Synchrotron-based phase contrast tomography for cardiovascular applications: from rodents to humans

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Dr. Hector Dejea

PIONEERING SYNCHROTRON SCIENCE

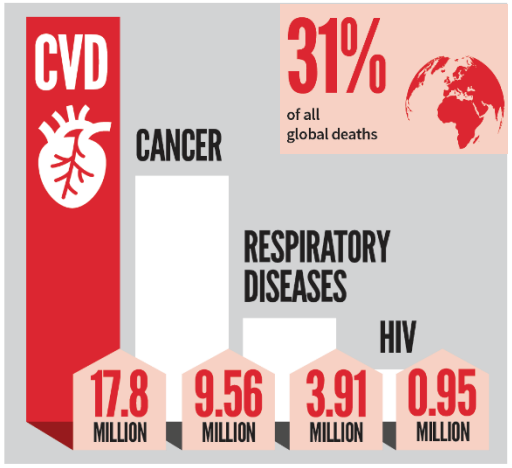
ESRF
The European Synchrotron

30 years of science

CARDIOVASCULAR DISEASE

Cardiovascular diseases are a group of disorders of the heart and blood vessels, commonly referred to as **heart disease** and **stroke**.

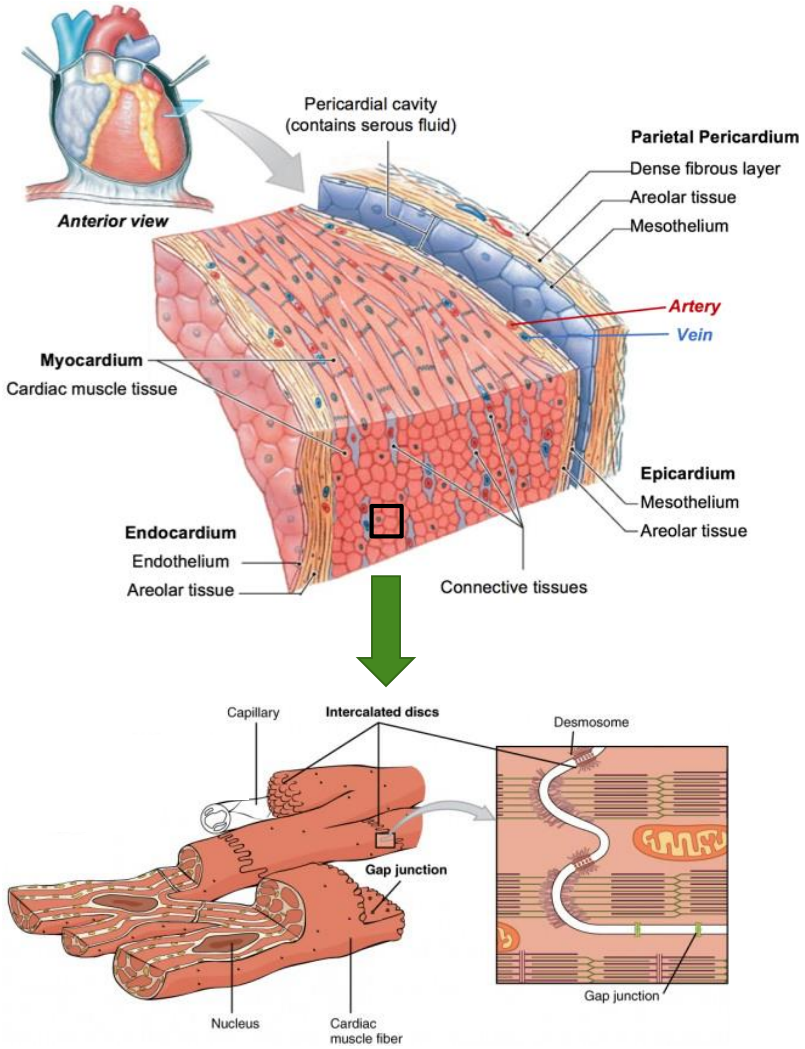
GLOBAL CAUSES OF DEATH



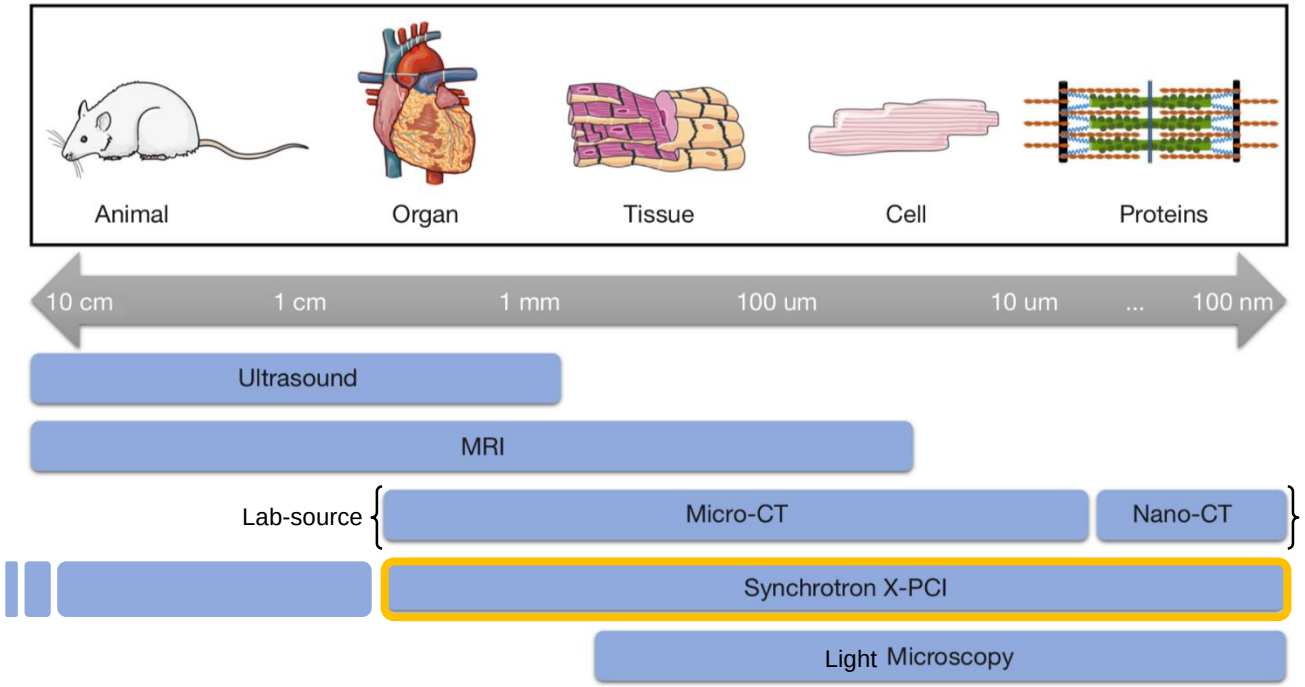
RISK FACTORS FOR CVD

- High Blood Pressure
- Unhealthy Diet
- High Cholesterol
- Diabetes
- Overweight & Obesity
- Tobacco
- Air Pollution
- Kidney Disease
- Physical Inactivity
- Harmful use of alcohol

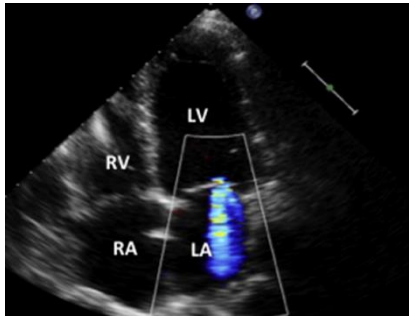
WORLD HEART FEDERATION



IMAGING THE CARDIAC ARCHITECTURE

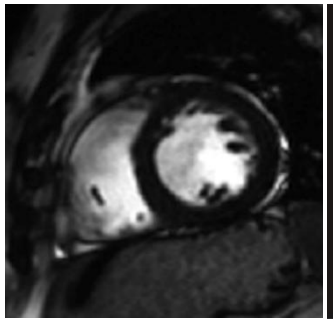


Ultrasound

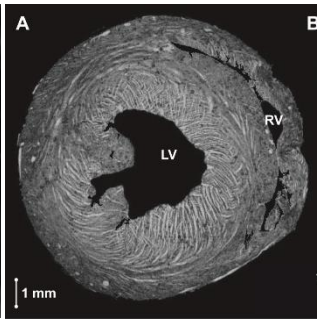


D'Alto et al., Int J Cardiol, 2018

Magnetic Resonance Imaging (MRI)

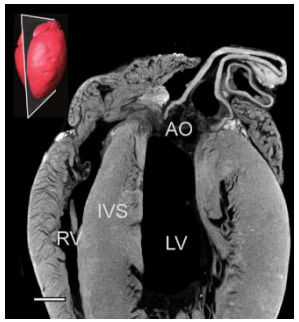


Romano et al., Radiology, 2018



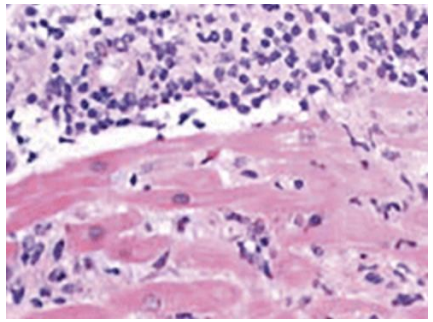
Gilbert et al., Am J Physiol Heart Circ Physiol, 2012

Micro-CT



Stephenson et al., PLoS One, 2012

Light microscopy

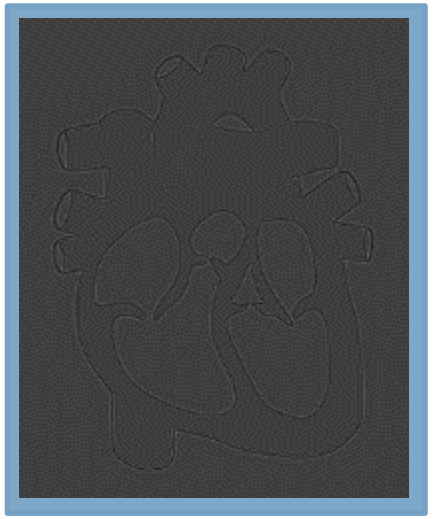


Smith et al., Radiographics, 2019

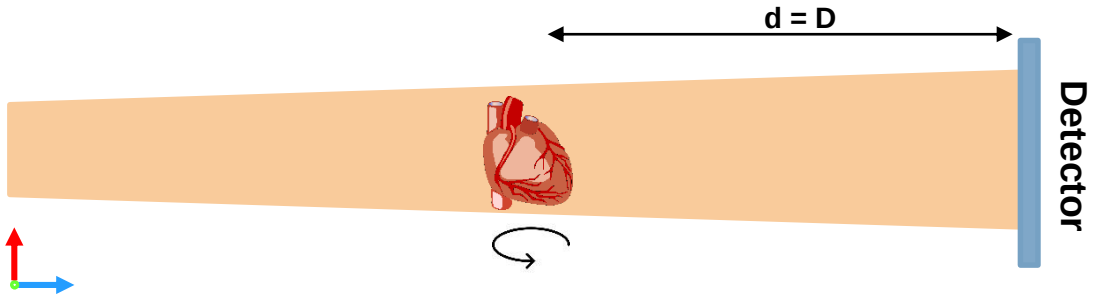
Dejea et al., Cardiovascular Diagnosis and Therapy, 2020

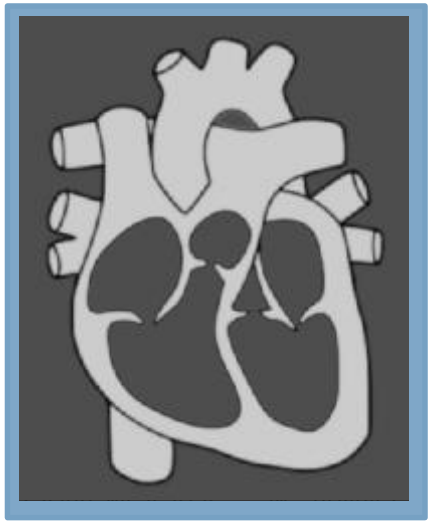
PROPAGATION-BASED X-RAY PHASE CONTRAST IMAGING (X-PCI)

Attenuation Contrast Imaging



Propagation–based Phase Contrast Imaging (PB X-PCI)





MULTISCALE *EX-VIVO* ANALYSIS OF CARDIAC STRUCTURAL REMODELLING IN WHOLE RAT HEARTS

Strategic Focus Area
Personalized Health and Related Technologies

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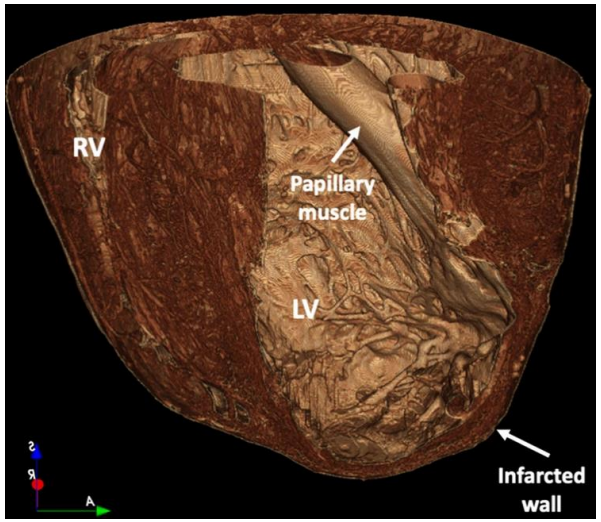

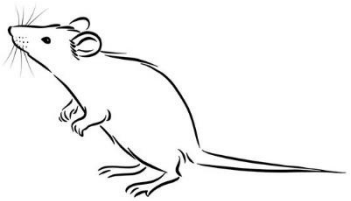

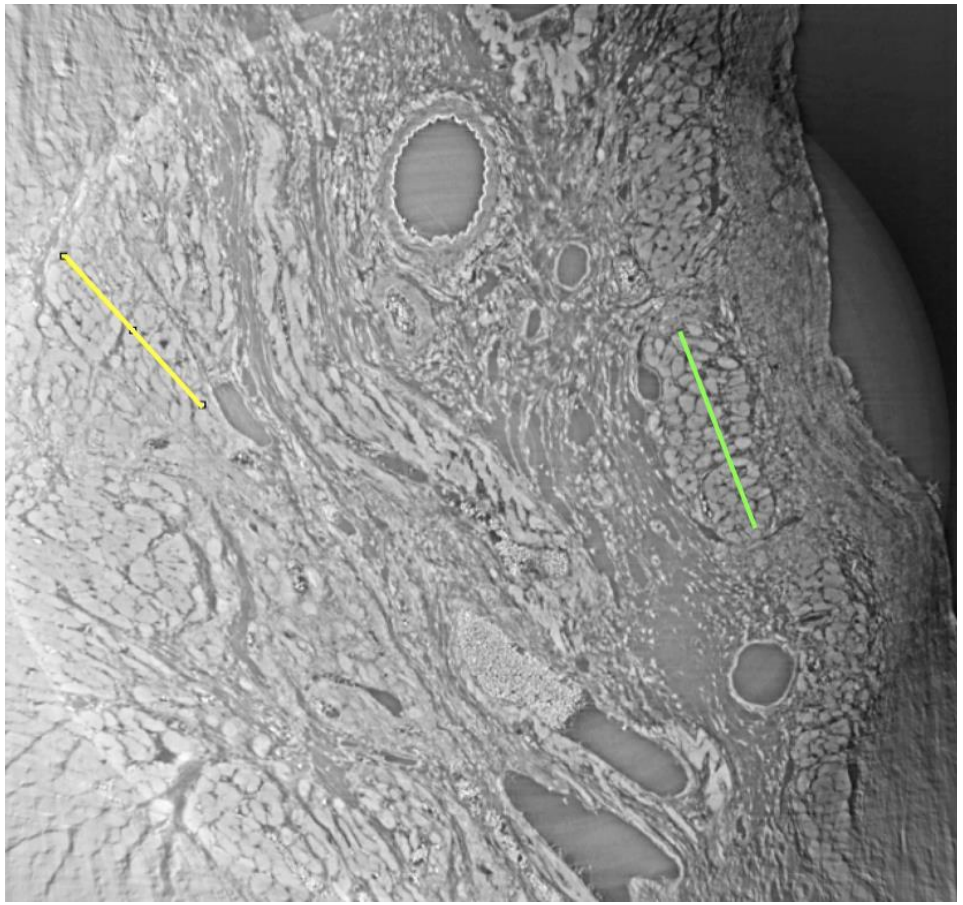

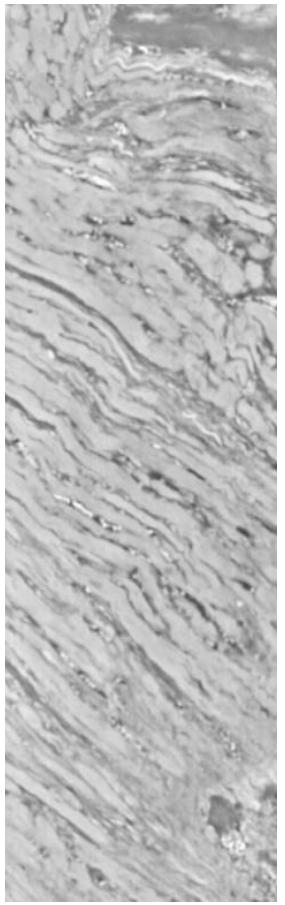

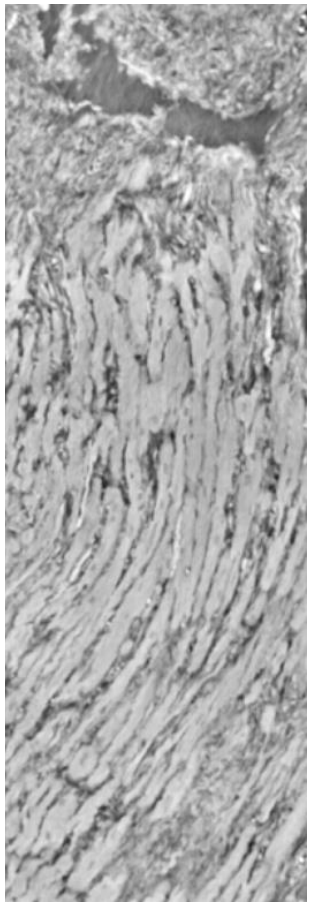

Planinc et al., Scientific Reports, 2021
Dejea et al., Scientific Reports, 2019

The European Synchrotron | ESRF

MULTISCALE X-PCI

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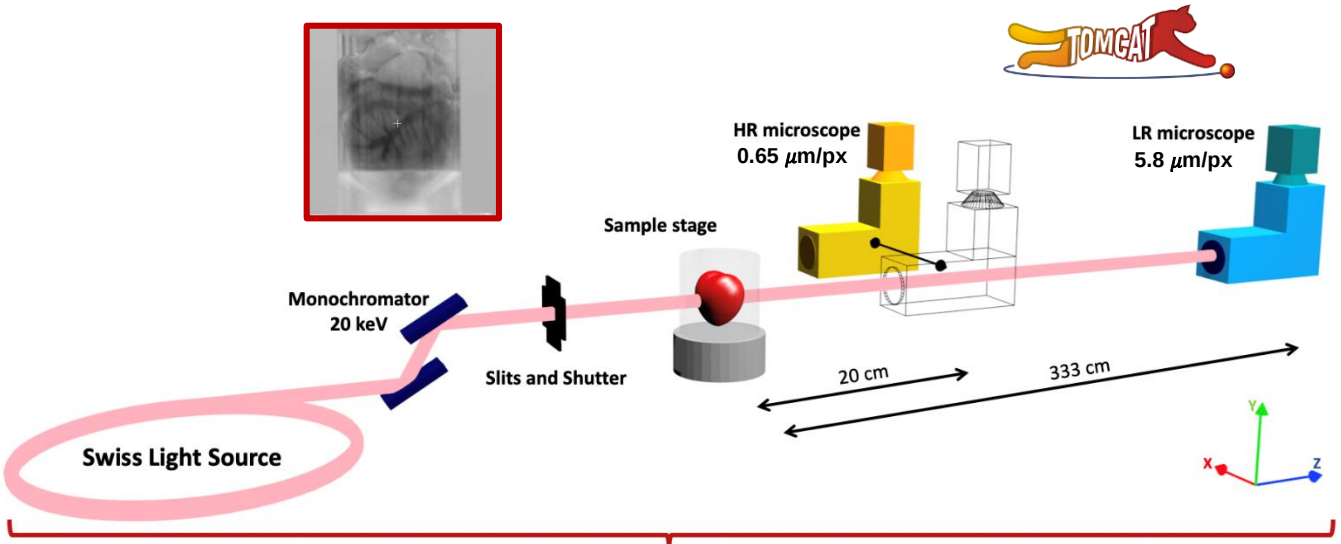

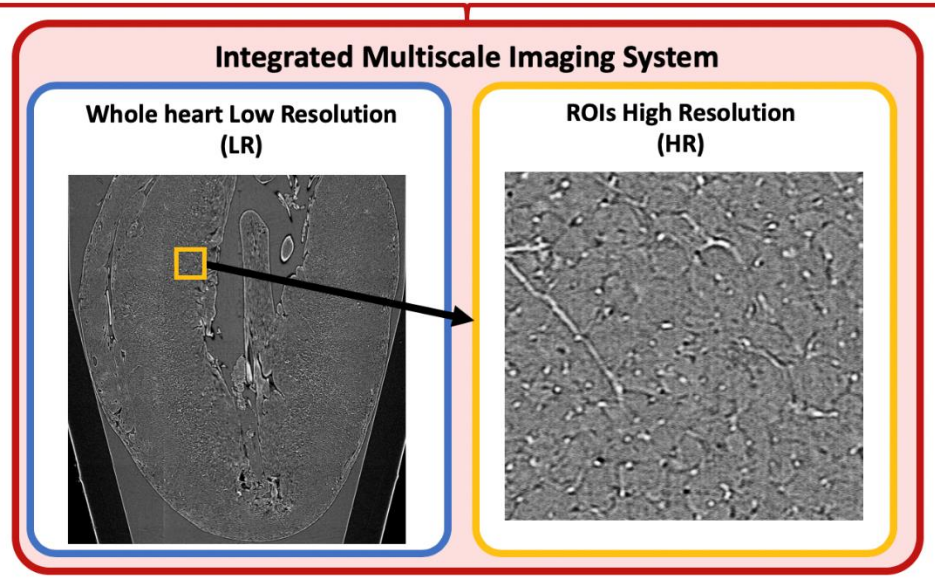

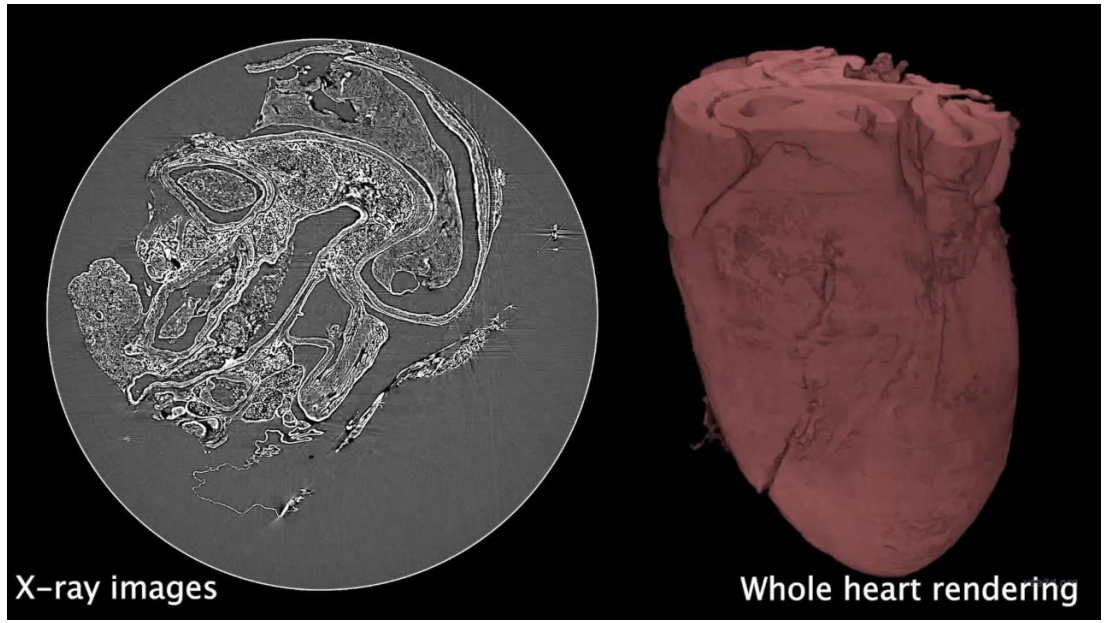

Dejea et al., Scientific Reports, 2019

MULTISCALE X-PCI – MYOCARDIAL INFARCTION IN RATS

Strategic Focus Area
Personalized Health and Related Technologies

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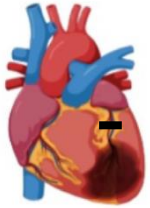
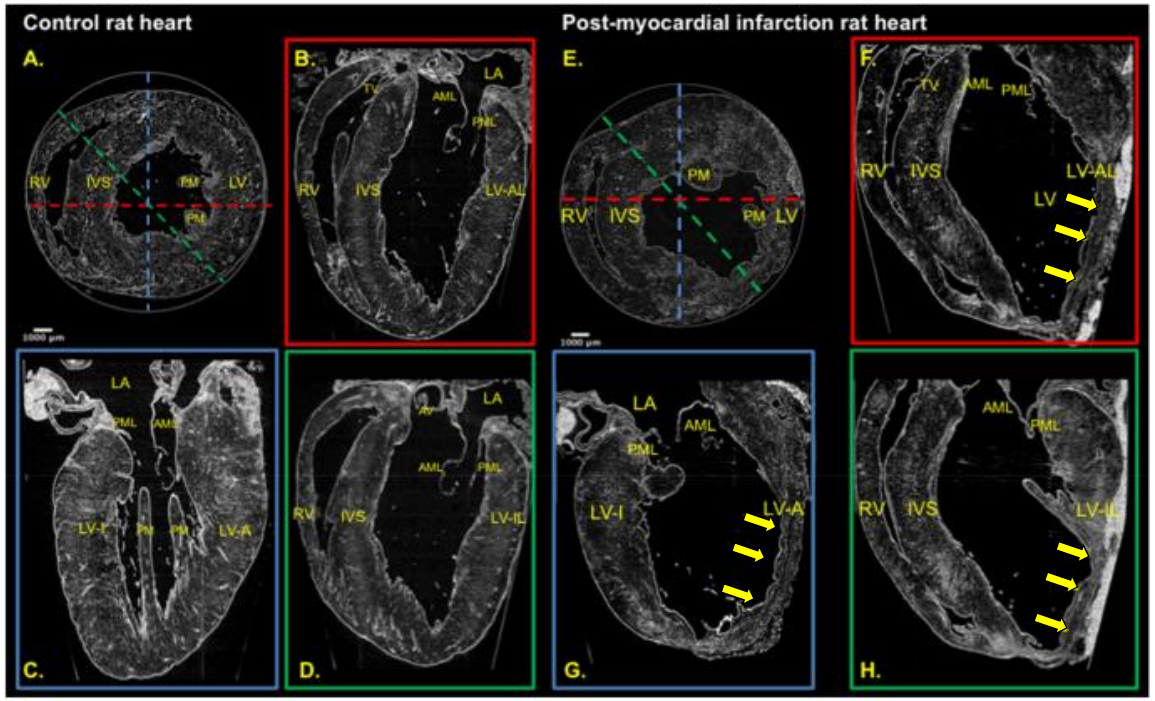
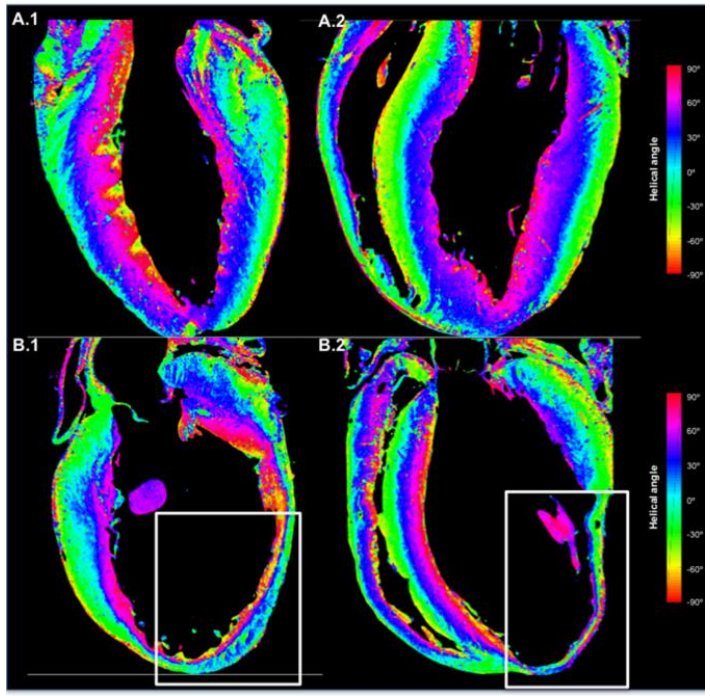
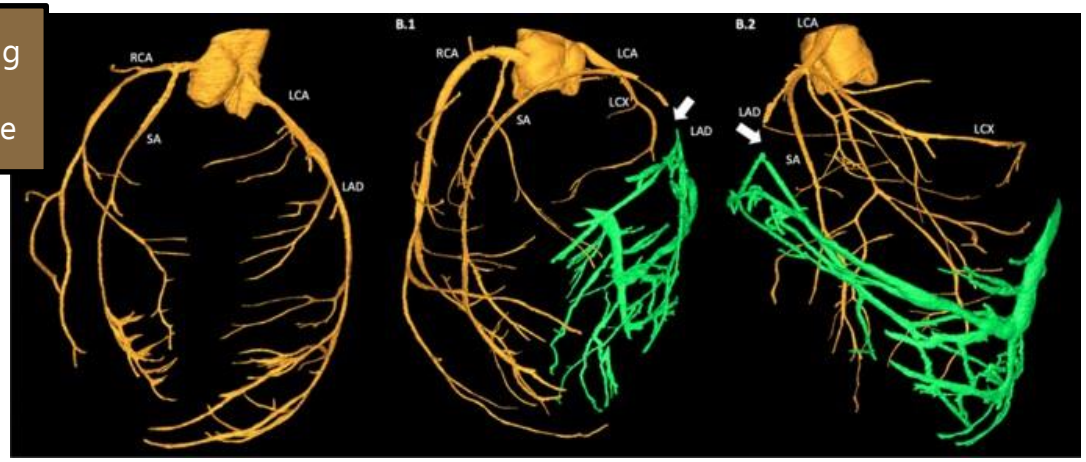


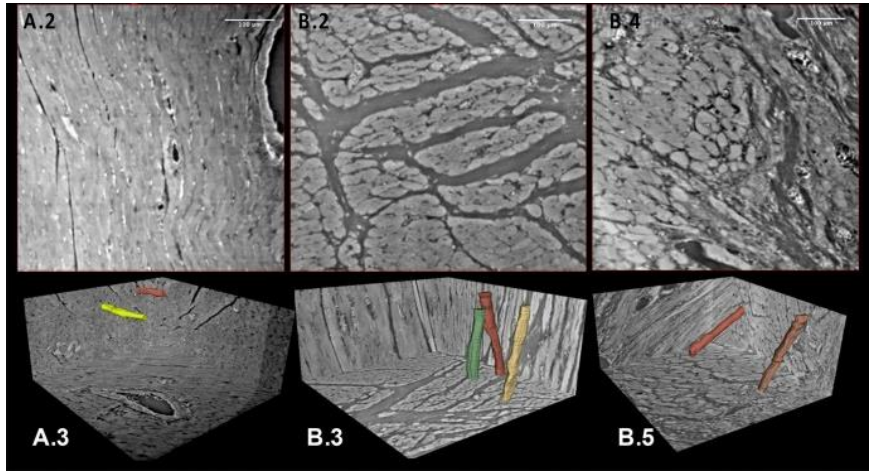




Quantification of helical angle

3D rendering of the vascular tree





Segmentation of individual cardiomyocytes

Average cross-sectional area:
- Control: 321 ± 75 µm^2
- LAD peri-MI area: 737 ± 127 µm^2
- LAD contralateral: 499 ± 141 µm^2

Planinc et al., Scientific Reports, 2021

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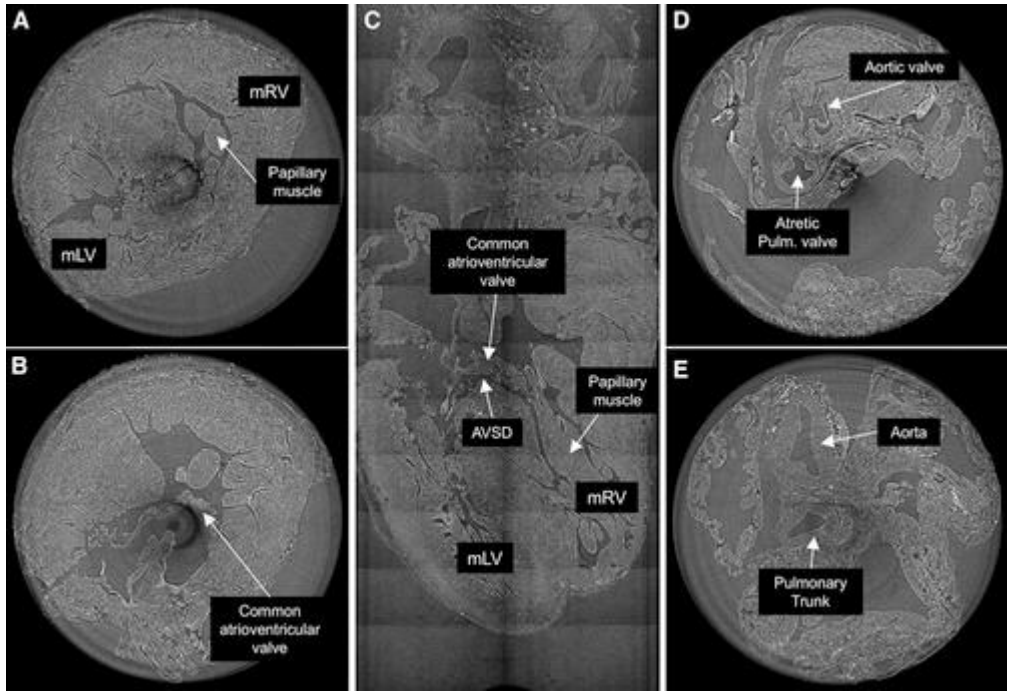
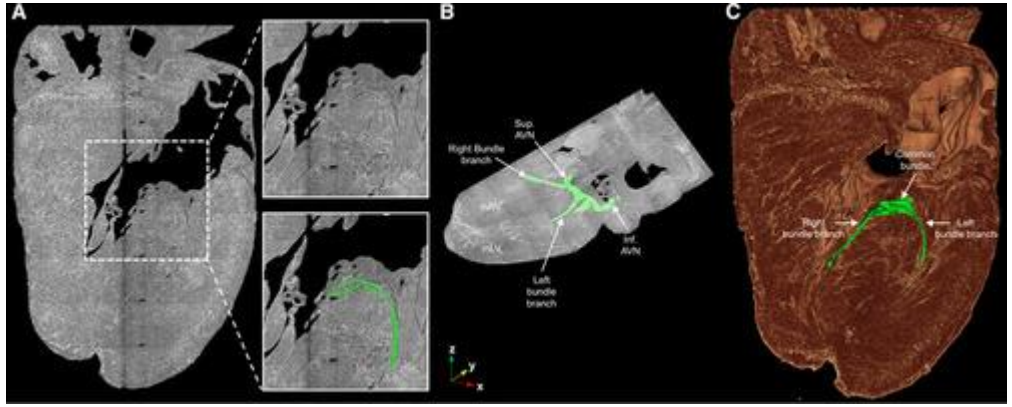
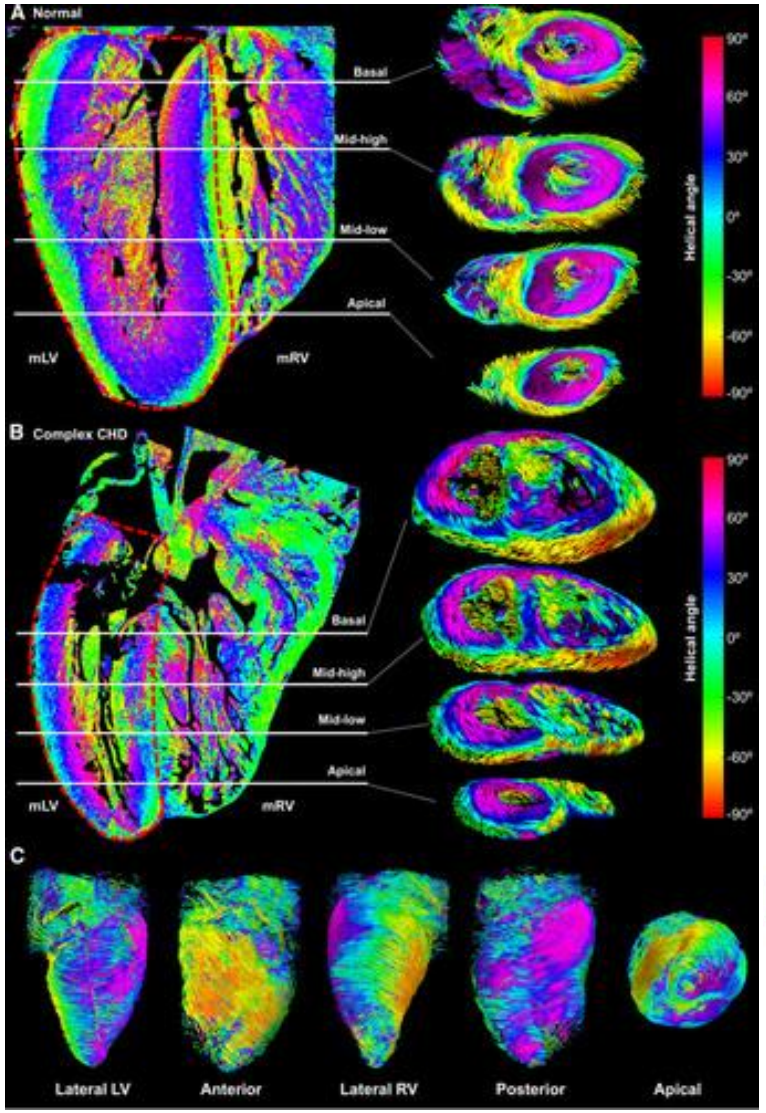
CONGENITAL HEART DISEASE IN HUMAN FETAL HEARTS

Fetal heart with complex CHD



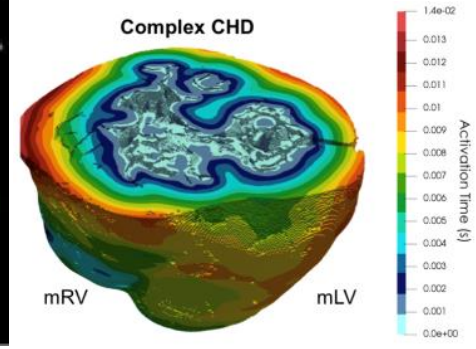
Conduction system





Quantification of helical angle

Simulation of electrical propagation



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P. Garcia-Canadilla et al, Circulation: Cardiovascular Imaging, 2018

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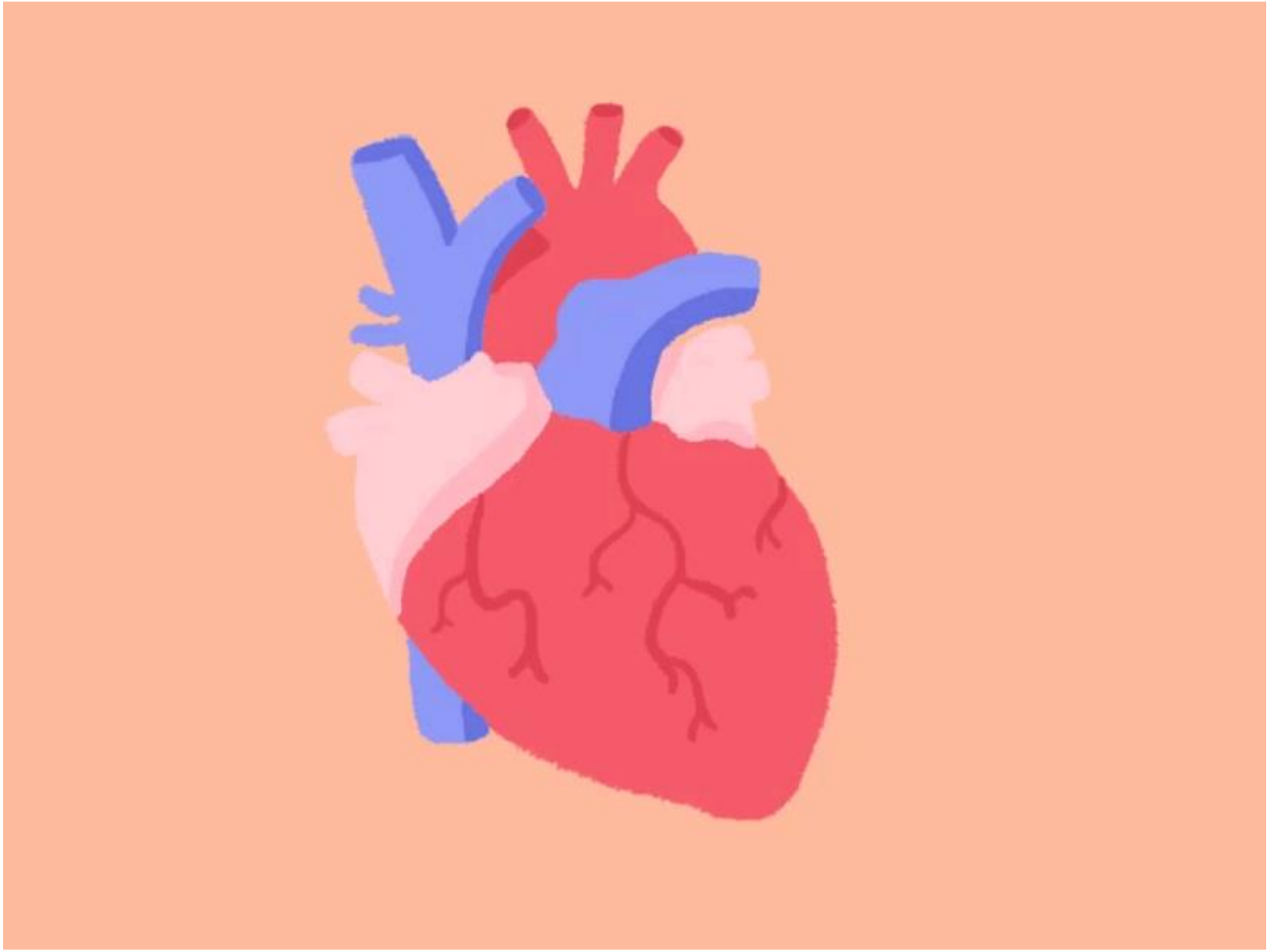
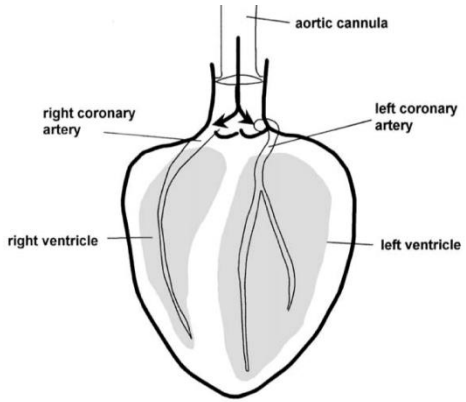
TOWARDS BEATING HEART STUDIES



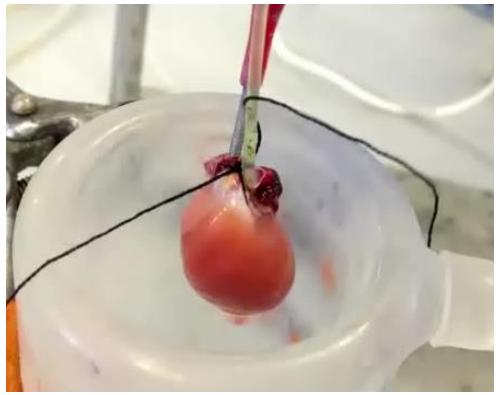
https://dribbble.com/shots/5510359-Beating-Heart

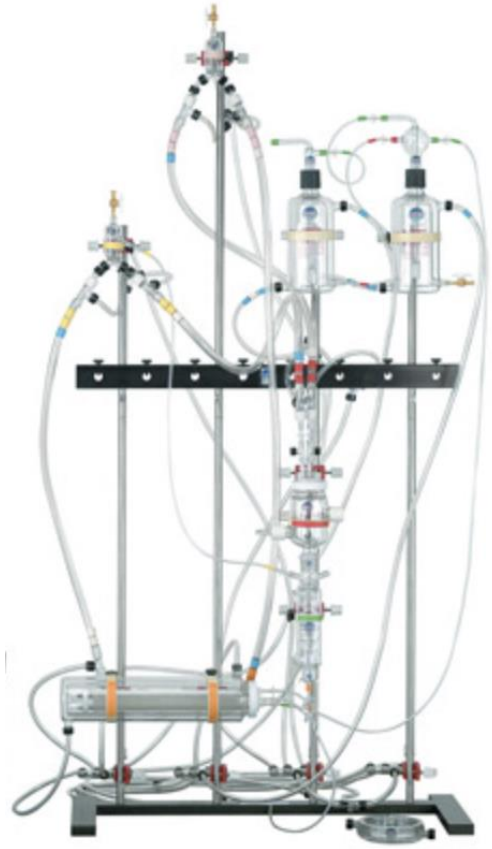
A TOMOGRAPHY-COMPATIBLE LANGENDORFF SYSTEM FOR THE STRUCTURAL CHARACTERIZATION OF THE CARDIAC CYCLE

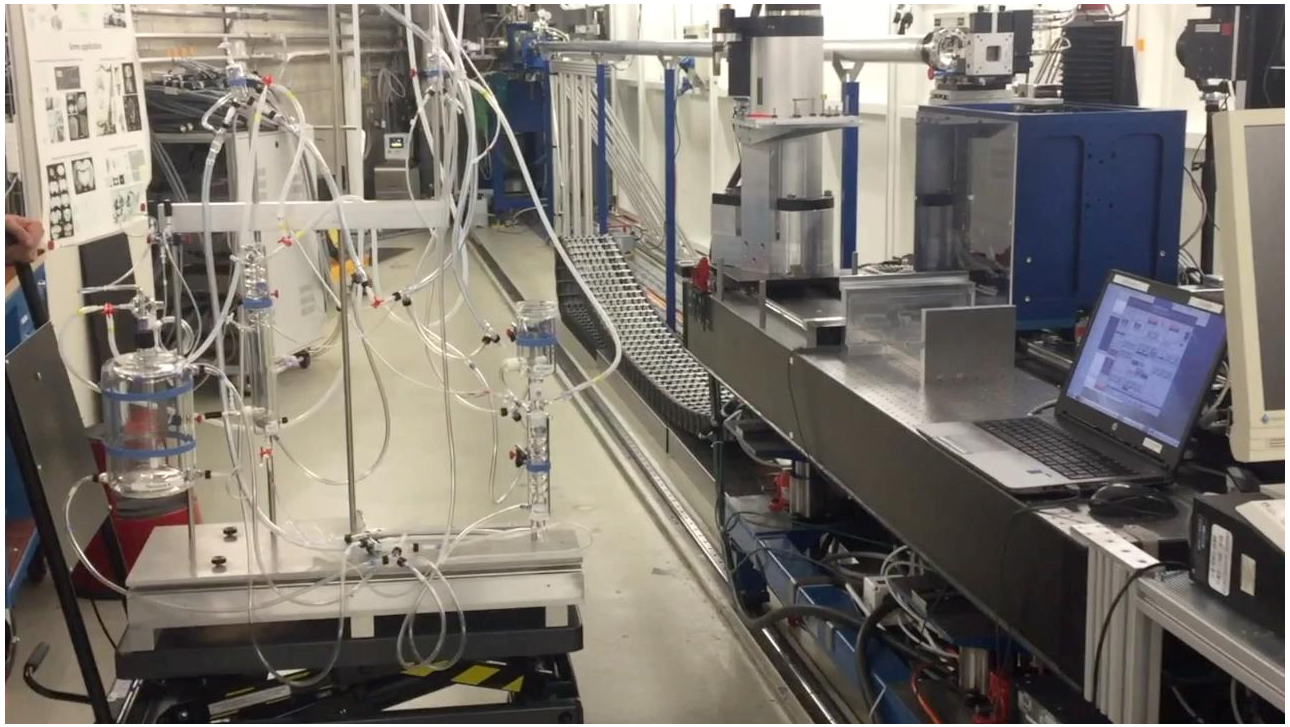
Strategic Focus Area
Personalized Health and Related Technologies



Dhein, The Langendorff heart, 2005

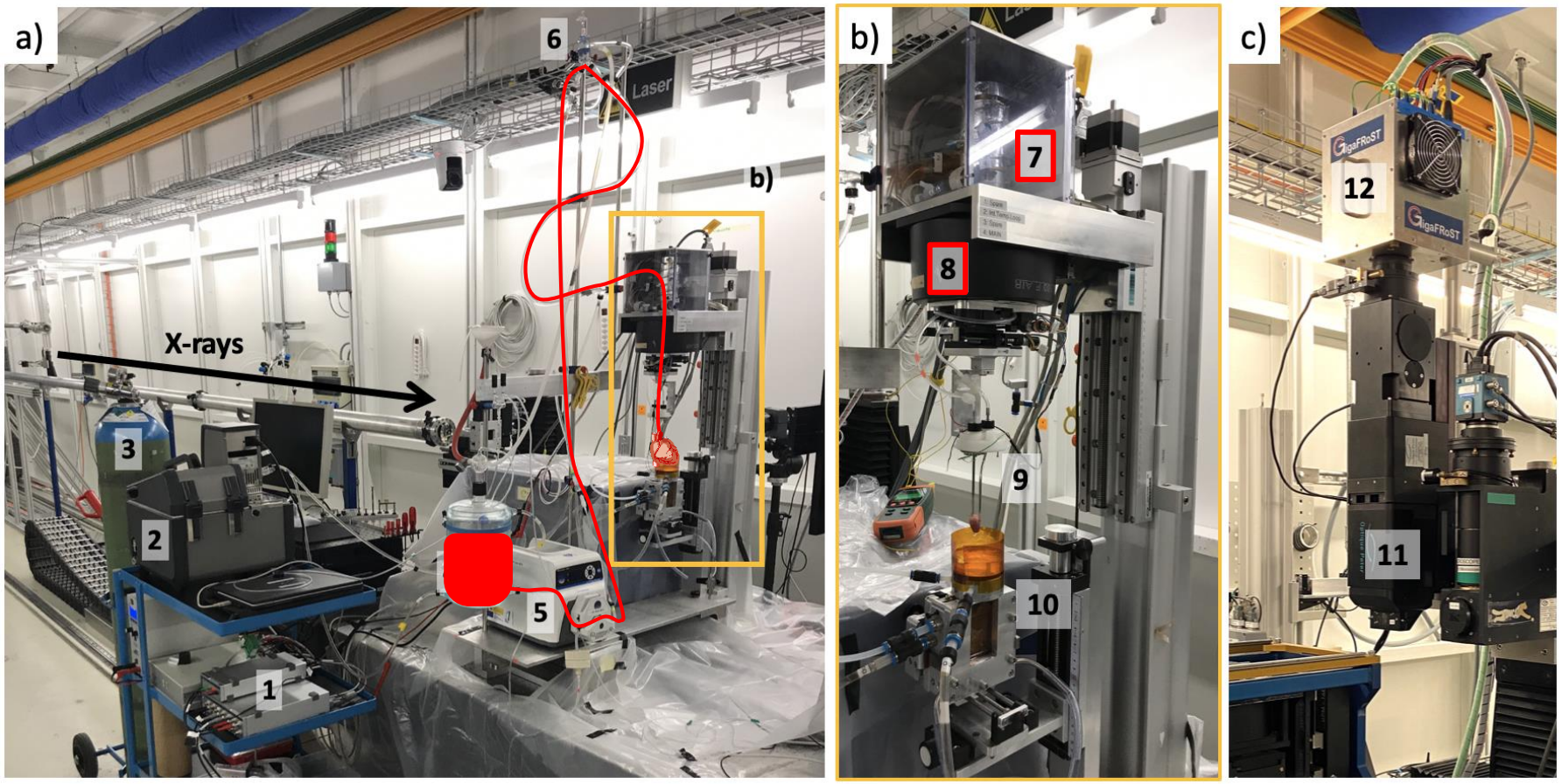






Dejea et al., Frontiers in Cardiovascular Medicine, 2022

SETUP AND ACQUISITION PROTOCOLS

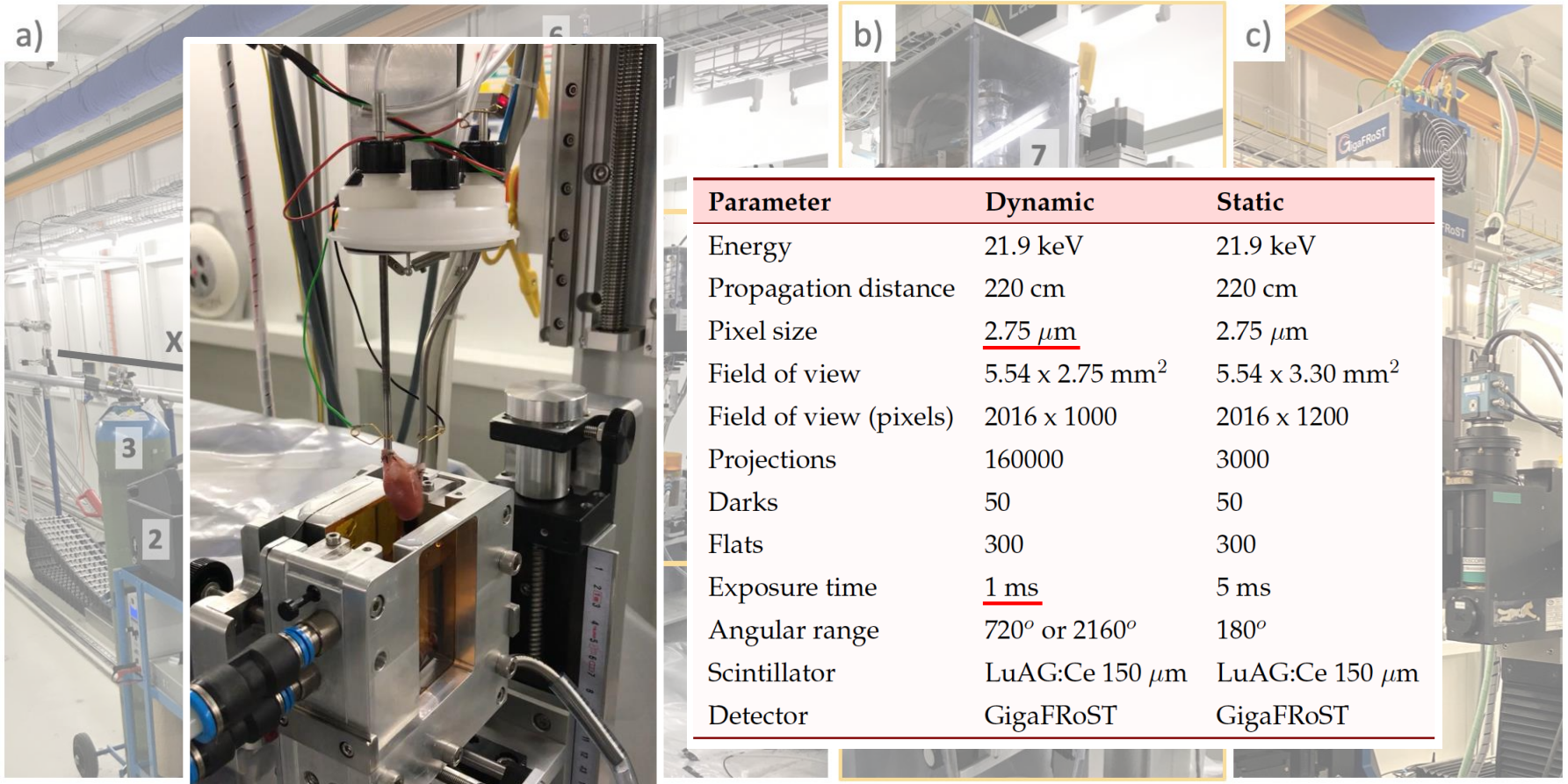


1: PowerLab data acquisition hardware.
2: Warm bath pump to keep the circuit at 37ºC.
3: 5% CO_2 gas bottle for perfusate oxygenation.
4: Perfusate reservoir.
5: Rotatory pump for perfusate circulation.
6: Compliance chamber.

7: Rotary union system.
8: Motor stage.
9: Modular sample holder with metallic cannulas.
10: Aquarium.
11: High-numerical aperture 4x macroscope[1].
12: GigaFRoST detector[2].

[1]Bührer et al, J Synchrotron Rad, 2019. [2]Mokso et al, J Synchrotron Rad, 2017.

SETUP AND ACQUISITION PROTOCOLS



Parameter	Dynamic	Static
Energy	21.9 keV	21.9 keV
Propagation distance	220 cm	220 cm
Pixel size	2.75 μm	2.75 μm
Field of view	5.54 x 2.75 mm^2	5.54 x 3.30 mm^2
Field of view (pixels)	2016 x 1000	2016 x 1200
Projections	160000	3000
Darks	50	50
Flats	300	300
Exposure time	1 ms	5 ms
Angular range	720^o or 2160^o	180^o
Scintillator	LuAG:Ce 150 μm	LuAG:Ce 150 μm
Detector	GigaFRoST	GigaFRoST

1: Pov
2: Wa
3: 5% CO_2 gas bottle for perfusate oxygenation.
4: Perfusate reservoir.
5: Rotatory pump for perfusate circulation.
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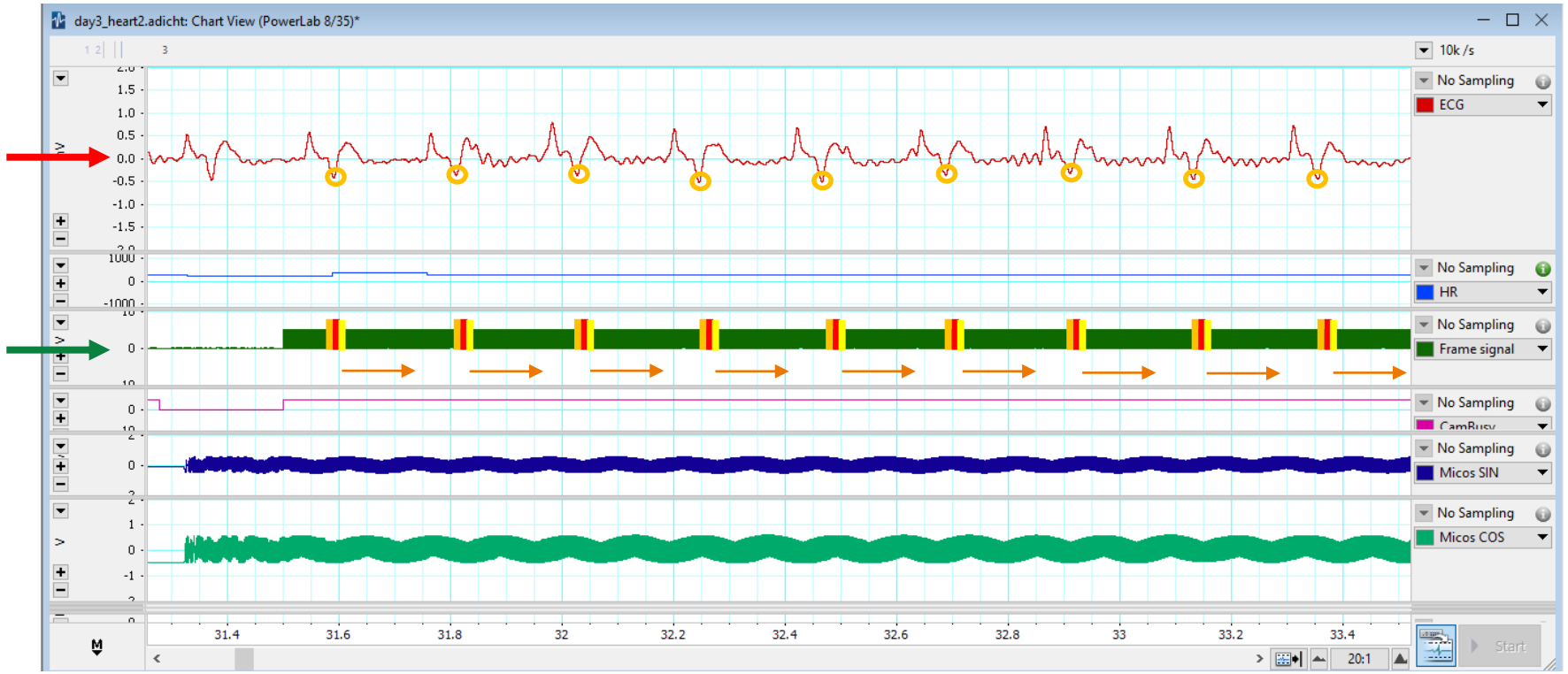
[1]Bührer et al, J Synchrotron Rad, 2019. [2]Mokso et al, J Synchrotron Rad, 2017.

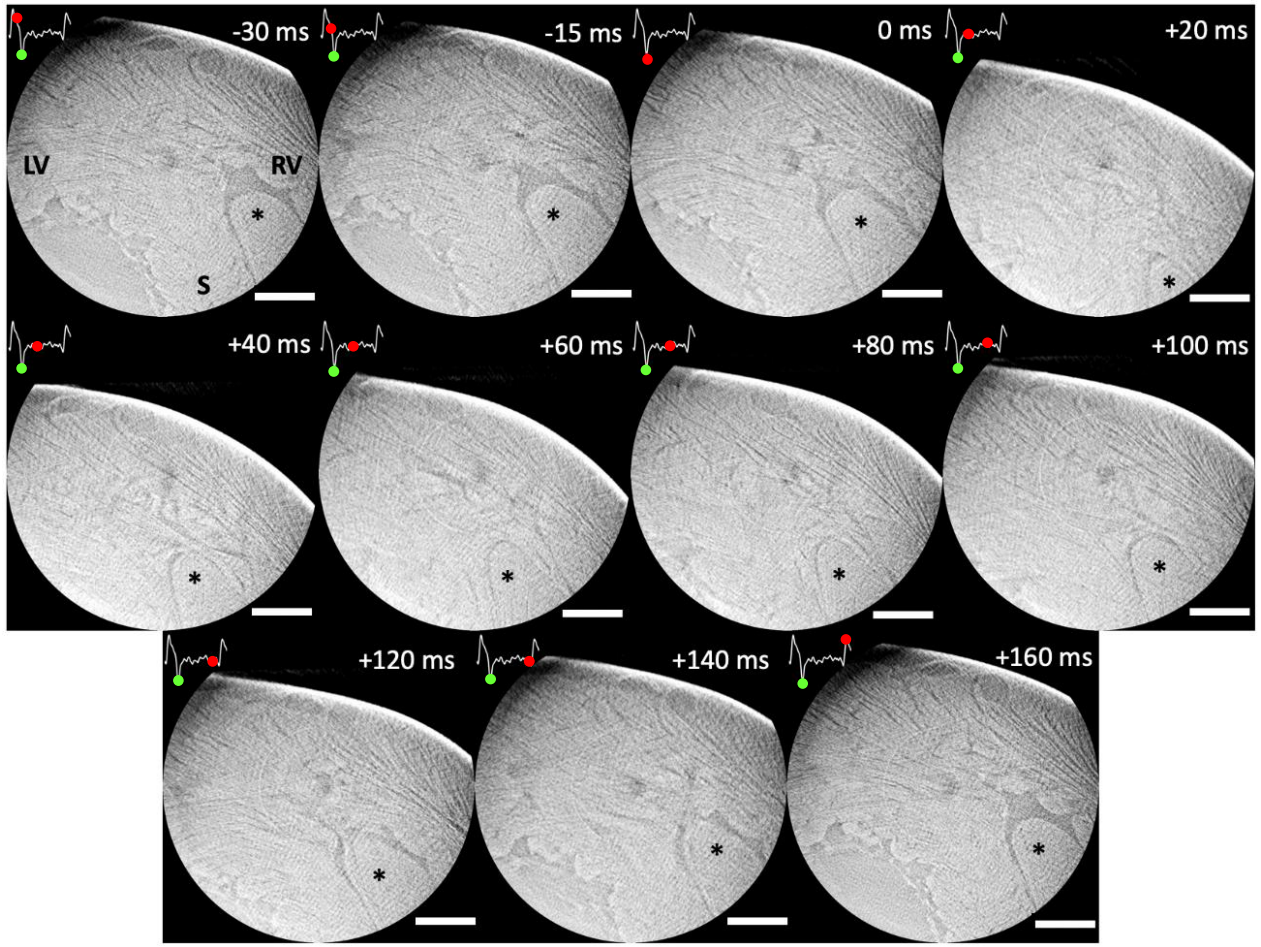
RETROSPECTIVE GATING AND RECONSTRUCTION

- Retrospective gating
  - Detection of start of contraction in ECG.
  - Dataset with corresponding projections and angles.
  - Apply time offset and create new dataset.
- Reconstruction
  - Dynamic flat field correction[1].
  - Gridrec algorithm[2] and Paganin[3].

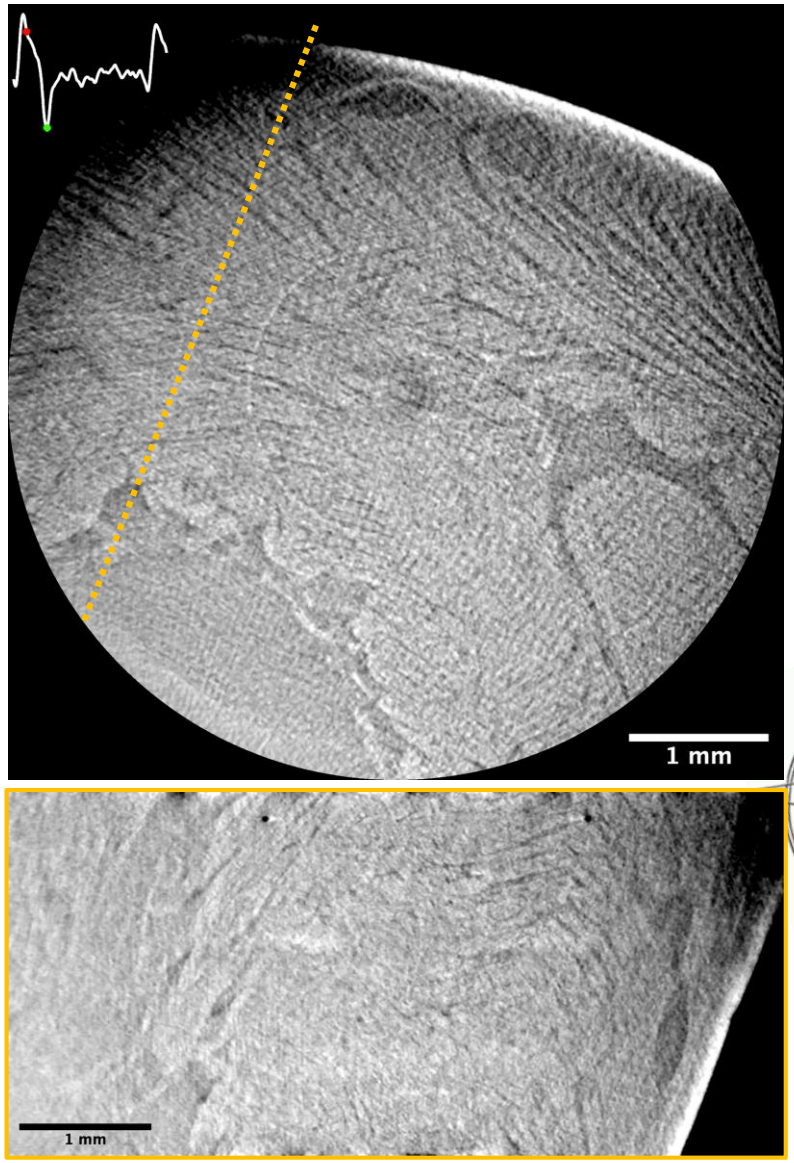


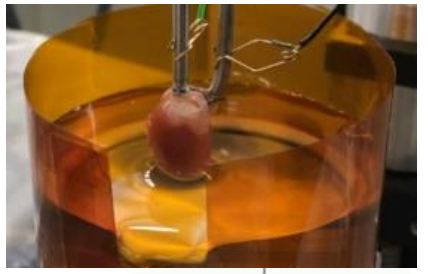
[1]Van Nieuwenhove et al, Opt Express, 2015. [2]Marone et al, J Synchrotron Rad, 2012, [3]Paganin et al, J Microsc, 2002.

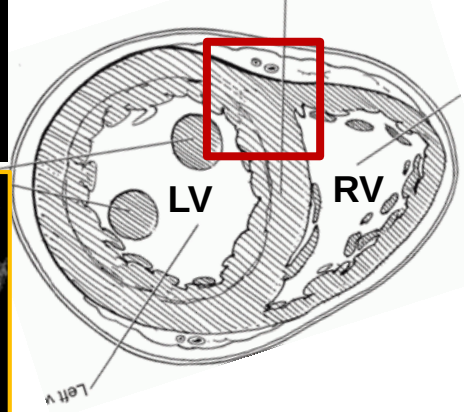
DYNAMIC BEATING HEART IMAGING



Time-series of a region of the beating rat heart. Start of the contraction at t = 0 ms. LV – Left Ventricle, RV – Right Ventricle, S – Septum, * - Right Ventricular Trabeculation Scale bar = 1 mm.





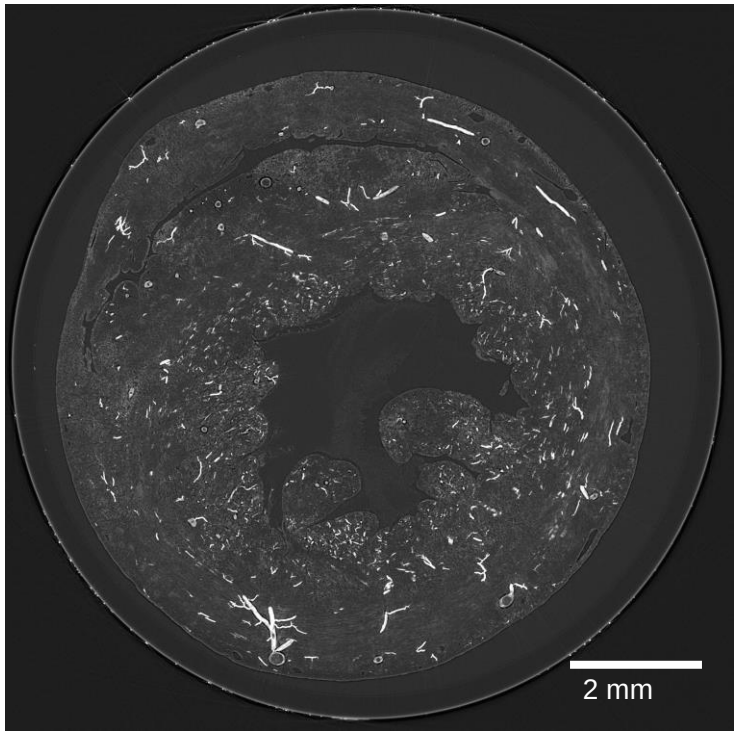


BEATING HEART STUDIES

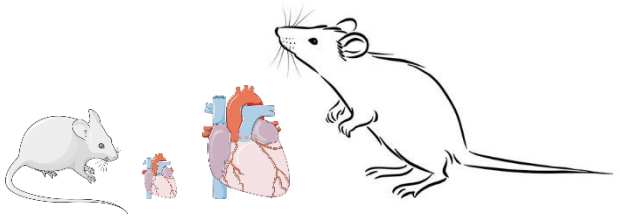
- Development of a unique tomography-compatible Langendorff system.
- Unprecedented dynamic high-resolution imaging of the beating heart.
- Arrest imaging indicates heterogeneous deformation during contraction.

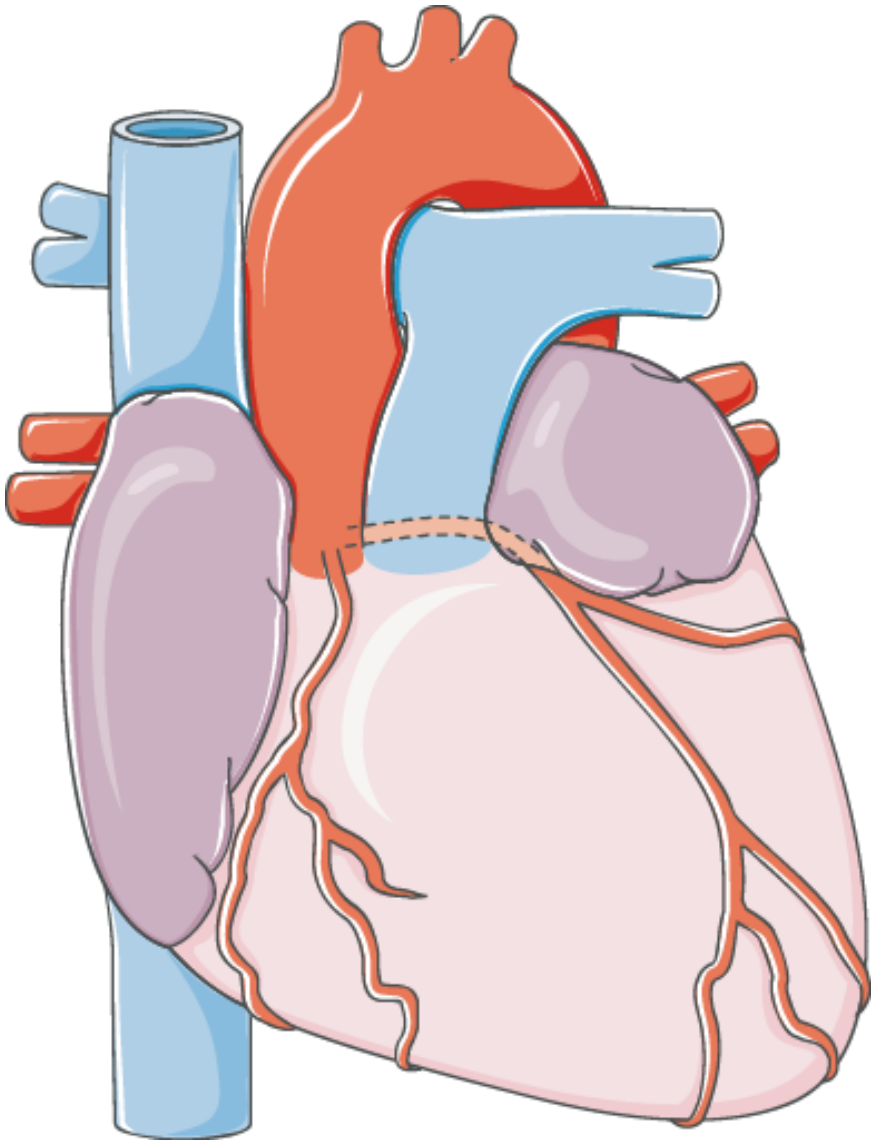
Outlook

- Overcome technical limitations with new equipment and iterative reconstruction algorithms.
- Investigation of dose effects on structure and function.
- Ischemia, pharmacology and angiography studies.

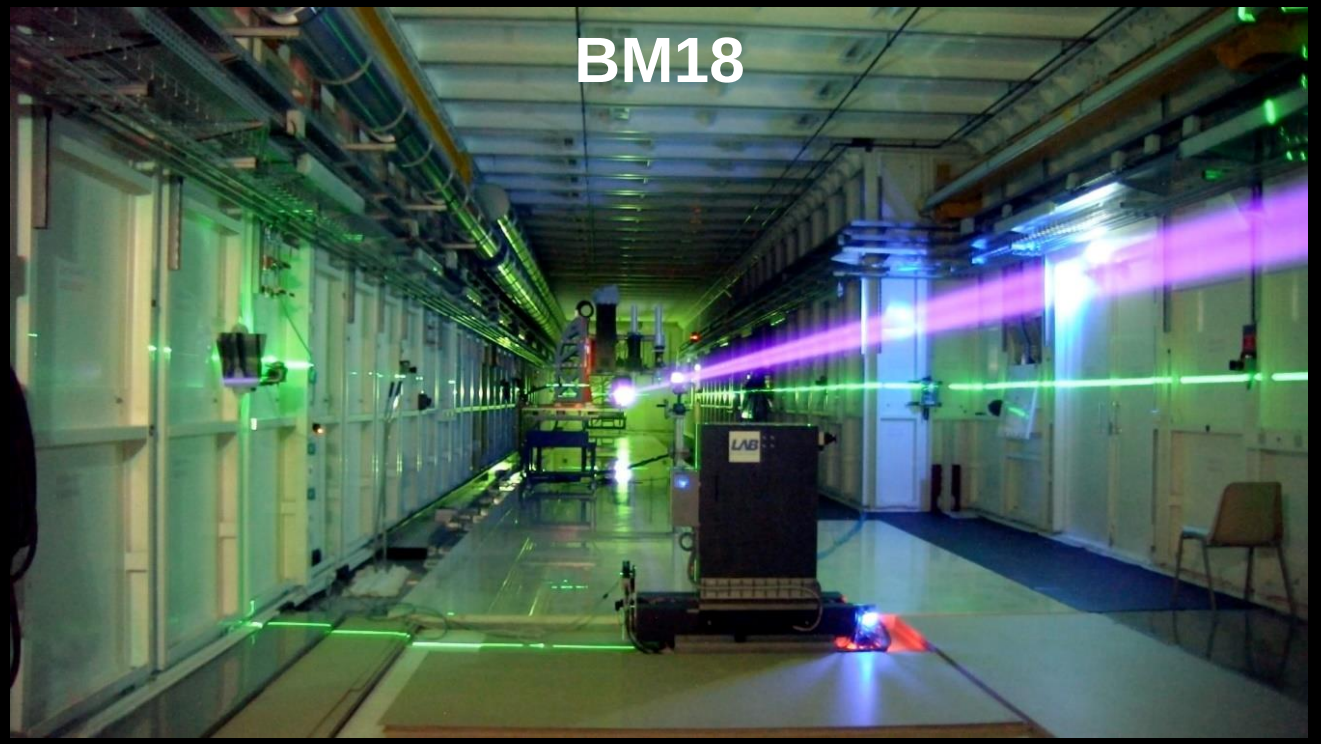


TOWARDS HUMAN STUDIES



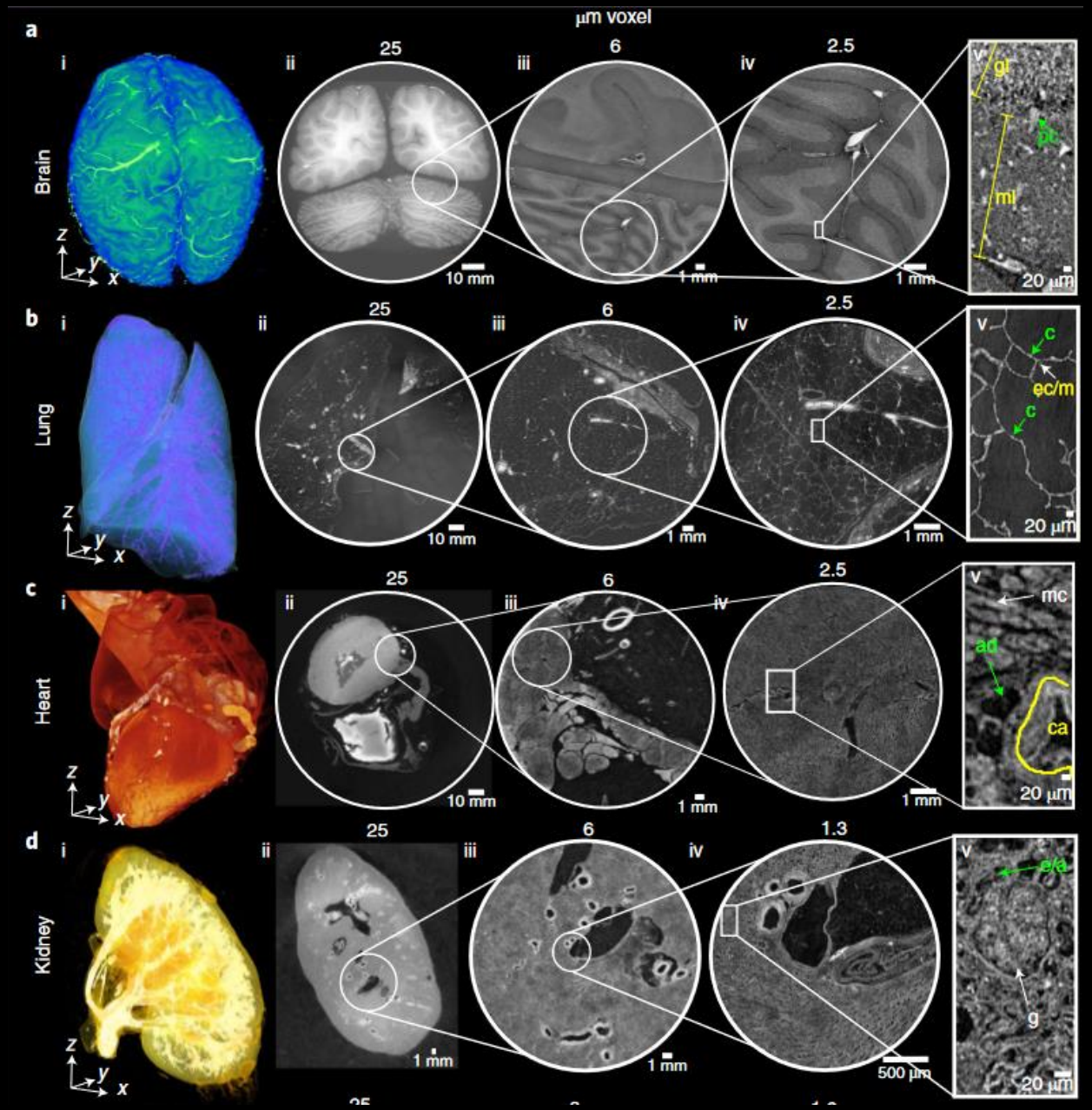


BM18: A BEAMLINE FOR HIERARCHICAL PHASE CONTRAST TOMOGRAPHY



Energy: 50-250 keV
Sample: 0.5m, 30 Kg (future 2.5m, 300 Kg)
Pixel size: 0.7 – 160 um
Propagation distance: 0-38 m

HIERARCHICAL PHASE CONTRAST TOMOGRAPHY (HIP-CT)



Human Organ Atlas Hub

https://mecheng.ucl.ac.uk/HOAHub/

Walsh et al., Nature Methods, 2021

HIP-CT PROTOCOL: SAMPLE PREPARATION

Autopsy → Formalin fix → EtOH series 50,60,70% → Mount in 70% EtOH-agar

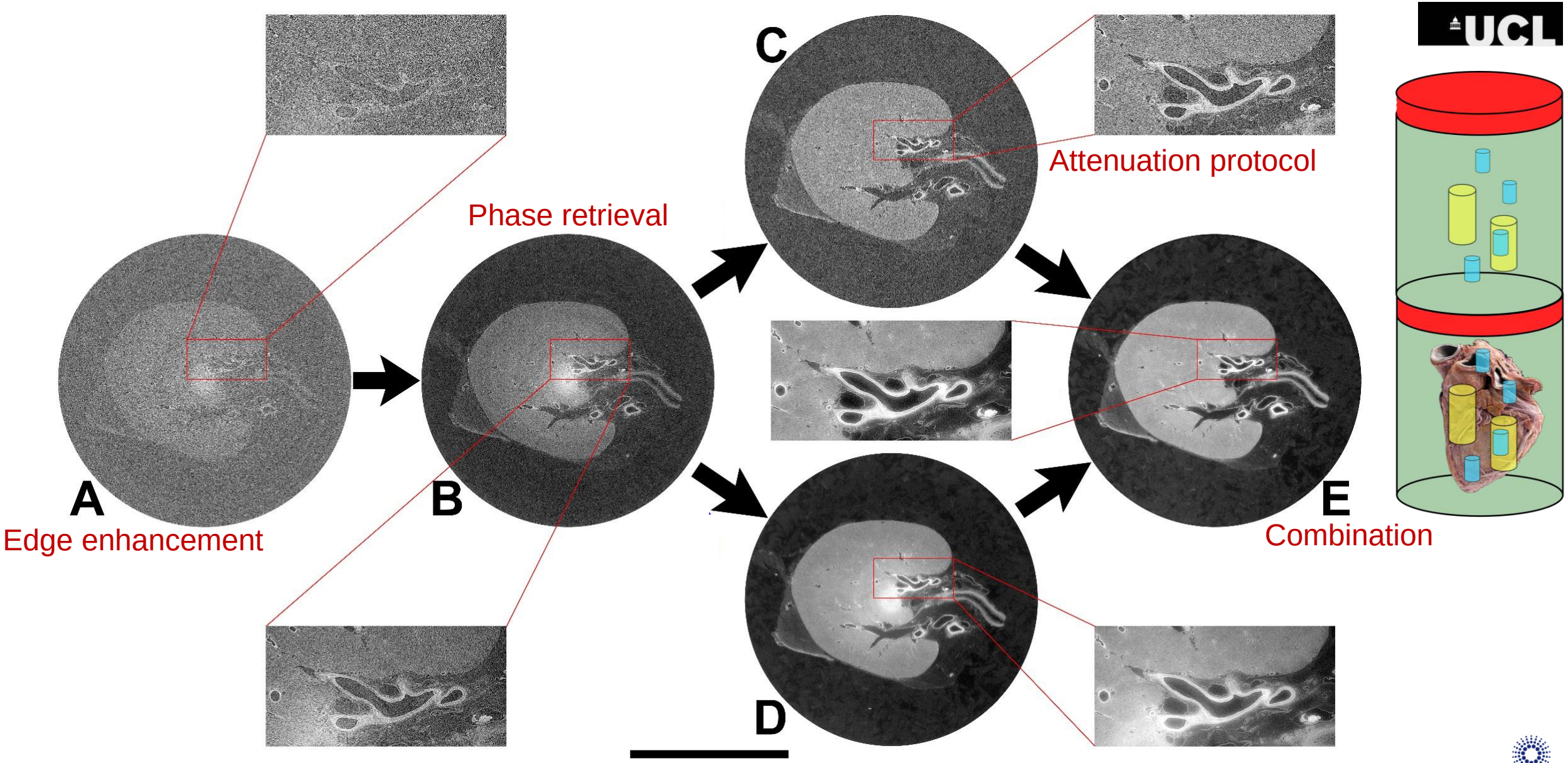
Approx. 20 days

Vacuum degassing

In-line degassing

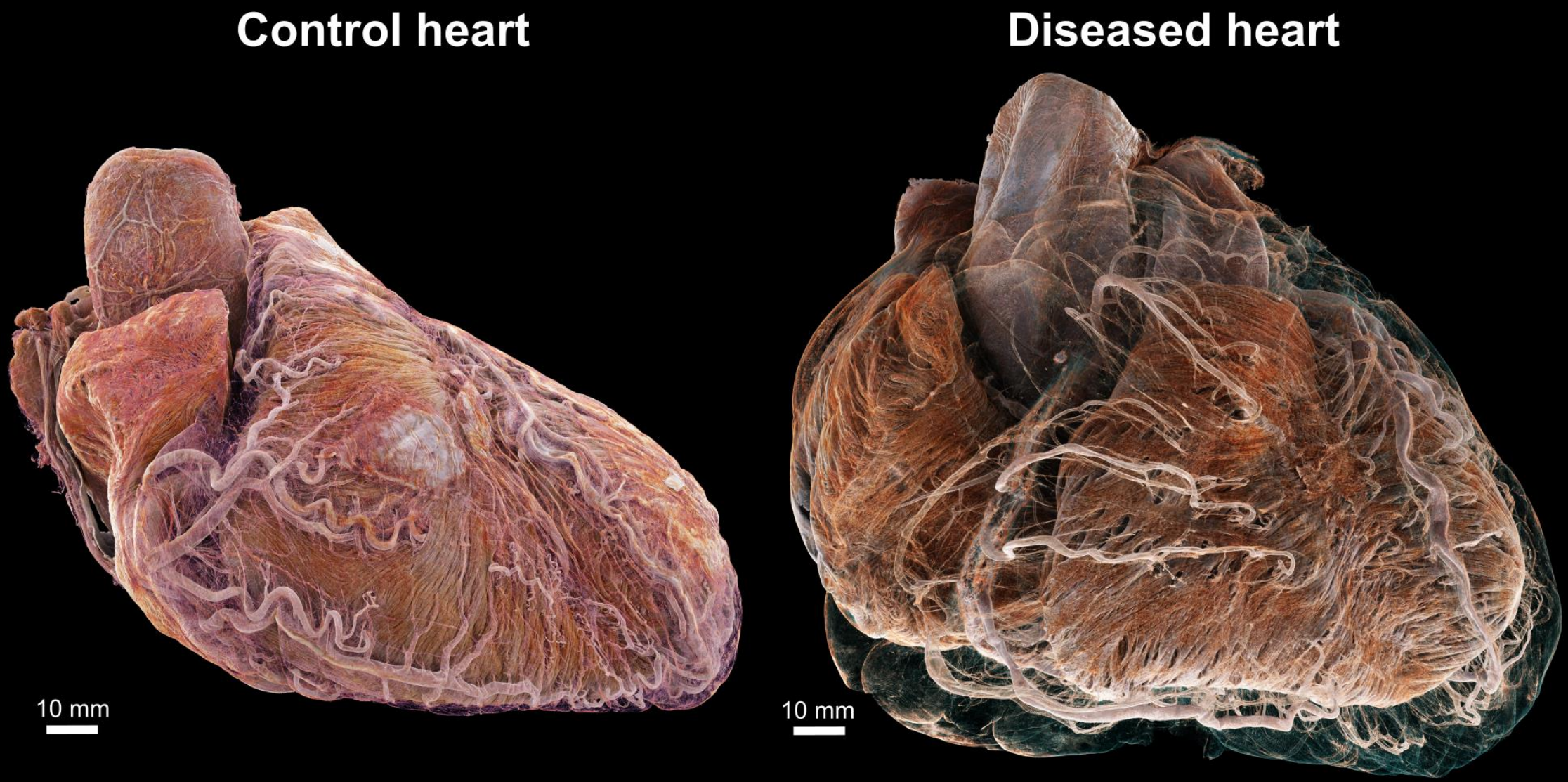
Walsh et al., Nature Methods, 2021
Brunet et al., Nature Protocols, 2023

COMBINING PHASE RETRIEVAL, ATTENUATION PROTOCOL AND DYNAMIC RANGE OPTIMIZATION



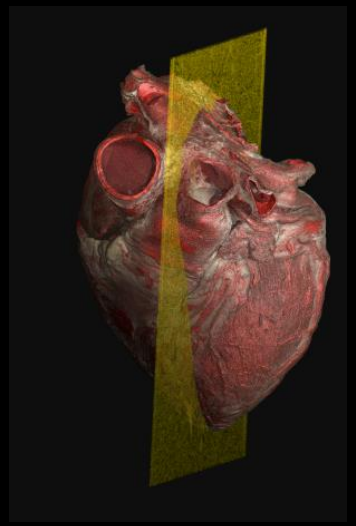
Walsh et al., Nature Methods, 2021
Brunet et al., Nature Protocols, 2023

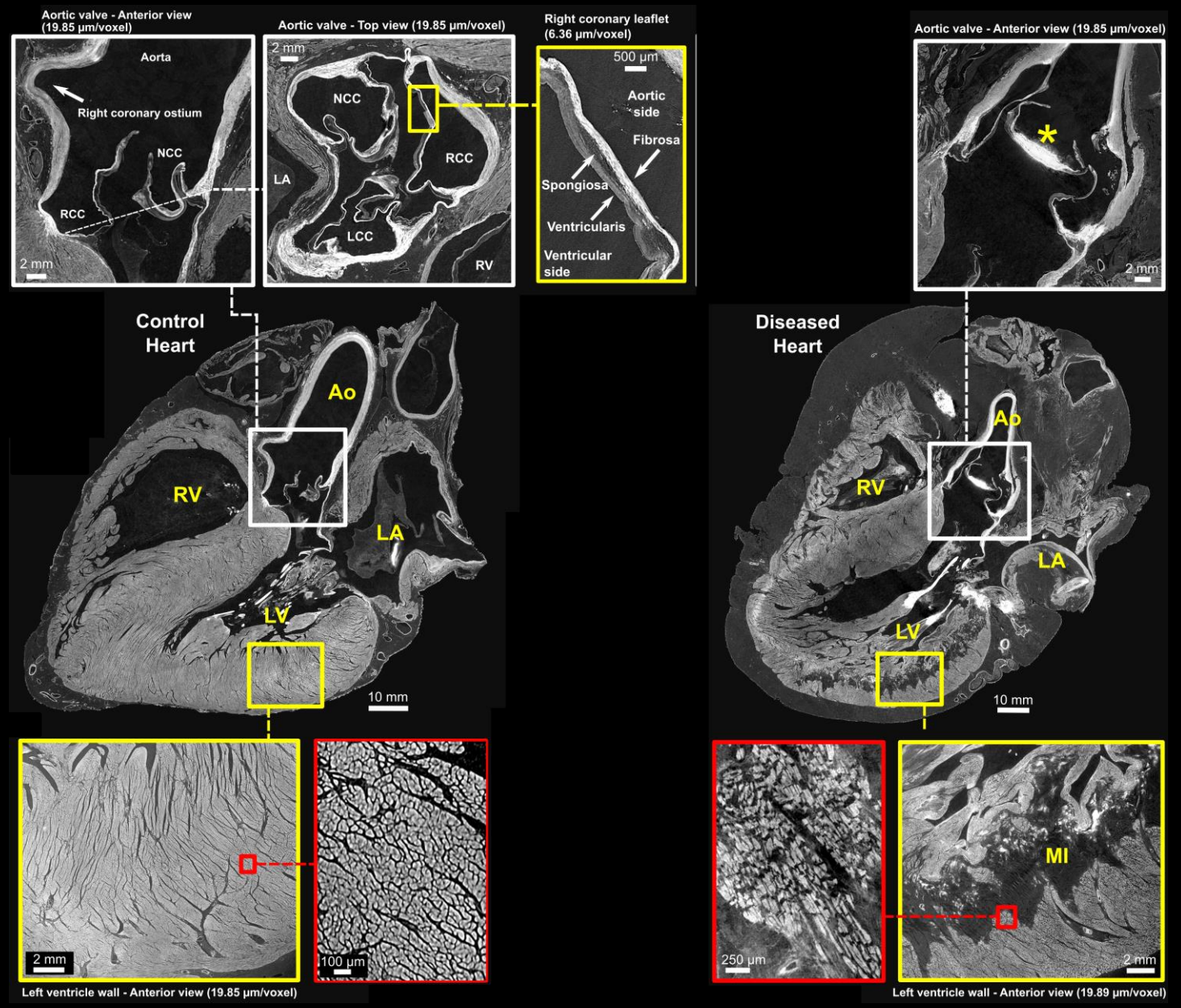
ADULT HUMAN HEARTS IN HEALTH AND DISEASE



Brunet et al., Radiology, 2024

ADULT HUMAN HEARTS IN HEALTH AND DISEASE





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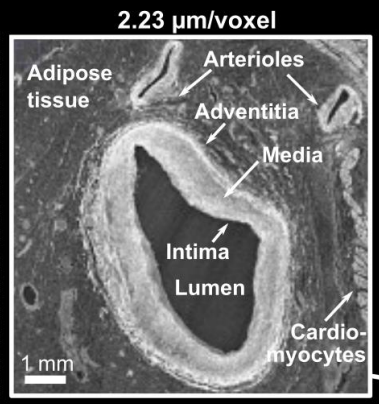
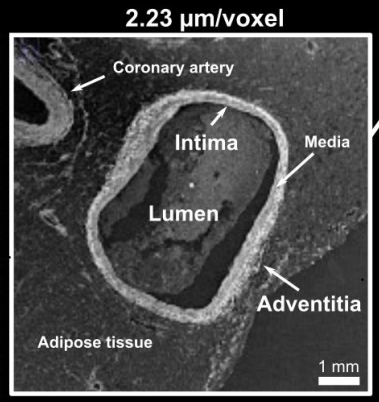
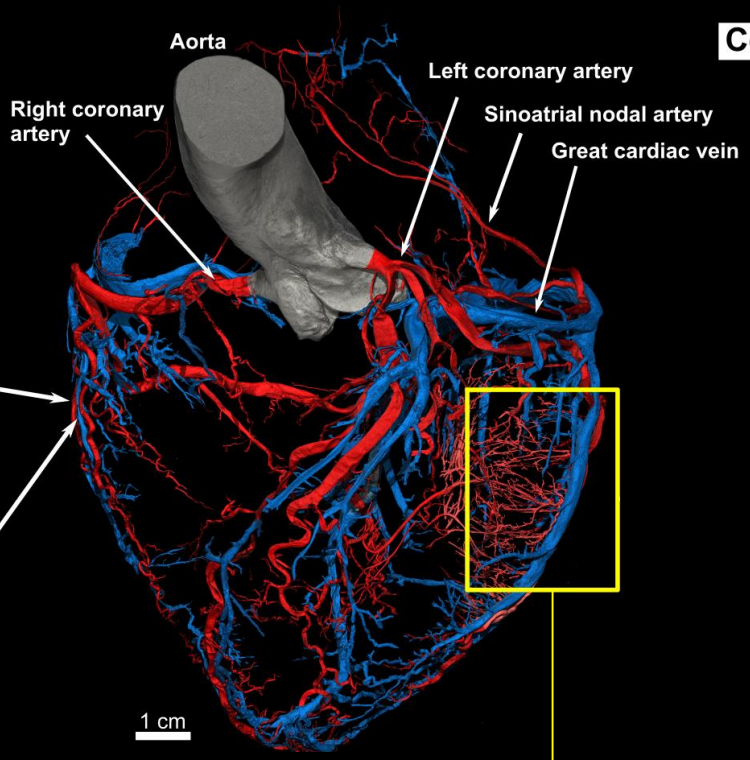
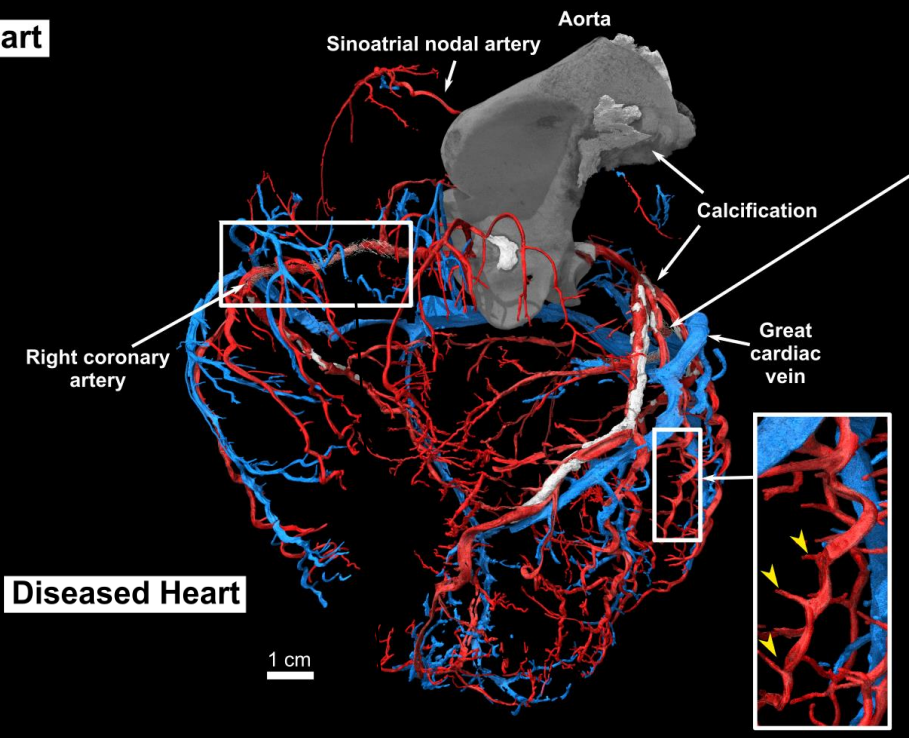
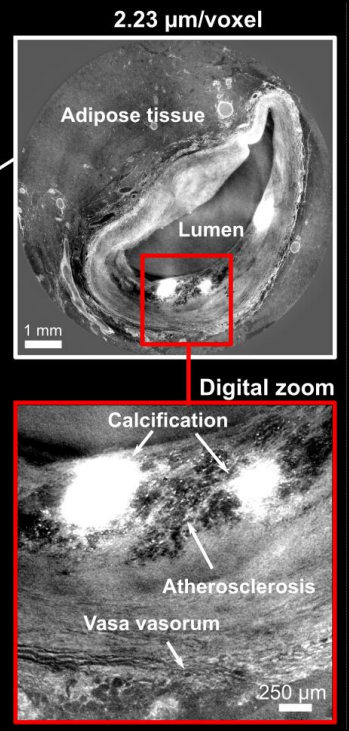
ADULT HUMAN HEARTS IN HEALTH AND DISEASE

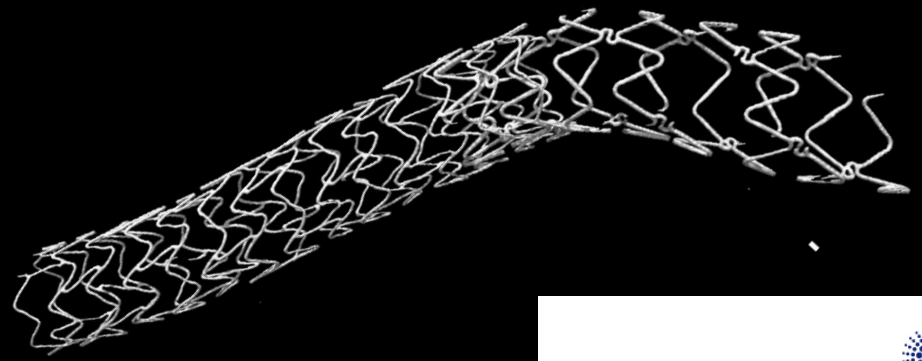












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The Human Organ Atlas

Public database with healthy and diseased organs

https://mecheng.ucl.ac.uk/HOAHub/
https://human-organ-atlas.esrf.eu/

Human Organ Atlas | EXPLORE | SEARCH

Patients

FO-20.129
male | 54 yo
died from COVID-19 21 days after hospitalisation, mechanical ventilation, pulmonary failure, renal failure,bacterial pneumonia with Klebsiella aerogenes, general brain edema, subarachnoidal and intracranial bleeding

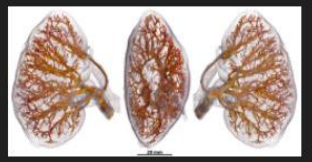
LADAF-2020-27
female | 94 yo | 45 kg | 140 cm
right sylvian and right cerebellar stroke, cognitive disorders of vascular origin, depressive syndrome, atrial fibrillation and hypertensive heart disease, micro-crystalline arthritis (gout), right lung pneumopathy (3 before death), cataract of the left eye, squamous cell carcinoma of the skin (left temporal region)

LADAF-2020-31
female | 69 yo | 40 kg | 145 cm
type 2 diabetes, pelvic radiation to treat cancer of the uterus, right colectomy (benign lesion on histopathology), bilateral nephrostomy for acute obstructive renal failure, cystectomy, omentectomy and peritoneal carcinoma with occlusive syndrome

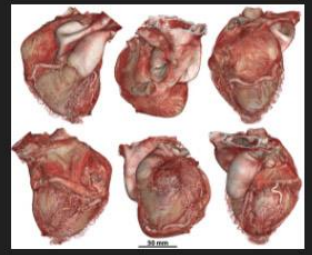
GLR-163
male | 77 yo
resection of the lower lobe segment 6 due to small pulmonary adenocarcinoma (1.4), coronary heart disease, arterial hypertension, chronic rheumatic disease (polymyalgia rheumatica)

Organs

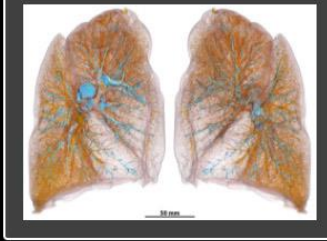
kidney



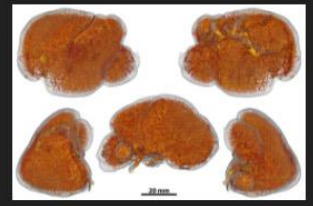
heart



lung

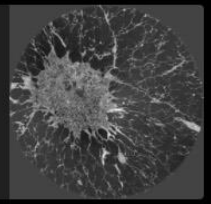


spleen

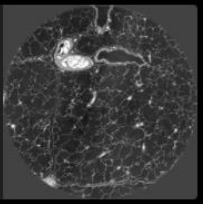


Datasets

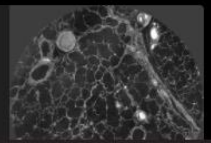
2.45um_VOI-01_upper-lobe-apical
Vertical column in local tomography at 2.45um pixe size performed by HiP-CT on the beamline BM05 of the left lung from the body donor LADAF-2020-27 using half-acquisition protocol.



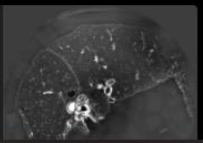
2.45um_VOI-02_lower-lobe-basal
Vertical column in local tomography at 2.45um pixe size performed by HiP-CT on the beamline BM05 of the left lung from the body donor LADAF-2020-27 using half-acquisition protocol.



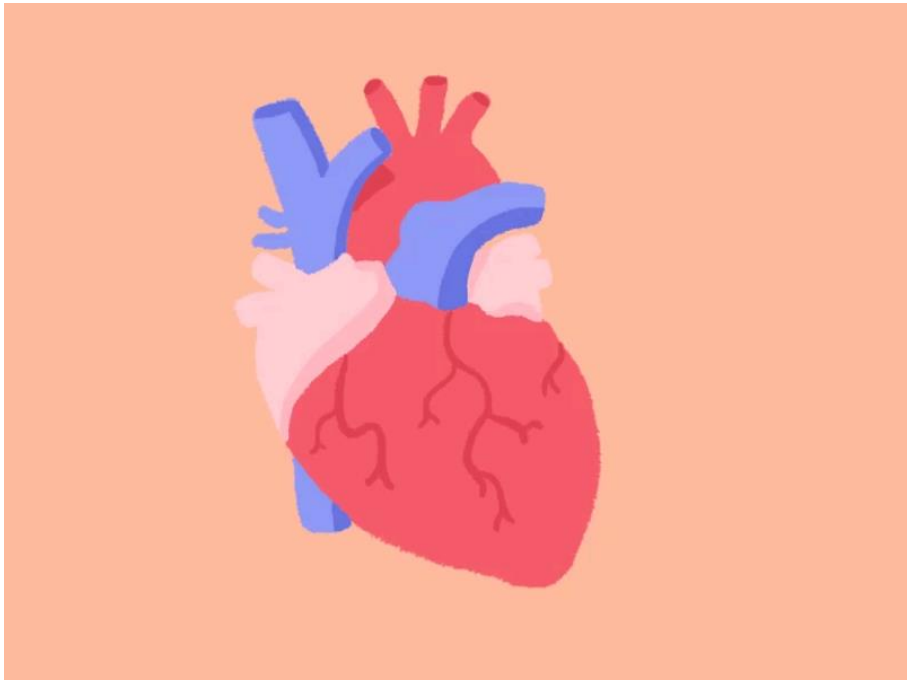
2.45um_VOI-06_lower-lobe-basal
Vertical column in local tomography at 2.45um pixe size performed by HiP-CT on the beamline BM05 of the left lung from the body donor LADAF-2020-27 using half-acquisition

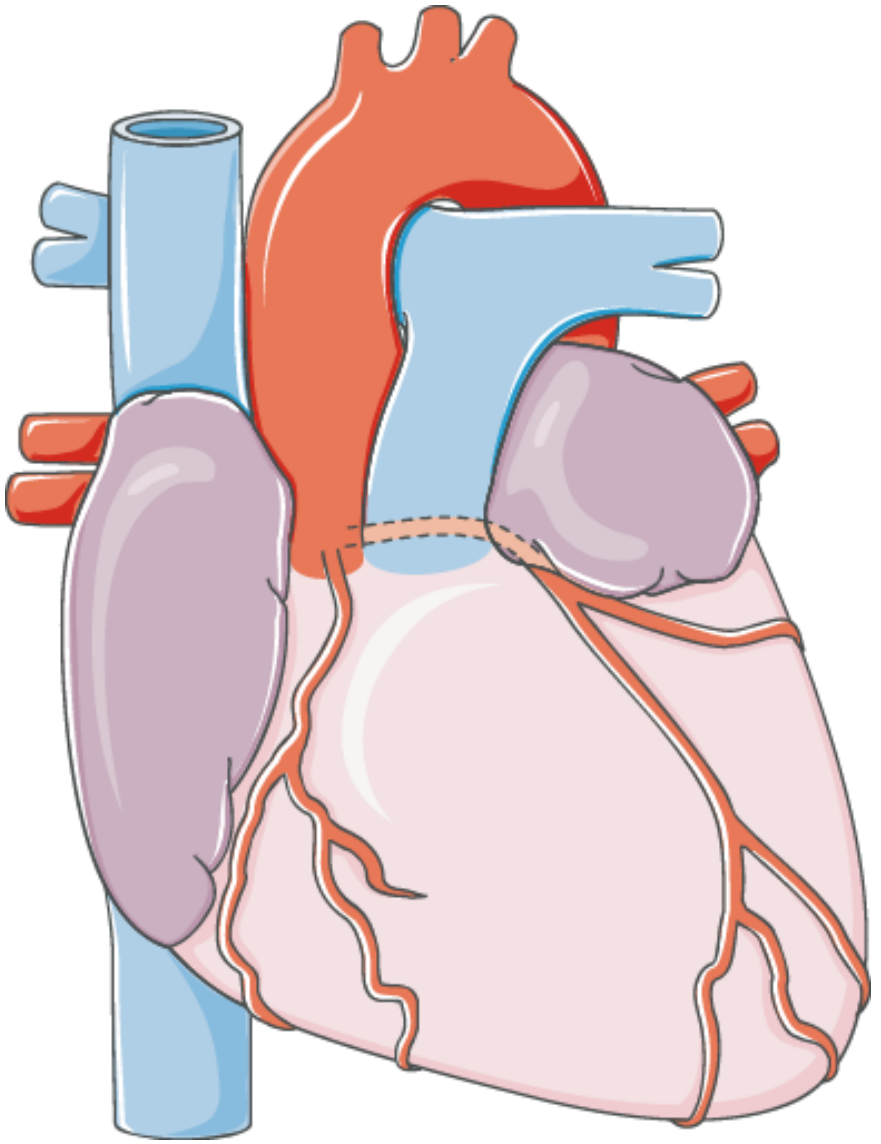


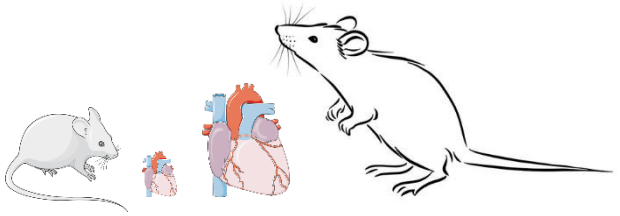
25.08um_complete-organ [2021-10-07 14:06:38]
Complete scan at 25.08um performed by HiP-CT on the beamline BM05 of the left lung from the body donor LADAF-



SUMMARY







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- Dr. Theresa Urban

- Prof. Dr. Alexandre Bellier

- Prof. Dr. Sarah Longnus

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PIONEERING SYNCHROTRON SCIENCE

THANK YOU FOR YOUR ATTENTION

HiP-CT: https://mecheng.ucl.ac.uk/hip-ct/
HOAHub: https://mecheng.ucl.ac.uk/HOAHub/
HOA database: https://human-organ-atlas.esrf.eu/

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Phase contrast radiograph