Cardiac Perfusion Imaging of Small Rodents using Cone-Beam Micro-CT

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Purpose

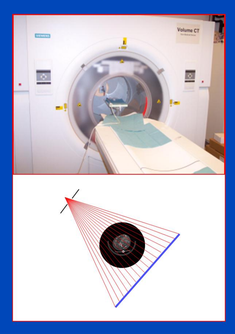
Cardiac perfusion studies using computed tomography are a common tool in clinical practice. The application of these techniques to the preclinical sector in general and to small laboratory animals in particular is a challenging task. Rodents for example commonly exhibit heart rates of up to 300 beats per minutes and respiratory rates of up to 200 respirations per minute resulting in high demands on hardware and the algorithms used for image reconstruction. These reconstructions have to be correlated to the cardiac and respiratory motion as these organs highly influence the flow of contrast agents. Longitudinal studies further call to reduce the administered radiation dose to a minimum in order to limit the metabolic inference to the animal. We therefor propose a low–dose scan protocol and an dedicated reconstruction method that allows to perform cardiac and respiratory correlated perfusion studies of free–breathing small animals.

Materials and Methods

The mice used in our studies are administered with an analgetic prior to all examinations. We use a retro–bulbar injection technique to deliver the contrast agent to the heart. Therefore, a needle is placed in retro–bulbar position to deliver the contrast agent. The needle is connected to a custom-made, high-precision pump. The extrinsic respiratory signal is derived using a pressure sensor beneath the mouse and the ECG is derived using small animal electrodes attached to the paws. Furthermore, the time of contrast media injection is recorded. This allows for a retrospective synchronization of all three gating signals with the acquired projection images. For longitudinal animal studies one needs to keep radiation dose at its absolute minimum and in general one cannot intubate the rodents. Hence the scans are carried out under free breathing conditions and the scans or the reconstructions need to be respiratory– and cardiac–gated as these organ movements inflict the temporal bolus evolution. The data necessary for image reconstruction cannot be acquired within one scan and a single bolus injection. Thus ten consecutive scans and hence N = 10 consecutive injections of boli with a size of 25 µL are performed. All measurements have been performed using a VolumeCT (Siemens Healthcare, Forchheim, Germany) allowing for a spatial sampling in the center of rotation of about 238 µm. The flat detector of this system allows to acquire 100 frames per second. We use a modification of the low–dose phase-correlated reconstruction method (LDPC) since it has proven to allow for the reconstruction of volumes without streak artifacts at very low dose [1].

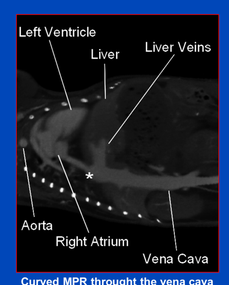
VolumeCT (VCT)

- 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



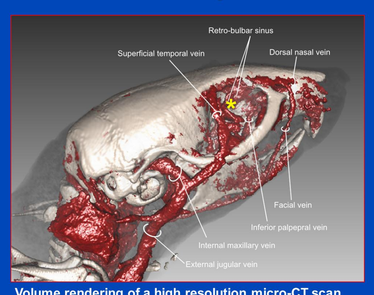
Contrast Injection

- 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.



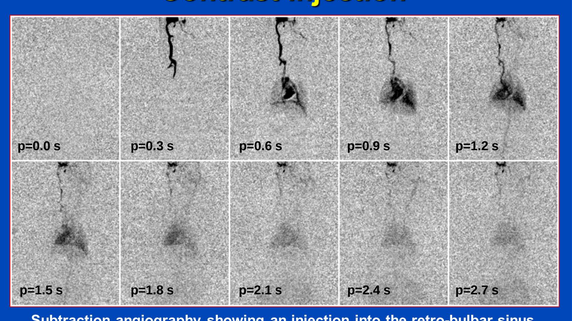
Curved MPR throught the vena cava of a mouse obtained from a high resolution micro-CT scan.

Contrast Injection



Volume rendering of a high resolution micro-CT scan with a spatial resolution of about 40 µm. The injection port is marked with a yellow asterisk.

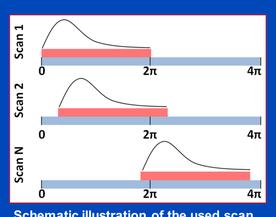
Contrast Injection



Subtraction angiography showing an injection into the retro-bulbar sinus.

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.*

Extrinsic Gating

- Respiration is monitored using a pneumatic pillow.
- Information on cardiac motion are obtained using electrodes attached to the paws.
- Timestamp of contrast injection/start of the perfusion is recorded.
- All signals are retro-spectively correlated to the acquired projections.
- Phase windows for image reconstruction are defined by c, r, p and corresponding window widths Δc, Δr, Δp.

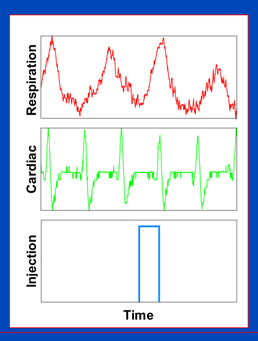
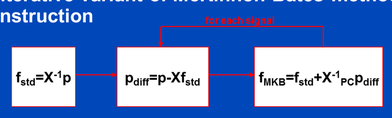


Image Reconstruction

- Use iterative variant of McKinnon-Bates method for reconstruction



- Refine images using edge-preserving spatio-temporal bilateral filtering

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

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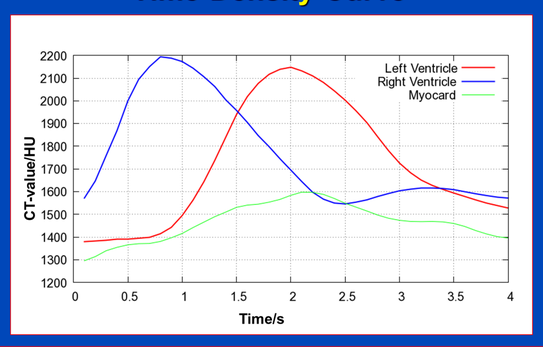
Time-Density-Curve



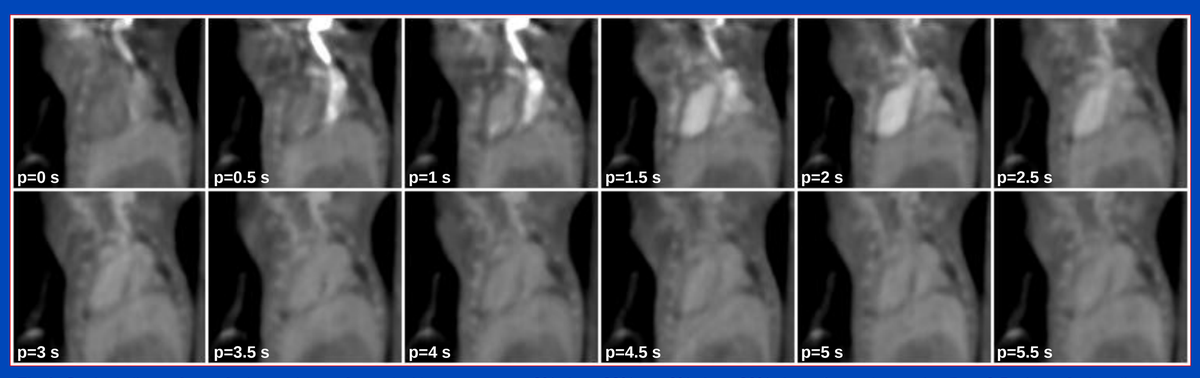


Fig 1: Sagittal slices of a perfusion series performed with a mouse. c = 0%, Δc = 20%, r = 0%, Δ r = 20%, Δ p = 1 s and step size δp = 0.5 s in perfusion direction. The contrast media arrives in the left ventricle after about 1 s, enters pulmonary circulation and arrives in the left ventricle after about 2 s as can be seen from the enhancement in the corresponding slices. This is followed by a transport of the contrast media into the body circulation. (C=1300HU, W=1000HU)

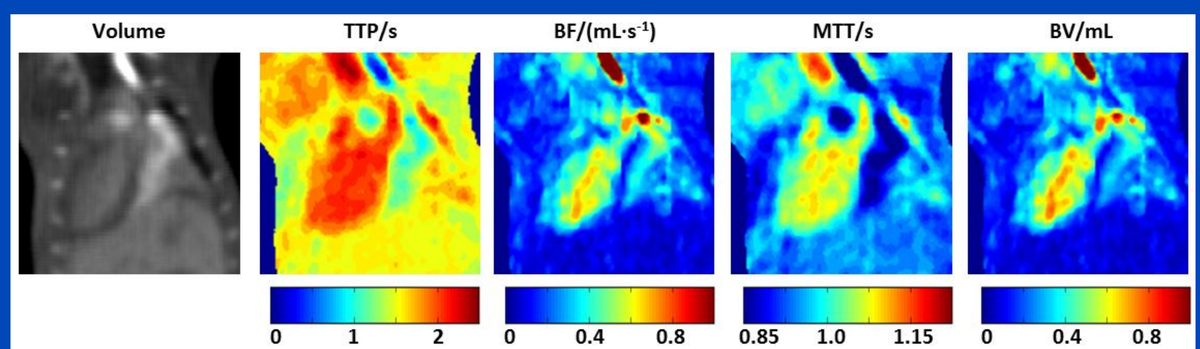


Fig 2: Volume slice of a mouse at t = 1 s (C=1300HU, W=1000HU) and the time to peak (TTP), blood volume (BV), mean transit time (MTT) and blood flow (BF) Maps calculate from these data. The contrast media arrives in the right ventricle after about 1 s and in the left ventricle after about 2 s. The peak blood flow appears in the external jugular vein with a flow of about 0.9 mL/s.

The algorithm shall only be briefly summarized here. LDPC itself is a modified McKinnon–Bates (MKB) algorithm and the resulting image is computed by iteratively correcting a prior image. The resulting images are further enhanced by an edge-preserving bilateral filter. The filtering is performed in six dimensions, i.e. three spatial dimensions and three temporal dimensions for cardiac and respiratory motion as well as bolus evolution.

Results

Figure 1 shows coronal slices of a reconstructed perfusion scan. Volumes were reconstructed in all temporal directions using step sizes of $\Delta c/2$, $\Delta r/2$ and $\Delta p/2$ for the cardiac, respiratory and temporal bolus evolution, respectively, to further limit the influence of the finite temporal resolution. The figure shows a perfusion series starting at the time of injection p=0 s and ending at p=5.5 s after the injection The flow of the contrast agent is clearly visible from the figure. The contrast arrives in the right ventricle, is transported to the respiratory circulation and arrives in the left ventricle. Image noise was measured in the difference images between to adjacent slices in z–direction to provide a fair comparison and to limit the influence of artifacts. The noise evaluation showed that image noise is no greater than 70 HU in any of the reconstructed volumes. Figure 2 shows kinetic information calculated from the perfusion series of a mouse, similar to what is known from clinical practice [2].

Conclusion

The proposed scan and injection protocol in combination with the proposed reconstruction method allows for the reconstruction of phase–correlated volumes in any desired cardiac and respiratory phase at any time after contrast media injection. The resulting images show no obvious streak artifacts and image noise is at a reasonable level to easily allow for the identification of anatomical structures. This boosts preclinical research as for the first time an easy and practical way of performing perfusion studies using small rodents was proposed.

References

[1] 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(3), pp. 1416-1424, 2011.

[2] A. Konstas, G. Goldmakher, T. Lee, and M. Lev. Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke, part 1: Theoretic basis. *American Journal of Neuroradiology*, vol. 30, pp. 662–668, 2009.

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