Relaxivity tissue differentiation among Gd-based contrast agents in ex-vivo mouse embryo imaging

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Introduction - The role of MRI in developmental biology, specifically in mouse embryo organogenesis and phenotyping, is significantly increasing due to technologies that allow for high image resolution and throughput [1]. The soft tissue contrast in MRI makes it a candidate for observing the normal development of the mouse embryo or alternatively genetic abnormalities that may affect organogenesis. Several studies, such as developing a mouse embryo atlas [2] and the analysis of genetic mutations in the heart during mouse embryo development [3] have been accomplished through the use of MR images. Recent studies have introduced gadolinium-based contrast agents into mouse embryos, ex-vivo, by dissolving some concentration of the contrast agent into a fixative solution of which the embryo is immersed for approximately a week. In addition, studies using different concentrations of a given contrast agent and immersion durations have been published using of Gd-DTPA ([Magnevist], Bayer, Toronto, Canada) [4] and gadoteridol ([ProHance], Bracco Diagnostics, Princeton, NJ) [5]. It is widely believed that all gadolinium-based contrast agents have identical tissue interactions and provide similar MRI images despite the differences in Gd-chelates. Analysis of the relationship of relativities (r1 and r2) at different concentrations of four clinical gadolinium-based contrast agents is presented for various mouse embryo organs.

Sample Preparation - C57BL/6 mice were mated and the detection of a vaginal plug the following morning was considered 0.5 dpc (days post coitum). Pregnant mice were sacrificed by cervical dislocation. The embryos were then dissected at 15.5 dpc and fixed in 4% paraformaldehyde (PFA) for ~ 1 week. Gadolinium contrast agents gadobenate dimeglumine ([MultiHance, Bracco Diagnostics, Princeton, NJ), gadodiamide ([Omniscan], GE Healthcare Canada, Mississauga, Canada), Magnevist and ProHance were dissolved into the PFA at concentrations of 1mM, 2mM, 4mM, and 8mM. After fixation the embryos were placed in a centrifuge tube filled with 1% agar into which the same concentration of the contrast agent was dissolved. A total of 16 mouse embryos were analyzed.

MRI Imaging - MR images of mouse embryos were acquired with a multi-channel 7.0-T MRI scanner (Varian Inc., Palo Alto, CA) with a 6cm diameter insert gradient set. The samples were imaged in parallel, 3 at a time, with a custom built array of three 14 mm solenoid coils with overwound ends. T1 and T2 mapping were created using a single sagittal slice (FOV 28 × 14 mm, 128 × 256 matrix size, 0.5 mm thickness). For T1 mapping an inversion recovery spin-echo was utilized using 16 TI's ranging from 10 – 2000 ms, TE = 7.47 ms , TR = 2100 ms, and NSA =2. T2 mapping was performed with repeated 2D spin echo acquisitions with 11 TE's ranging from 8-100ms, TR = 2000 ms and NSA =2. The high resolution whole volume images of 4 mM Omniscan and MultiHance treated mouse embryos were acquired with a 3D gradient echo sequence with a TR = 50 ms, TE = 5.06 ms, 60º flip angle and NSA = 4 for an 11 hour scan. The FOV = 14 × 14 × 25 mm with a matrix of 780 × 432 × 432 for an isotropic resolution of $(32\ \mu m)^3$ without zero filling or extrapolation.

Methods – In the T1 and T2 maps, regions of interests were selected in the agar, heart, brain and liver of each mouse embryo to determine the average T1, T2 and subsequently relaxation rates, R1 and R2, within each organ. An embryo not subjected to any contrast agent was used as the control ($R1^0$, $R2^0$). (R1 - $R1^0$) and (R2 - $R2^0$) values of each organ were fitted to a linear-model as a function of contrast agent concentration for each Gd-based contrast agent to determine the relaxivity (r1, r2).

Results – The results separated the tested contrast agents into two groups. One group, ProHance and Omniscan, demonstrated no variance in relaxivity (r1) between the four tissues analyzed (Figure 1a –only Omniscan shown) as the calculated r1's were equal within their uncertainties. The opposite is true for the second group Magnevist and MultiHance, where the r1's were statistically different between all four tissue types (Figure 1b – only MultiHance shown). However, all four contrast agents showed similar r2 data for all embryo tissue types (Figures 1c and 1d, only Omniscan and MultiHance shown). In terms of high resolution imaging, the first group of Omniscan (Figure 2a) and ProHance demonstrates poor contrast in T1 – weighted images compared to MultiHance (Figure 2b) and Magnevist.

Discussion – The fact that this study produced two distinct behaviors of two classes of Gd- based contrast agents may be explained by accessibility. ProHance and Omniscan are non-ionic molecules while Magnevist and MultiHance are ionic. The iconicity of the gadolinium chelate may dictate its ability to penetrate organ membranes or its ability to stick to the tissue. The phenomenon may be attributable to the physical characteristics of the contrast agent solution. MultiHance and Magnevist solutions both have significantly higher osmolality, viscosity and density than ProHance and Omniscan.

Conclusion – The results show that all Gd-based contrast agents are not the same in the context of ex-vivo mouse embryo imaging. Based on our analysis, those pursuing T1-weighted sequences should avoid ProHance and Omniscan, while those using T2 or T2* weighted sequences can use any of the Gd-based contrast agents. How this phenomenon extends beyond mouse embryo imaging is yet to be investigated.

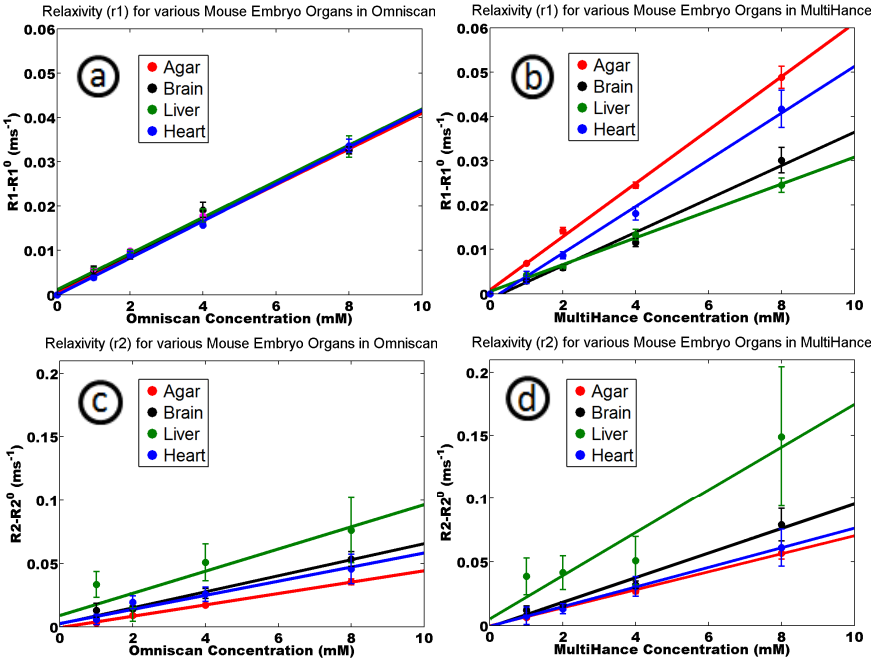

Figure 1: Relaxivity (r1) data and linear model fits of (a) Omniscan and (b) MultiHance for 4 tissue types as a function of concentration. Corresponding r2 data is shown in (c) and (d).

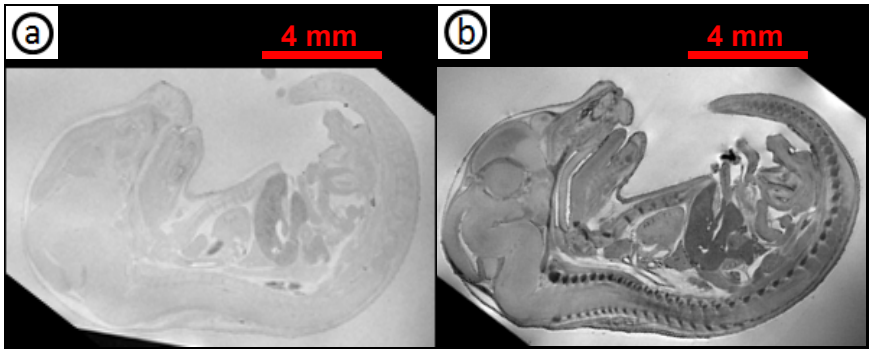

Figure 2: T1-weighted 3D gradient echo images of a E15.5 mouse embryo prepared with (a) Omniscan and (b) MultiHance.

References
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