced blood oxygenation in the distal capillaries. The ^{129}Xe RBC chemical shift is sensitive to such oxygenation variations.

Goals: We aim to test whether enhanced oxygenation zones in PH could be detected by regional RBC shift mapping via ^{129}Xe CSI.

Approach: ^{129}Xe CSI was performed in healthy volunteers and patients with pre-capillary PH. RBC shift maps were computed via spectral fitting and were compared between disease groups.

Results: RBC shift maps in PH patients exhibit distinct patterns, consistent with physiological theory.

IMPACT

This work offers a proof-of-concept that mapping the ^{129}Xe RBC chemical shift could be valuable in assessing PH. Compared to current gold standard diagnostic techniques, ^{129}Xe CSI is less invasive and, with further optimization, may permit localization of vascular occlusion.

ABSTRACT

INTRODUCTION Inhaled hyperpolarized ^{129}Xe exhibits a distinct resonance as it diffuses into the red blood cells (RBCs) of the pulmonary capillaries, allowing MR imaging and spectroscopy of the distal pulmonary vasculature. Recent work has shown that ^{129}Xe MRI of RBC transfer is a surrogate measure of capillary blood volume. Moreover, dynamically acquired ^{129}Xe whole-lung spectra exhibit oscillations in the amplitude of the RBC resonance that reflect the cumulative effect of blood flow, impedance, and pulmonary capillary compliance. When combined, ^{129}Xe MRI and dynamic MRS offer indirect sensitivity to elevated pulmonary vascular resistance (PVR)¹, typical in pre-capillary pulmonary hypertension (PH)². Elevated PVR in pre-capillary PH is driven by localized thickening and stiffening of the pulmonary arterioles³. Downstream of such occlusions, the blood flow through the capillary bed is

reduced, leading to longer transit times and paradoxically enhanced blood oxygenation^{4,5}. However, since cardiac output must be conserved, blood flow in unobstructed vascular branches increases. In these regions, transit times are shortened, and their capillary blood oxygenation is commensurately decreased. Such variations in blood oxygenation impact the chemical shielding of ¹²⁹Xe dissolved in the capillary RBCs and its binding to hemoglobin, thereby altering its chemical shift⁶. Specifically, RBC chemical shift increases with blood oxygenation⁷. Thus, in patients with pre-capillary PH, we expect to observe regions of significantly elevated RBC shift, complemented by larger regions of low shift, as illustrated in Figure 1. To this end, regional mapping of the RBC chemical shift may offer direct sensitivity to pre-capillary PH pathology and localization of arteriole occlusion. Here, we use hyperpolarized ¹²⁹Xe lung CSI to generate such RBC chemical shift maps and compare them in healthy volunteers and pre-capillary PH patients.

METHODS Healthy volunteers (n=4) and pre-capillary PH patients (n=6) underwent consortium-standard ¹²⁹Xe gas exchange imaging and dedicated global spectroscopy⁸. Additionally, they underwent a breath-hold ¹²⁹Xe CSI scan with elliptical sampling, 22.5mm isotropic resolution, dissolved/gas-phase flip angle=16.1°/0.1°, TR=9.8ms, and 256 points per FID. Spectra in all CSI voxels were fit with a Lorentzian profile for the RBC and gas-phase resonances, and a Voigt profile for the membrane resonance, using least-squares regression in MATLAB (version 2023a)^{9,10}. Within each voxel, the RBC chemical shift was calculated as the difference between the center frequencies of the gas-phase and RBC peaks, yielding a regional shift map. Maps were interpolated to match the resolution of each subject's gas exchange image and then registered to it. Lung boundaries were identified by applying the gas exchange mask, generated by neural network segmentation and edited by expert readers¹¹. For each masked CSI map, heterogeneity in the distribution of RBC chemical shift values was quantified by the interquartile range (IQR).

RESULTS On whole-lung spectroscopy, healthy subjects had a mean RBC shift of 218.3ppm, while pre-capillary PH patients had a mean RBC shift of 217.4ppm. CSI maps of RBC shift in healthy subjects tended to be relatively homogeneous, with narrow distributions about well-defined central peaks (Figure 2A). By contrast, in PH patients, CSI RBC shift maps tended to have striking regions of very high shift, complemented by reduced shift across the rest of the lung (Figure 2B). Concordantly, their distributions of shift values tended to be broader, with larger concentrations of extreme values on both ends. This observation was substantiated by calculating the IQR of the shift

distributions in each map (Figure 3). While all healthy subjects had an IQR<1ppm, all but one PH subject had an IQR>1ppm.

DISCUSSION This work demonstrates that, while there may only be modest differences in RBC chemical shift measures from whole-lung spectroscopy between disease groups, regional mapping of ^{129}Xe RBC chemical shift yields distinct patterns in pre-capillary PH, compared to healthy volunteers. Notably, regions of paradoxically high RBC shift are hypothesized to occur distal to occlusions in the pre-capillary arterioles supplying these regions. However, several technical advances are needed to improve the fidelity of these shift maps. In particular, the inherently low resolution in ^{129}Xe CSI, combined with additional under-sampling, makes accurate localization of vascular occlusion in PH challenging. Achieving the ideal balance between CSI undersampling artifact reduction and image resolution for localization will require further optimization of the k-space trajectories and filters. Nonetheless, this work suggests that, once optimized, RBC chemical shift mapping via ^{129}Xe CSI may permit non-invasive detection of localized precapillary occlusions in PH, potentially facilitating more targeted application of highly invasive gold standard diagnostic methods. Such localization will be particularly valuable in diagnosing chronic thromboembolic pulmonary hypertension (CTEPH), where pre-capillary occlusion is driven by blood clots that may be treated surgically.

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FIGURES

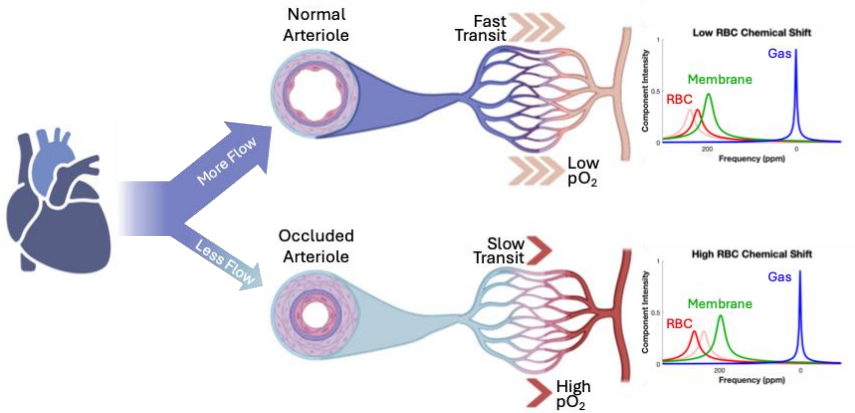
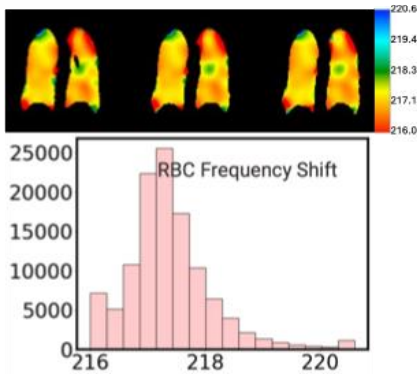


Figure 1. In pre-capillary PH, arterioles that are occluded carry a smaller proportion of the cardiac output, leading to slower blood transit through the capillary bed, which paradoxically enhances blood oxygenation. The unobstructed arterioles then carry the bulk of the cardiac output, reducing transit time through the distal capillaries, and decreasing capillary blood oxygenation. Elevated blood oxygenation increases the ^{129}Xe RBC chemical shift, while lower oxygenation decreases it.

A

Healthy (ppm)



B

Pre-Capillary PH (ppm)

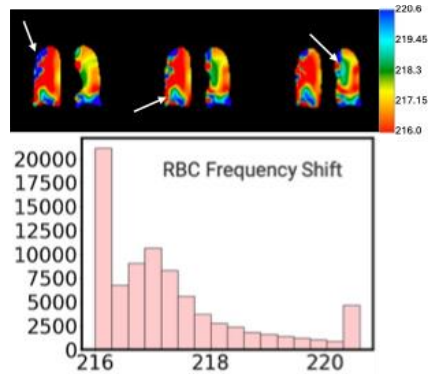


Figure 2. Representative ^{129}Xe RBC chemical shift maps in A) healthy subject 1 and B) pre-capillary PH subject 4. In the healthy subject, the shift map is relatively homogeneous with a narrowly concentrated distribution about the mean. In the PH patient, there are notable regions of very high chemical shift, hypothesized to be distal to arteriolar occlusion. RBC shift is significantly lower in the rest of the lung, thought to reflect shorter transit times and lower oxygenation, due to more blood flow. The resulting distribution is much broader with larger concentrations on the extreme ends.

A

Healthy	
Subject	RBC Shift IQR (ppm)
1	0.74
2	0.96
3	0.67
4	0.91

B

Pulmonary Hypertension	
Subject	RBC Shift IQR (ppm)
1	6.93
2	6.98
3	1.47
4	1.51
5	0.79
6	1.12

Figure 3. Table of interquartile ranges corresponding to the distribution of RBC chemical shift values from CSI maps in A) healthy volunteers and B) PH subjects. In healthy subjects the IQR of the RBC shift distribution is lower, indicative of narrow distributions with few extreme values. By contrast, the PH patients exhibit substantially higher RBC shift IQR values. This is indicative of broader distributions with higher concentrations in the tails, reflecting the regions of extremely high shift, complemented by low shift throughout the rest of the lung.

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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