2009A1879 / Medical Bio EX

Application of a novel bismuth nanoparticle contrast agent to synchrotron X-ray imaging

Project Leader James Pearson, Department of Physiology, Monash University
Team: Keiji Umetani, Mikiyasu Shirai, Takashi Sonobe, Mat Jenkins.
Performed at BL28B2

Research purpose and background

Cardiovascular disease causes much of the morbidity and mortality in the developed world. In particular, chronic vascular diseases such as atherosclerosis and hypertension kill many people every year as a result of stroke, myocardial infarction and chronic kidney disease. An even greater number of patients undergo X-ray imaging to determine the extent of vascular dysfunction or occlusion with the aid of contrast agents based on iodinated compounds. While X-ray angiography and computed tomography require ionizing radiation, magnetic resonance imaging does not. Clinical X-ray angiography provides the best spatial and temporal resolution of arterial vessels (200-300 microns), and can be implemented for imaging any organ system. On the other hand, MR imaging can take minutes to record when cardiac and respiratory gating are employed to minimize the motion artefacts that limit this modality's utility for vascular imaging. More importantly, in order to understand the pathophysiology of many cardiovascular diseases it is important to be able to resolve smaller arterial vessels, the so-called resistance vessels. In organs such as the heart, lung and kidney visualizing small vessels by clinical angiography requires selective arterial infusion of contrast media to (i) distinguish arterial vessels within the complex vascular networks and (ii) achieve a sufficiently high concentration of iodine in the small vessel to enable detection. Many of us now believe that synchrotron X-ray imaging has become the gold standard for vascular imaging, as it is now possible to visualize 20-80 μm diameter vessels with iodinated agents.

Rabin *et al*. [1] report that 0.5 M solutions of the inert bismuth sulphide nanoparticles (BSN) produced similar X-ray absorption to that of iodinated contrast media (350 mg/ml iodine) routinely use in the clinic, and by us at Spring-8. Low resolution CT images were included in that study to demonstrate radiopacity of the heart, aorta and large arteries in mice. Unlike commercial iodinated agents, bismuth nanoparticles in solution are equi-osmolar with blood and low viscosity. Further, these authors reported a circulation time for a bolus of nanoparticles lasting several hours, before the particles were removed by the liver. We speculate that the high X-ray absorption of bismuth nanoparticles and long circulation times could provide higher resolution synchrotron microangiography images than is currently achievable with iodinated agents. Even at 33 keV, well below the K-edge of Bi, the X-ray attenuation of Bi is at least 5 times that of soft tissue. Since a single bolus injection of bismuth sulphide nanoparticles circulates for an extended period of time it might be possible to achieve continuous image recordings of the vasculature under different drug administration protocols in the same animal.

Experimental / analytical method

The main objectives of this study was to determine whether bismuth sulphide nanoparticles can provide more detailed and higher resolution images of the microvasculature than is currently achievable with iodinated agents, and to determine which organ systems are amenable to imaging in the mouse. BSN was dissolved in phosphate buffered saline and warmed to 37 ^{o}C under sonication for 30 min. In mice (C57Bl6, 10 weeks old) anaesthetized with pentobarbitone (50 mg/kg) we injected a 100 μl bolus of BSN through an arterial cannula (carotid artery) and

recorded images with the SATICON imaging and shutter system described in our earlier proposals (field of view 9.5 mm square).

Research results

BSN was injected into mice by remote injection, but arterial vessels were not clearly defined in the angiograms of any mouse. Imaging of a glass container with BSN stock solution revealed that radiopaque particles were present. Hence we found that BSN in our hands did not remain radiopaque in the *in vivo* mouse body for several hours as originally claimed, and that 0.5 M solution was insufficient for accurate recording of small vessel calibre.

Current and future issues / challenges

Further work in our lab is required to improve the BSN formulation for dynamic X-ray imaging requirements. Our collaborator Dr Massimiliano Massi (Curtin University of Technology, Australia) has now formulated an improved bismuth sulphide particle solution that remains soluble for extended periods. Subsequent to inhouse testing of the new particle solution's stability under simulated physiological conditions, in the presence of citrates and phosphates, we will attempt further testing of X-ray opacity *in vivo*.

Reference

[1] Rabin O, Manuel Perez J, et al. *Nat. Mater*. 5:118-22, 2006.

Status of publication and patent

It is hoped that a publication will be possible after further testing of modified particle solutions.

Keywords and annotations

contrast angiography – method of enhancing visualization of the structure and function of the vasculature by increasing blood X-ray absorption by infusion of contrast agents.