In–vivo Coronary Micro–CT of Small Animals

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Introduction

As cardiovascular diseases (CVD) are the leading cause of death worldwide, they are of high importance in healthcare as well as in preclinical research, where a variety of cardiac disease small animal models are used. However, clinical image quality of computed tomography (CT) of the heart and especially coronary CT angiography (CCTA) used in daily routine diagnostics is superior to small animal micro-CT imaging. This is caused by the fact that anatomical structures in a murine model are 50 to 200 times smaller than in humans whereas physiological respiratory and cardiac rates are 5 to 10 times higher [1]. The imaging of small structures like the coronary arteries with a diameter of 20 µm at a heart rate of up to 600 bpm is challenging as in micro-CT an increase in spatial resolution results in an decrease in temporal resolution and vice versa. Therefore, we built the prototype of a small animal micro–CT system dedicated to murine cardiovascular imaging (Fig. 1).

Materials and Methods

CT System

The prototype of a high speed micro–CT system was equipped with a micro–focus x–ray source with transmission target (L10951, Hamamatsu Photonics K. K., Shimokanzo, Iwata City, Japan), providing a tube voltage of up to 110 kV and a tube current of up to 800 µA at 50 W. The power–dependent focal spot–size varies between 15 µm at 6 W and 80 µm at 50 W.

The CMOS x–ray detector used is a Dexela 2923 MAM (Perkin Elmer, Salt Lake City, USA) with a 150 µm high–resolution CsI scintillator, providing 3888 × 3072 pixels with 74.8 µm pixel pitch. To account for the high cardiac and respiratory rates of small animals, the detector achieves a frame rate of up to 86 fps in the 4 × 4 binning mode. The spatial resolution of the system can be estimated to 49 µm in the 4 × 4 binning mode assuming a 20 µm focal spot using

$$\Delta^2 = \left(\frac{R_\mathrm{D}}{R_\mathrm{F}+R_\mathrm{D}}W_\mathrm{F}\right)^2 + \left(\frac{R_\mathrm{F}}{R_\mathrm{D}+R_\mathrm{F}}W_\mathrm{D}\right)^2,$$

with W_F and W_D being the used focus size and the detector aperture, respectively.

Animal Experiments

Four healthy mice were examined after administration of 100 µL of a blood pool contrast agent (ExiTron nano 12000, nanoPET Pharma GmbH, Berlin, Germany) using a tube voltage of 60 kV and a tube current of 800 µA. To maximize angular sampling and minimize blurring during readout, the detector was operated in the fast 4 × 4 binning mode and rotation was limited to 60°/s. All animals were scanned for 348 s with a total amount of 30.000 projections.

Materials and Methods

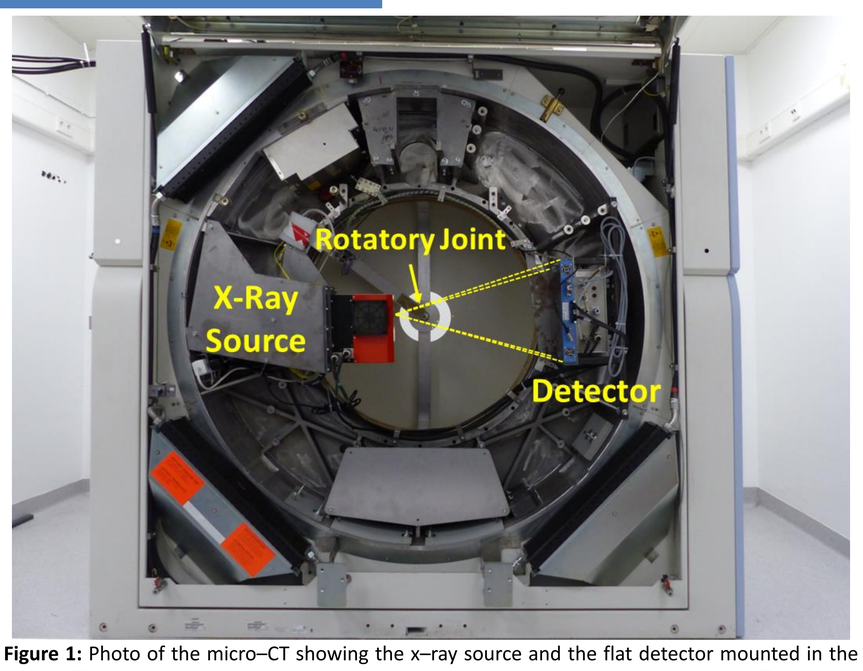

Figure 1: Photo of the micro–CT showing the x–ray source and the flat detector mounted in the gantry. The yellow, dashed lines indicate the cone–beam geometry of the system. The focus–isocenter–distance R_F = 90 mm and the detector–isocenter–distance R_D = 500 mm result in a magnification factor of 6.6. Using a 29 × 23 cm² detector the diameter of the field of measurement is 44 mm.

Results

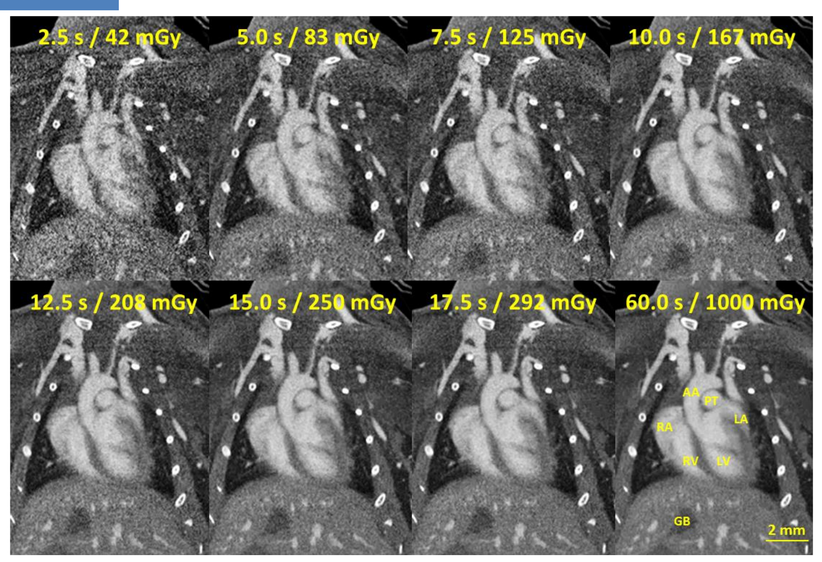

Figure 2: Standard ungated reconstructions of one scan of a healthy mouse acquired with the 4 × 4 binning mode and a focal spot–size of 80 µm. The amount of raw data used for the reconstructions was varied to match an effective acquisition time of 2.5 s to 60 s. Image quality with an acquisition time of 2.5 s suffers from high noise, even if the main anatomical structures are visible. For diagnostic use in preclinical research, images with an effective acquisition time of 12.5 s to 60 s are sufficient. (AA = aortic arch, RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, PT = pulmonary trunk, GB = gallbladder) C = 0 HU, W = 1500 HU

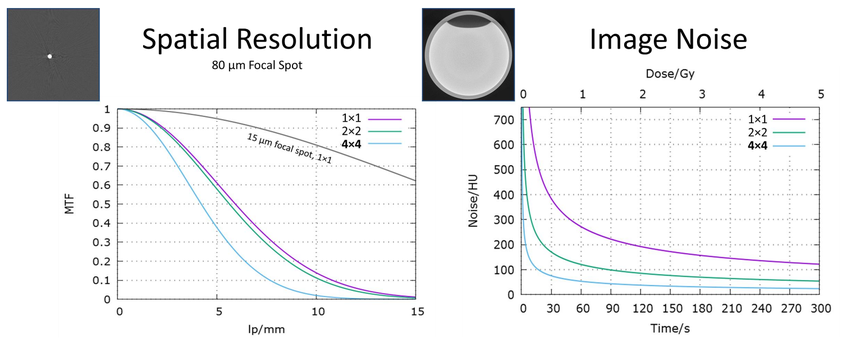

Figure 3: Image quality of the micro–CT system is shown as modulation transfer function measured in a tungsten wire (left) and image noise measured in a water cylinder (right). While a focal spot–size of 80 µm and the 4 × 4 binning mode were used for the presented in-vivo measurements, the maximum spatial resolution using the smallest focal spot of 15 µm and the 1 × 1 binning mode is shown as reference.

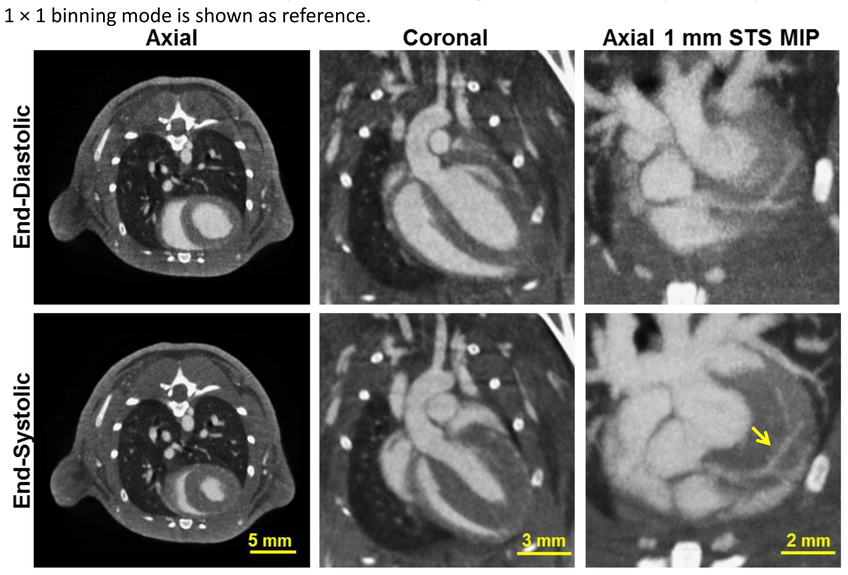

Figure 4: Reconstruction of the vasculature and heart of a mouse in two cardiac phases shown in axial and coronal plane as well as MIP. The left anterior descending coronary artery (LAD) is clearly visible in the MIP (arrow). In all phases, at least one diagonal branch of the LAD can be tracked. C = 0 HU W = 1500 HU

Reconstruction

Standard as well as phase-correlated reconstructions into 10 equally distributed cardiac phases were performed using the high–performance implementation of the Feldkamp–algorithm [3] (RayConStruct®–IR, RayConStruct, Nürnberg, Germany) on a sufficiently sized grid with a voxel size of 49 µm.

Results

Standard reconstructions of a healthy mouse are shown in figure 2 with varied scan time and dose. The image quality parameters spatial resolution and image noise are shown in figure 3. Reconstructions indicate that image quality using effective measurement times of 12.5 s to 60 s are sufficient for preclinical research. Measurement of the image noise indicates that the optimum in the trade–off between image quality and acquisition time in the used 4 × 4 binning mode is in the order of 30 s. Phase–correlated reconstructions representing two exemplary cardiac phases of one mouse are shown in figure 4. The contrast of the blood in the left atrium to the surrounding myocardium was measured to be 370 HU, while the noise measured in a homogeneous region of the myocardium is 62 HU. Overall dose measured with a pencil ionization chamber positioned in a 16 mm PMMA phantom is 17 mGy/s. The spatial resolution at 2% modulation transfer function, determined in the scapular bone is 10 lp/mm. The image quality presented in the axial slices in figure 4 is sufficient to determine functional parameters like ejection fractions or for the measurements of myocardial wall thickness. Moreover, the large vessels like aortic arc, pulmonary trunk and the carotid artery are clearly delimited in the coronal plane and can clearly be delimited from the surrounding walls and tissue, allowing e.g. for the identification of anomalies, aneurysms or calcifications. The left anterior descending coronary artery is visible in all cardiac phases. Up to two vascular branches are visible in the reconstructions. The fast moving right coronary artery cannot be clearly depicted with the current acquisition modes.

Conclusion

The presented high resolution phase–correlated reconstructions demonstrate in–vivo CT imaging of coronary arteries in mice for the first time. Even though the dose in the presented acquisition scheme is relatively high, there are many dose reduction techniques available to enable longitudinal studies, e.g. dose-efficient low-dose phase-correlated [3] reconstructions or motion compensation [4] techniques. In conclusion, it was demonstrated that future micro–CT systems can emerge as a powerful tool for in–vivo cardiovascular imaging.

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