MRI Tissue Window Chamber System for Validation and Optimization of Dynamic Contrast Enhanced Tumor Imaging

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Purpose: Currently two important goals of cancer research are, (1) to understand how cancer cells spread from a primary tumor into normal tissues, and (2) developing methods by which to track treatment effects on tumor architecture and total tumor burden in an animal or human subject. An important obstacle to the attainment of both goals has been the inability to effectively image tumors in their normal environment deep within the body [1]. High resolution Magnetic Resonance (MR) imaging holds significant promise in this context allowing longitudinal studies to be performed on the same subject. However with deep tumor MR imaging there is no means by which to validate *in vivo* methods and results, especially those of a dynamic nature such as permeability quantification using contrast agents. In Ref. [2] and [3] an experimental setup was described for combined optical and MR image acquisition. We report here on the design and fabrication of a MR and light microscope compatible dorsal skinfold window chamber, and initial time course data following Gd injection. Such a system is necessary to facilitate validation of the MR images with the light microscope. The findings could then be extended to images obtained with deep MRI.

Materials and Methods:

Window chamber and integrated RF-coil design: Delrin® plastic was machined into two complementary plates held together by clips. The plate containing the viewing window was machined with grooves for the glass cover slip and a removable MR-coil. Figures 1 a) and b) show, respectively one window chamber plate (companion plate not shown), and the coil placed on its removable mount. The mount simply plugs onto the window chamber plate when MR imaging is performed. The RF-coil twists into the outer groove around the glass coverslip bed. The coil consists of an inductively-coupled receive-only 1.2 cm diameter single loop, made of copper and tuned to NMR frequency with four lumped capacitances. This design provides good magnetic coupling to a small sample ROI, ensuring an enhanced sensitivity as compared to a conventional mouse volume coil. The coil is removable, so that several MRI compatible chambers may be implanted on different subjects at once, and then successively MR imaged by simply transferring the coil.

Animal Preparation: Mice were anesthetized and a longitudinal dorsal skinfold was gently sandwiched between the two Delrin chamber plates. A 1.2 cm circular area of skin was removed from one side of the fold, then 4 µl of PBS containing 8×10^5 fluorescent FG tumor cells was injected and a sterile glass coverslip was secured over the exposed tissue. Two weeks later for MR imaging, the mouse was anesthetized with ketamine-medetomidine and silastic tubing (Dow Corning 0.64 mm ID) filled with normal saline was advanced 1 cm into the left external jugular vein. The mouse was secured to a Plexiglas stand and gently wrapped in a soft towel next to a rubber bladder filled with warm water. Dynamic MR imaging was commenced and approximately 3 mmol/kg (240 µL of a 20x dilution in saline) of Gd-BOPTA (Multihance®, Bracco Diagnostics) was slowly injected via the jugular catheter into the mouse.

MRI: MR images were acquired on a 3T clinical system (General Electric). Dynamic study was performed using a 3D TRICKS pulse sequences allowing to cover the volume of interest with a 5.2 s temporal resolution (FOV=2.6 cm, Mx=126×96, TR=16.6ms, TE=4.3µs, FA=30º, BW=10.7kHz, 12 slices, Sl.Th.=0.8mm). Partial Fourier encoding of 0.75% was chosen to improve temporal resolution. For comparison with optics, a better in plane resolution was achieved using a T_1 weighted 2D Fast Spin Echo sequence (FOV=2.6 cm, Mx=256×256, TR=550ms, TE=17ms, ETL=2, BW=31.25 kHz, Sl.Th.= 1 mm, Tacq=4:42 min).

Optical: In order to compare with the MRI findings, chamber tissues were imaged to high resolution (1 micron) using a light microscope. For fluorescence imaging the mouse was comfortably secured within perforated plastic restraining tube, and the tube was placed within a custom designed holder. The window chamber was bolted to the holder via a stainless steel plate, and the chamber window was both brightfield and fluorescence imaged at various magnifications using a Nikon intravital fluorescent dissecting microscope.

Results and Discussion:

Figure 2 displays the T_1-weighed spin echo image a) and the corresponding optical image b). Those were obtained on a tumor-free mouse, just focusing on the vasculature details. Note the vasculature pattern that is very similar in both images. Figure 3 a) shows a blended brightfield and fluorescence image of a human pancreatic tumor growing in the window chamber. Figure 3 b) displays the contrast uptake with respect to time (at 5.2 s resolution) in the tumor and the surrounding tissue. The tumor signal enhancement occurs sooner than for the healthy tissue and tends to reach a plateau while still increasing in healthy tissue. This observation is consistent with a higher permeability coefficient of tumor as usually reported by DCE-MRI data analysis [1]. For comparison two MR images extracted from the dynamic data set are displayed in c). The pre-injection image exhibits poor contrast whereas the 3 min post-injection image evidences the tumor enhancement. The signal transient drop at the beginning of the dynamic scan and the overall kinetics are amenable to DCE-MRI analysis.

Conclusion and Perspectives: Good correlation between MR and optical imaging was obtained, using the MR compatible window chamber apparatus described here. In this perspective a quantitative validation of permeability measurement should be possible, and might greatly benefit for DCE-MRI in general. The proposed design incorporating a highly sensitive RF coil tightly coupled to the sample of interest is a key feature since it allows sufficient SNR to achieve a temporal resolution of a few seconds. The removable design means that multiple animal studies can be performed with the identical coil, making comparisons easier. We believe such an apparatus will be of great help in view of DCE-MRI validation.

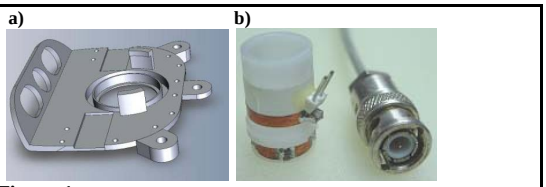

Figure 1: MR-compatible mouse window chamber design
a) Window chamber plate
b) Detachable coil and mount. BNC connector shown for scale

References:

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2. Gmitro AF, et al., Proc. ISMRM **15** (2007): 132
3. Gmitro AF, et al., Proc. ISMRM **14** (2006): 51

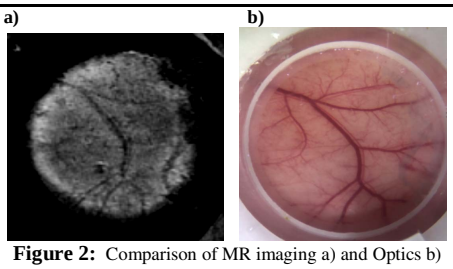

Figure 2: Comparison of MR imaging a) and Optics b)
No tumor cells were injected in this mouse
Window diameter is 12mm

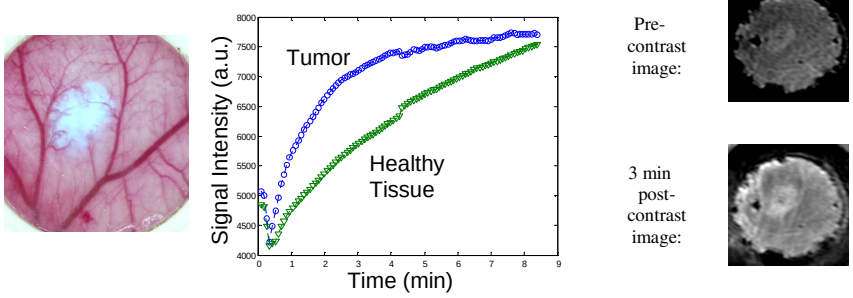

Figure 3: a) Human pancreatic tumor (FG) visible as a white mass in the nu/nu mouse dorsal skinfold MRI window chamber. b) Time intensity curves corresponding to the tumor and healthy tissue. c) Corresponding pre and 3min-post MR images. The tumor can be seen in the middle of the chamber along with areas of vascular pooling