High-Resolution Contrast-Enhanced Magnetic Resonance Angiography of the Mouse Circle-of-Willis

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Introduction: In clinical practice, magnetic resonance angiography (MRA) is an extremely valuable tool for non-invasively evaluating neurovascular pathology, such as atherosclerosis, aneurysms and arteriovenous malformations (AVMs). In the laboratory, transgenic mouse models for these diseases are available; however, translation of MRA techniques for use with MR microscopy has been thwarted by the lack of spatial resolution and low signal-to-noise ratios. The best *in vivo* spatial resolution reported to date has been 100 μm^3 isotropic voxels [1,2]. In this work we use a surface-conjugated Gadolinium (SC-Gd) liposomal blood pool contrast agent [3] to achieve adequate signal-to-noise to facilitate high-resolution (50x50x100 μm^3) MRA of the mouse brain. Images generated at this resolution are able to demonstrate anatomic detail in the mouse that begins to approach anatomic detail seen in clinical MRA of humans. We present here a survey of the normal vascular anatomy of the C57/BL6 mouse as visualized by this high-resolution MRA technique.

Materials and Methods: Five C57BL/6J mice (~25 g) were used for the study. Free-breathing animals were anesthetized with isoflurane delivered by nose-cone. The body temperature was maintained at 36 ± 0.2 °C. SC-Gd was administered via the tail vein at a Gadolinium dose of 0.08 mmol/kg. Imaging was performed using a 35 mm quadrature volume coil with a 7T GE EXCITE MRI system. A voxel size of 50 x 50 x 100 μm^3 was acquired using a 3D SPGR sequence with the following parameters: TE = 3 ms; TR = 20 ms; FA = 30°; FOV = 20 x 20 x 8 mm^3; Image matrix = 384 x 384 x 80; NEX = 4; BW = 15.6 kHz; total scan time was 43 minutes. Maximum intensity projection (MIP) images were created and analyzed using Vitrea® software.

Results and Discussion: The prior *in vivo* report demonstrated first order vessel within the Circle of Willis [2]. In the current *in vivo* work, not only are these vessels more clearly seen, but the demonstrated neurovascular tree more closely approximates that shown in a prior 14-hour ex-vivo study [4]. Numerous second and third order vessels, communicating vessels, and perforating vessels are demonstrated. A few examples of the fine vasculature that could be visualized is presented below.

Circle of Willis: Typical large vessel anatomy was observed: including the vertebral arteries (VA), basilar artery (BA), anterior inferior cerebellar arteries (AICA), internal auditory arteries (IAA), superior cerebral arteries (SCA), posterior cerebral arteries (PCA), middle cerebral arteries (MCA), posterior communicating arteries (PCOM), internal carotid arteries (ICA), and anterior cerebral arteries (ACA) (Figure 1).

Higher-Order Arteries: In the posterior circulation, pontine perforating arteries that arise from the basilar artery are demonstrated (Figure 2). In the anterior circulation, the lateral hypothalamic arteries (LHA) and olfactory arteries (OA) arise from the A1 segments of the ACAs, which then fuse to form the typical azygous configuration of the second-order A2 segment (azACA). The azACA supplies the medial orbitofrontal artery (MOF), which has a cortical and olfactory branch and anterior internal frontal artery (AIF) (Figure 3). The azACA then becomes the azygous pericallosal artery (azPA), which supplies the middle and posterior internal frontal arteries (MIF, PIF) before terminating in the retrosplenial artery (RS).

Venous system: While most previous *in vivo* MRA in the mouse has utilized time of flight contrast, a blood pool contrast agent was used in this work. In the presence of the agent, the vessel signal is not dependant on in-flowing unsaturated spins; therefore, the veins are clearly visible. The superior sagital sinus (SSS), the great vein of Galen (GVG), and the thalamostriate vein (TSV) can all be seen, along with numerous small tributaries (Figure 3).

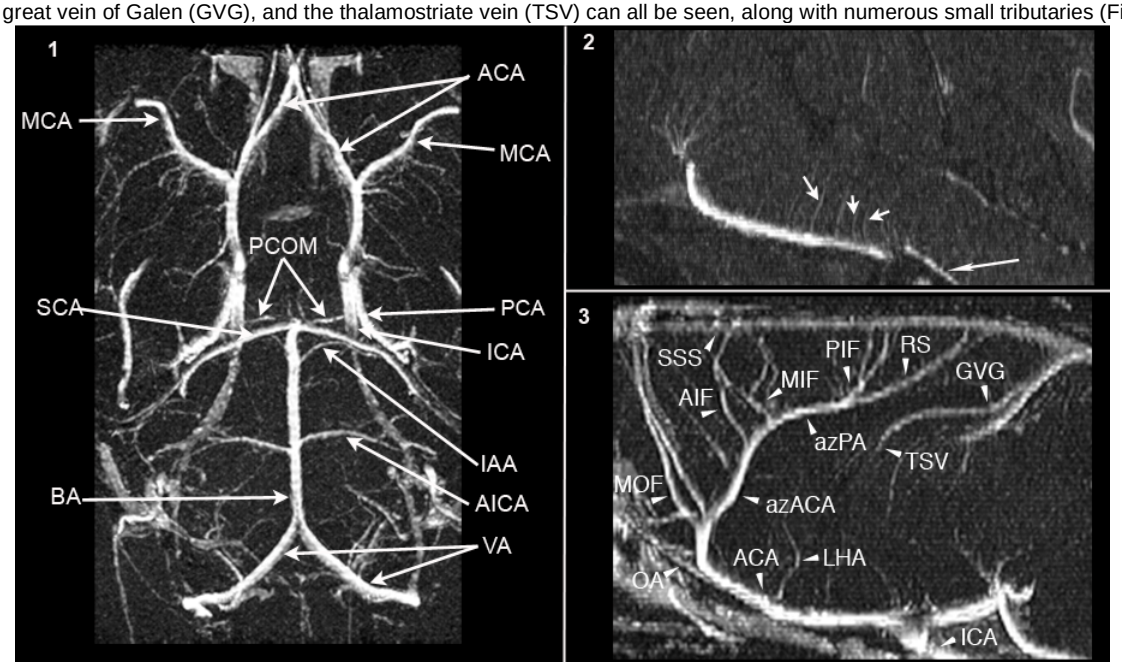

*Figure: **(1)** Axial maximum intensity projection (MIP) image demonstrating the Circle of Willis in a mouse brain; **(2)** Sagittal MIP image demonstrating the pontine arteries (short arrows) arising from the basilar artery and, the posterior spinal artery (long arrow); **(3)** Sagittal MIP image demonstrating the branches of the anterior cerebral artery and the venous system.*

References: [1] Brubaker LM, et al. Cancer Res. 2005; 65: 8218-23. [2] Beckmann N, et al. 1999; 140: 442-50. [3] Ghaghada KB, Ojerholm E, Howles G, Johnson GA, Mukundan S. (*Manuscript in preparation*). [4] Dorr A, et al. Neuroimage. 2007 ; 47: 510-7.

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