New Imaging Approaches for Screening and Diagnosis of PH

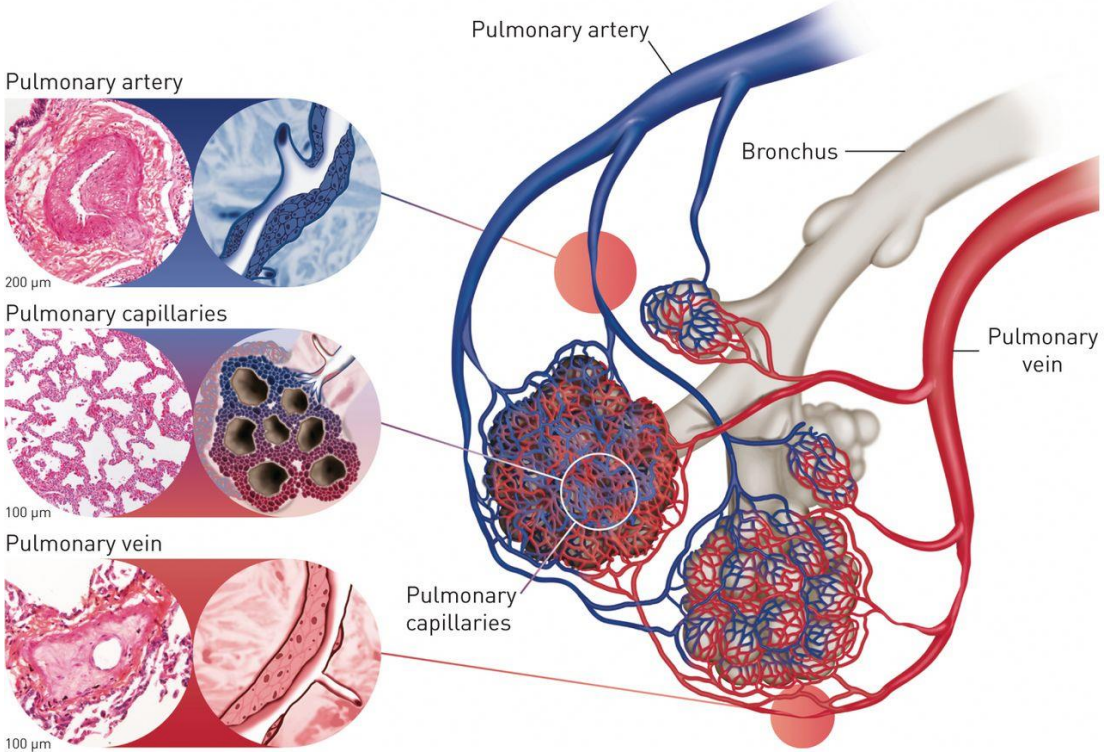
Sudarshan Rajagopal, MD, PhD
Associate Professor in Medicine and Biochemistry
Co-Director, Pulmonary Vascular Disease Center
Duke University School of Medicine

Duke Heart

Disclosures / Funding

- Research
  - NIH
  - American Heart Association
  - United Therapeutics, Actelion
- Consulting
  - Actelion, United Therapeutics, Merck, Liquidia, APIE Therapeutics, Aerami, Gossamer Bio, Insmed, TotalCME, Visterra

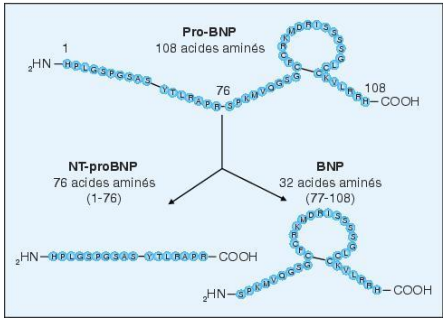
Pulmonary Vascular Disease



European Respiratory Journal 2016 47(5): 1518-1534

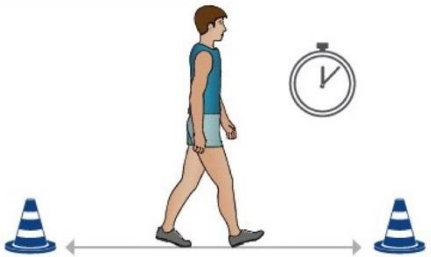
Current Biomarkers in PH

BNP / NTproBNP



- Reflects degree of stress on the right heart
- Can be affected by changes in volume alone
- Can be affected by left heart failure
- Specific effects of sex and obesity
- Not specific for PAH

Six Minute Walk Test



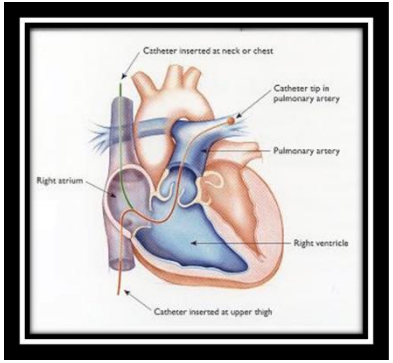
- Straightforward to do clinically
- Frequently values are not corrected for age, height and weight
- Can be affected by other health factors
- Not specific for PAH

CMR / Echocardiography



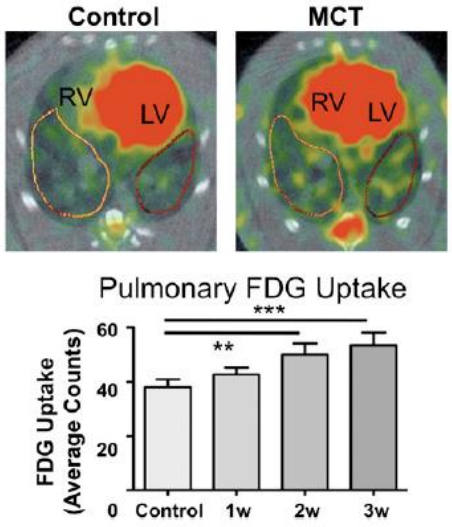
- Noninvasive
- Echo - common screening tool for PAH
- Frequently cannot provide estimate of left-sided filling pressures
- Indirect assessment of PVD

Right Heart Catheterization



- Gold standard for diagnosis
- Invasive
- Typically only at rest
- Interpretation requires additional studies
- Indirect assessment of PVD

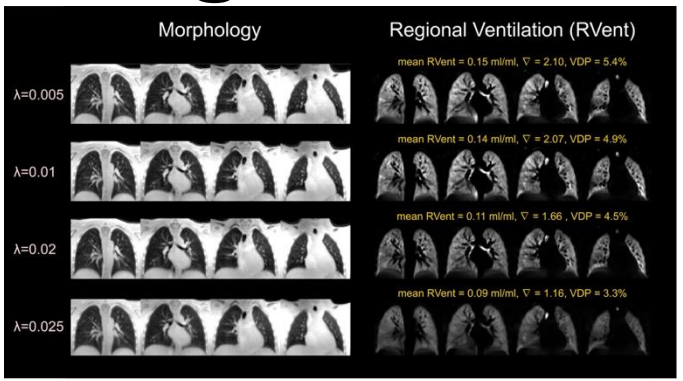
Emerging approaches to image the pulmonary vasculature



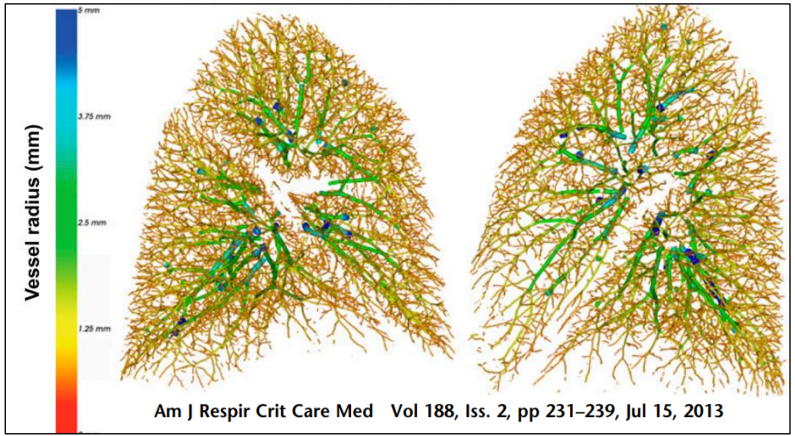
Marsboom *et al.* AJRCCM 2012



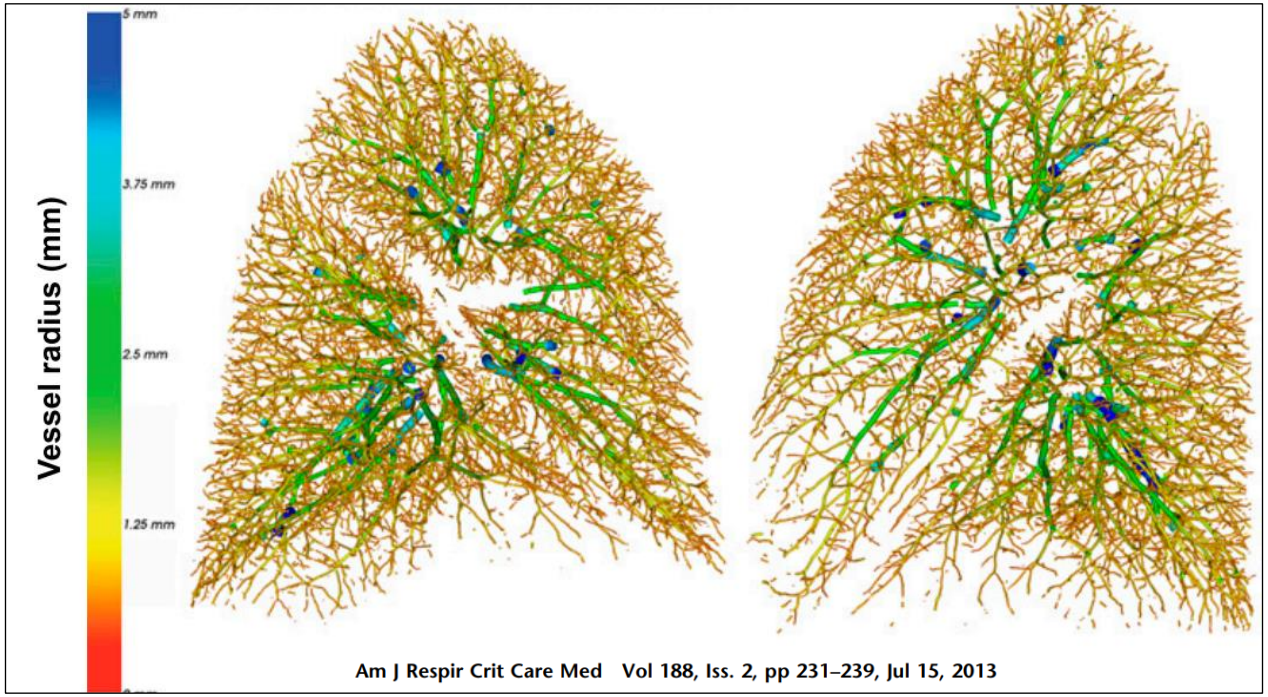
From Martine Remy-Jardin



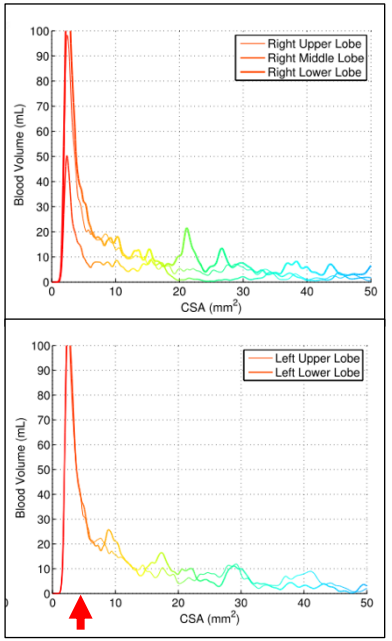
Magnetic Resonance in Med, DOI: (10.1002/mrm.30416)



Total blood vessel volume (TBV) *(PA & PV down to approximately 1mm in diameter)*
Volume of vessels < 5mm² (BV5)



Am J Respir Crit Care Med Vol 188, Iss. 2, pp 231–239, Jul 15, 2013

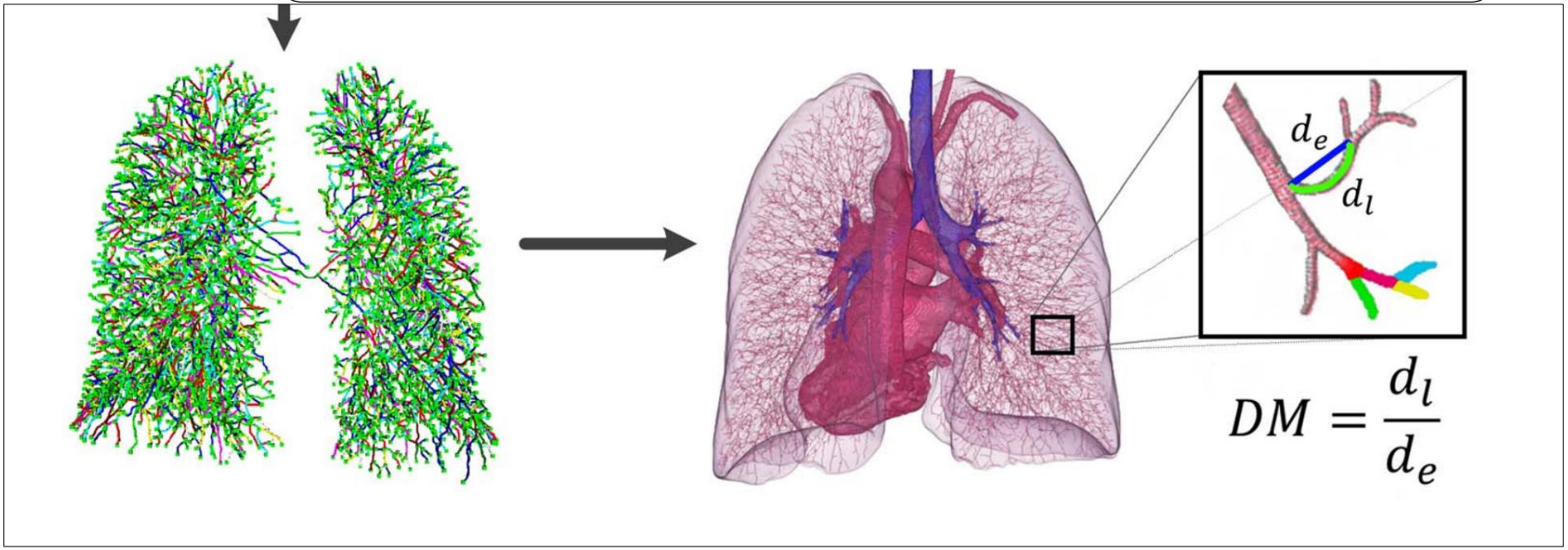


Distribution of blood vessel volume as a function of the cross-sectional area (CSA) of the vessels.

Blood vessel morphology

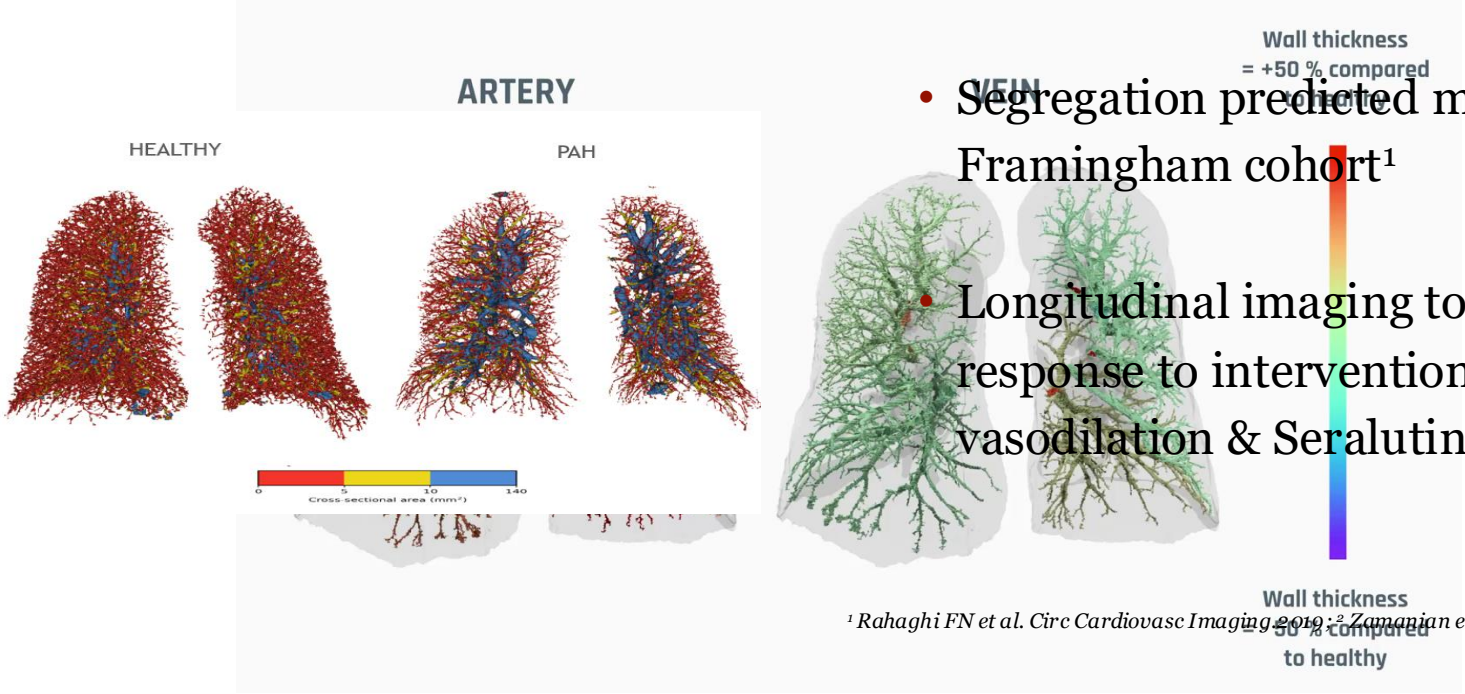
Tortuosity *(measure of twistedness of blood vessels)*

3D fractal dimension *(parameter measuring the complexity of the lung vascular tree)*



Helmberger M, Pienn M, Urschler M, Kullnig P, Stollberger R, et al. (2014)
PLoS ONE 9(1): e87515. doi:10.1371/journal.pone.0087515

Functional Respiratory Imaging: Beyond diagnosis



- Segregation predicted mortality in Framingham cohort[1]
- Longitudinal imaging to assess response to interventions such as NO vasodilation & Seralutinib[2]

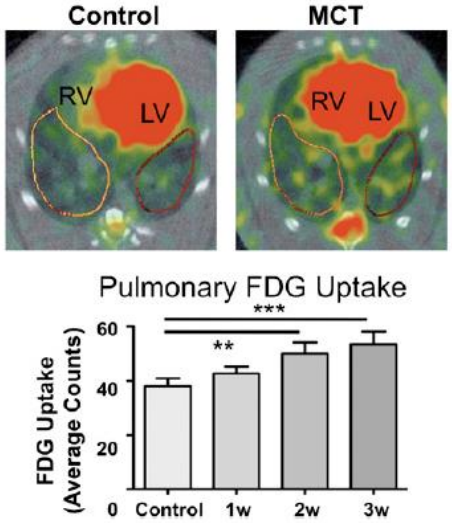
[1] Rahaghi FN et al. Circ Cardiovasc Imaging 2019; [2] Zamanian et al. Abstract ERS 2023

Image courtesy B Lavon, Fluidda

Lung Positron Emission Tomography in PAH

Increased glucose uptake:

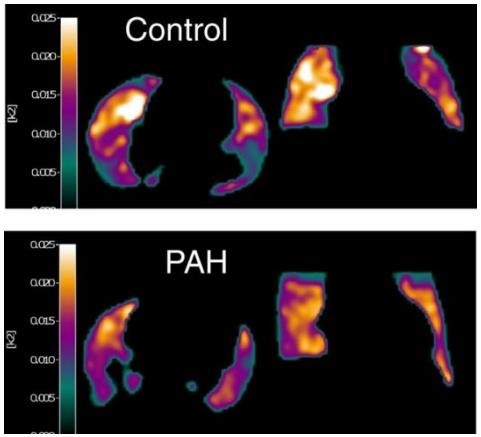
^{18}F-FDG



Marsboom *et al.* AJRCCM 2012

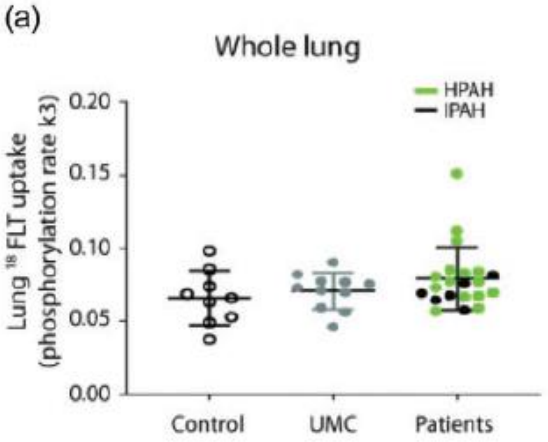
Oxygen uptake:

^{11}C-Acetate



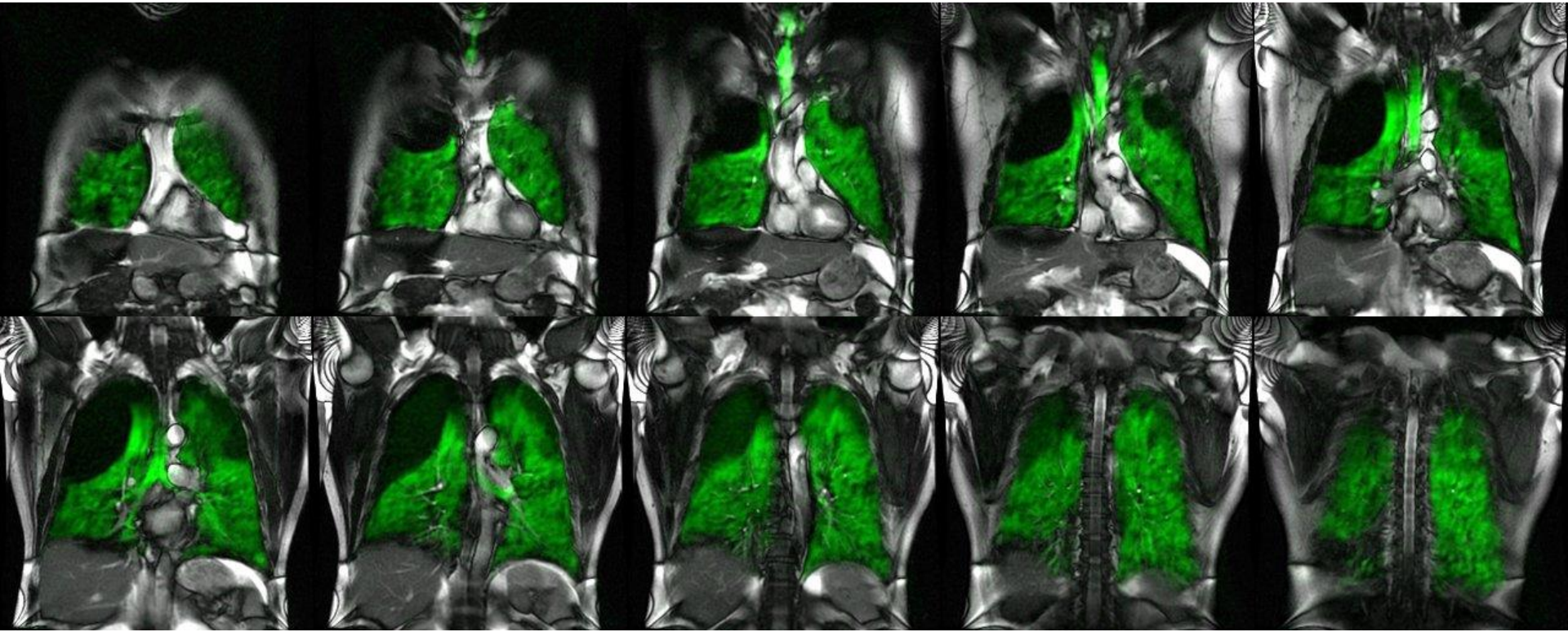
Proliferation:

^{18}F-FLT



Botros et al. Pulm Circ 2021

Hyperpolarized ^{129}Xe MRI – Adding Function to Structure



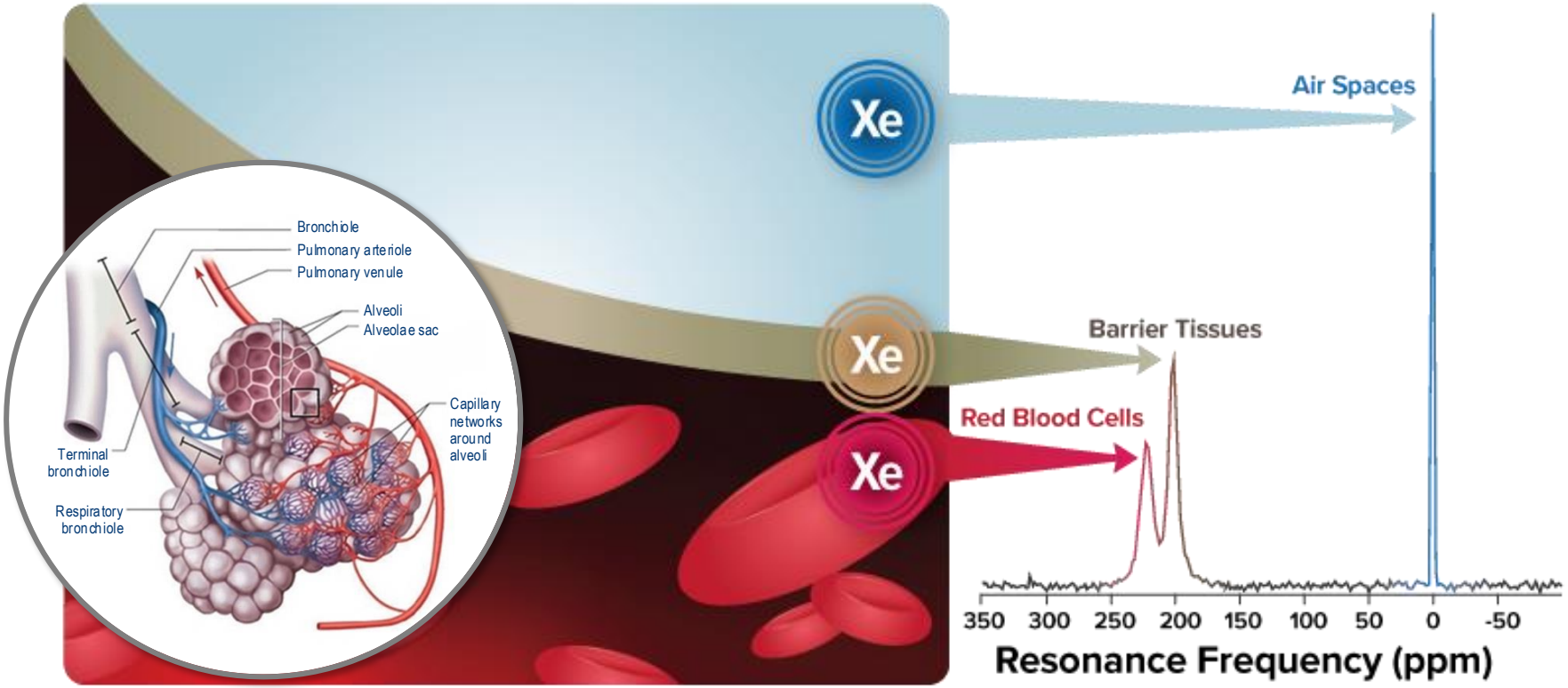
Signal Source is ^{1}H (water)

^{1}H density ~100 Mol/liter

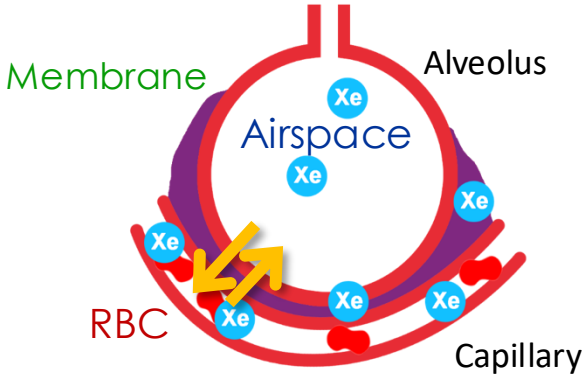
Signal Source is ^{129}Xe

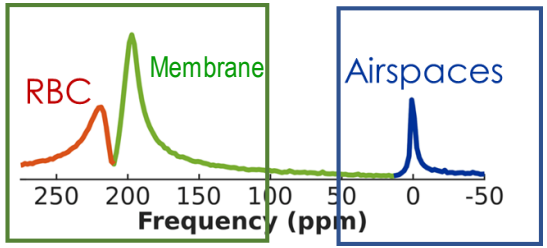
^{129}Xe density ~0.01 Mol/liter

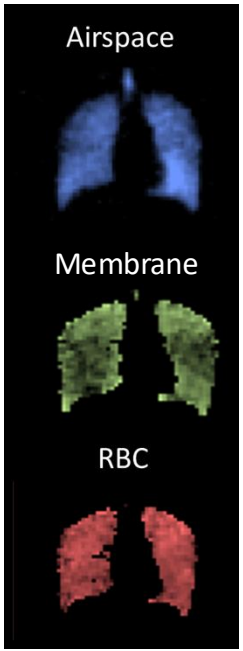
^{129}Xe Enables Evaluation of Gas Exchange



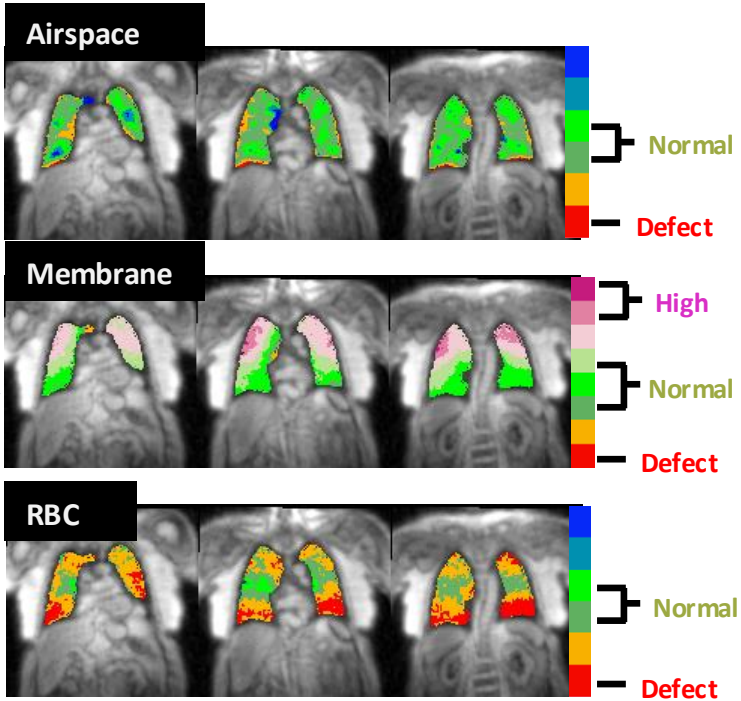
Gas exchange with Hyperpolarized ^{129}Xe





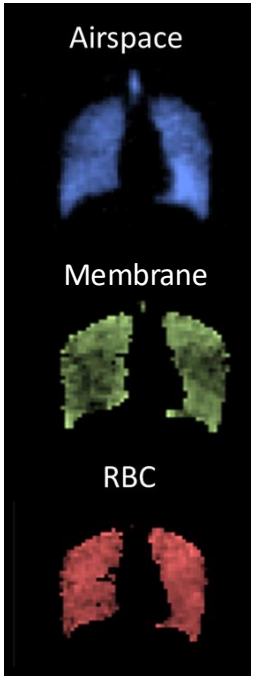


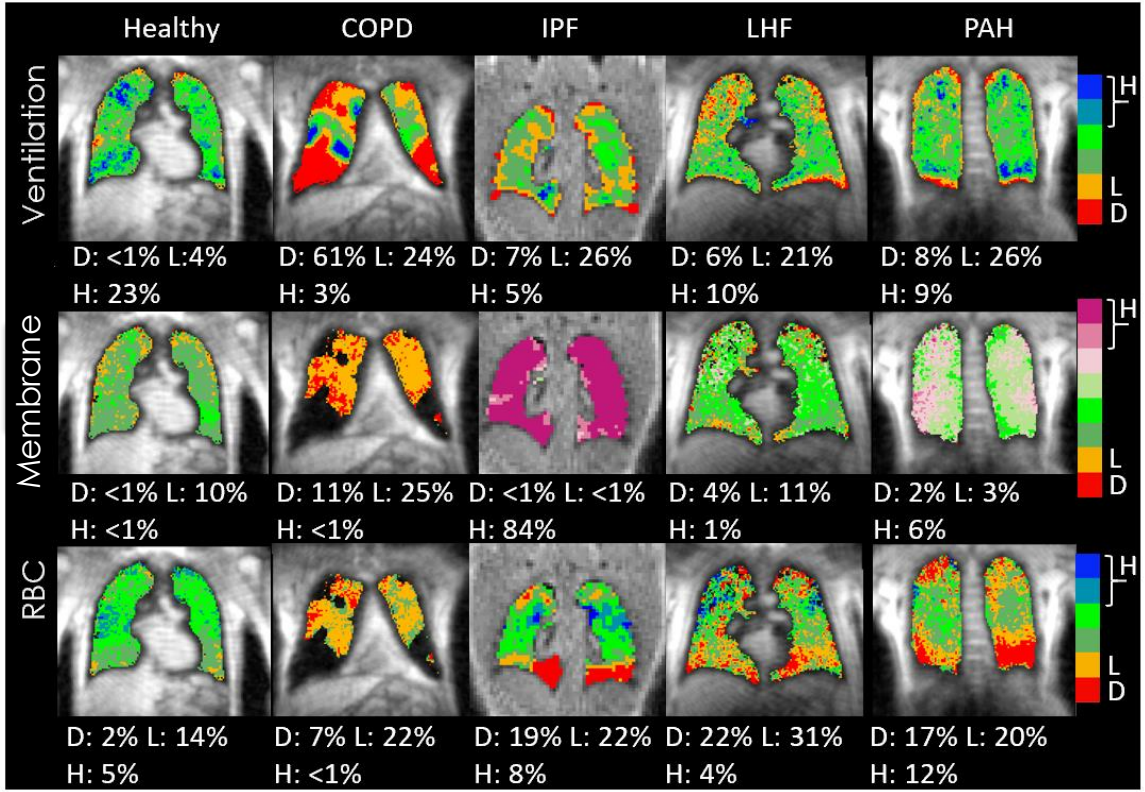
Quantitative Mapping



Slide Courtesy of Bastiaan Driehuys

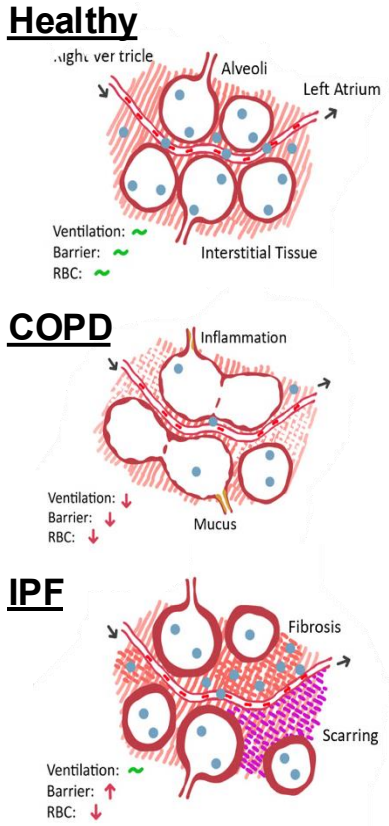
Imaging features correspond with disease physiology



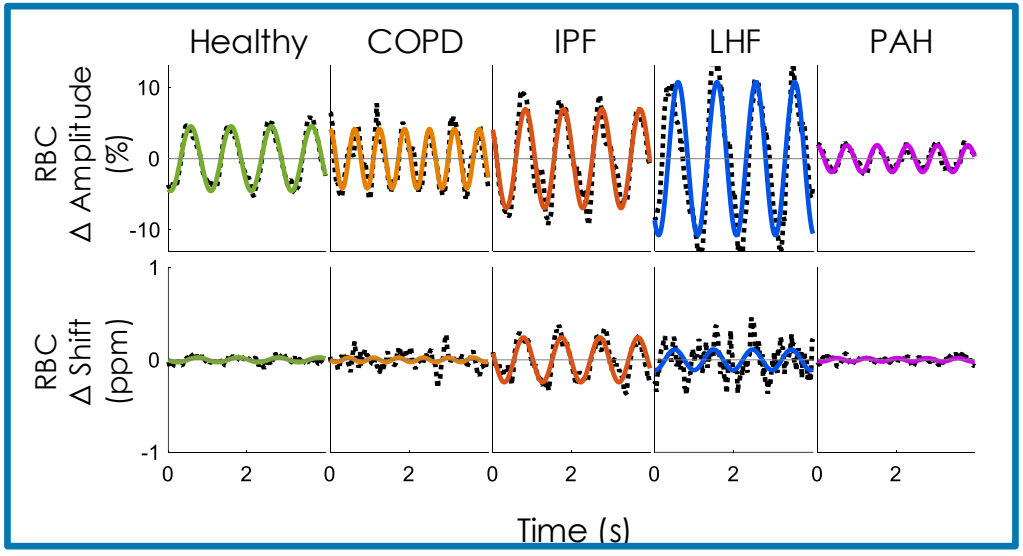


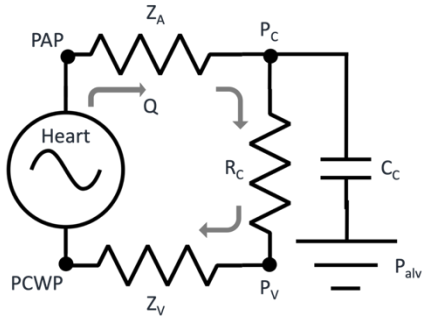
***COPD** = chronic obstructive pulmonary disease; **IPF** = idiopathic pulmonary fibrosis; **LHF** = left heart failure; **PAH** = pulmonary arterial hypertension*

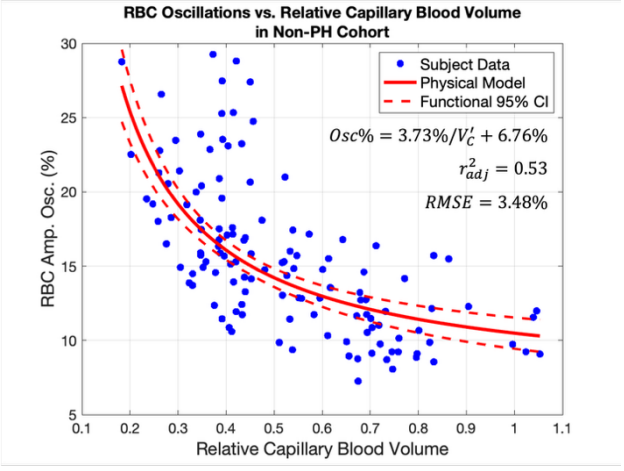
Wang et al., *Eur Respir J.* (2019)



Xenon signals report on hemodynamics



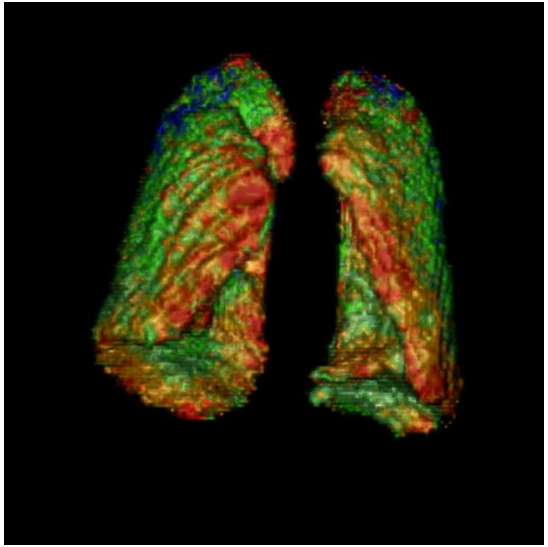




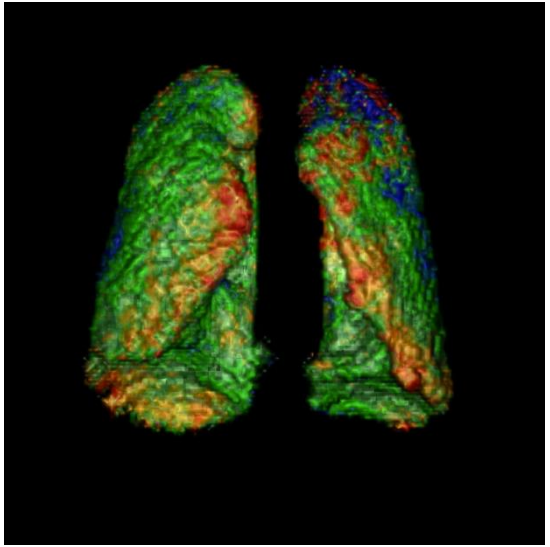
Costelle et al., 2025

Improvement in RBC Transfer with inhaled treprostinil

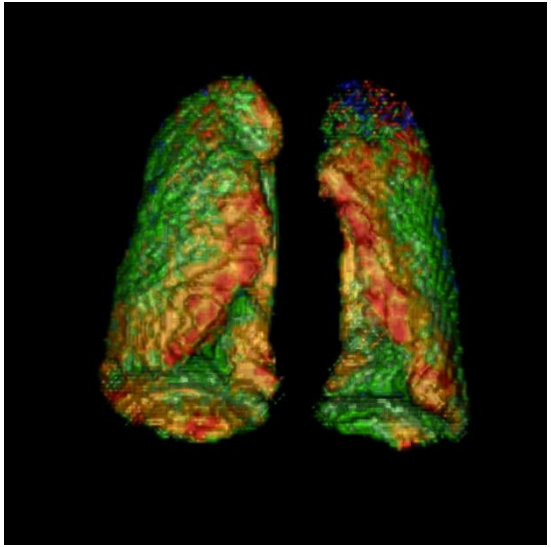
Pre-drug



15-min post



3hrs post



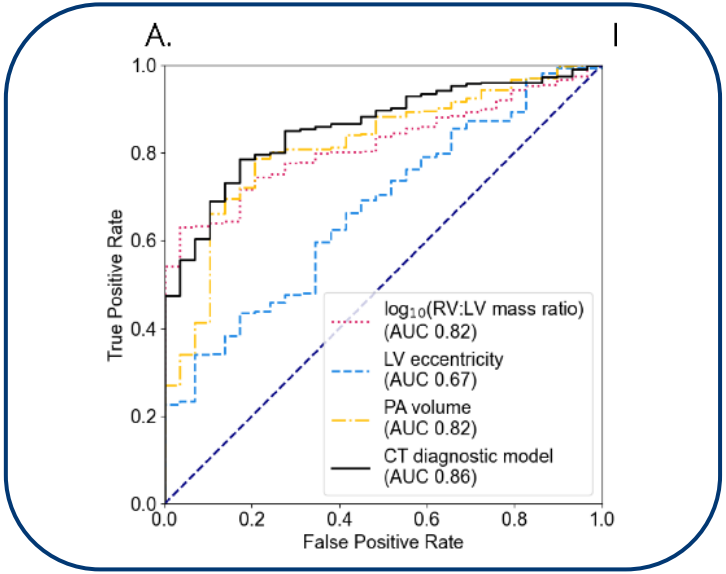
Alenezi et al., 2025

Can AI Help Humans with PH Diagnosis?



AI and CTPA: automation of vessel and biventricular segmentation to aid diagnosis prediction





(validation cohort n=500)

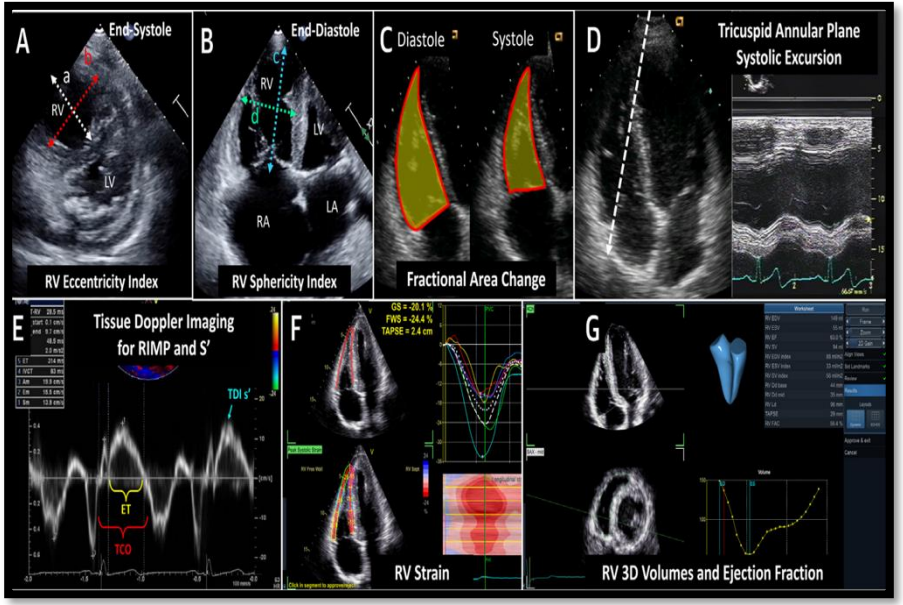
ASPIRE REGISTRY
DONALD HEATH SHEFFIELD
PULMONARY HYPERTENSION RESEARCH

Sharkey M et al *Front Cardiovasc Med* 2022 Sep 26:9:983859.

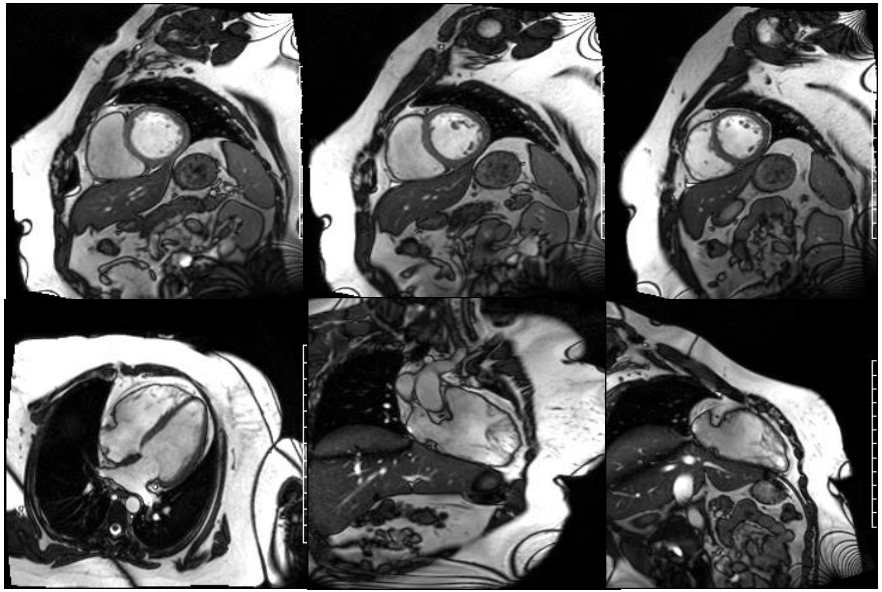
CARDIOVASCULAR IMAGING IN PULMONARY HYPERTENSION

Comprehensive imaging exists, but it is expertise-dependent

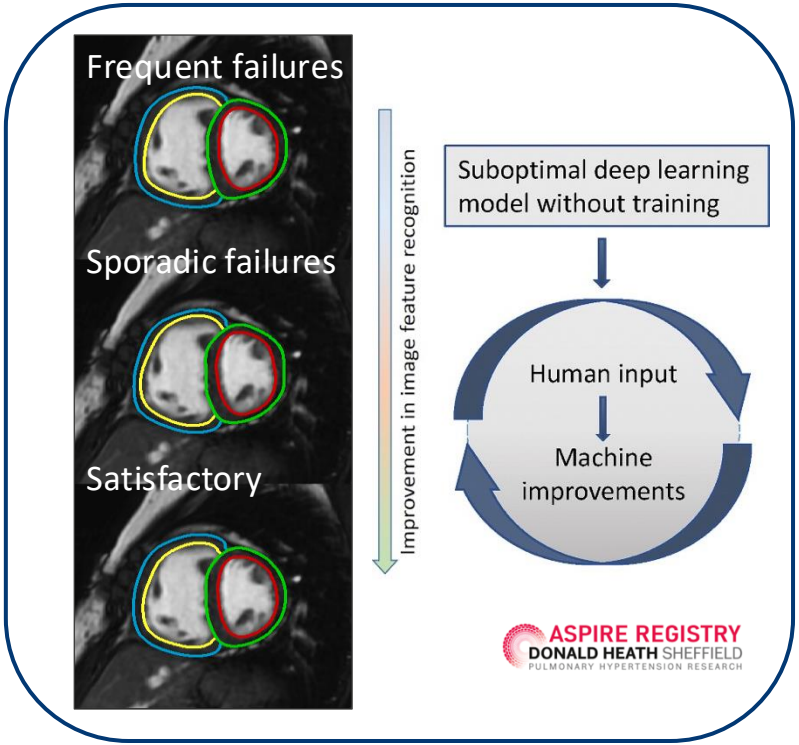
Echo: many measurements, many views

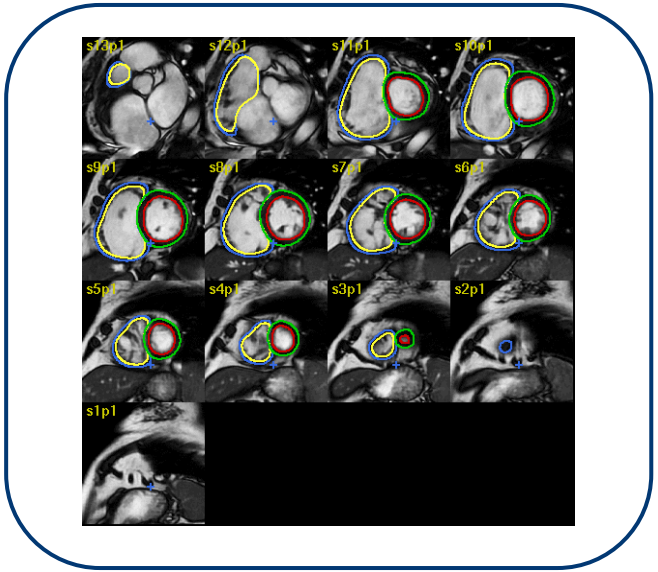


CMR: gold standard for RV, limited access



Using AI to improve and automate biventricular segmentation



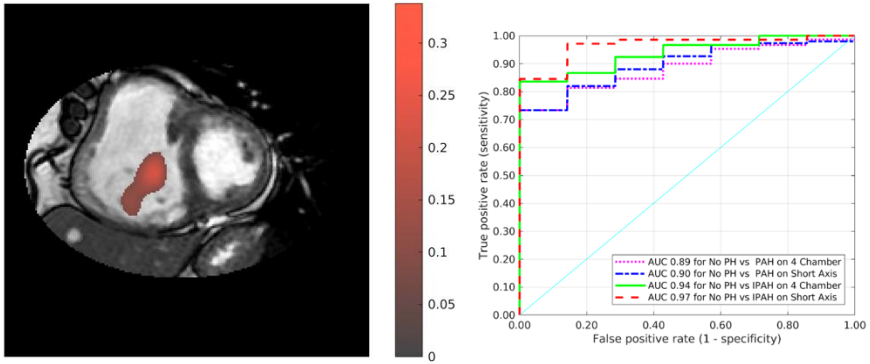


(n=5051 MRI in 3782 patients)

Alabed S et al, *Radiology* 2022 Oct;305(1):68-79

Using feature extraction on MRI to diagnose PH and predict outcome

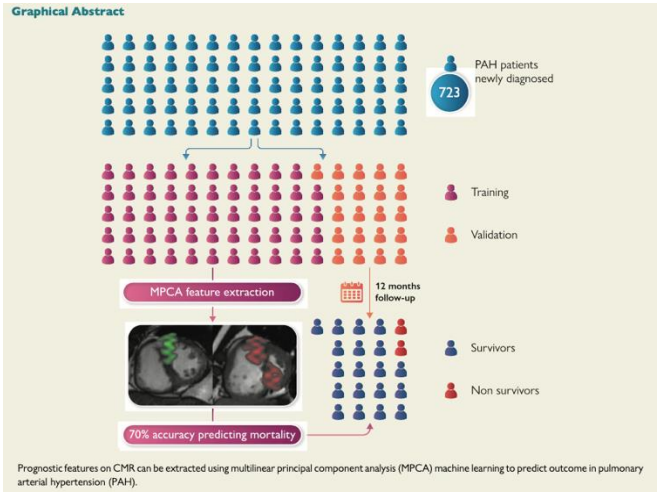
Diagnosis[1] (treatment naïve)



Physiological feature extraction
Supervised by binary outcome

ASPIRE REGISTRY
DONALD HEATH SHEFFIELD
PULMONARY HYPERTENSION RESEARCH

Mortality[2] (1-yr newly diagnosed PAH)



When used in combination with REVEAL 2.0, CMR metrics and MPCA AUC for 1 year mortality 0.83

1. Swift AJ *et al. Eur Heart J Cardiovasc Img* 2020; 2. Alabed S et al, *Eur Heart J Digit Health* 2022

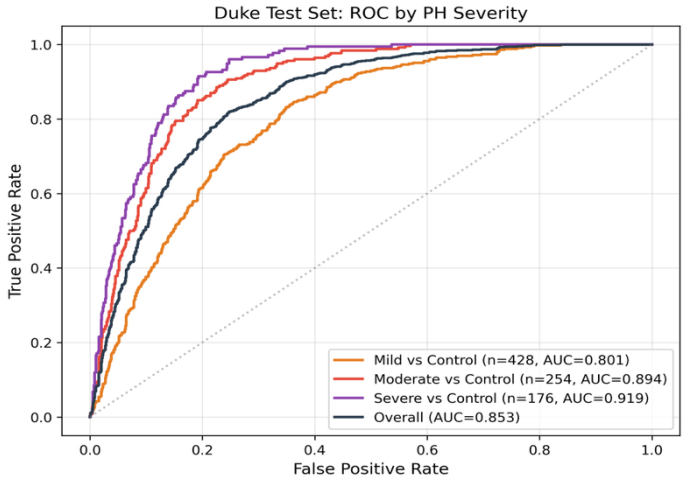
Similar approaches now applied to echo

Discrimination scales with hemodynamic severity

Severity defined by mPAP and PVR per 2022 ESC/ERS

Alenezi et al., submitted

DUKE

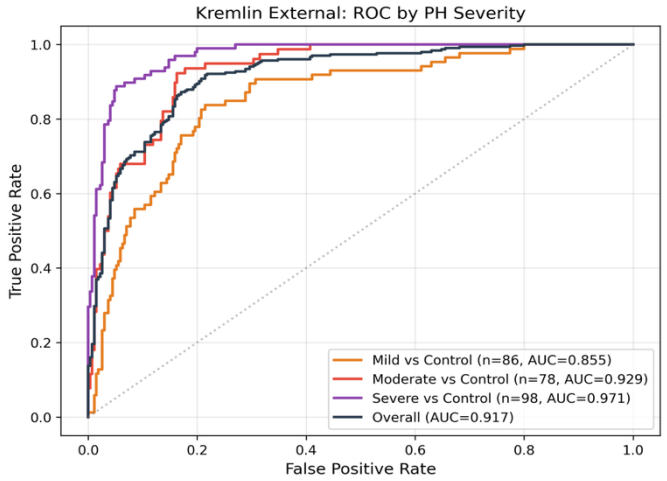


AUROC 0.801 0.894 0.919

Mild *Moderate* *Severe*

Discrimination increases with disease severity

KREMLIN-BICÊTRE (France)



AUROC 0.855 0.929 0.971

Mild *Moderate* *Severe*

Discrimination increases with disease severity

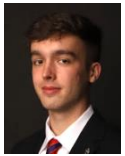
Acknowledgements

- WSPH Task Force 6
  - Slides from David Kiely, Martine Remy-Jardin, Deepa Gopalan, Harm Bogaard and others
- Collaborators and Colleagues
  - Duke – Fawaz Alenezi, Bastiaan Driehuys
  - AI in echo
    - Us2.ai: Cyril Equilbec, Matt Frost, Carolyn Lam
    - Fabrice Bauer, Francois Haddad

The Team and Collaborators at Duke University


Bastiaan Driehuys


David Mummy


Drew Clements


Hong Qin

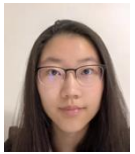

Suphachart Leewiwatwong


Anna Costelle


Seth Lee


Andrew McHorse


Fuyao Li


Kunyu Du


Jennifer Korzekwinski

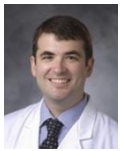

Cody Blanton


Alex Sents




Team CAMRD


Joe Mammarapallil


Rob Tighe


Aparna Swaminathan


Lake Morrison

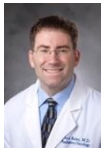

Loretta Que


Sudarshan Rajagopal


Fawaz Alenezi


Tony Huang


Azfar Ali


Christopher Kelsey


Kamran Mahmood

Funding Sources:

NHLBI R01-HL-105643

NHLBI R01-HL-126771

NHLBI R01- HL-153872

NHLBI R01-HL-153641

Genentech

Boehringer Ingelheim

United Therapeutics

Duke

NONE OF THESE ACTUALLY LOOK AT THE PULMONARY CIRCULATION!

Vascular remodeling of the small pulmonary arteries and measures of vascular pruning on computed tomography

Andrew J. Synn[1], Constance De Margerie-Mellon[2], Sun Young Jeong[3], Farbod N. Rahaghi[4], Iny Jhun[5], George R. Washko[4], Raúl San José Estépar[6], Alexander A. Bankier[7], Murray A. Mittleman[8], Paul A. VanderLaan[9] and Mary B. Rice[1]

Pulmonary Circulation 2021; 11(4) 1–9

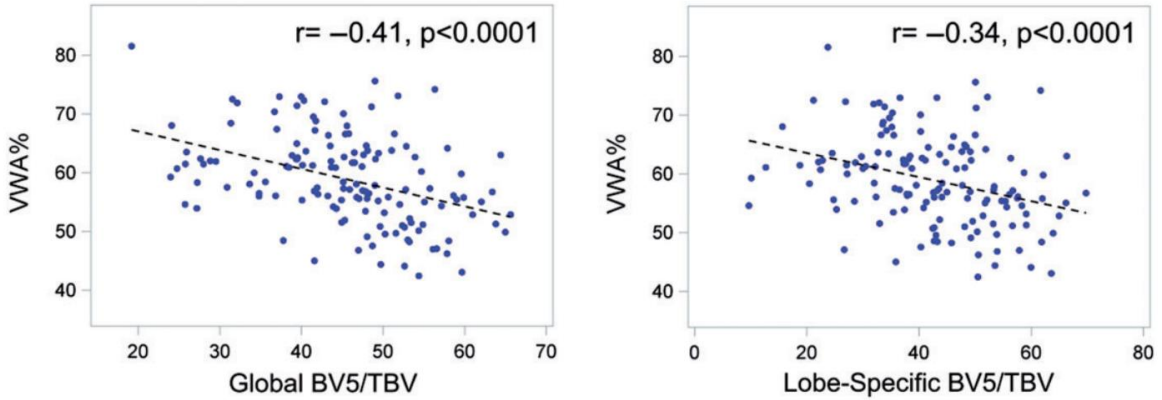
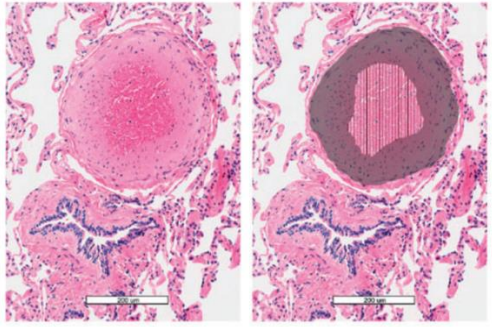


Fig. 3. Correlation of vascular pruning on CT (BV5/TBV) with histologic vascular remodeling (VWA%).

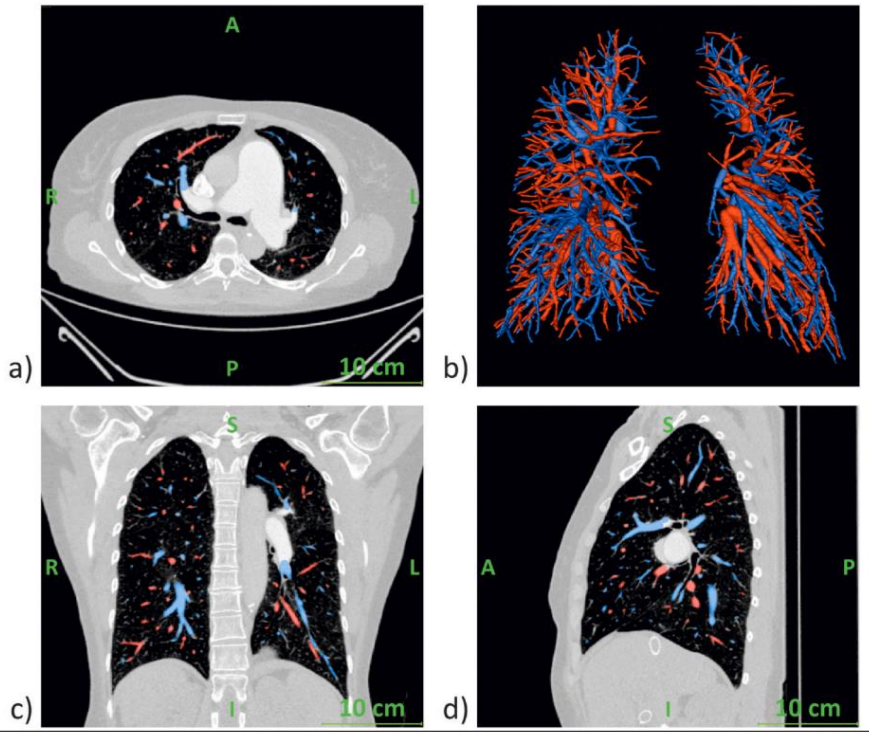


Morphometric evidence of arterial remodeling

Among individuals who underwent resection for lung adenocarcinoma, more severe CT-based vascular pruning was associated with greater histologic arterial remodeling. These findings suggest CT imaging may be a non-invasive indicator of pulmonary vascular pathology.

CT-derived lung vessel morphology correlates with prognostic markers in precapillary pulmonary hypertension

J Heart Lung Transplant 2024;43:54–65

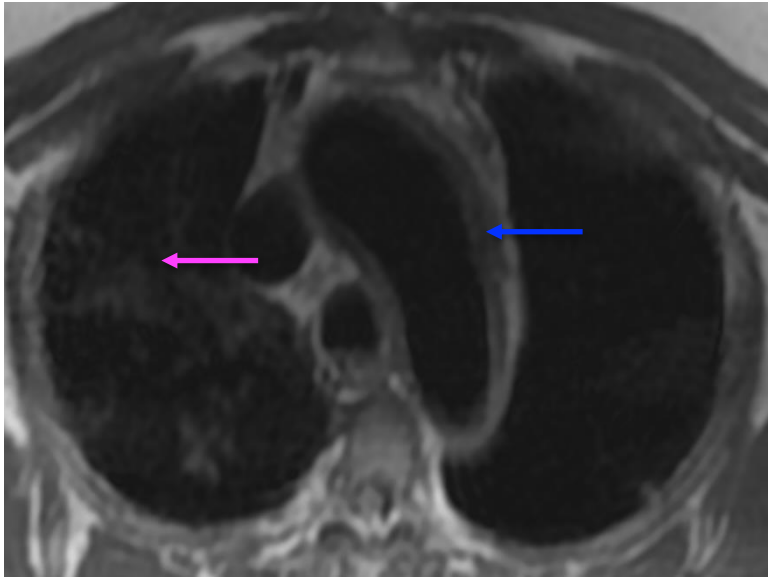


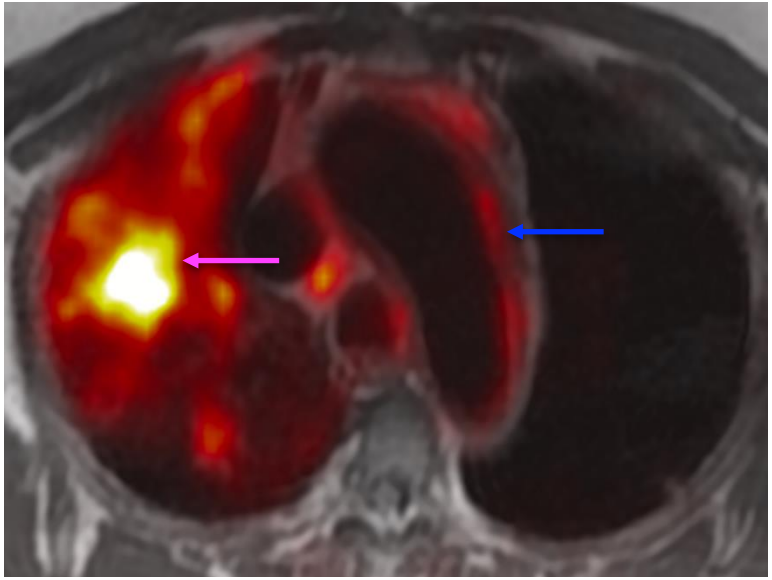
risk stratification of precapillary PH

CONCLUSIONS: The ratio of the number of arteries over veins with diameters between 6 and 10 mm is significantly correlated with prognostic markers in pulmonary hypertension and predicts low and high mortality risk.

^{18}F-FETO (Active Tak)

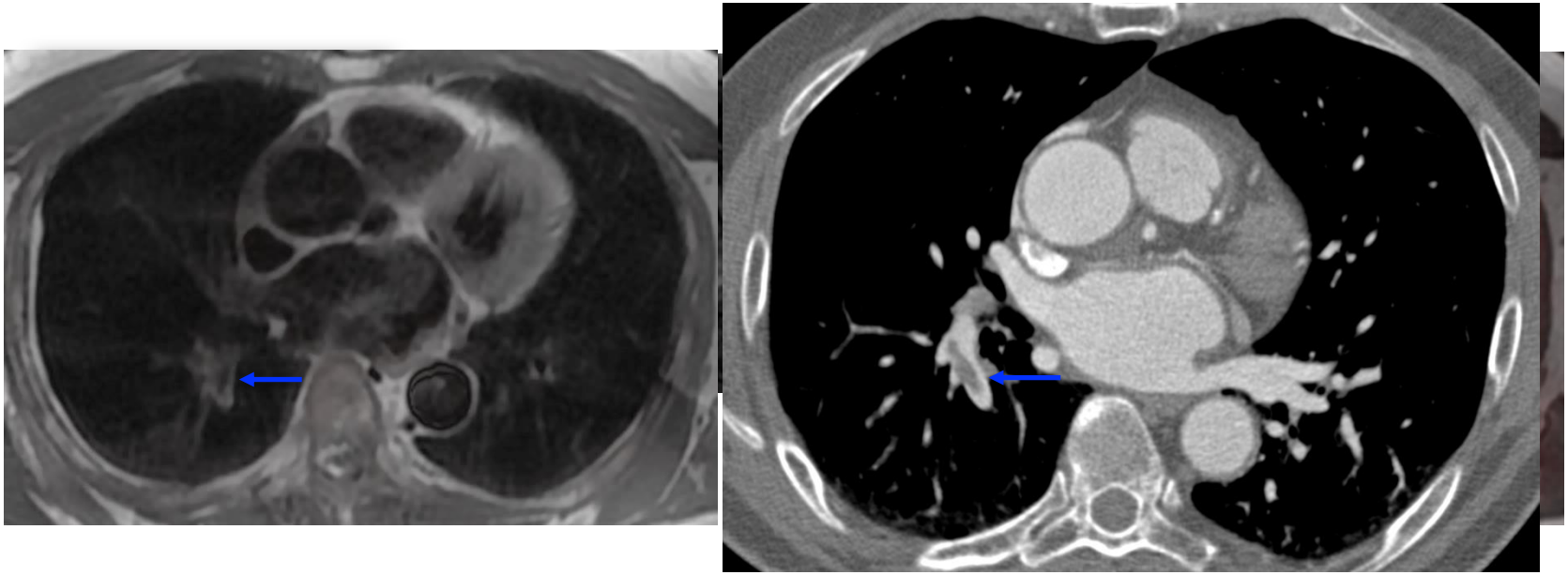
PET-MR in vasculitis :Vessels & Lung



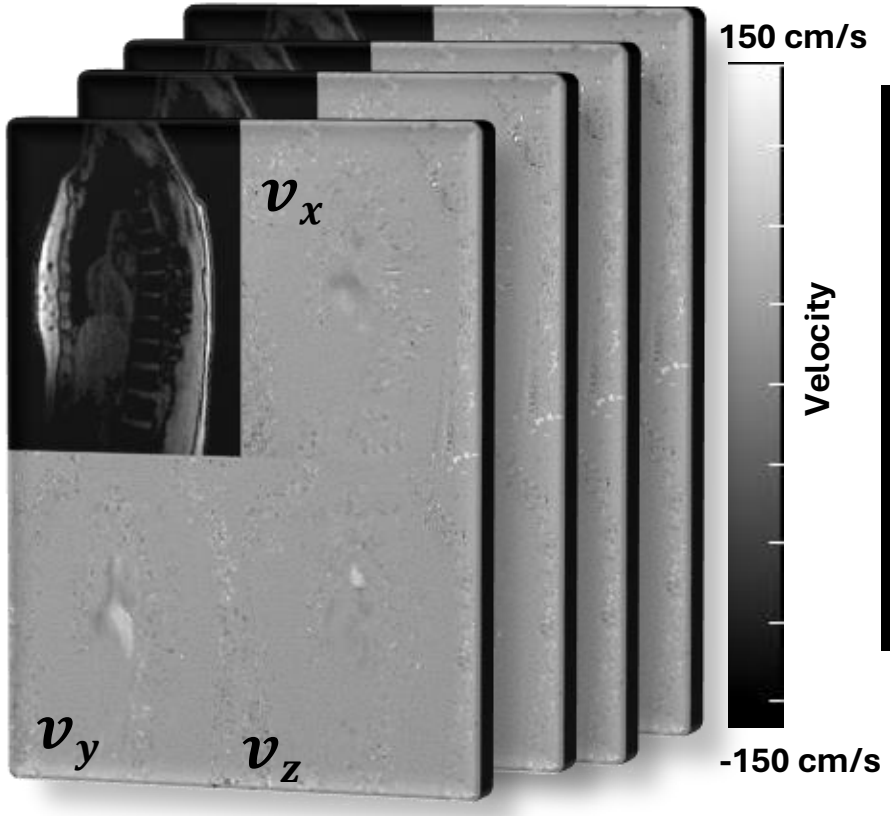


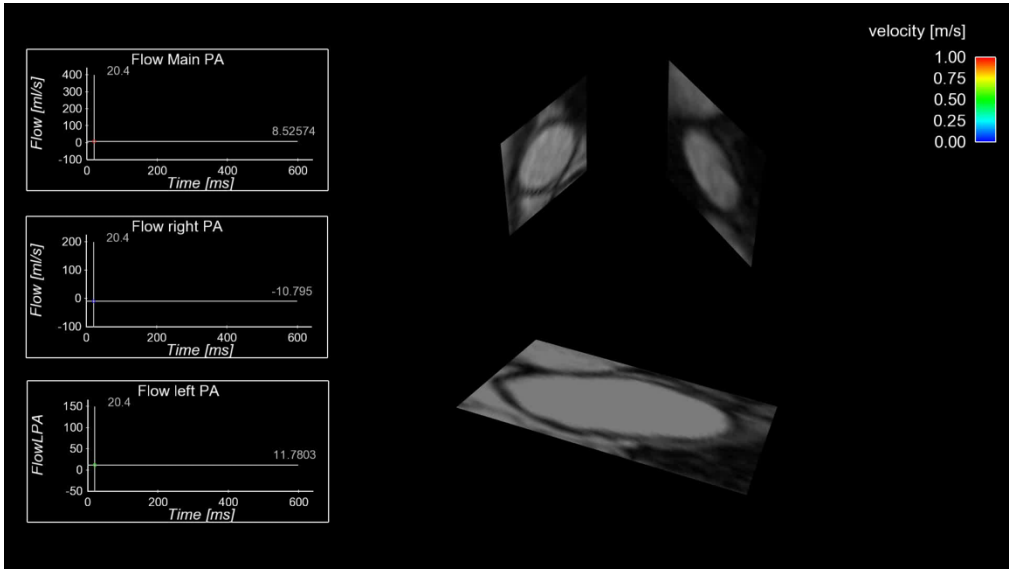
Tracer: ^{18}F-FETO

PET-MR in antiphospholipid syndrome: Cardiac & Pulmonary vascular



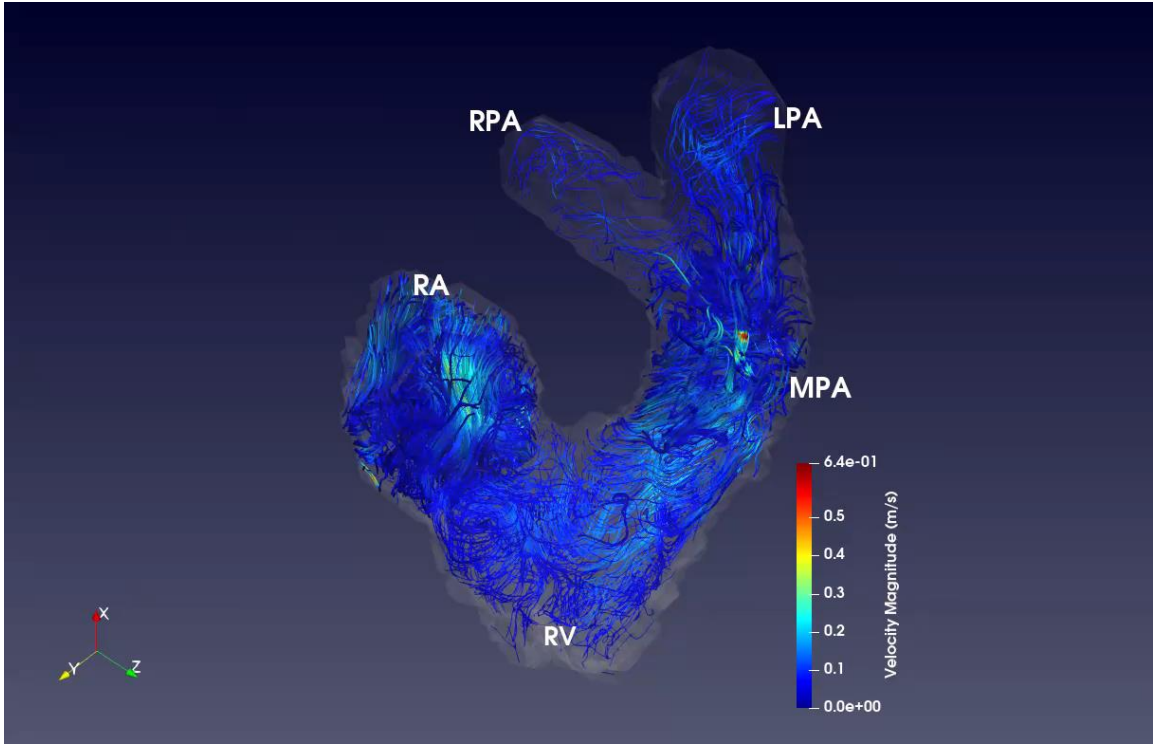
4D Flow MRI





4D Flow through Healthy Pulmonary Artery (PA)

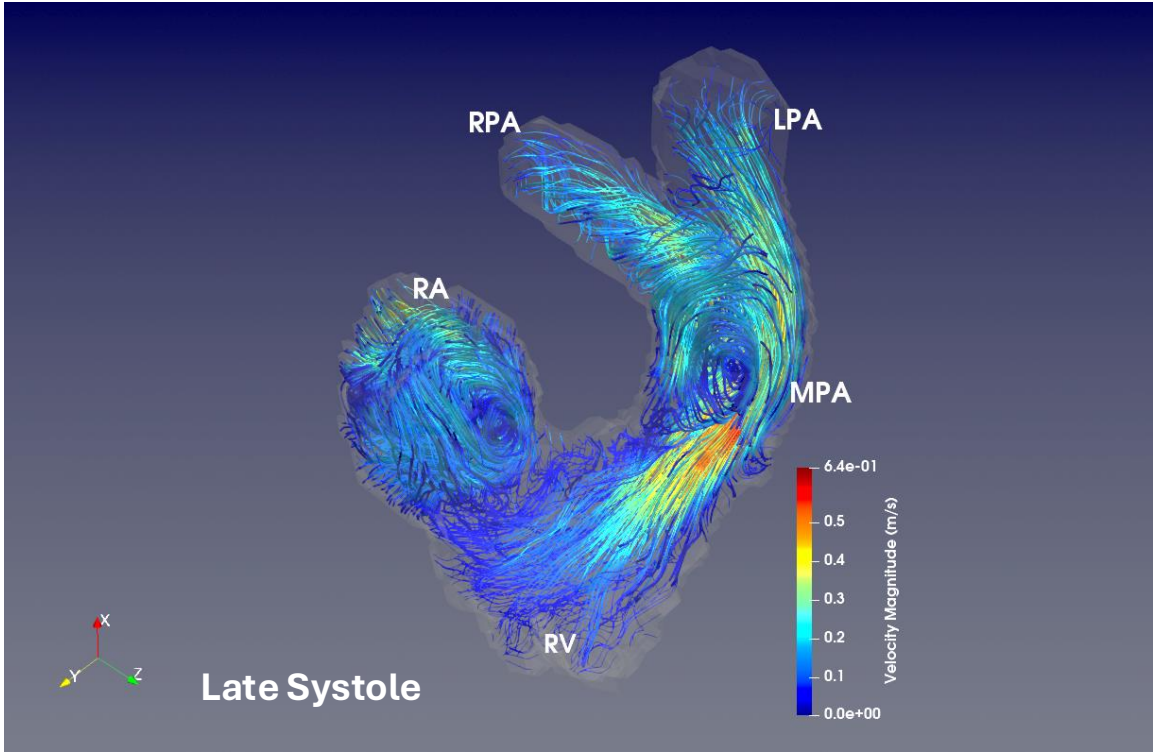
In vivo 4D Flow MRI Blood Flow in the right heart in PAH



39-Year-Old Female with Pulmonary Arterial Hypertension

Abbreviations: RV: Right ventricle. RA: Right Atrium. MPA: Main Pulmonary Artery. LPA: Left Pulmonary Artery. RPA: Right Pulmonary Artery.

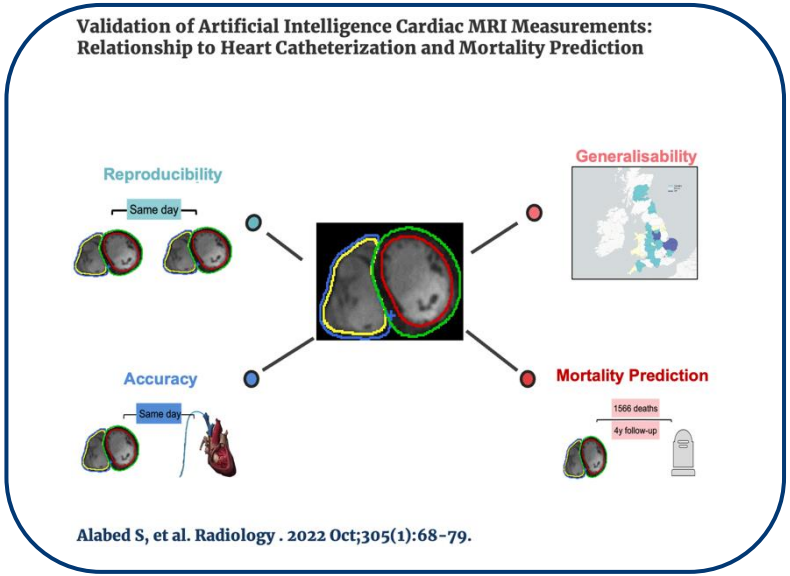
In vivo 4D Flow MRI: 3D Blood Flow in the right heart

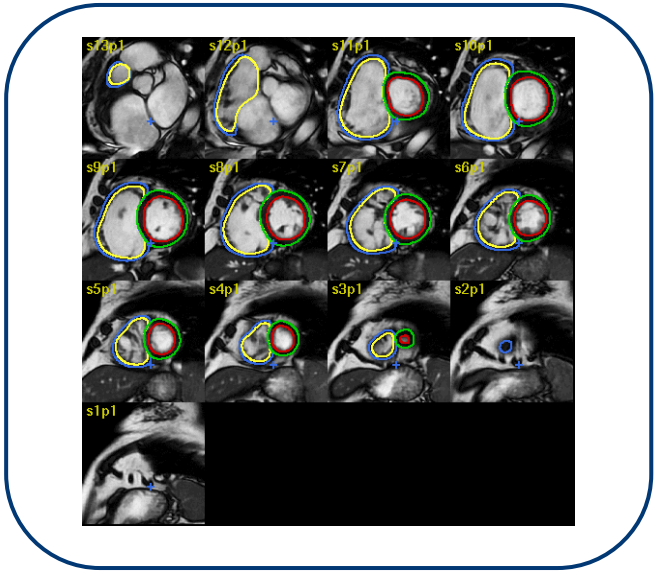


39-Year-Old Female with Pulmonary Arterial Hypertension

Abbreviations: RV: Right ventricle. RA: Right Atrium. MPA: Main Pulmonary Artery. LPA: Left Pulmonary Artery. RPA: Right Pulmonary Artery.

Using AI to improve and automate biventricular segmentation





Stronger correlations with haemodynamics, **higher repeatability** on scan-rescan testing and at least equivalent **mortality prediction** compared to manual contours

Alabed S et al, *Radiology* 2022 Oct;305(1):68-79