Preclinical X-Ray Computed Tomography

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dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Is CT a Molecular Imaging Modality?

Imaging Modality	Molecular Sensitivity	Reference
PET	10^{-11}-10^{-12} mol/L	1
SPECT	10^{-10}-10^{-11} mol/L	1
Bioluminescence Imaging	10^{-9}-10^{-11} mol/L	2
Ultrasound	10^{-8} mol/L	3
MRI	10^{-3}-10^{-5} mol/L	1
CT	10^{-3} mol/L	4

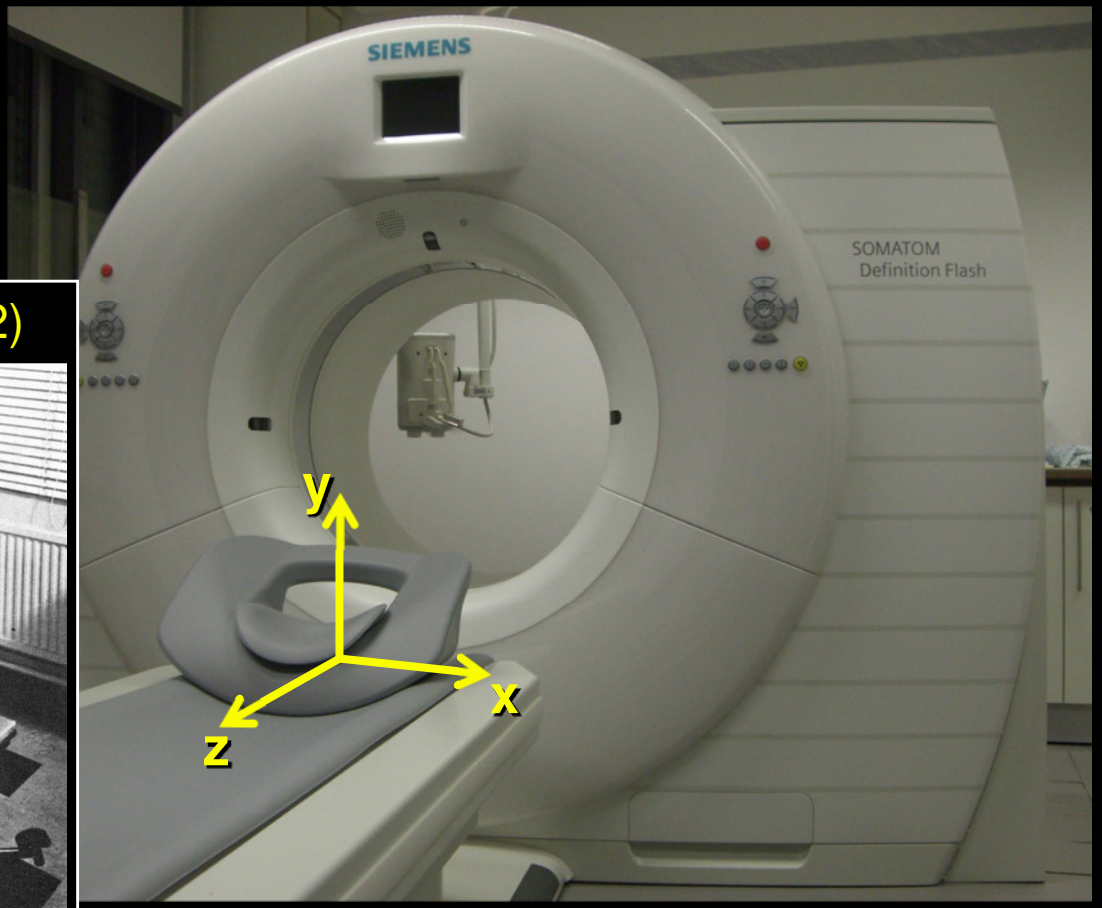
1 C. S. Levin, "New Imaging Technologies to Enhance the Molecular Sensitivity of Positron Emission Tomography," Proc. IEEE 96(3), 439-467 (2008).

2 D. S. Wang, M. D. Dake, J. M. Park, and M. D. Kuo, "Molecular Imaging: A Primer for Interventionalists and Imagers," J. Vasc. Interv. Radiol. 17, 1405-1423 (2006).

3 G. Schmitz, "Ultrasonic imaging of molecular targets," Basic Res. Cardiol. 103, 174-181 (2008).

4 L. Fass, "Imaging and cancer: A review," Molecular Oncology 2, 115-152 (2008).

Siemens 2·2·64=256-slice dual source cone-beam spiral **CT**(2008)



1152 views per rotation in 0.28 s

2·64×(736+480) 2-byte channels per view

600 MB/s data transfer rate

5 GB data size typical

EMI parallel beam scanner (1972)

180 views per rotation in 300 s

2×160 positions per view

384 B/s data transfer rate

113 kB data size

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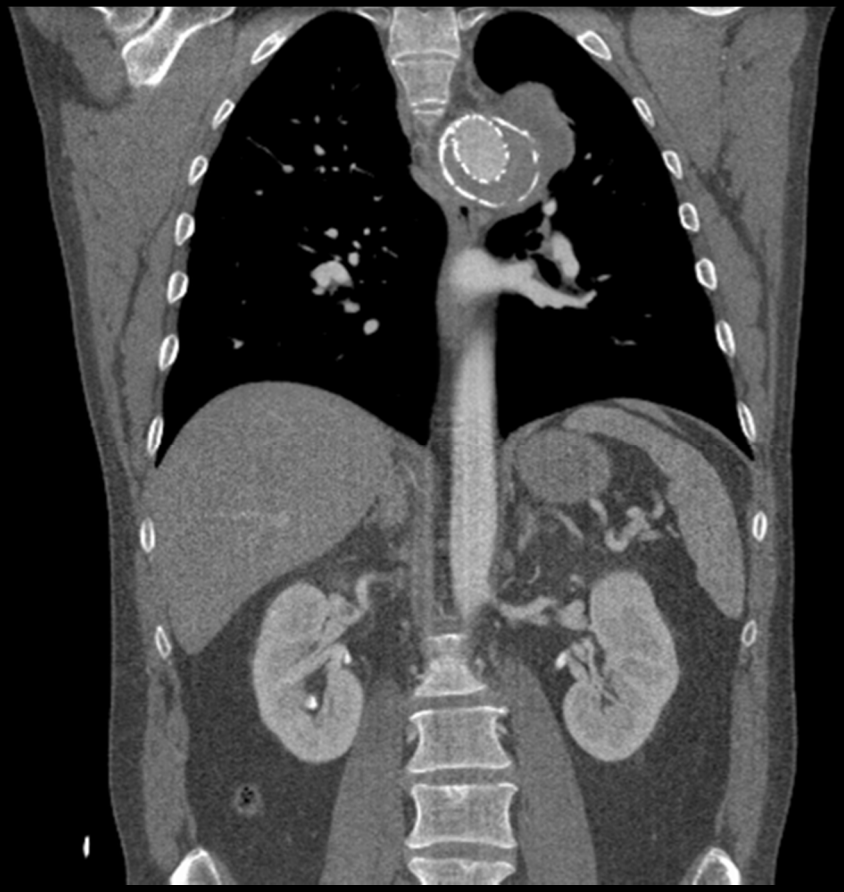
Siemens 2·2·64=256-slice dual source cone-beam spiral **CT**(2008)



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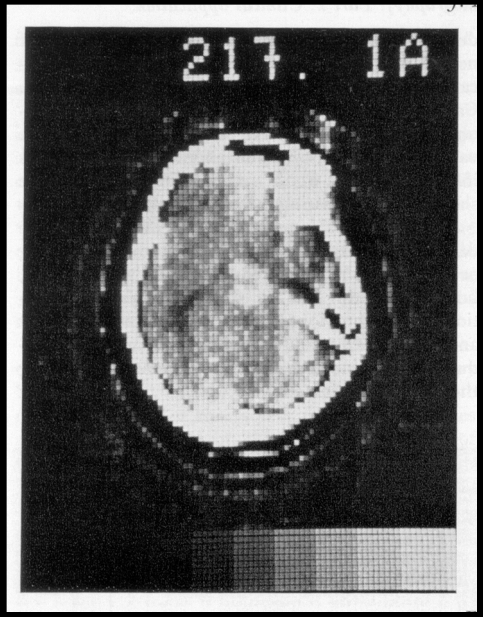

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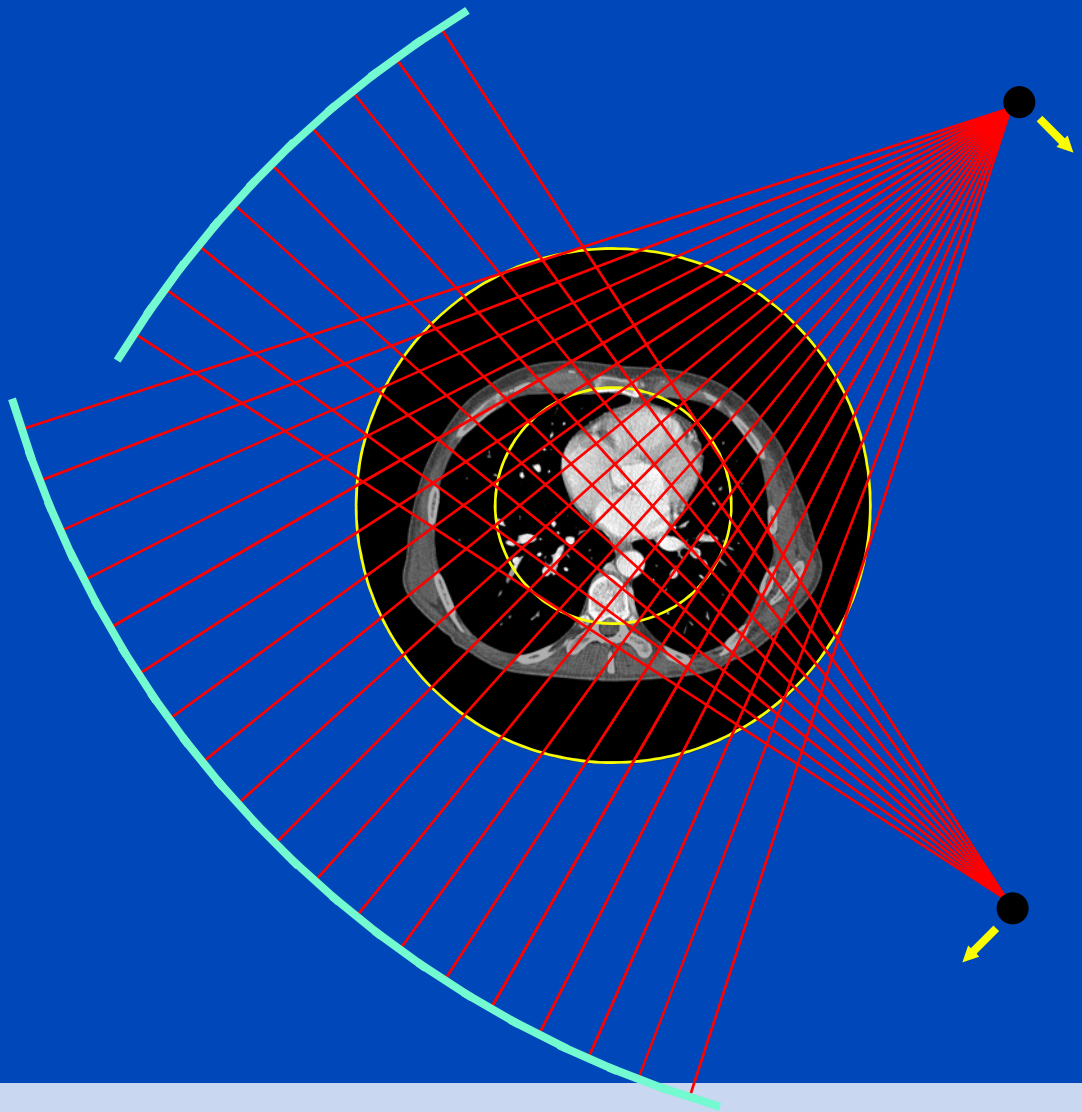
GE Discovery

Toshiba Aquilion ONE Vision

Philips Brilliance iCT

Siemens Definition Flash

Multi-Threaded CT Scanners and Dual-Source-CT



Siemens SOMATOM Definition Flash dual source cone-beam spiral CT scanner

Dual-Source-CT

Flash Mode

280 ms Rotation

Partial scan reconstruction

70 ms temporal resolution

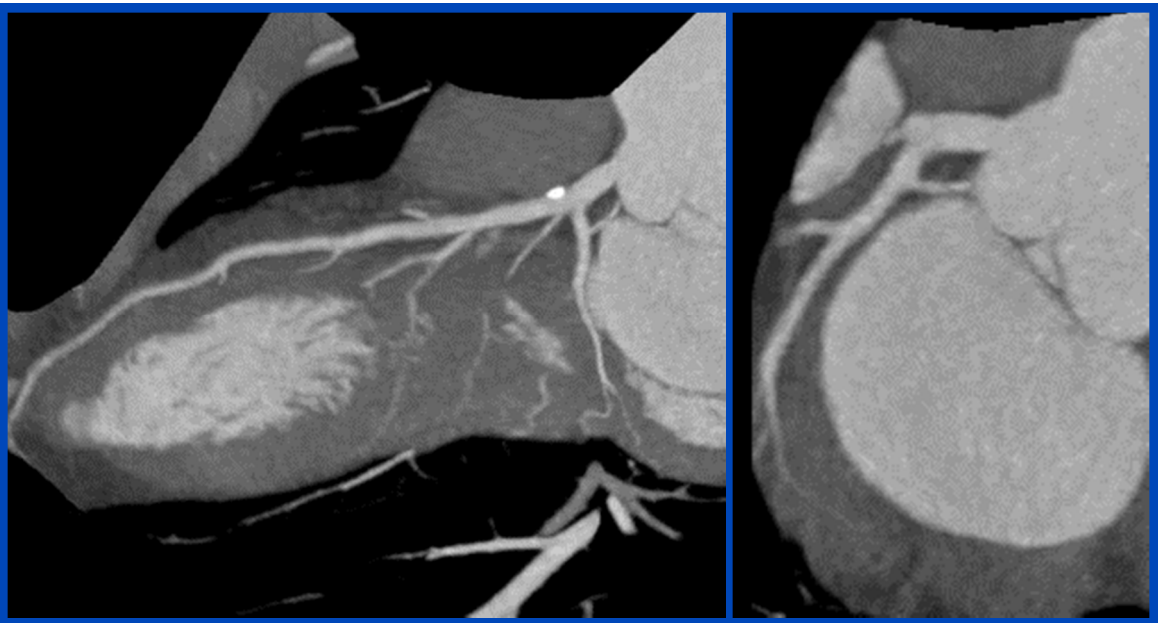
Pitch = 3.2 (43 cm/s)

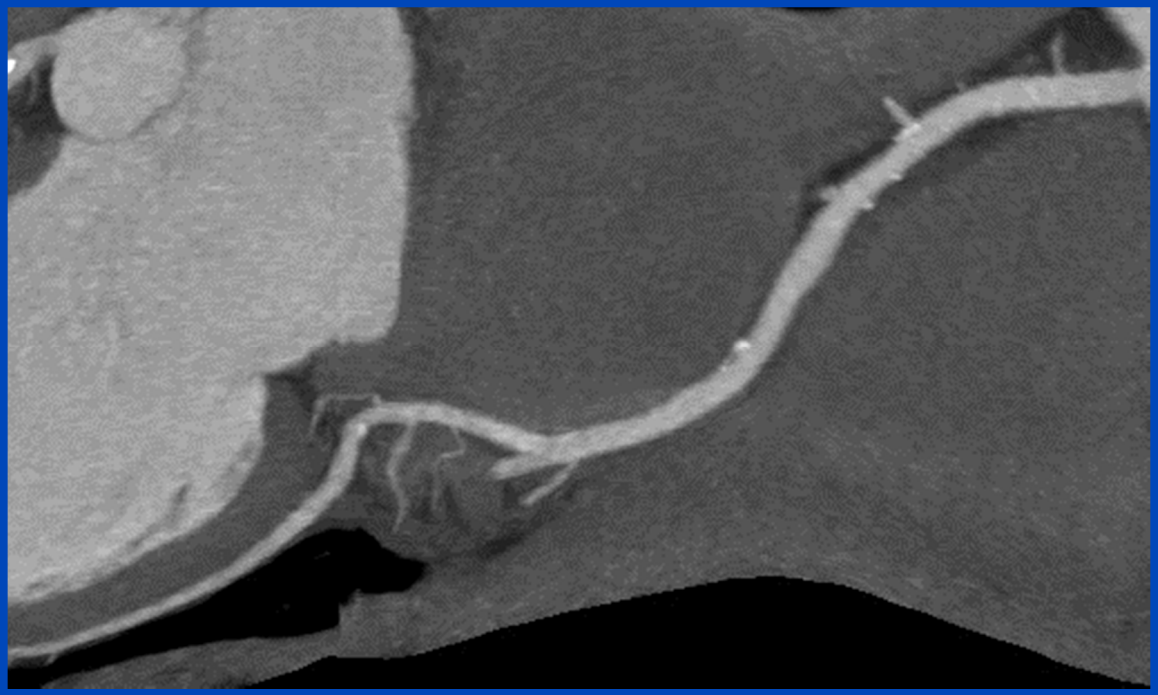
320 mAs, 100 kV

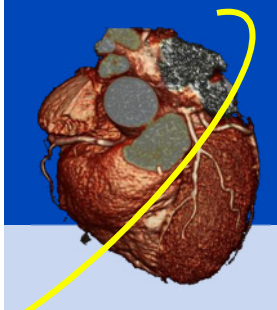
10.6 cm scan range

DLP = 64 mGy·cm

D_{eff} = 0.89 mSv







Data courtesy of Dr. Stephan Achenbach, Erlangen, Germany

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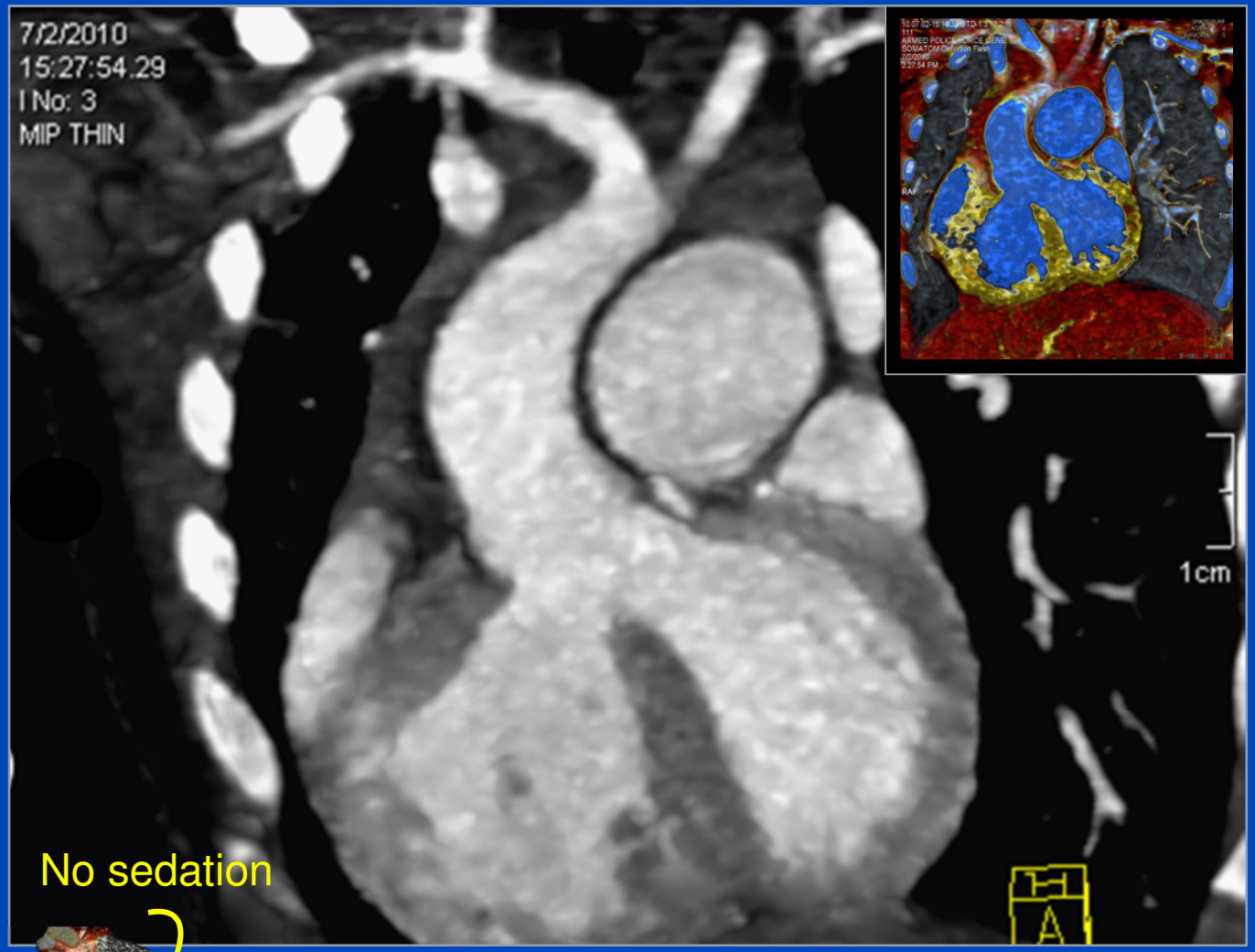
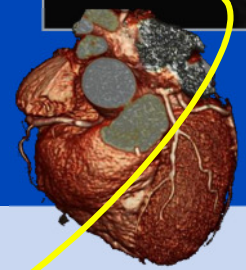


No sedation



Courtesy of Armed Police Forces Center/ Beijing, China

Child, 12 months

Temporal resolution: 75 ms
Collimation: 2·64×0.6 mm
Spatial resolution: 0.6 mm
Scan time: 0.23 s
Scan length: 78 mm
Rotation time: 0.28 s
80 kV, 36 mAs / rotation

Flash Spiral

Eff. dose: 0.05 mSv

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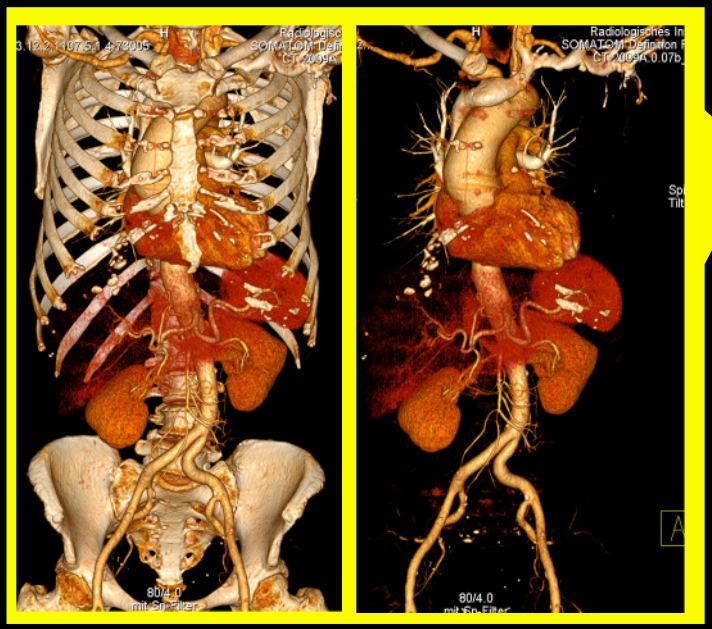
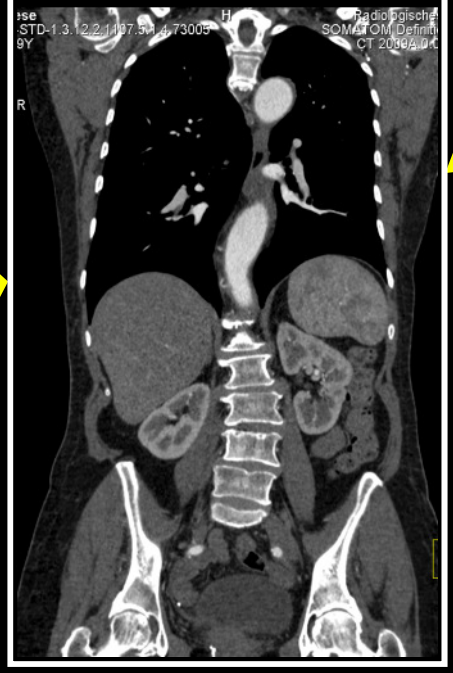
Examples

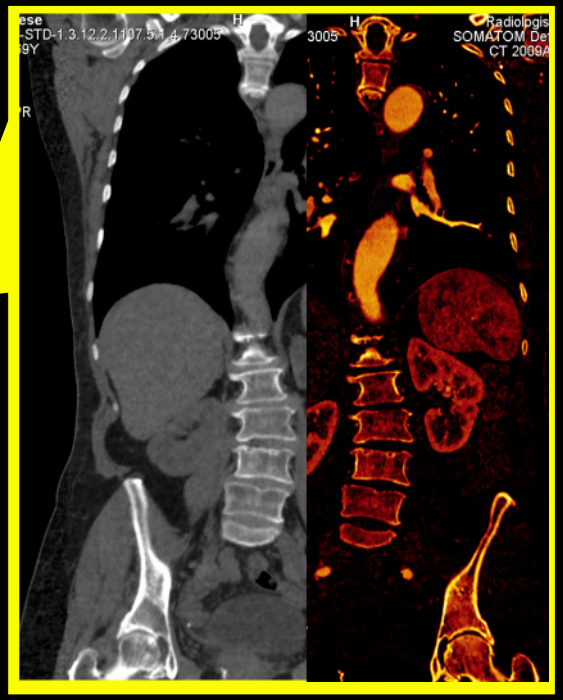
(Slide Courtesy of Siemens Healthcare)

DE bone removal



Single DECT Scan





Virtual non-contrast and Iodine image

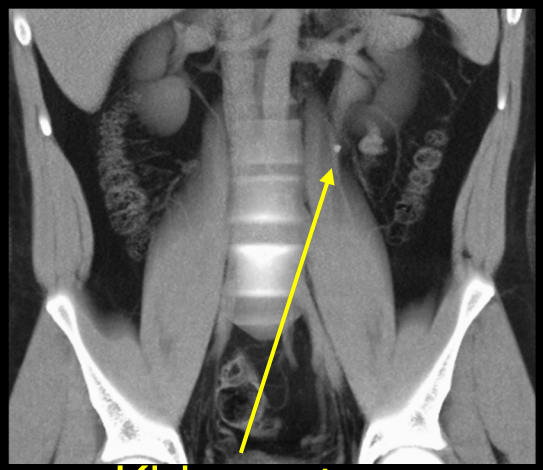
Dual Energy whole body CTA: 100/140 Sn kV @ 0.6mm

Courtesy of Friedrich-Alexander University Erlangen-Nürnberg

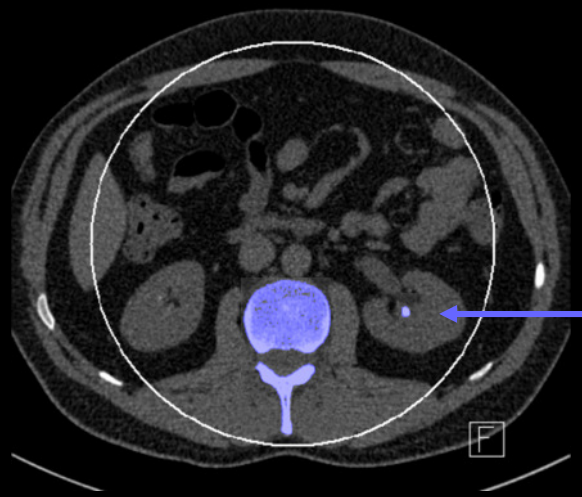
DECT Today: Widely Available via DSCT

(Slide Courtesy of Siemens Healthcare)

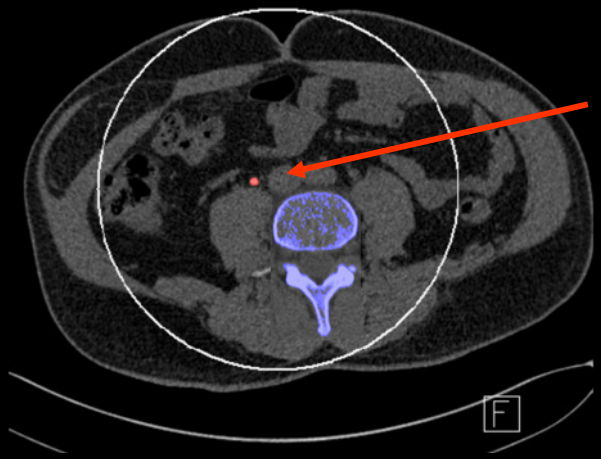
- **"Spectroscopy": more specific tissue characterization**
  → Detection and visualization of calcium, iron, uric acid, …..



Kidney stones



Calcium-oxalate-stone



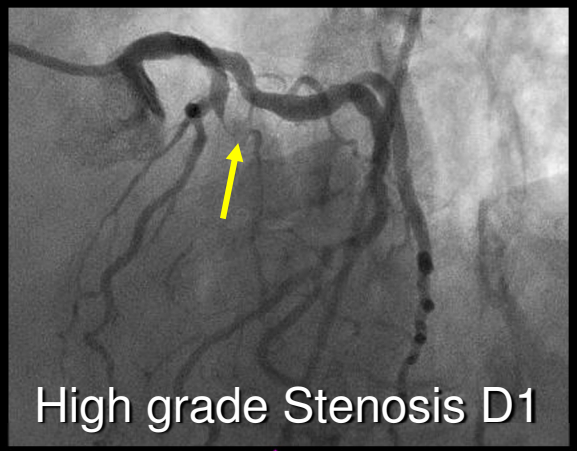
Uric acid-stone

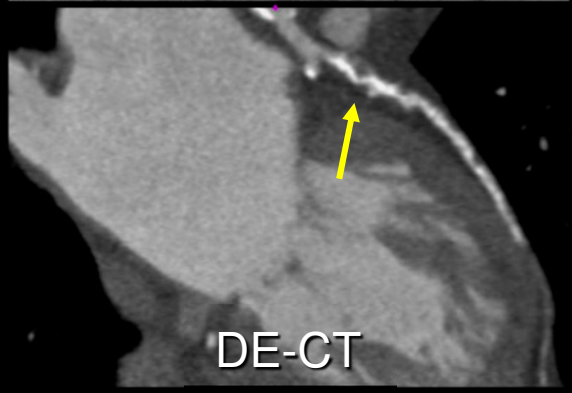
Courtesy of Klinikum Großhadern, LMU München

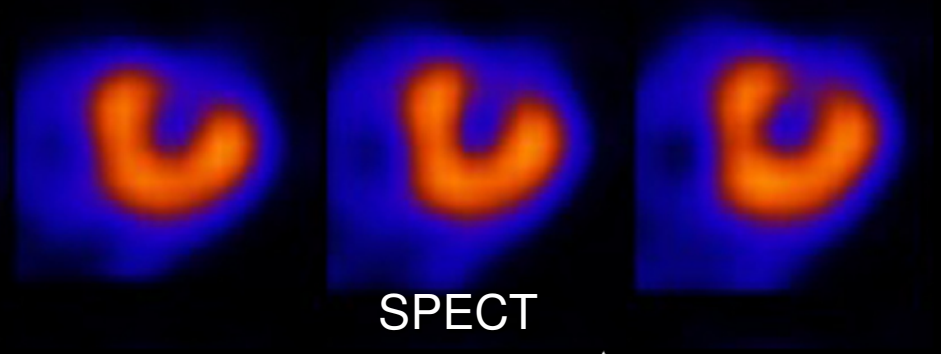
DECT Today: Widely Available via DSCT

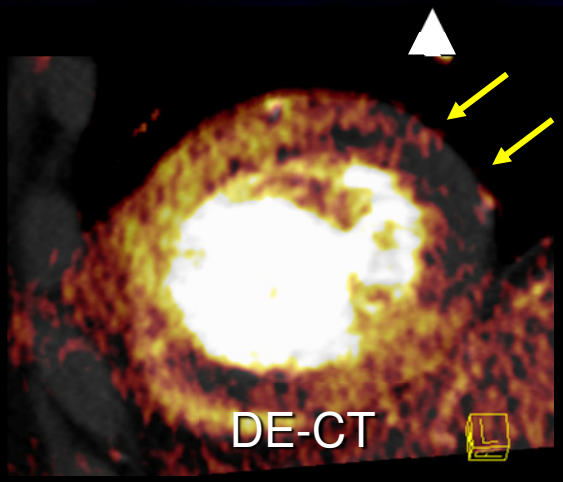
(Slide Courtesy of Siemens Healthcare)

- **New approach: Detection, visualization and quantification of iodine**
  → Characterization of perfusion defects in the myocardium
  → Hemodynamic relevance of coronary artery stenosis:
  Coronary CTA = morphology, local blood volume = function





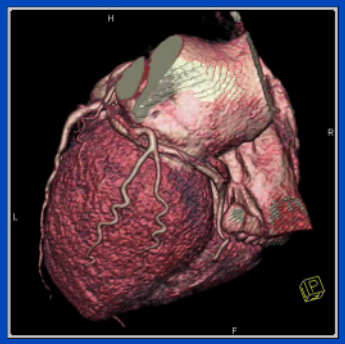


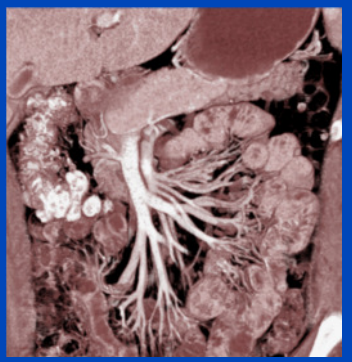


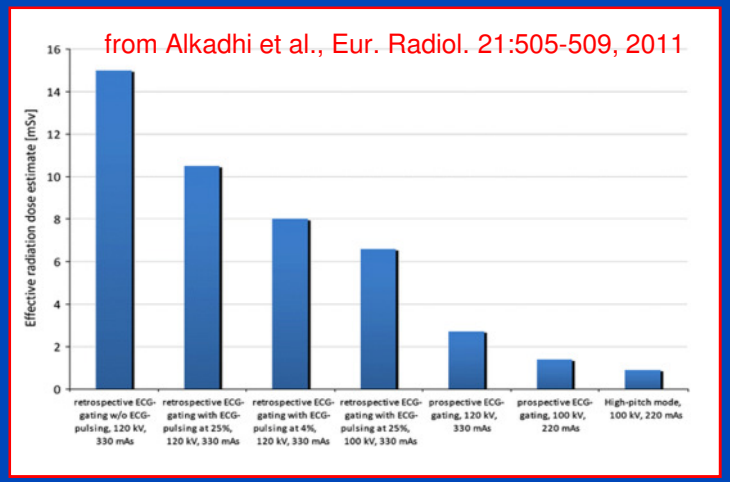
Courtesy of MUSC, Charleston, USA

Clinical CT (also used Preclinically)

- **Many specialized applications**
  - Dedicated injection protocols (test bolus, bolus tracking, shuttle modes, …)
  - CT angiography (CTA)
  - Cardiac CT and cardiac CT angiography (CCTA)
  - Dual energy CT
  - Perfusion CT
  - CT colonoscopy
  - …
- **Sophisticated dose management**
  - Tube current modulation
  - Automatic exposure control
  - Protection of organs at risk
  - Dose decreased by an order of magnitude
  - Iterative image reconstruction
  - …
- **Image quality**
  - Low contrast (5 HU), low noise (5 … 50 HU)
  - submillimeter isotropic spatial resolution
  - …







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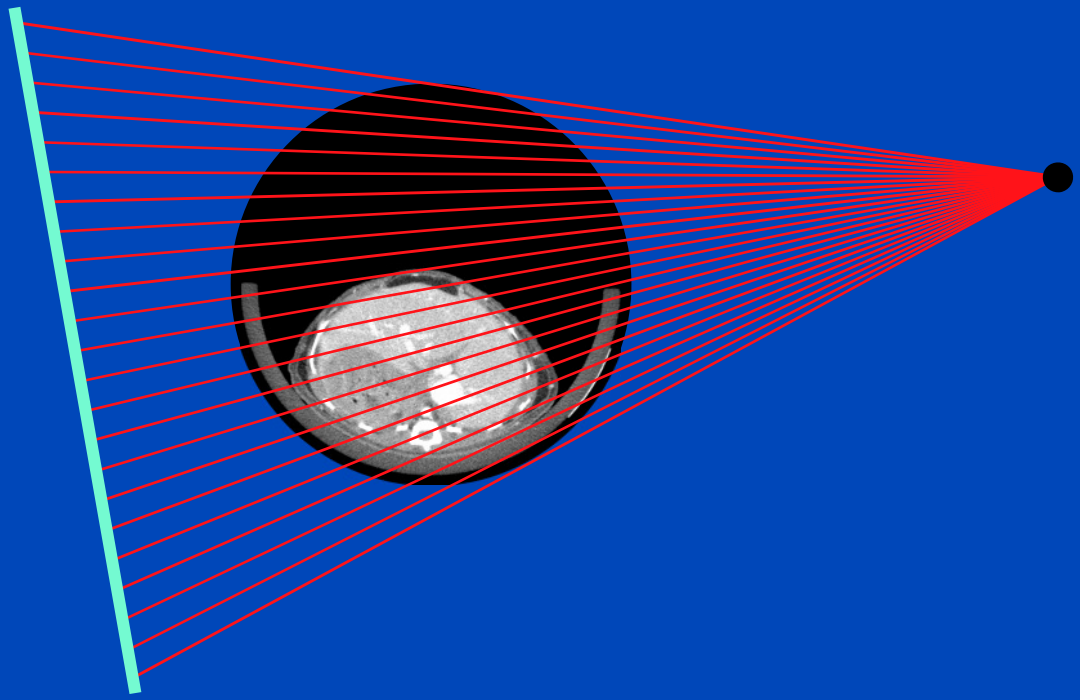
Preclinical Micro-CT



GE eXplore Locus Ultra

- Fully sealed: yes
- Voltage: 70-140 kV
- Detector size: 1024×1024
- Detector type: integrating
- Detector integration: < 6 ms
- Detector readout: >100 fps
- Pixel pitch: 200 µm
- Spatial resolution (at best): 45 µm

Siemens Inveon

- Fully sealed: yes
- Voltage: 35-80 kV
- Detector size: 4064×4064
- Detector type: integrating
- Detector integration: >10 ms
- Detector readout: <1 fps
- Pixel pitch: 25 µm
- Spatial resolution (at best): 10 µm

SkyScan 1176

- Fully sealed: yes
- Voltage: 20-90 kV
- Detector size: 4000×2672
- Detector type: integrating
- Detector integration: -
- Detector readout: >5 fps
- Pixel pitch: 9 µm
- Spatial resolution (at best): 9 µm

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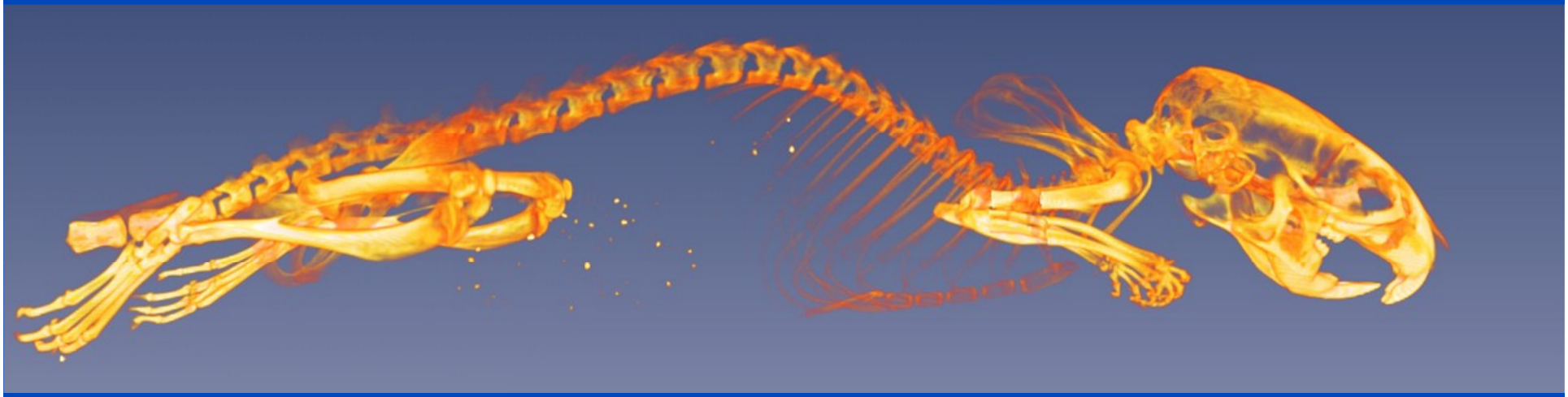
CT Imaging TomoScope

- Fully sealed: yes
- Voltage: 35-80 kV
- Detector size: 1024×1024
- Detector type: integrating
- Detector integration: 40 ms
- Detector readout: 25 fps
- Pixel pitch: 100 µm
- Spatial resolution (at best): 40 µm

MARS CT

- Fully sealed: yes
- Voltage: 40-80 kV
- Detector size: 256×256
- Detector type: photon counting
- Detector integration: 10 ms
- Detector readout: 100 fps
- Pixel pitch: 55 µm
- Spatial resolution (at best): 30 µm



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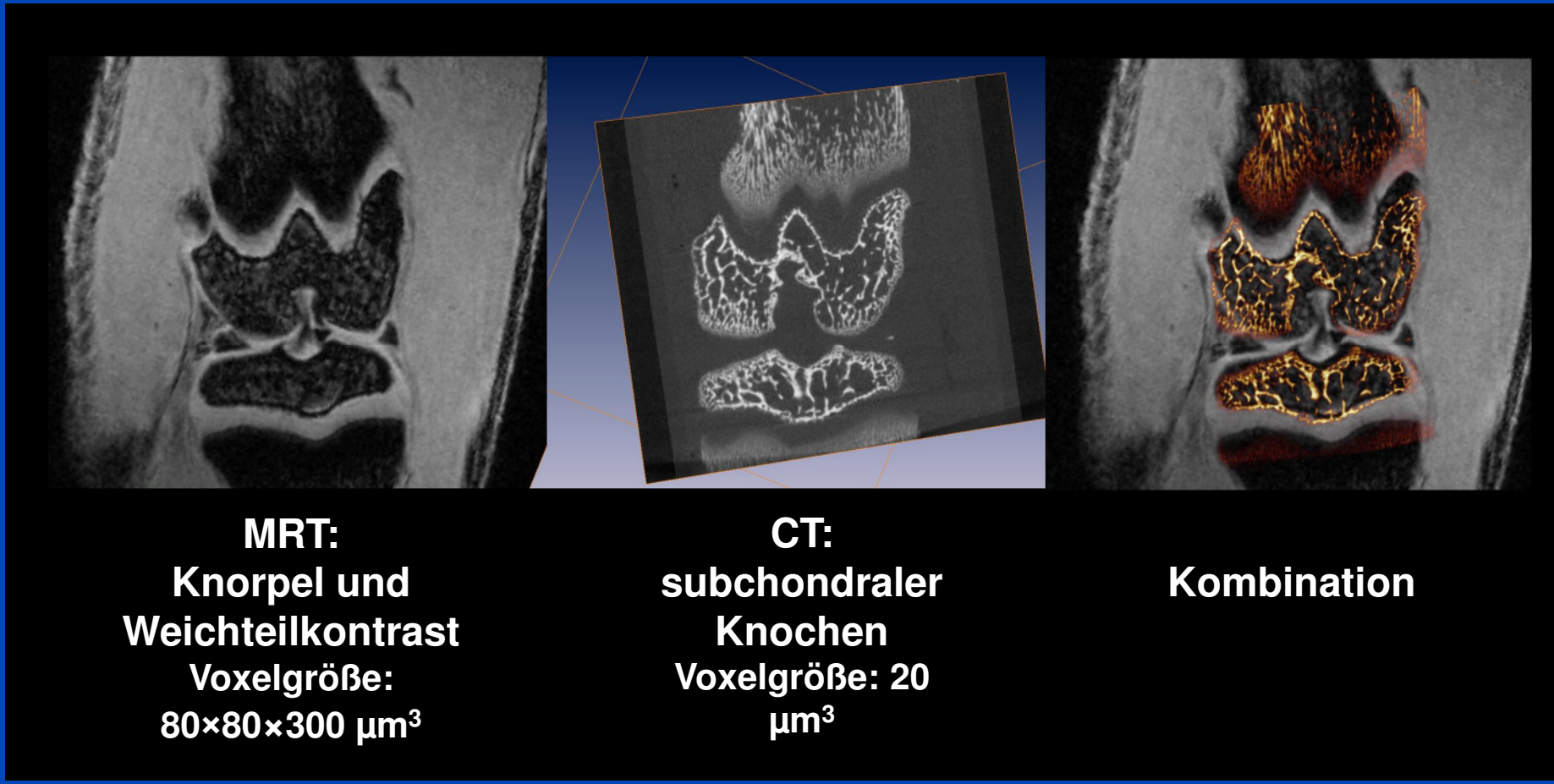
Micro-MR/CT



MRT:
Knorpel und Weichteilkontrast
Voxelgröße:
80×80×300 µm³

CT:
subchondraler Knochen
Voxelgröße: 20 µm³

Kombination

A. Hess, et al. IZKF, FAU Erlangen.

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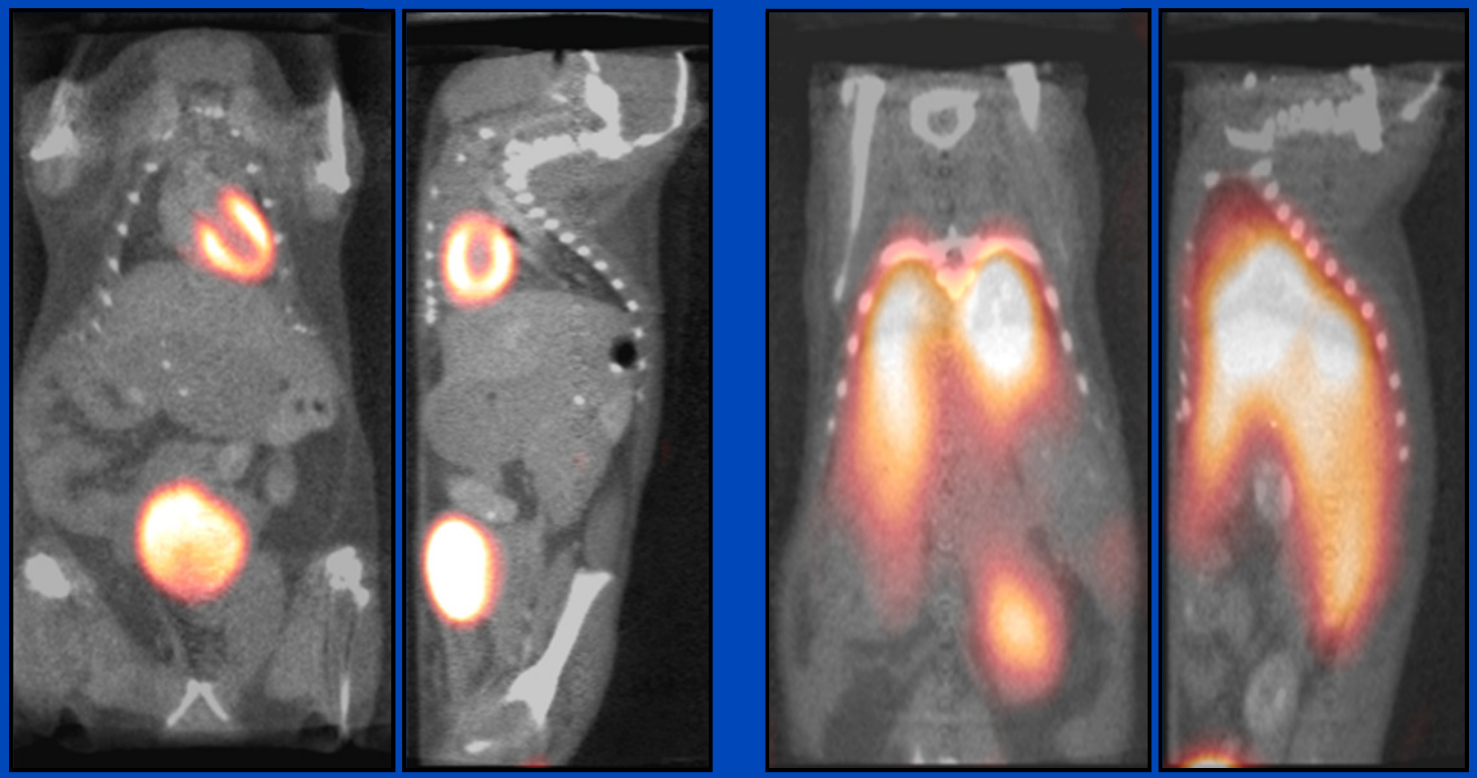
Micro-PET/CT



^{18}F gelabelte Melanomzellen

University of California, Davis

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Preclinical Micro-CT

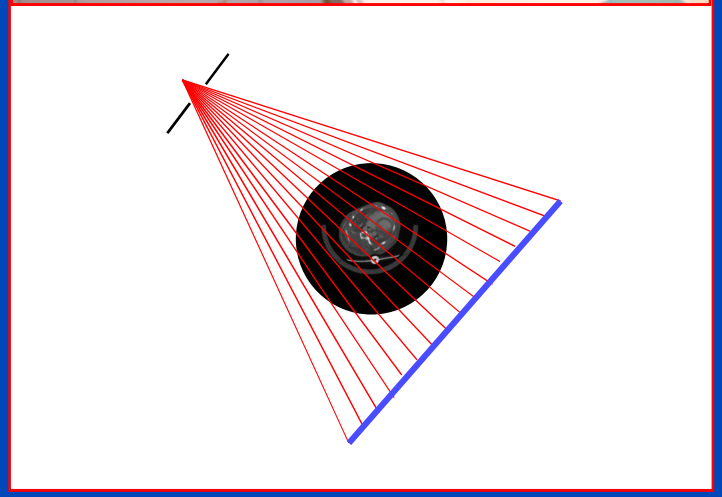
- Mainly focuses on high spatial resolution
  - 5 to 100 μm spatial resolution
  - 50 to 500 HU image noise
  - limited low contrast resolution (due to flat detector)
- Dose levels
  - often very high (500 mGy or more are typical)
  - nearly no dose reduction during the last decade
- Special applications
  - typically restricted to post processing
  - no real-time imaging (slow scans)
  - no mapping of clinical CT applications to micro-CT today
- Molecular imaging
  - CT often serves as the anatomical reference for other modalities

The Future of Micro-CT

- Today's small animal micro-CT systems do not reflect the state-of-the-art in CT
- New developments in micro-CT technology (hardware, algorithms) limited to independent research groups
- Developments in contrast agents (nanoparticles, …) are highly promising.
- Micro-CT vendors seem to make only minor changes.

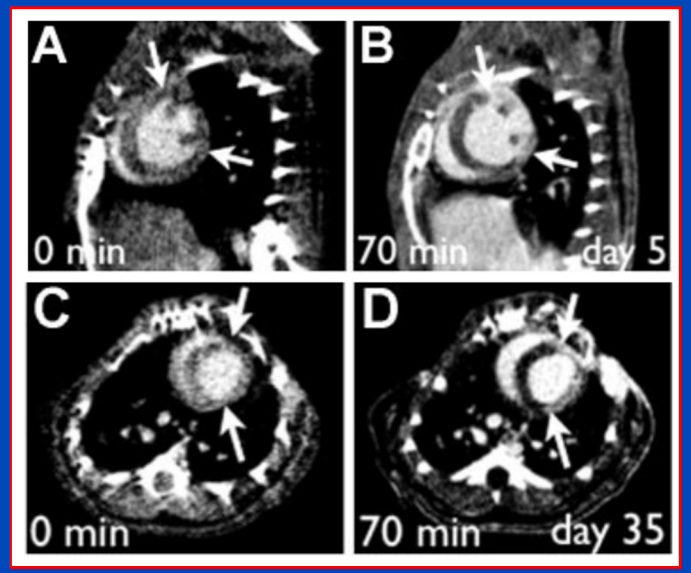
Cardiac Perfusion of Small Animals

- VolumeCT (Siemens Healthcare, Forchheim, Germany)
- X-ray source:
  - Focal spot size: 400 µm × 400 µm
  - Tube voltage range: 80 kV – 140 kV
  - Tube current range: 10 mA – 50 mA
- Detector:
  - Varian flat panel detector
  - 1024×768 pixel (2×2 binning)
  - 1024×192 @ 100 fps
  - 388 µm pixel size
  - Spatial sampling: 238 µm
  - 10 ms integration time
- Protocol:
  - Scan time: 20 s
  - Rotation speed: 18 °/s
  - Number of projections: 2000
  - Estimated dose: 50 mGy



Cardiac Perfusion of Small Animals Prior Art

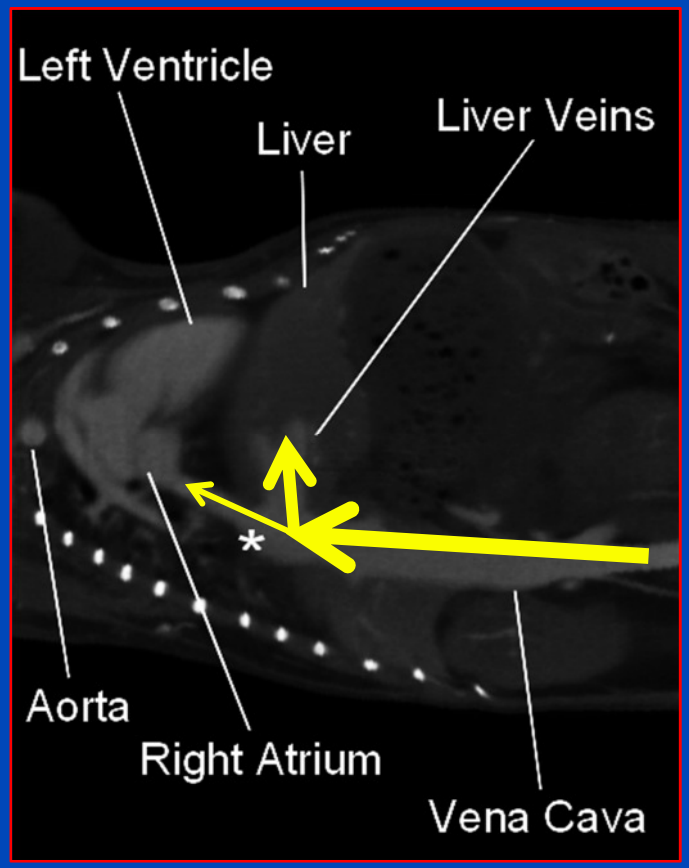
- High resolution (100 µm) imaging of the thoracic region.
- No phase-correlation and thus motion artifacts occur.
- Administration of more than 1 mL of contrast agent within 70 min.



Nahrendorf M, Badea C, Hedlund LW, Figueiredo JL, Sosnovik DE, Johnson GA, Weissleder R. High–resolution imaging of murine myocardial infarction with delayed-enhancement cine micro-CT. American Journal of Physiology: Heart and Circulatory Physiology. 2007; 292:H3172–H3178.

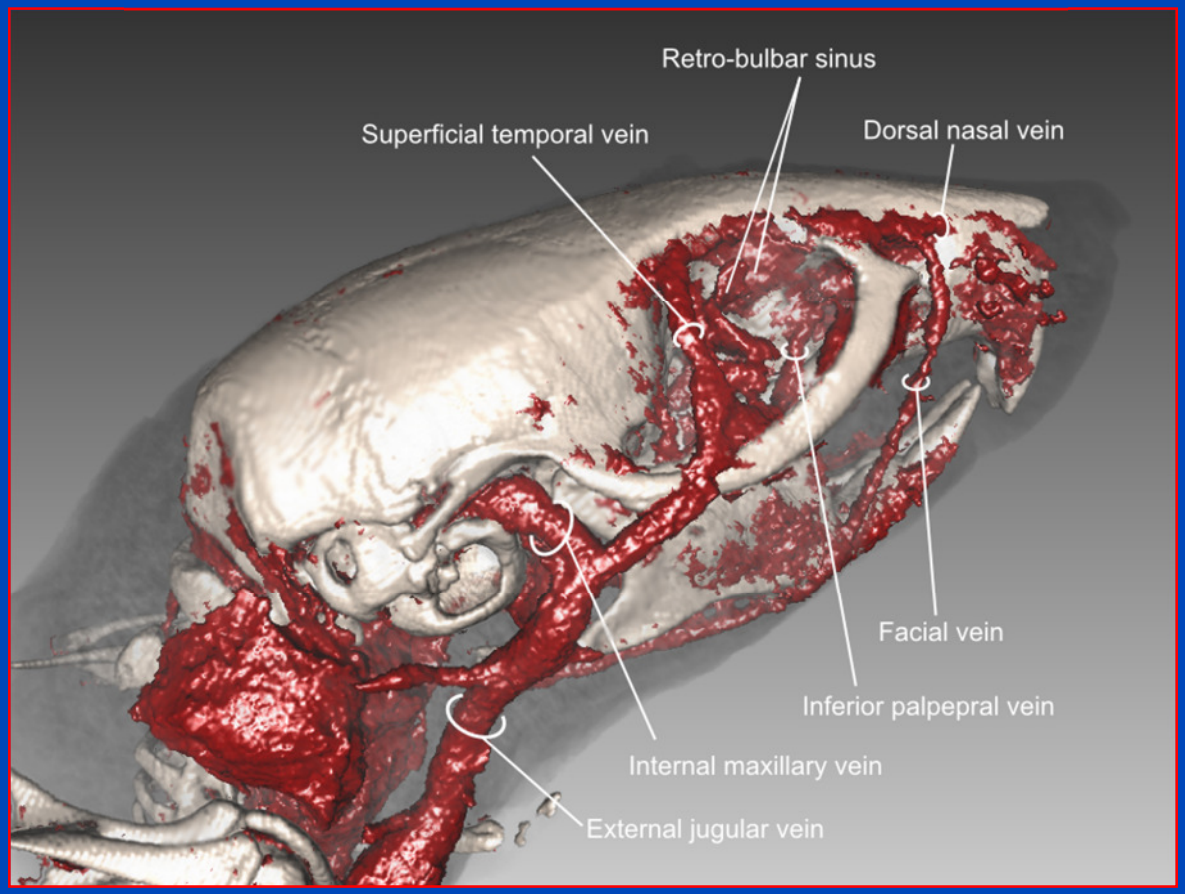
Contrast Injection

- We wish to inject boli of 25 µL.
- Clinical contrast agents are highly viscous (up to 8.7 mPa·s).
- Retrograd blood flow from the vena cava to the liver veins near the diaphragm.
- Bolus is dissolved before it arrives in the heart.
- Another route for contrast injection is required.
- We propose to inject into the **retro-bulbar sinus**.



Curved MPR throught the vena cava of a mouse obtained from a high resolution micro-CT scan.

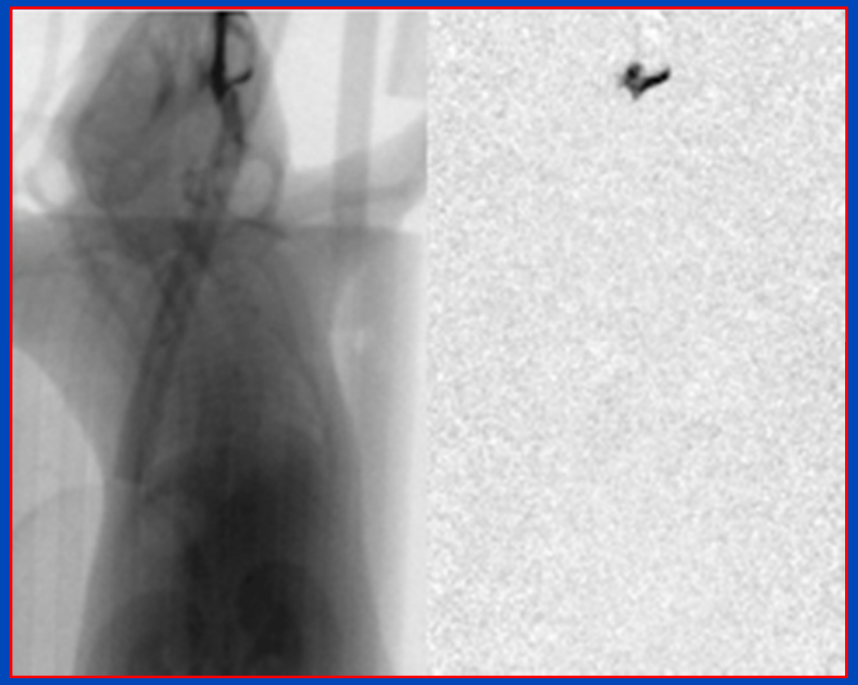
Contrast Injection



Volume rendering of a high resolution micro-CT scan with a spatial resolution of about 40 µm.

Contrast Injection

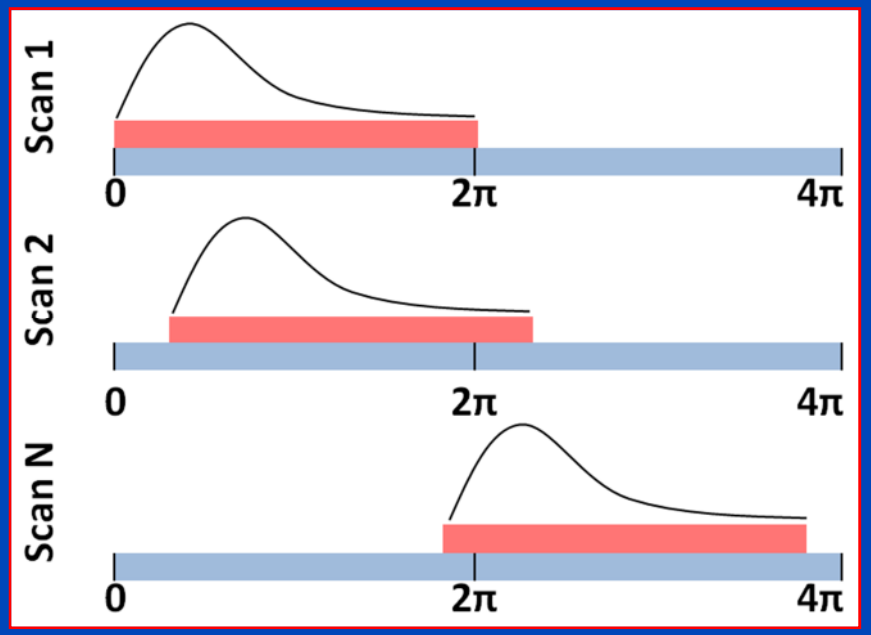
- Injection into the retro-bulbar sinus is verified using digital subtraction angiography.
- Imeron 300 is used as contrast agent.
- Contrast agent arrives in the right ventricle 1.5 s after the injection.
- Contrast agent is in the left ventricle after about 2.0 s.
- Enhancement of the aorta visible after about 2.5 s.



Left: acquired projection images.
Right: digital subtraction angiography.

Scan Protocol

- We perform N=10 scans each over 360° within 20 s.
- 2000 projections are acquired in every scan.
- Each scan starts at a different angle. We thus ensure to cover the complete angular range.
- We inject 25 µL per scan and 250 µL in total.



Schematic illustration of the used scan protocol. This is inspired by *Badea CT, Johnston SM, Subashi E, Qi Y, Hedlund LW, Johnson GA. Lung perfusion imaging in small animals using 4D micro–CT at heartbeat temporal resolution. Medical Physics. 2010; 37:54–62.*

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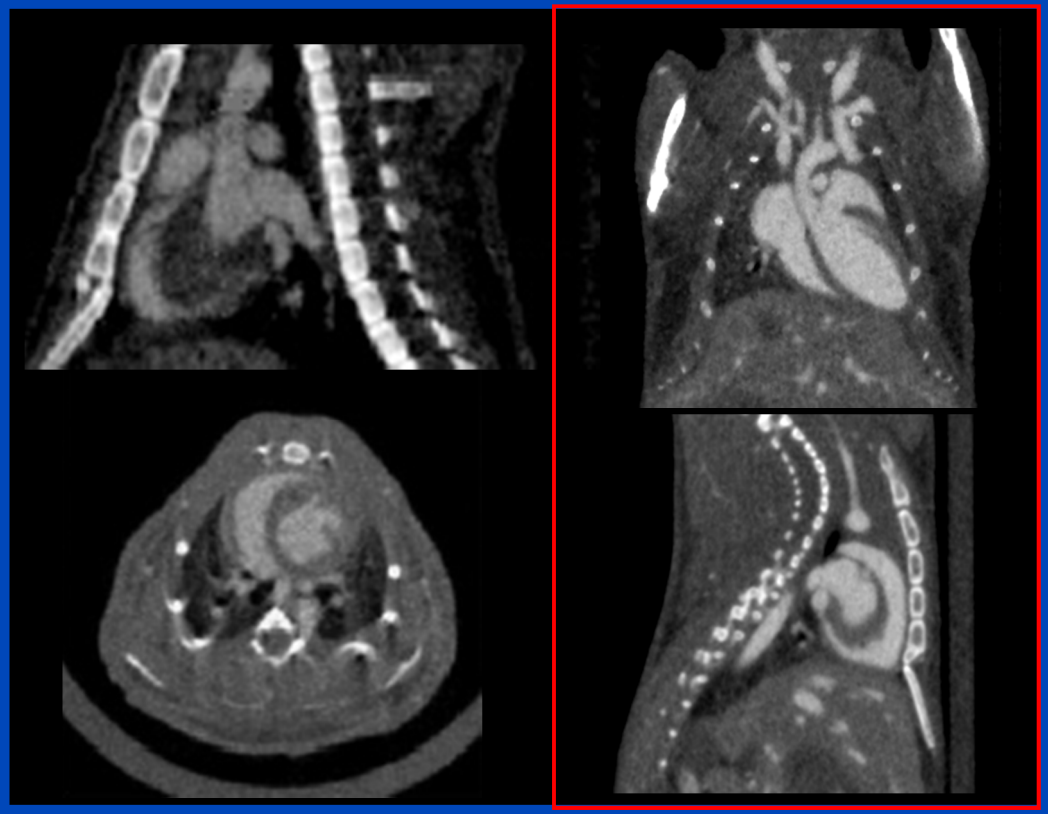
Image Reconstruction Prior Art

Conventional Recon
1840 mGy, 90 µm, 12 phases

Dedicated Iterative Recon
500 mGy, 80 µm, 50 phases



C. Badea, B. Fubara, L. Hedlund, and G. Johnson, "4D micro–CT of the mouse heart," *Molecular Imaging*, vol. 4, no. 2, pp. 110–116, Apr./Jun. 2005.

S. Sawall, F. Bergner, R. Lapp, M. Mronz, M. Karolczak, A. Hess, and M. Kachelrieß, "Low-dose cardio-respiratory phase-correlated cone-beam micro-CT of small animals," *Medical Physics*, vol. 38, no. 3, pp. 1416-1424, Feb. 2011.

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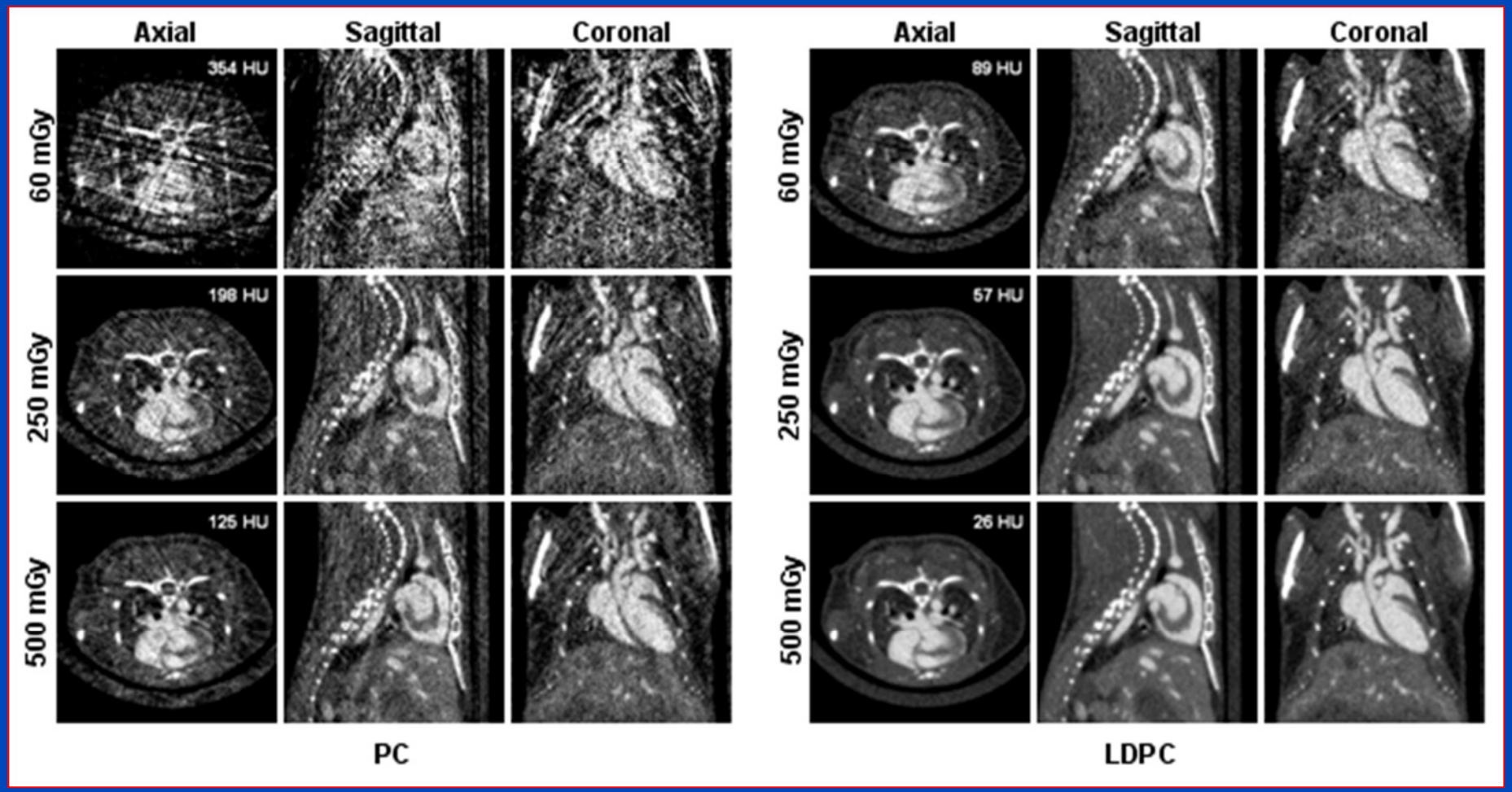
Image Reconstruction Prior Art



S. Sawall, F. Bergner, R. Lapp, M. Mronz, M. Karolczak, A. Hess, and M. Kachelrieß, "Low-dose cardio-respiratory phase-correlated cone-beam micro-CT of small animals," *Medical Physics*, vol. 38, no. 3, pp. 1416-1424, Feb. 2011.

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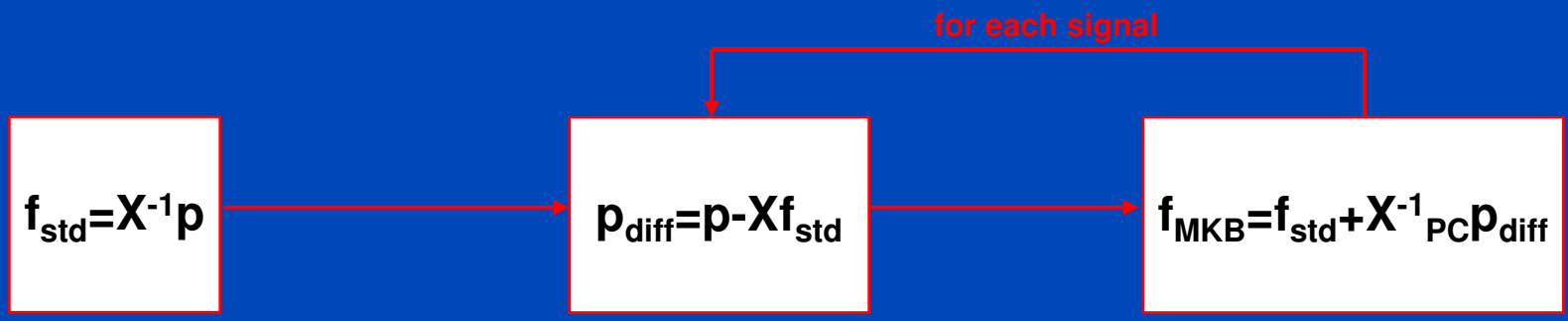
Modified McKinnon-Bates Algorithm



- Use image based on all projections as prior (standard image)
- Calculate rawdata difference for desired motion phases
- Perform correction

Standard image f_{std} reconstructed from all projections.

McKinnon-Bates reconstruction f_{MKB}.

G. C. McKinnon and R. Bates, "Towards imaging the beating heart usefully with a conventional CT scanner," *IEEE Transactions on Biomedical Engineering*, vol. BME-28, no. 2, pp. 123–127, Feb. 1981.

dkfz.

Edge Preserving Spatio-Temporal Postprocessing

Six-dimensional bilateral filtering (three spatial and three temporal dimensions)

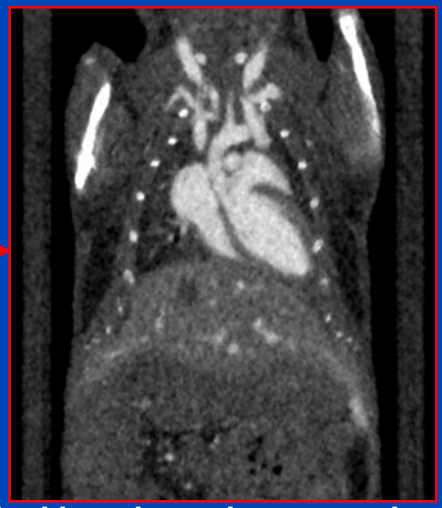
$$f_{\mathrm{PLDPC}} = B f_{\mathrm{MKB}} = \frac{\int dt^6 D(x,t) R(x,t) f(t)}{\int dt^6 D(x,t) R(x,t)}$$

Standard image reconstructed from all projections.

Modified MKB

Modified McKinnon-Bates reconstruction.

6D Filter



Final low-dose phase-correlated (PLDPC) image.

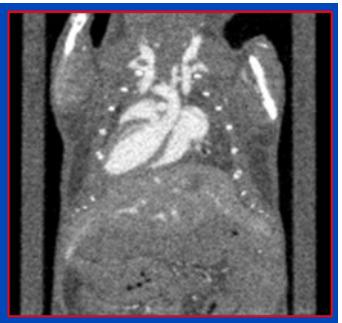
S. Sawall, F. Bergner, R. Lapp, M. Mronz, M. Karolczak, A. Hess, and M. Kachelrieß, "Low-dose cardio-respiratory phase-correlated cone-beam micro-CT of small animals," *Medical Physics*, vol. 38, no. 3, pp. 1416-1424, Feb. 2011.

dkfz.

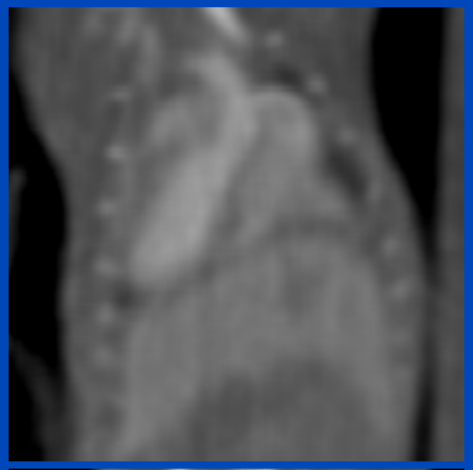
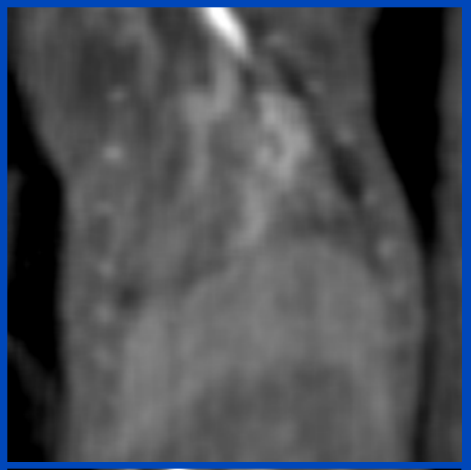
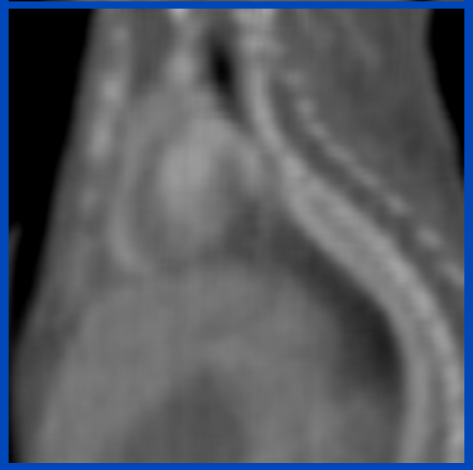
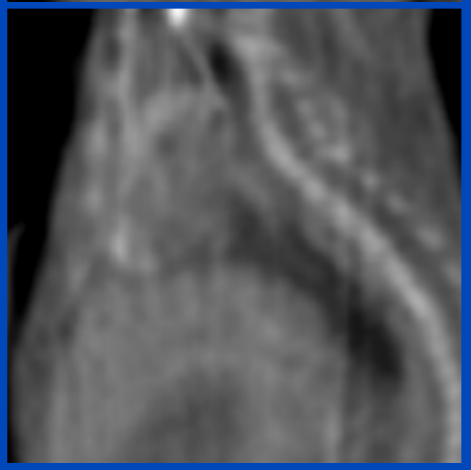
Results

	Mouse 1	Mouse 2
Respiratory rate	120 rpm	115 rpm
Cardiac rate	265 bpm	250 bpm
Contrast agent	Imeron 300	Imeron 300
Administered volume	10×25 µL	10×25 µL

Mouse 1



This is how the images would look like at 80 µm spatial resolution.

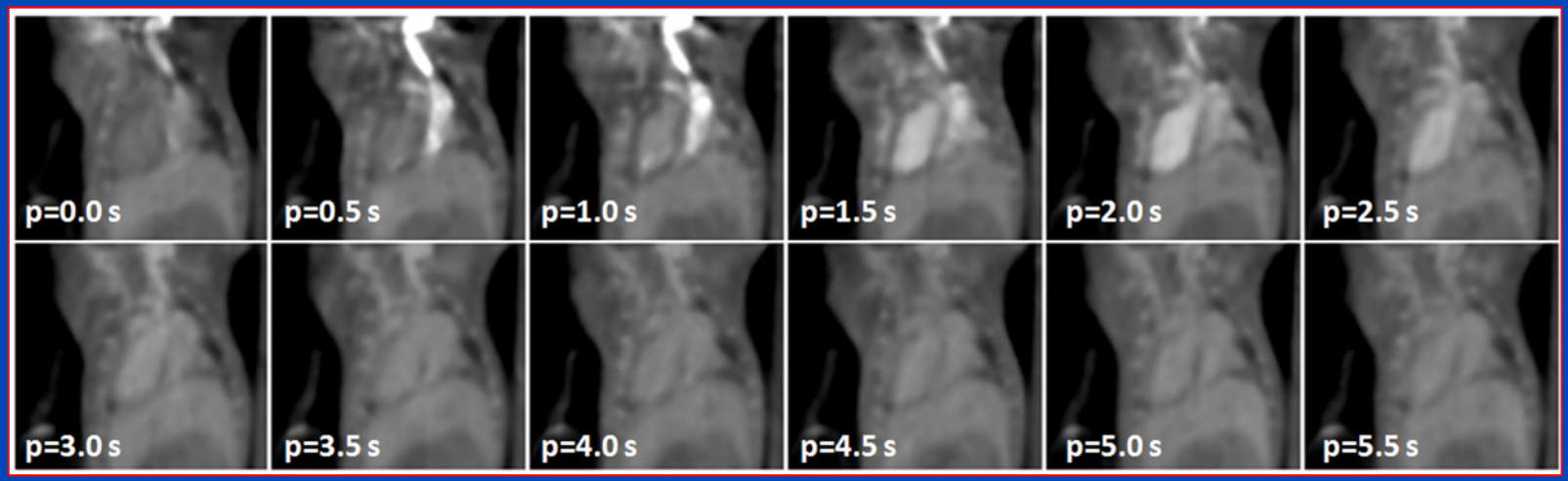
	Respiration	Cardiac Motion	Perfusion
Coronal			
Sagittal			

Δr = 20%, Δc = 20%, Δp = 0.5 s (600 HU / 700 HU)

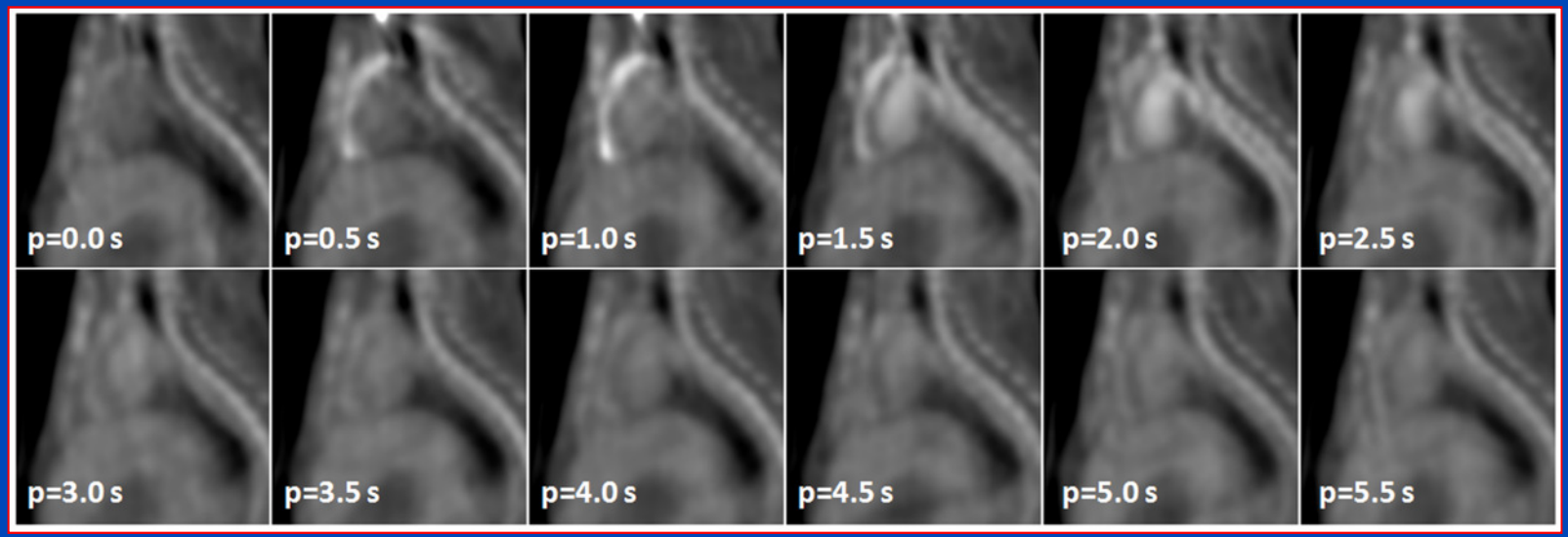
dkfz.

Mouse 2

Coronal



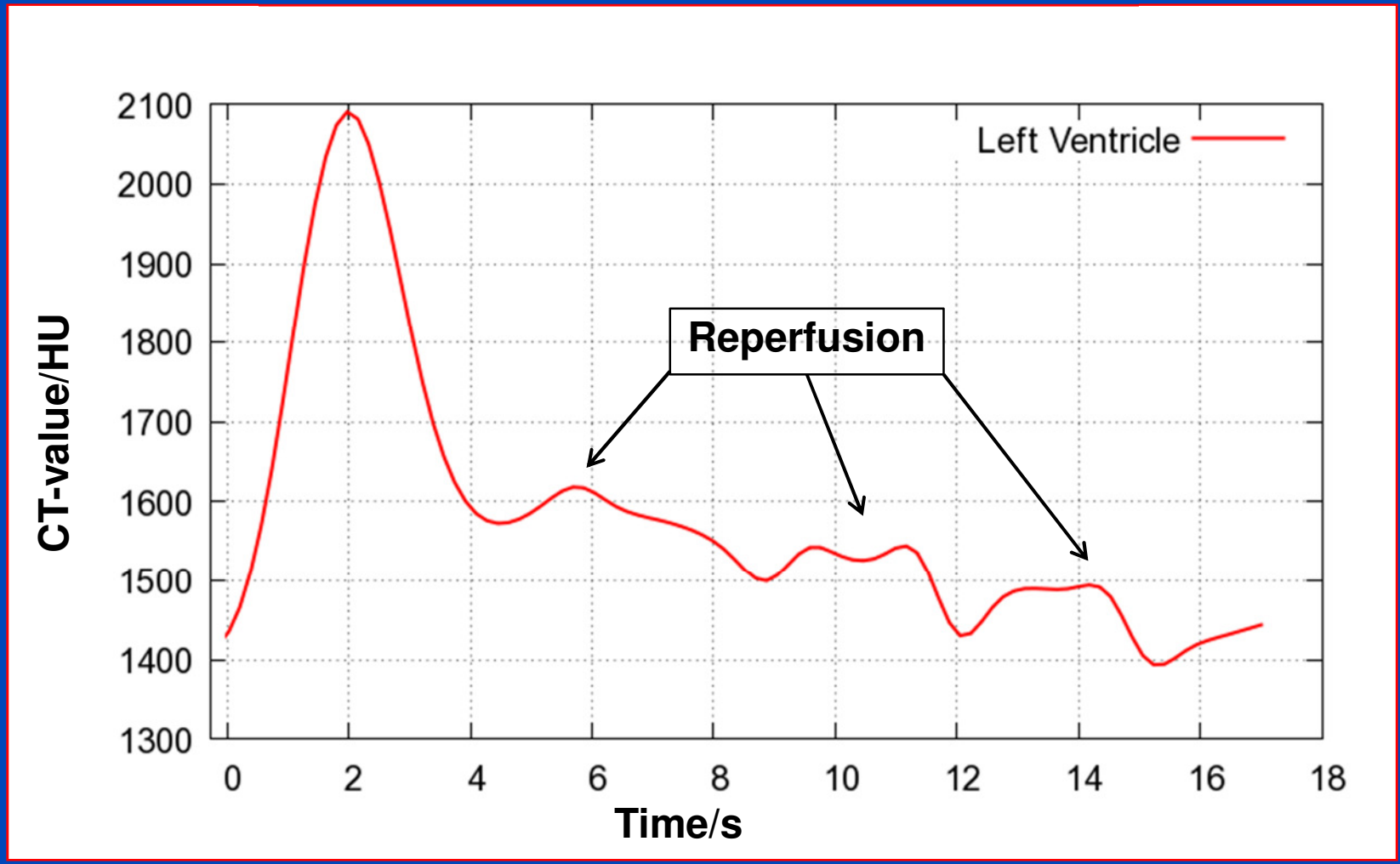
Sagittal



r=0%, Δr=20%, c=20%, Δc=20%, Δp=0.5 s (600 HU / 900 HU)

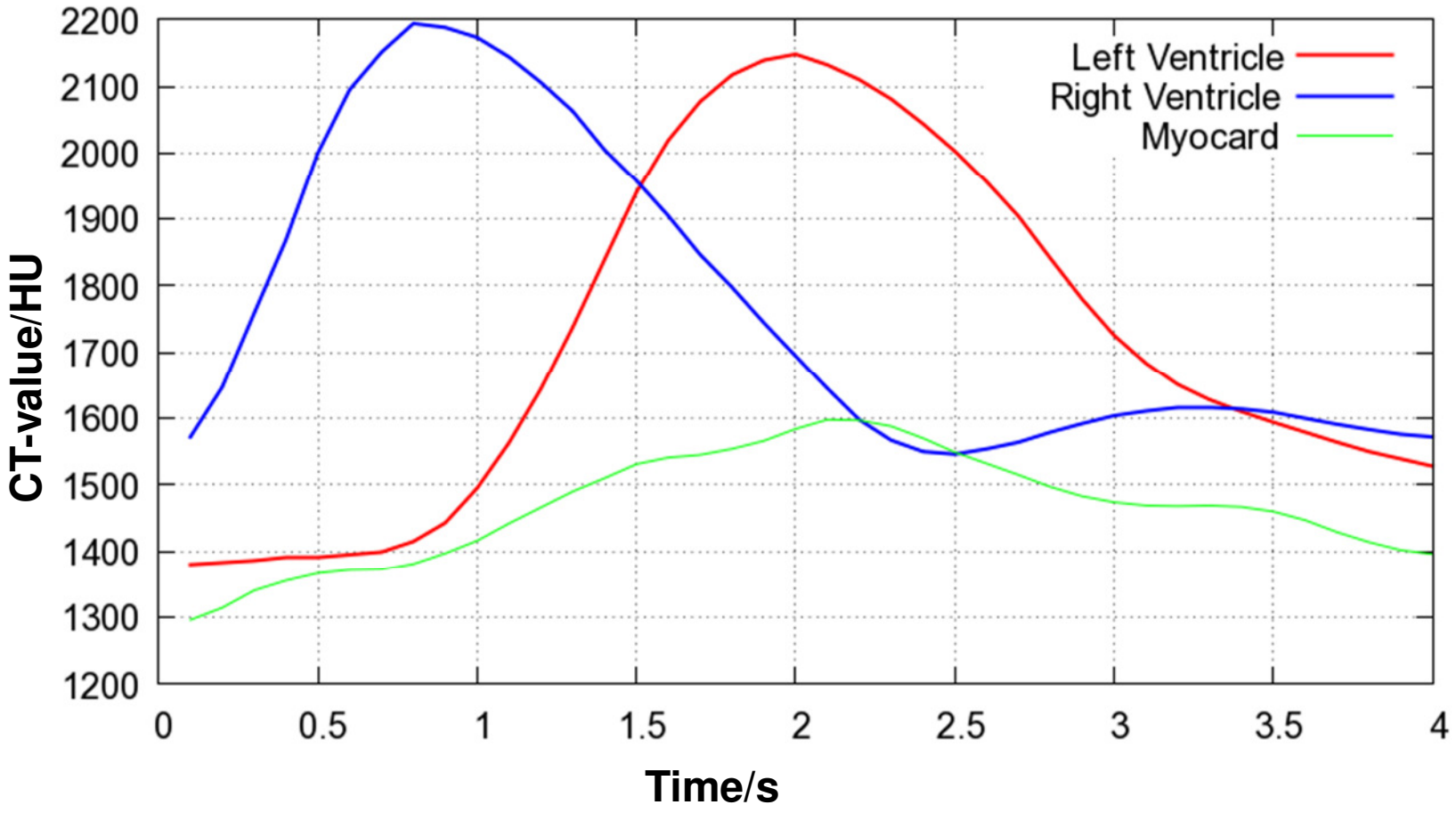
dkfz.

Time-Density-Curve



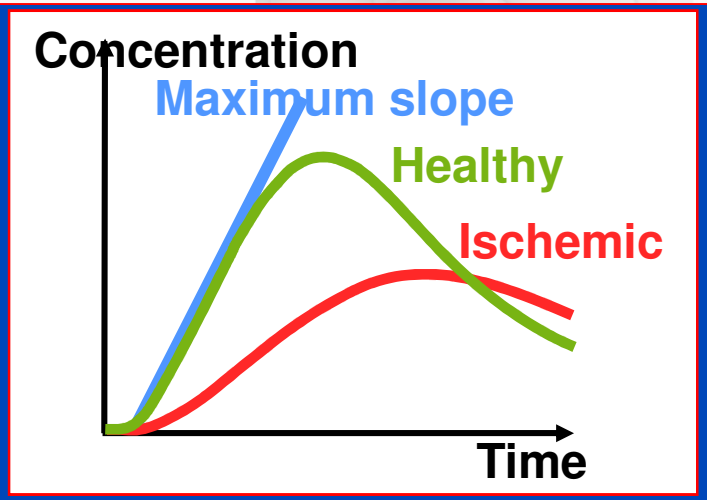
dkfz.

Time-Density-Curve



Clinical Case

Clinical Examinations



Preclinical Examinations

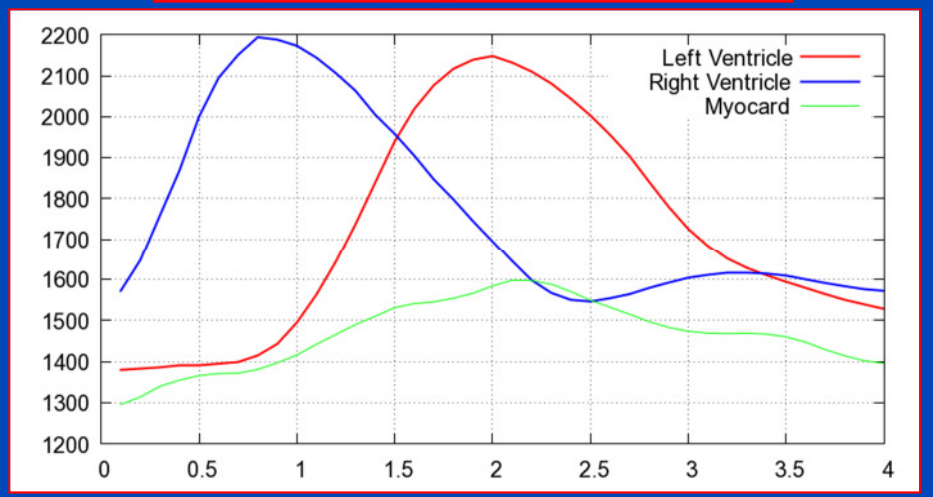


Image of the Siemens SOMATOM definition Flash and the acquired curves courtesy of Siemens Healthcare, Forchheim, Germany.

dkfz.

Summary

- Technology that is mature in diagnostic CT does not arrive in dedicated small animal systems
- Preclinical micro-CT is mainly used as an anatomical reference
- Therefore, it does a good job in reliably providing anatomical images


Thank You!
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