MICRO-CT CONTRAST AGENTS FOR DETECTION OF MURINE NON-ALCOHOLIC FATTY LIVER DISEASE

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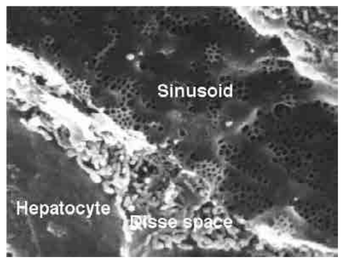
RATIONALE AND AIM

Contrast enhanced micro-computed tomography (micro-CT) represents a potential technique for detection and staging progression of murine non-alcoholic fatty liver disease (NAFLD). One objective of this study was to compare Mvivo™ BIS and Fenestra® LC X-ray contrast agents in their ability to detect fatty liver disease in a non-alcoholic steatohepatitis (NASH) mouse model. It was hypothesized that liver of NASH mice should have a compromised micro-CT enhancement profile compared to normal mice.

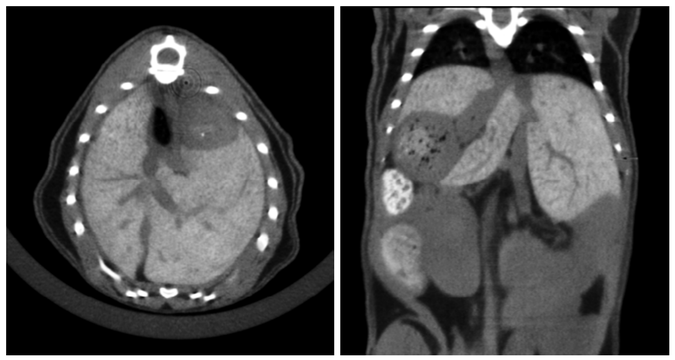
Mvivo™ BIS bismuth(III) oxide

Mvivo™ BIS bismuth(III) oxide nanoparticles are used for anatomical micro-CT imaging of liver and spleen.[1] The nanoparticles have a size of 300 nanometers and do not pass through fenestrae of liver sinusoids which have a size under 200 nanometers. Mvivo™ BIS nanoparticles are instantaneously taken up by kupffer cells in liver after tail vein IV injection and can be used for anatomical liver imaging since 15% murine liver is composed of kupffer cells.[2] The starch covered nanoparticles are composed of BIS bismuth(III) oxide and can be administered at very low doses due the high X-ray attenuation coefficient of bismuth.



Sinusoidal blood vessel of a rat liver with fenestrated endothelial cells. These fenestrae in Sprague Dawley rats and C57BL/6 mice have an approximate size of 160 and 140 nm respectively. Image courtesy of Prof. Robin Fraser, University of Otago, NZ.

Figure 1: Axial view (left) and coronal view (right) of micro-CT anatomical images representing liver and spleen (coronal) 20 minutes after injection of Mvivo™ BIS (IV dose of 1 ml/kg) in normal C57Bl/6 mouse.



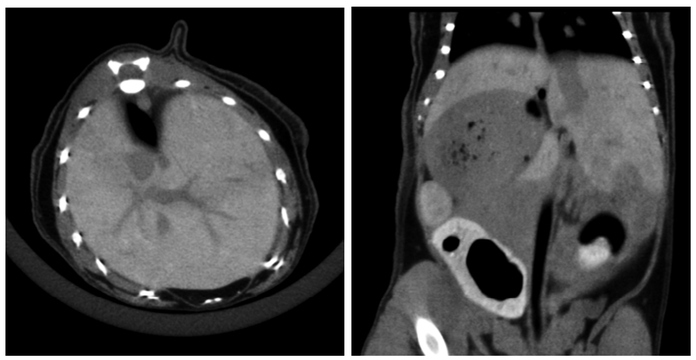
Fenestra® LC

Fenestra® LC contrast agent is an oil-in-water emulsion used for anatomical and functional imaging of liver. The emulsion contains lipomimetic iodinated triglycerides (ITG).

The lipid spheres of Fenestra® LC nanoemulsion act as the delivery vehicle for ITG and have an average size under 150 nanometers which allows them to pass through fenestrae of liver sinusoids and access hepatocytes. It is thought that the lipid spheres mimic chylomicron remnants by incorporating apoliporotein E (APO-E) from plasma for selective targeting of hepatocytes.

Fenestra® LC can be used for functional imaging of liver since the biomimetic targeting, endocytosis, metabolism and elimination of triglycerides in the emulsion depends on intracellular and extracellular liver lipase catalysis and other functional metabolic processes of healthy liver.[3] In healthy mice, 70% of the total Fenestra® LC dose is localized to hepatocytes as soon as 30 minutes after IV administration.[3] The Fenestra® LC nanoemulsion remains in organism for up to 24 hours before being eventually eliminated by hepatobiliary system.

Figure 2: Axial view (left) and coronal view (right) of micro-CT images representing liver and spleen (coronal view) 24 hours after injection of Fenestra® LC (IV dose of 6 ml/kg) in normal C57Bl/6 mouse.



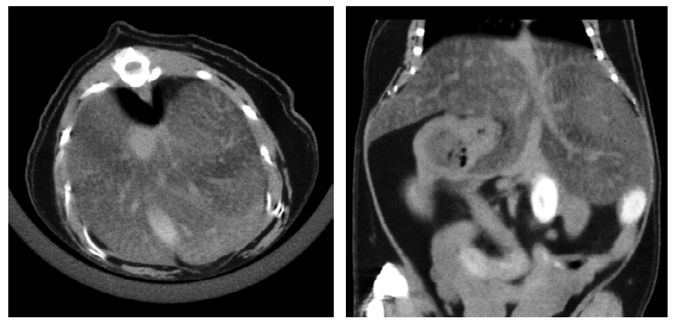
METHODS

Animals we're provided by laboratory of Prof. Dr. med Ulf Peter Neumann at the clinic for general, visceral and transplant surgery at the University of Aachen. To induce NASH, C57BL/6 neonatal mice were fed a high-fat, high fructose and high-cholesterine diet (western diet) for 30 weeks alongside control mice of same age and sex. Micro-CT measurements were obtained using a dual energy gantry-based flat-panel micro-computed tomography scanner (TomoScope 30s Duo; CT Imaging, Erlangen, Germany) in the laboratory of Prof. Twan Lammers at the Institute for Experimental Molecular Imaging at RWTH Aachen University. The dual-energy X-ray tubes of the micro-CT were operated at voltages of 40 and 65 kV with currents of 1.0 and 0.5 mA. Mvivo™ BIS contrast agent was administered at a dose of 1 ml per kg via tail vein IV injection followed by acquisition of microCT measurements 20 minutes post injection in both control and NASH mice. Fenestra® LC was administered at a dose of 6 ml per kg with tail vein IV injection followed by acquisition of microCT images 24 hours post injection in both control and NASH mice.

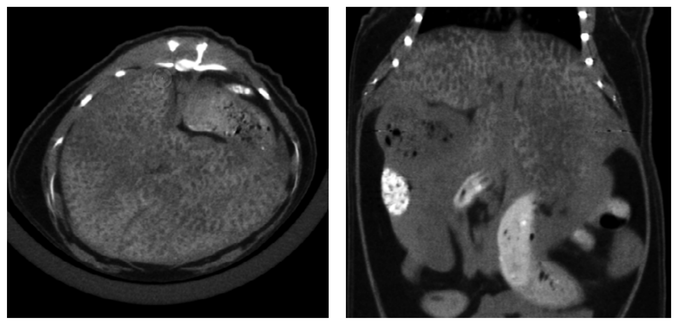
RESULTS

In normal mice, both Fenestra® LC and Mvivo™ BIS provide micro-CT contrast enhancement in the mouse liver and the ability to delineate liver blood vessels through a negative contrast enhancement effect. In healthy mice, Mvivo™ BIS provides a stronger spleenic and spleen to liver CT enhancement ratio compared to Fenestra® LC (Fig. 1,2). With Fenestra® LC, the contrast agent remained in liver blood vessels 24 hours after injection in NASH mice suggesting that the hepatobiliary system of the compromised NASH mouse liver could not take up the triglycerides of the Fenestra emulsion (Fig. 3). Injection of Mvivo™ BIS in NASH mice provides contrast enhancement in spleen and gives non-uniform contrast enhancement in liver suggesting that the contrast agent can be used for monitoring changes in anatomy of liver RES compartment during progression of fatty liver disease. Further work will need to be done to determine if these contrast agents can be used for early detection and monitoring the progression of NAFLD.

Figures 3: Axial view (left) and coronal view (right) of micro-CT images representing liver blood vessels 24 hours after injection of Fenestra® LC at an IV dose of 6 ml/kg in NASH induced C57Bl/6 mice.



Figures 4: Axial view (left) and coronal view (right) of liver and spleen (coronal view) representing RES compartments 20 minutes after IV injection of Mvivo™ BIS.



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2. Sitia G , et al. PLoS Pathog. 2011 Jun;7(6):e1002061.
3. Bakan DA, Weichert JP, Longino MA, Counsell RE. Invest. Radiol. 2000; 35:158.

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