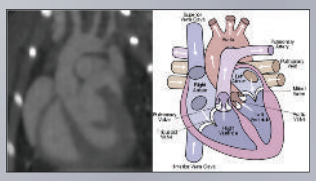
In vivo evaluation of a myocardial infarction in small animals using a novel CT blood pool imaging agent

Alexander Kraupner[1], Danielle Franke[1], Stefan Sawall[2], Jan Kuntz[2], Jan Beckendorf[3], Johannes Backs[3], Marc Kachelrieß[2], and Andreas Briel[1]

[1]*nanoPET Pharma GmbH, Berlin, Germany*
[2]*Medical Physics in Radiology, German Cancer Research Center (DKFZ), Heidelberg, Germany*
[3]*Heidelberg University Hospital, Heidelberg, Germany*

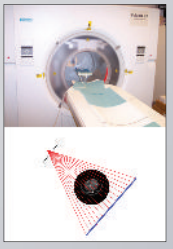


Introduction & Objective

Cardiac imaging in small animals is rather challenging because in these subjects the heart and its vasculature are relatively small. Therefore, an imaging agent that provides high contrast and a prolonged blood half-life is required[1]. Additionally, for the evaluation of cardiovascular function, differentiation between the ventricle lumen and the myocardium is indispensable. In this work we present a novel CT imaging agent, which provides optimal blood pool properties and the feature of myocardial uptake. Consequently, the agent allows *in vivo* visualization and evaluation of a myocardial infarction.

Materials & Methods

Contrast-enhanced micro-CT imaging was performed using a novel iodine-based blood pool imaging agent consisting of a polymeric nanostructure with a mean hydrodynamic diameter of 180 nm and a high iodine content of ~200 mg/mL. The nanostructures were synthesized according to Fessie et al [2], formulated according to physiological conditions and finally sterilized. *In vivo* imaging studies were performed on standard wild type mice using 125 µL of the imaging agent per 25 g mouse (intravenous injection). The acute myocardial infarction was induced by a ligation of the left anterior descending artery (LAD). The images were acquired using a VolumeCT (Siemens Healthcare, Forchheim, Germany) with the following settings: 80 kV tube voltage, 50 mA tube current, 6 mm Al prefiltration, 800 projections, 1024 × 192 pixels/projection and a spatial sampling in the isocenter of 238 µm. High quality CT images were obtained using a noise-reducing LDPC (low-dose phase-correlated) image reconstruction method [3].



Results & Discussion

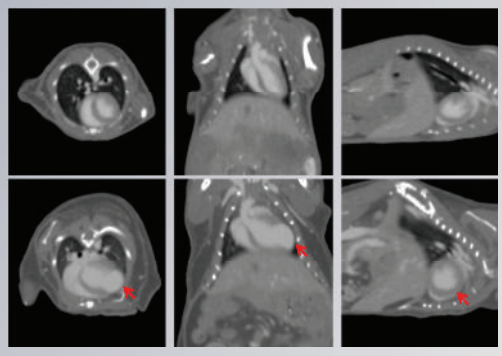


Fig. 1: CT images obtained during the blood pool phase showing axial, coronal and sagittal slices (from left to right) of the thorax/abdominal region of the mouse (C/W=100 HU/2000 HU). The upper images show a healthy control mouse while the lower images show the mouse with myocardial infarction. The red arrows indicate the infarct region.

In vivo results in mice show that the nanoparticulate formulation provides a very high contrast enhancement in the vascular system. The imaging agent is distributed rapidly in the vascular system and reaches the maximum contrast enhancement of about 800 HU immediately after injection (see Fig. 2). The blood half-life is graphically estimated and found to be approximately 120 min. This very high blood half-life and high contrast enhancement indicates the optimal blood pool properties of the imaging agent and allows the visualization of the vascular system down to very fine blood vessels in the whole body of the mouse. Fig. 1 shows the cardiac region during the blood pool phase of the imaging agent. In contrast to the healthy mouse, the infarcted mouse shows an unusual contrast enhancement in the infarcted part of the myocardium. The myocardial uptake appears after the imaging agent has been cleared from the blood and has accumulated in the liver/spleen. The high contrast in the liver also offers the possibility of liver imaging up to several hours post injection (p.i.). The maximum contrast enhancement in the myocardium of about 360 HU is reached between 3 - 4 h p.i. with a uniform distribution of the imaging agent throughout the healthy myocardium. In contrast to the healthy mouse, the infarction can be clearly indicated by the differentiation between the non-enhanced and enhanced regions of the myocardium (see Fig. 3). The imaging agent is mainly excreted via the liver (mononuclear phagocyte system (MPS)) and is cleared completely from the body within 24 h, enabling the possibility of multiple injections and allowing studies where daily injections are required. The high iodine concentration, which allows high signal intensities at low injection volumes, reduces possible negative hemodynamic effects. Indeed, no adverse effects were observed after injection reflecting the optimal biocompatible properties of the novel CT blood pool imaging agent.

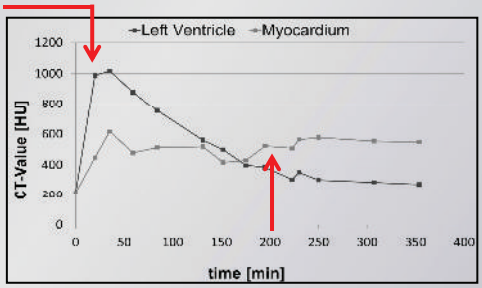


Fig. 2: Time-attenuation curves for the left ventricle and myocardium post injection of the novel nanoparticulate imaging agent.

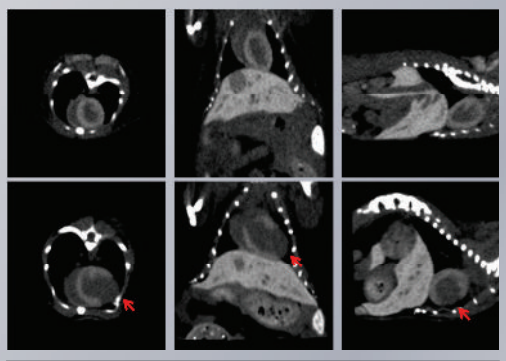


Fig. 3: CT images obtained during the myocardial uptake phase showing axial, coronal and sagittal slices (from left to right) of the thorax/abdominal region of the mouse (C/W=500 HU/850 HU). The upper images show a healthy control mouse while the lower images show the mouse with myocardial infarction. The red arrows indicate the infarct region (non-enhanced region).

Conclusion

In this study we report on an iodine-based nanoparticulate CT imaging agent, which provides optimal blood pool properties as well as high contrast enhancement in the myocardium. Due to the agent's high iodine concentration and long blood half-life, enhanced vascular imaging can be performed where the vasculature can be visualized down to very fine vessel structures. In particular for myocardial imaging, the blood pool phase allows an estimation of functional parameters, e.g. the ejection fraction, while the enhancement phase allows for the estimation of infarct severity and size.

References

[1] Kraupner et al.; World Molecular Imaging Congress Meeting Program; 2013
[2] Fessi et al.; Nano Int J Pharm; 1989; 55; 1:R1-R4
[3] Sawall et al.; Med Phys; 2011; 38(3): 1416-24