University of Sheffield

POLARIS
Polarised lung and respiratory imaging Sheffield
POLARised Imaging Systems

# Methods for and applications of hyperpolarised $^{129}$Xe gas MRI

Jim Wild

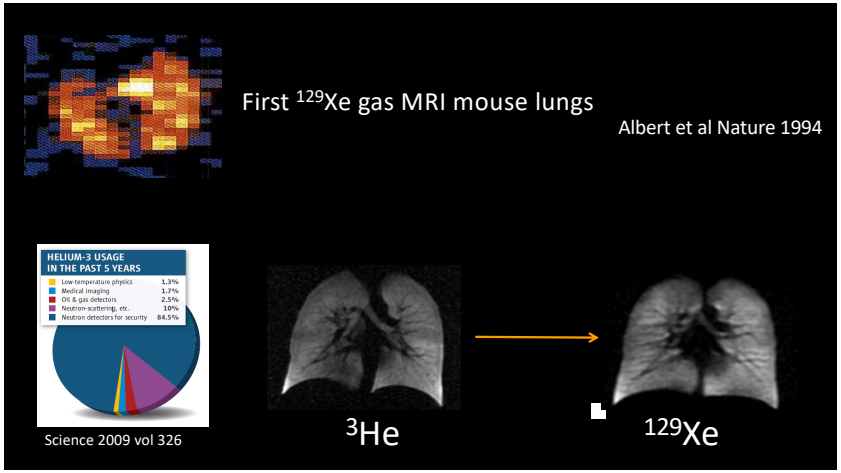
Aarhus October 2024

1

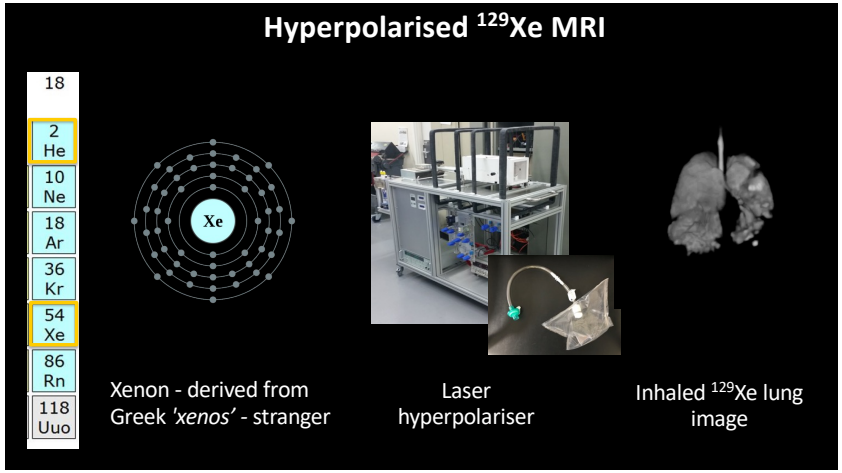
## Overview

- $^{129}$Xe MRI – background physics and engineering
- $^{129}$Xe MRI acquisition and quantification methods
- Pathophysiological sensitivity – ventilation, microstructure, gas exchange - quantitative metrics
- Few examples of clinical utility

2


First $^{129}$Xe gas MRI mouse lungs
Albert et al Nature 1994
HELIUM-3 USAGE
IN THE PAST 5 YEARS
Low-temperature physics 1.3%
Medical imaging 1.7%
Oil & gas detectors 2.5%
Neutron-scattering, etc. 10%
Neutron detectors for security 84.5%
Science 2009 vol 326
$^{3}$He
$^{129}$Xe

3


Hyperpolarised $^{129}$Xe MRI
18
2 He
10 Ne
18 Ar
36 Kr
54 Xe
86 Rn
118 Uuo
Xe
Xenon - derived from Greek *'xenos'* - stranger
Laser hyperpolariser
Inhaled $^{129}$Xe lung image

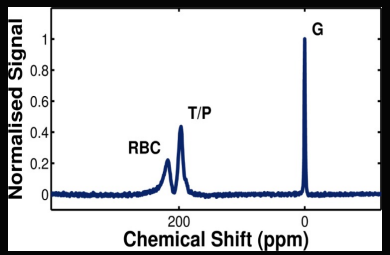
4

## NMR properties


| Property | $^{1}$H | $^{3}$He | $^{129}$Xe | $^{19}$F |
|---|---|---|---|---|
| Nuclear spin, $I$ | 1/2 | 1/2 | 1/2 | 1/2 |
| Gyromagnetic ratio, $\gamma$ (MHz/T) | 42.58 | -32.44 | -11.78 | 40.07 |
| T2* in gas phase | | 14-28 ms | 30-50 ms | ~4 ms |
| T1 in gas phase<br>T1 dissolved in blood /tissue | - | 20 s | 40 s<br>2-10 s | ~12 ms |
| ADC in healthy lungs ($cm^2s^{-1}$) | - | ~ 0.2 | ~ 0.04 | ~0.015 ($C_3F_8$) |
| Cost (£/L) | - | ~ 500? | ~ 150 (EN ~80%) | |
| | | | ~ 20 (NA ~ 26%) | 2 (>10L needed) |
| T1 gas in air | | 40 s | 20 s | |

5

## $^{129}$Xe solubility and chemical shift

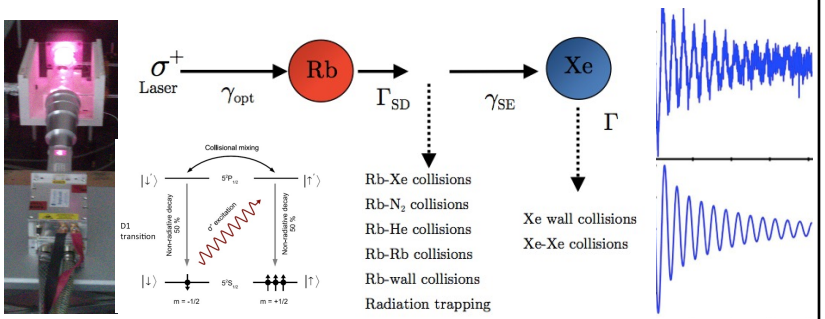




$^{129}$Xe lung spectrum

| Solvent | Ostwald Solubility Coefficient, λ | Chemical shift, δ (ppm) |
|---|---|---|
| Distilled $H_2O$ | 0.083 | 190 |
| Saline | 0.078 – 0.093 | 194 – 196 |
| Olive oil | 1.79 – 1.83 | 198 |
| Adipose tissue | 1.715 | 191 |
| Plasma | 0.091 – 0.103 | 192 – 197 |
| RBCs | 0.19 – 0.27 | 216 – 222 |

6

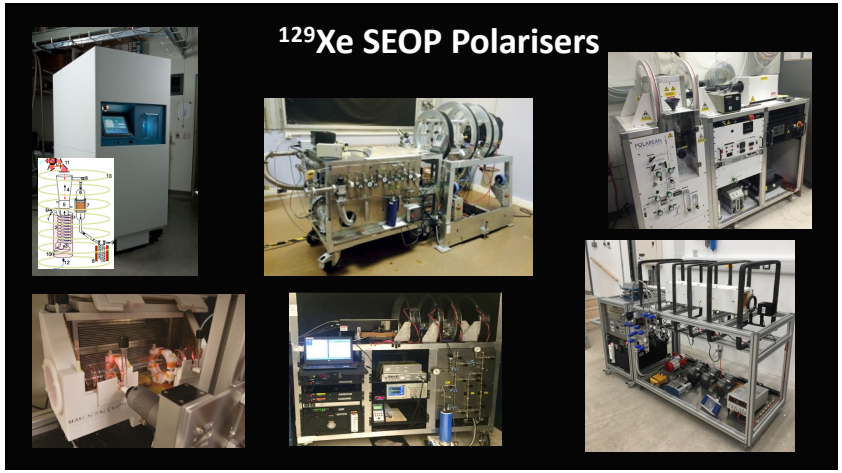
## $^{129}$Xe hyperpolarisation with spin exchange optical pumping




**Laser power - IN** **Nuclear spin polarisation - OUT**

7

## $^{129}$Xe SEOP Polarisers

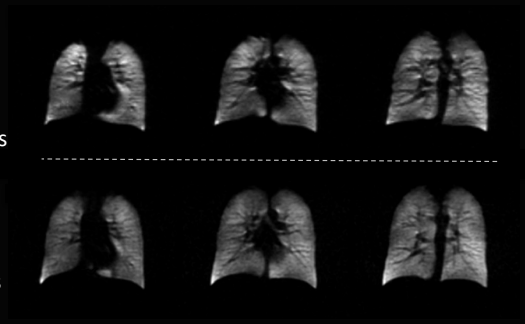


8

## HP $^{129}$Xe Gas MRI – $B_0$ dependence

3 T
35.4 MHz
T2* 18-24 ms

1.5 T
17.7 MHz
T2* 25-52 ms

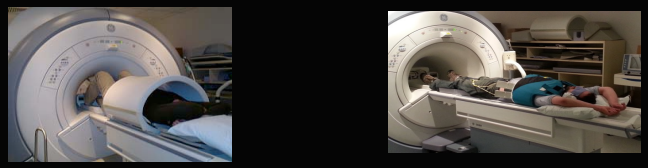


**Low FA spoiled gradient echo**

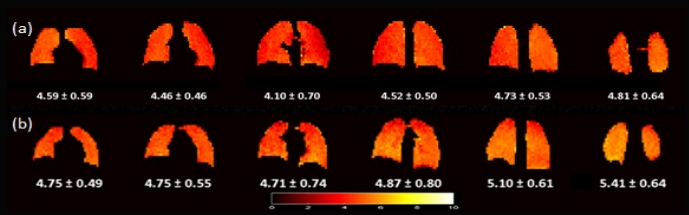
X. Xu et al., Magn Reson Med, 68, 6 (2012).

9

## RF coils for $^{129}$Xe – T/R

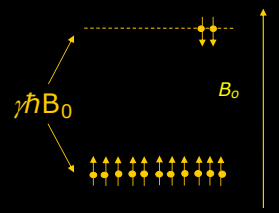







10

## Best use of hyper- polarisation




small flip angles with spoiled sequences

$$S(n) = S_0 \sin\alpha(\cos(\alpha))^{n-1}$$

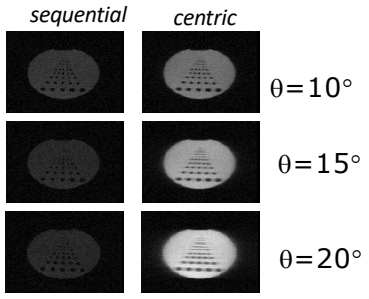
11

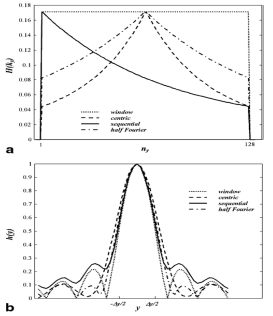
## Polarisation constraint

$M_y(n) = M_0(\cos\theta)^{n-1}\sin\theta\ \exp(-NT_R/T1(p0_2))$

RF k-space filter $H(k_y)$

$$\tan(\alpha_{opt}) = \left(\sqrt{(N/2)-1}\right)^{-1}$$




$k_y$-filter

PSF

*Magn Reson Med, 47, 687 , 2002.*

12

## Variable flip angle spoiled gradient echo

Use a progressively increasing F.A. to maintain constant transverse magnetisation $M_{xy}$

use ALL the Longitudinal magnetisation up – most efficient use of polarisation

For a given *N*; SNR $\propto \sin\theta_1$ $\theta(n) = \arctan\left(\frac{1}{\sqrt{N-n}}\right)$

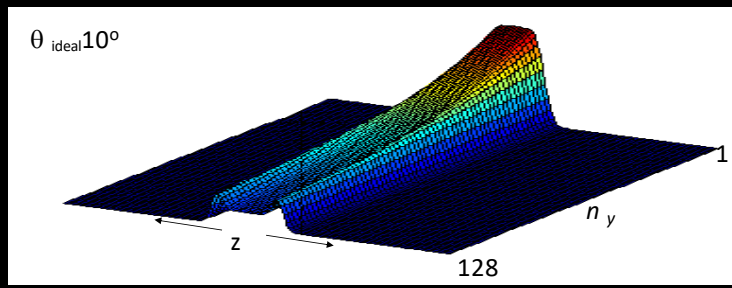
VFA technique introduces no additional blurring :
$H(k_y)$ = constant

$$\tan(\alpha_{opt}) = \left(\sqrt{(N/2)-1}\right)^{-1}$$

Zhao et al J Magn Reson B. 1996;113(2):179-83

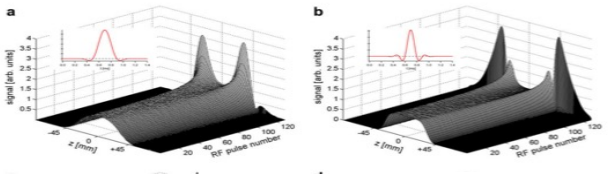
13

## 2D or 3D?




14

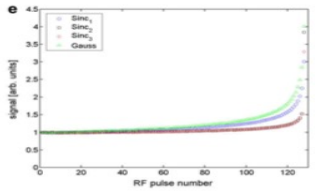
## Slice profile effects with variable flip angle




Compensate by :

• discarding data

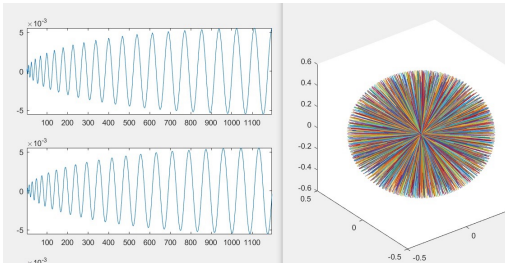
• pulse –pulse slice profile modulation

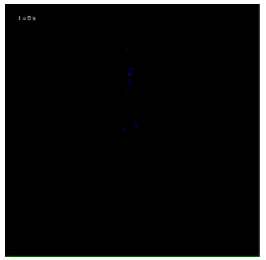



Journal of Magnetic Resonance 202 (2010) 180–189

15

## Non Cartesian sampling

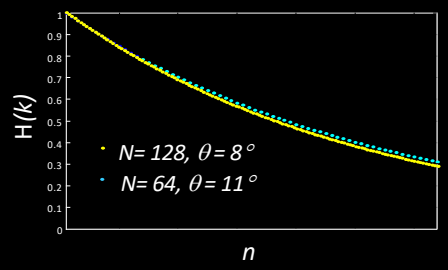




- short TE for dissolved $^{129}Xe$
- undersampling and view sharing for dynamic imaging

16

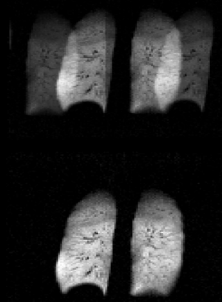
## RF undersampling – flip angle




Undersampling – increase the FA when reducing N to overcome the SNR penalty (SNR √N)

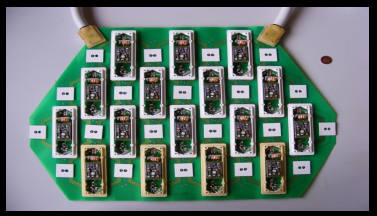
17

## Parallel Imaging – efficient use of polarisation



R=2

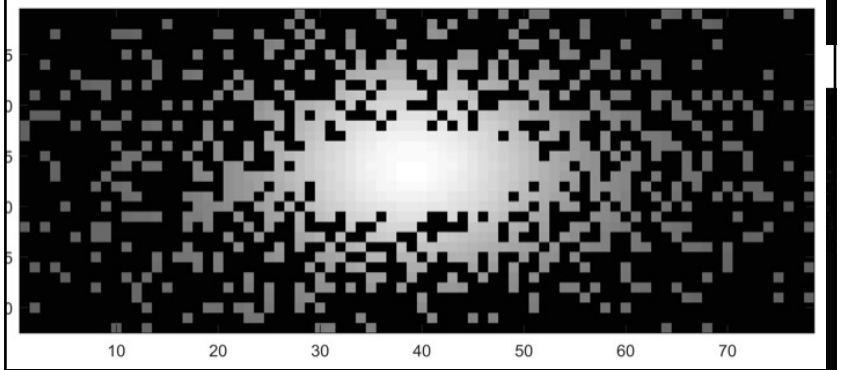
R= 4



Deppe et al Magn Reson Med. 2011 Dec;66(6):1788-97.

18

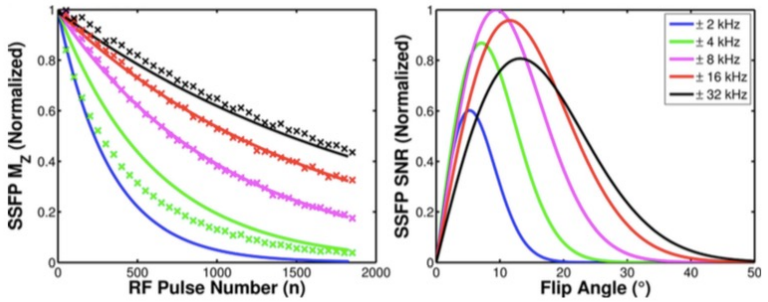
## Image acceleration with 3D Compressed Sensing




Collier et al Magn Reson Med. 2019 Jul;82(1):342-347. Ajraoui et al Magn Reson Med. 2010 Apr;63(4):1059-69

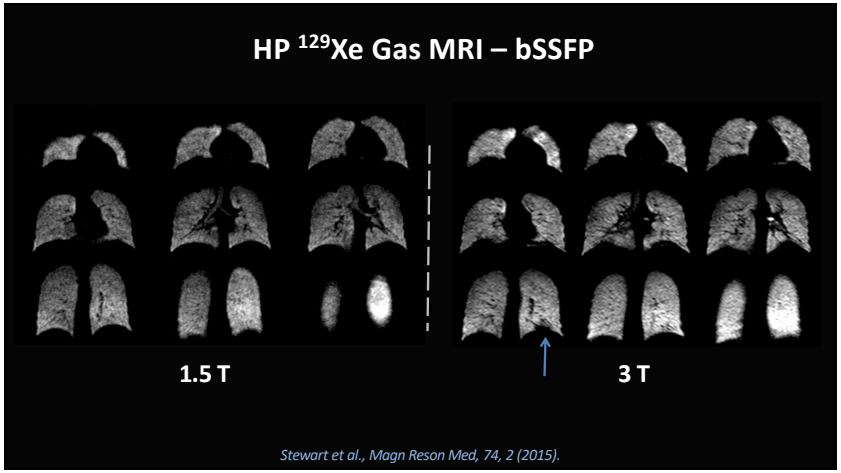
19

## Recycle magnetisation - SSFP

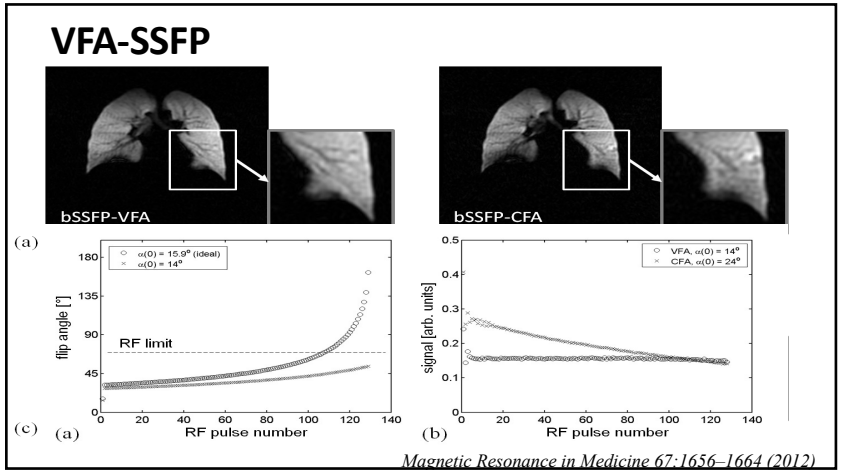



*Wild et al J MagnReson, 183 (2006) 13–24,* *N. J. Stewart et al., Magn Reson Med,74, 2 (2015).*

20

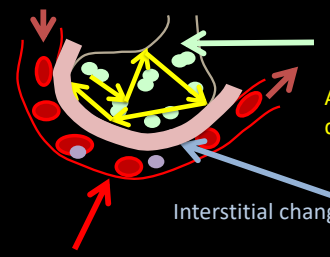

HP 129Xe Gas MRI – bSSFP
1.5 T
3 T
Stewart et al., Magn Reson Med, 74, 2 (2015).

21


VFA-SSFP
bSSFP-VFA
bSSFP-CFA
(a)
(c)
(a)
(b)
flip angle [°]
RF limit
RF pulse number
signal [arb. units]
RF pulse number
Magnetic Resonance in Medicine 67:1656–1664 (2012)

22

## $^{129}$Xe MRI - assessment of structure and function



Lung ventilation

Acinar microstructure – Brownian diffusion weighted MRI (DW-MRI)

Interstitial changes – dissolved xenon diffusive exchange

Xenon up take in RBCs - capillary perfusion

23

## Ventilation defect percentage (VDP = 1 - VV/TLV)

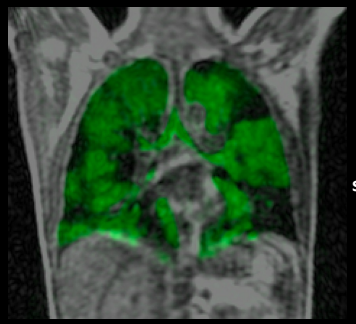
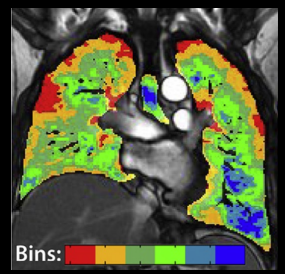


Image segmentation

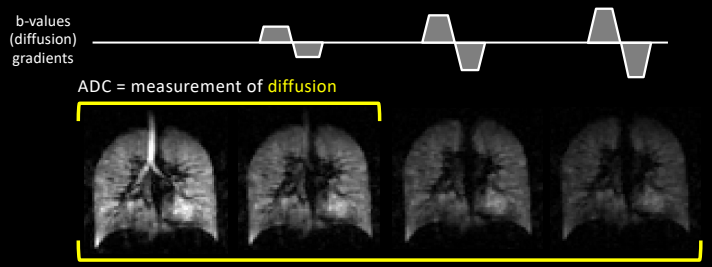



Ventilation Image
$^{1}$H Proton MRI

Ventilation Mask
$^{1}$H Proton Mask

24

## Diffusion weighted $^{129}$Xe MRI – interleaved acquIsition

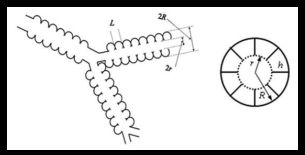



Multiple b-values - sample non-mono exponential diffusion e.g. 0, 10, 20, 30 …s/cm2

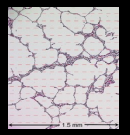
- In vivo theoretical gas diffusion models to extract lung morphometry parameters from the non-mono exponential signal decay

25

## $^{3}$He and $^{129}$Xe - 3D alveolar morphometry from diffusion MRI



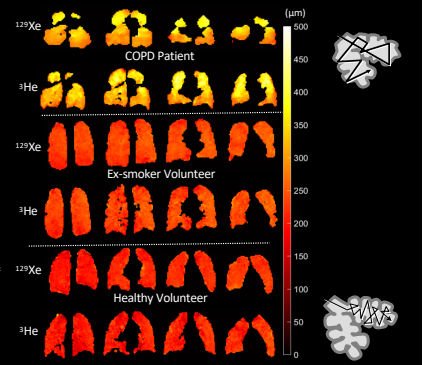
Cylinder model
Sukstanski et al Magn Reson Med. 2012 Mar;67(3):856-66.



$$\frac{S_b}{S_0} = \int_0^\infty p(D) e^{-bD} dD = e^{[-b \cdot DDC]^\alpha}$$

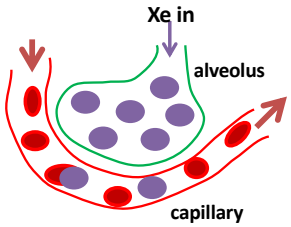
$$Lm_D = \int_0^\infty \sqrt{2\Delta D}\, p(D)\, dD$$

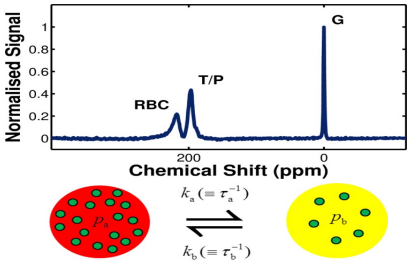
Stretch exponential model
Chan, et al. (2016). Magn Reson Med doi:10.1002/mrm.26279




26

## Dissolved-Phase $^{129}$Xe



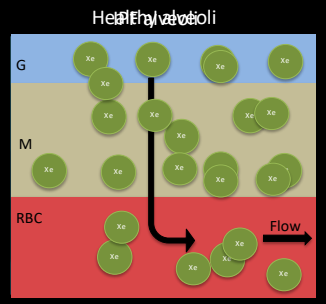

Considerations

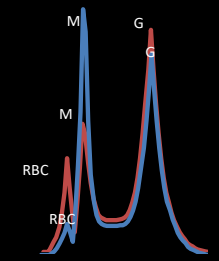
- Small dissolved signal ~ 2% of gas
- Short $T_2$* of dissolved $^{129}$Xe ~1-2ms (chemical exchange) [1,2]

*[1] J. P. Mugler III et al., Proc ISMRM, 1347 (2012). [2] X. Xu et al., Proc ISMRM, 4119 (2013).*

27

## Gas Transfer MRI




G = gas, M = membrane, RBC = red blood cells

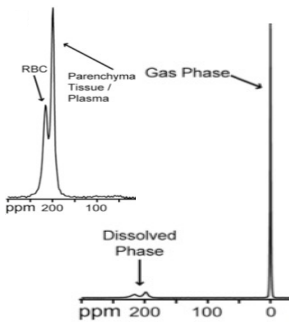
*Weatherley et al, Thorax 2019 74(5):500-502*
*Collier et al, Magn Reson Med 2021 85(5):2622-33*

28

## $^{129}$Xe dissolved phase imaging

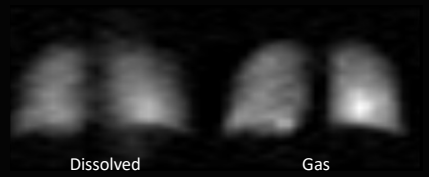
• short T2* (< 2ms) due to chemical exchange effects between RBC and tissue/plasma
• large gas signal contaminates (but also acts as a signal reservoir by gas exchange in lungs – can use larger FA)

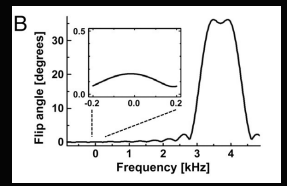
**Use:**
UTE (radial/spiral/ 3D radial)
Frequency selective RF pulses




29

## Dissolved-Phase $^{129}$Xe imaging



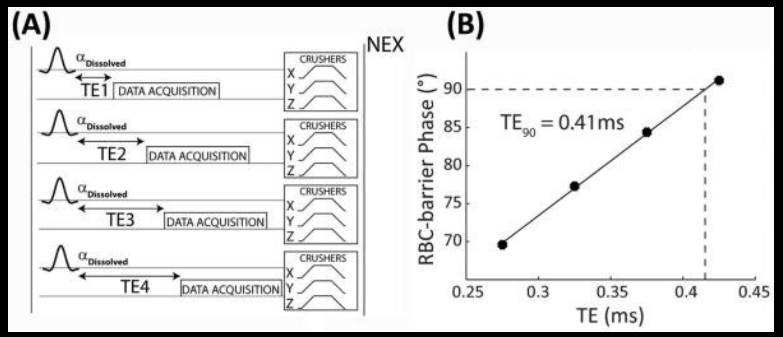




- gas & dissolved $^{129}$Xe separated in frequency direction [1]
- narrow band RF pulses for selective dissolved excitation [2]

[1] J. P. Mugler et al., PNAS, 107, 50 (2010). [2] Leung et al MRM

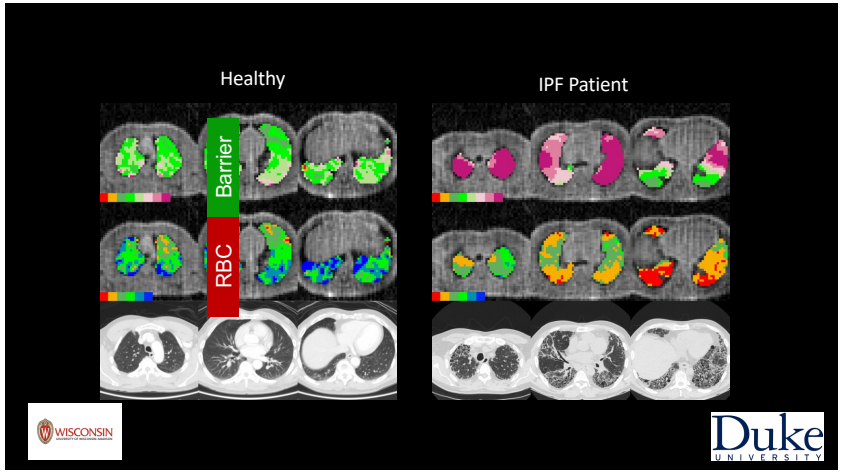
30

## 3D single point DIXON imaging

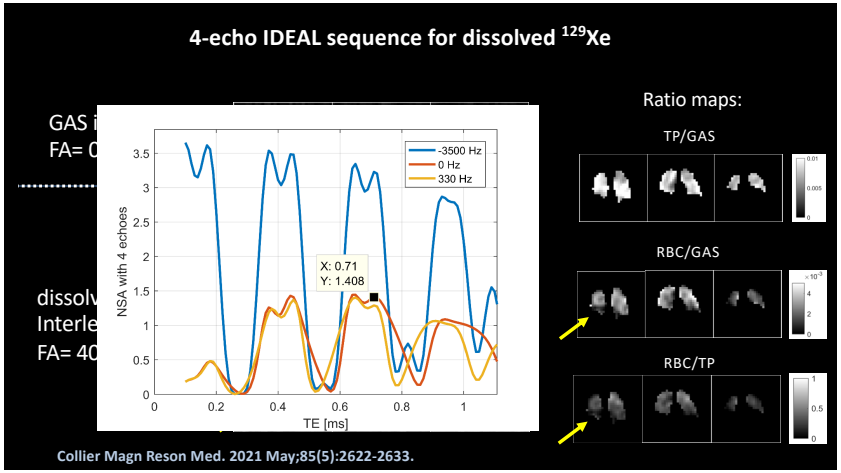



Kaushik et al Magn Reson Med. 2016 Apr;75(4):1434-43.

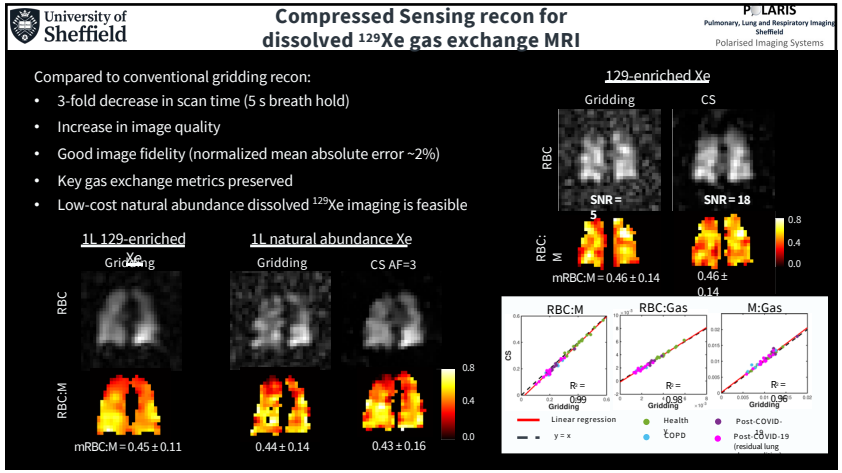
31




32

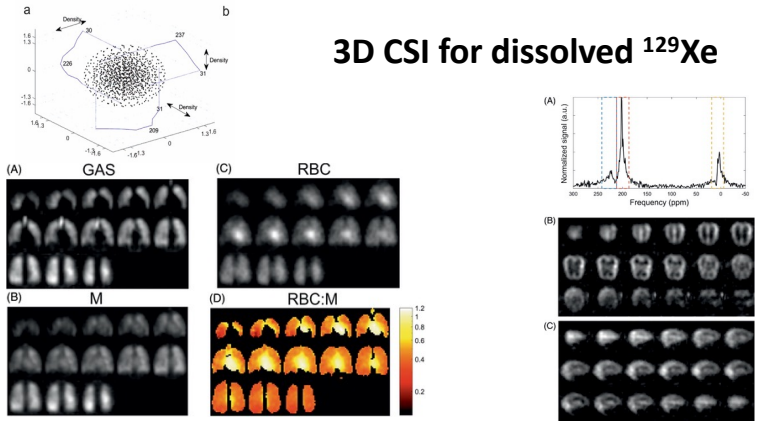

4-echo IDEAL sequence for dissolved $^{129}$Xe
GAS i
FA= 0
dissolv
Interle
FA= 40
NSA with 4 echoes
TE [ms]
X: 0.71
Y: 1.408
-3500 Hz
0 Hz
330 Hz
Ratio maps:
TP/GAS
RBC/GAS
RBC/TP
Collier Magn Reson Med. 2021 May;85(5):2622-2633.

33


University of Sheffield
Compressed Sensing recon for dissolved $^{129}$Xe gas exchange MRI
LARIS
Pulmonary, Lung and Respiratory Imaging Sheffield
Polarised Imaging Systems
Compared to conventional gridding recon:
3-fold decrease in scan time (5 s breath hold)
Increase in image quality
Good image fidelity (normalized mean absolute error ~2%)
Key gas exchange metrics preserved
Low-cost natural abundance dissolved $^{129}$Xe imaging is feasible
129-enriched Xe
Gridding
CS
RBC
RBC:M
SNR = 5
SNR = 18
mRBC:M = 0.46 ± 0.14
0.46 ± 0.14
1L 129-enriched Xe
1L natural abundance Xe
Gridding
CS AF=3
mRBC:M = 0.45 ± 0.11
0.44 ± 0.14
0.43 ± 0.16
RBC:M
RBC:Gas
M:Gas
Linear regression
y = x
Health
COPD
Post-COVID-
Post-COVID-19 (residual lung

34

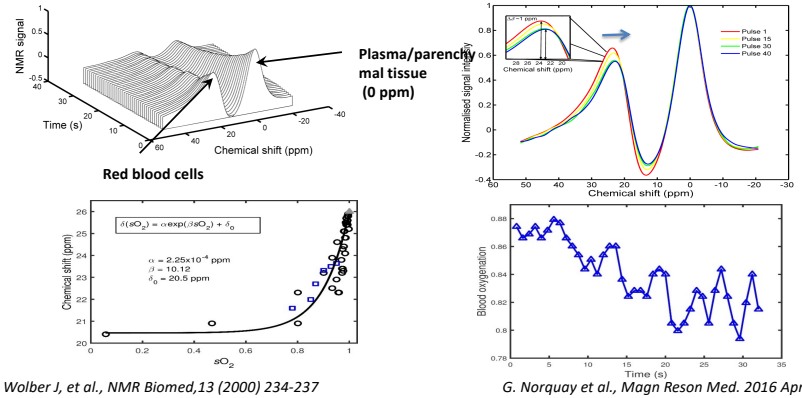
## 3D CSI for dissolved $^{129}$Xe




Collier et al Magn Reson Med. 2023 Jun;89(6):2217-2226. doi: 10.1002/mrm.29602.

35

## $^{129}$Xe chemical shift as a probe of oxygenation

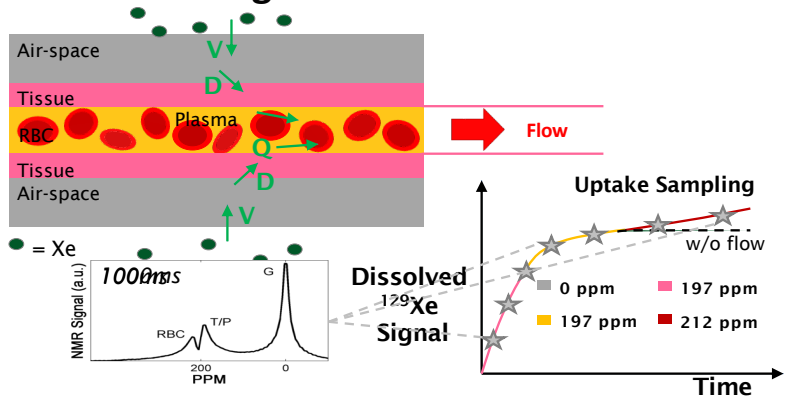



*Wolber J, et al., NMR Biomed,13 (2000) 234-237*

*G. Norquay et al., Magn Reson Med. 2016 Apr 8*

36

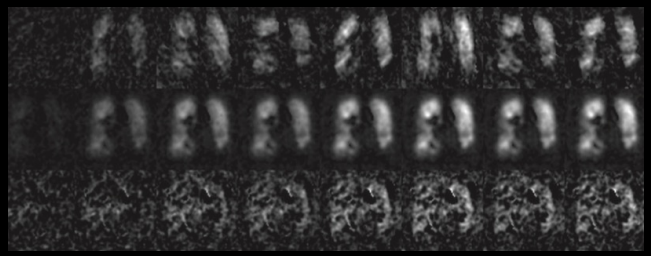
## Gas-exchange MR with dissolved $^{129}Xe$




[1] N. J. Stewart et al., Magn Reson Med, 74, 1 (2015). [2] S. Patz et al., New J Phys, 13, 015009 (2011).

37

## Dynamic spectroscopic imaging of xenon uptake



Kern et al Magn Reson Med. 2019 Apr;81(4):2360-2373.

38

## Clinical applications where lung MRI can add value

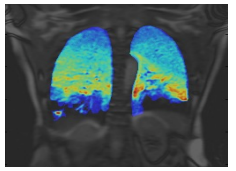
- Paediatrics and Infants : CF and BPD
- Assessment of interventions in asthma and COPD
- Diseases of gas exchange

39

## Imaging tools for pulmonary disease

Better understanding of lung ***physiology*** and disease mechanisms

Early detection, ***diagnosis***

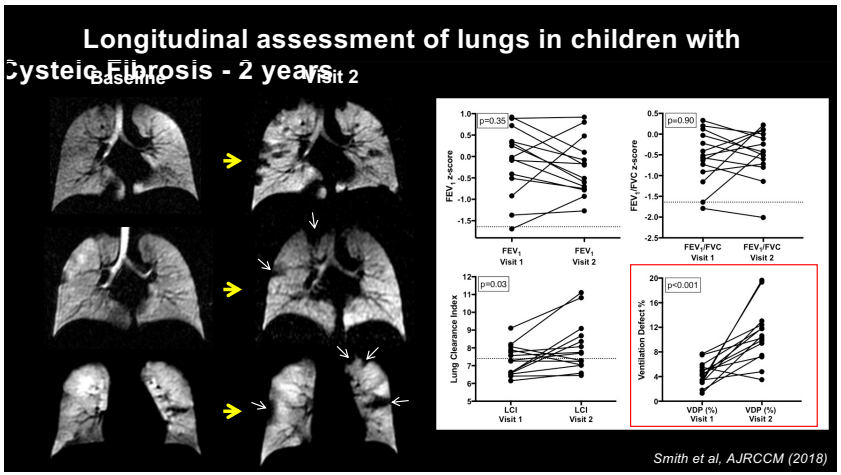


Better, personalised and ***regionally targeted treatments***

Sensitive ***regional markers*** of therapy and progression

40

## Longitudinal assessment of lungs in children with Cysteic Fibrosis - 2 years




*Smith et al, AJRCCM (2018)*

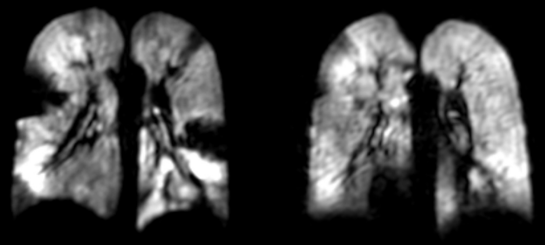
41

## Paediatric non CF bronchiectasis - IV antibiotics

13 year old cross country runner

↓ race times

FEV1 normal



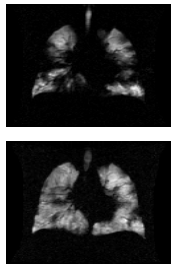
Baseline

Post 2 weeks of IV therapy

42

# Asthma - treatment response mapping

Mean baseline





Post Bronchodilator

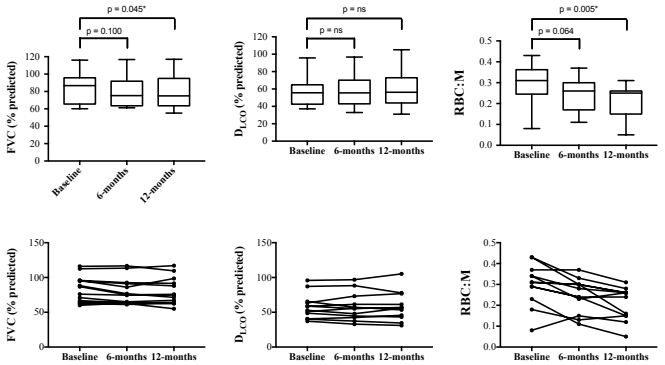
**Asthmatic pre and post bronchodilator**

ΔVVF (post – pre)


Horn et al Radiology 2017

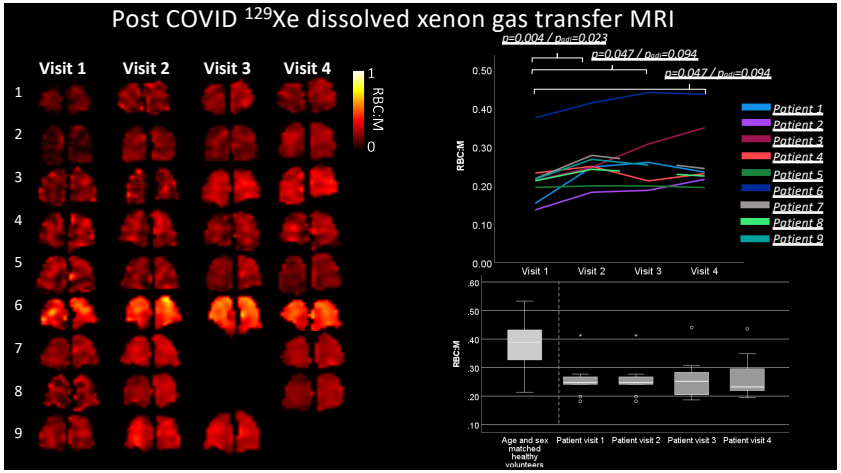
43

# $^{129}$Xe spectroscopic imaging and PFTs – longitudinal sensitivity

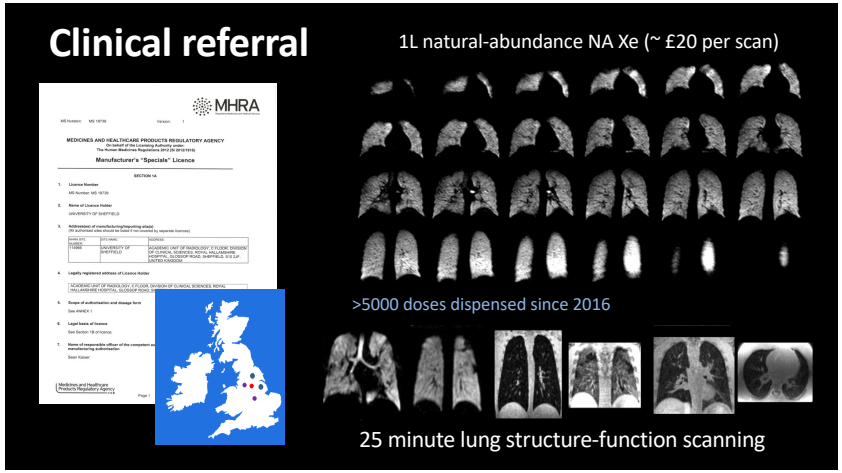



Weatherley et al – Thorax. 2018 Nov 2. pii: thoraxjnl-2018-211851.

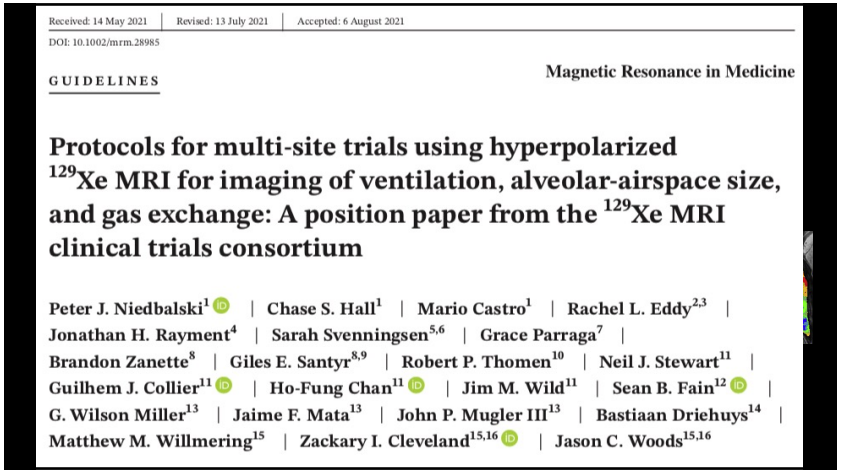
44


Post COVID 129Xe dissolved xenon gas transfer MRI
Visit 1
Visit 2
Visit 3
Visit 4
RBC:M
p=0.004 / pBonf=0.023
p=0.047 / pBonf=0.094
p=0.047 / pBonf=0.094
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Age and sex matched healthy volunteers
Patient visit 1
Patient visit 2
Patient visit 3
Patient visit 4

45


Clinical referral
1L natural-abundance NA Xe (~ £20 per scan)
MHRA
MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
Manufacturer's "Specials" Licence
>5000 doses dispensed since 2016
25 minute lung structure-function scanning

46



Received: 14 May 2021 | Revised: 13 July 2021 | Accepted: 6 August 2021
DOI: 10.1002/mrm.28985

GUIDELINES

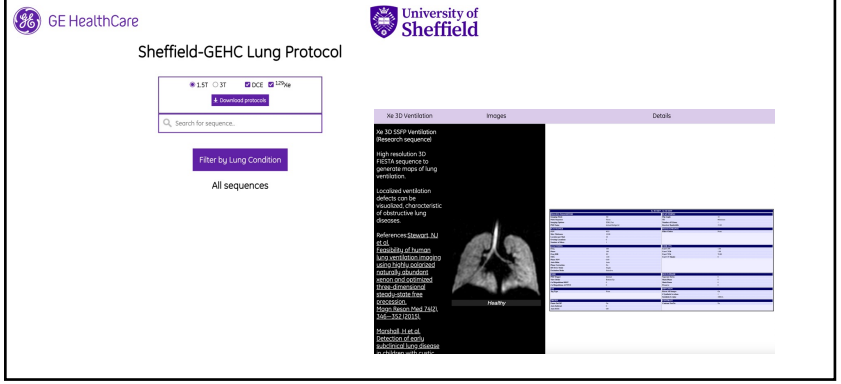
Magnetic Resonance in Medicine

**Protocols for multi-site trials using hyperpolarized $^{129}$Xe MRI for imaging of ventilation, alveolar-airspace size, and gas exchange: A position paper from the $^{129}$Xe MRI clinical trials consortium**

Peter J. Niedbalski[1] | Chase S. Hall[1] | Mario Castro[1] | Rachel L. Eddy[2,3] | Jonathan H. Rayment[4] | Sarah Svenningsen[5,6] | Grace Parraga[7] | Brandon Zanette[8] | Giles E. Santyr[8,9] | Robert P. Thomen[10] | Neil J. Stewart[11] | Guilhem J. Collier[11] | Ho-Fung Chan[11] | Jim M. Wild[11] | Sean B. Fain[12] | G. Wilson Miller[13] | Jaime F. Mata[13] | John P. Mugler III[13] | Bastiaan Driehuys[14] | Matthew M. Willmering[15] | Zackary I. Cleveland[15,16] | Jason C. Woods[15,16]

47

https://polaris-sheffield.github.io/sheffield-lung-protocol/




48

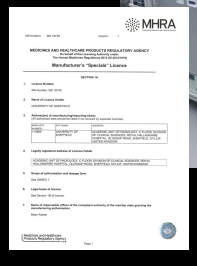
## Logistical considerations for $^{129}$Xe MRI

**Cost**
- **RF coils & broad band RF amplifier ~ £150 k**
- **Gas polariser ~ £300 k**
- **Gas ~ £20/L**

**Technical support**
- **MR physicist and MR radiographer**

**Clinical interest**
- **Respiratory medicine / pharma**

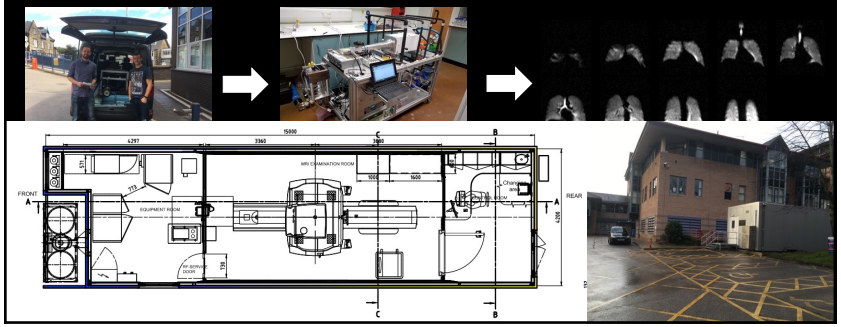
- **Regulatory licencing**




49

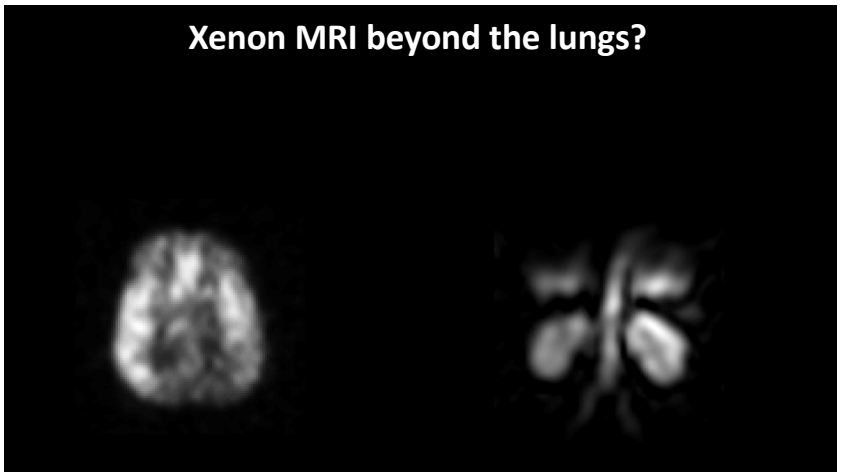
## Accessibility and portability of technology

- $^{129}$Xe lung imaging at novice clinical imaging centre
- no specialist equipment is needed for polarizer installation




50

## Xenon MRI beyond the lungs?

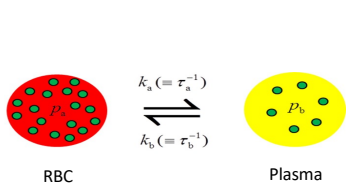


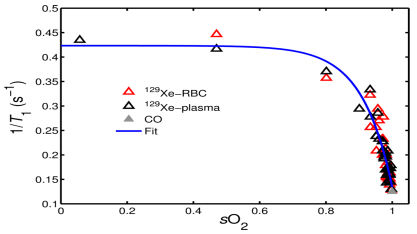
51

## Dissolved $^{129}$Xe - T1 in blood

$T_1$ of $^{129}$Xe in oxygenated blood is sufficiently long for transport to distal organs

| **oxyHb $^{129}$Xe-blood $T_1$** | **7.7 s** |
|---|---|
| deoxyHb $^{129}$Xe-blood $T_1$ | 2.4 s |

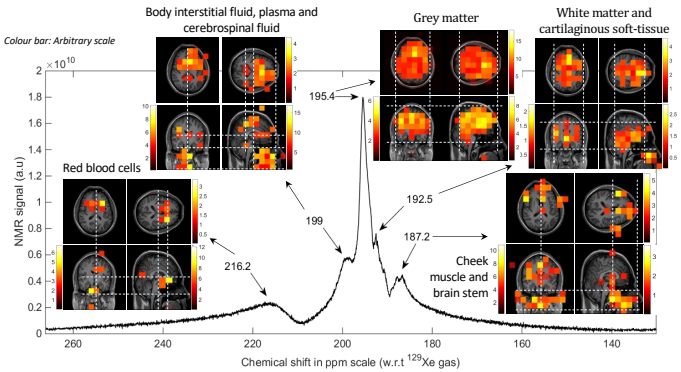



*G. Norquay et al., Magn Reson Med, 74, 2 (2015).*

52

## $^{129}$Xe brain chemical shift imaging

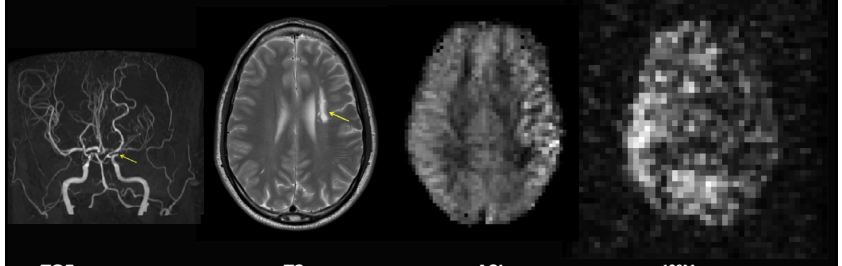



Xenon 1 L with ~30% polarisation

Rao et al. Mag Res Med (2016) 10.1002/mrm.26241

53

## $^{129}$Xe brain - Stroke (3 months post)



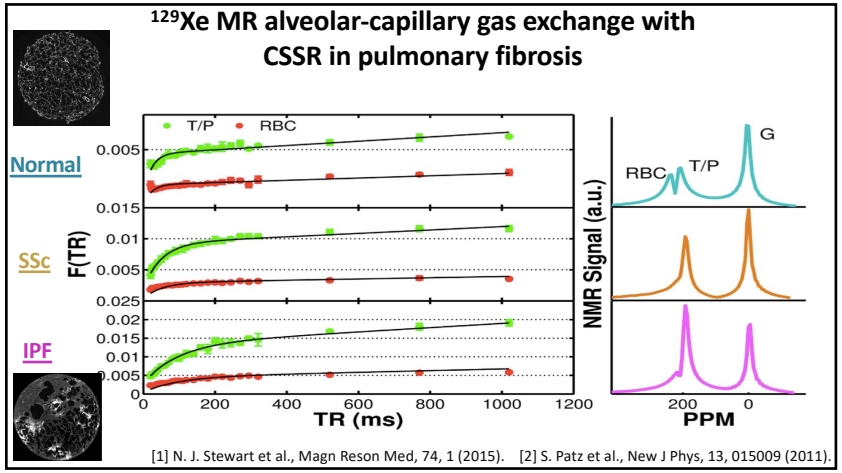

Rao et al, JMRI 2019

54

https://www.sheffield.ac.uk/polaris

https://polaris-sheffield.github.io/sheffield-lung-protocol/

55




56