Quantitative MRI may help detect bone repair in a piglet model of Legg-Calvé-Perthes disease

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Introduction: Legg-Calvé-Perthes disease (LCPD) is an idiopathic, pediatric hip disorder caused by reduced blood flow (ischemia) to the femoral head, which leads to bone marrow and bone necrosis [1]. The avascular necrosis stage of LCPD is followed by spontaneous revascularization, infiltration of fibrovascular tissue, bone resorption and fragmentation, and new bone formation [1]. While gadolinium contrast-enhanced MRI (CE-MRI) is the clinical standard in diagnosing femoral head ischemia, non-invasive imaging methods to detect femoral head repair are limited [2]. Furthermore, alternatives to CE-MRI are desired given concerns about the use of gadolinium contrast agents in children [3]. It has been shown that non-contrast-enhanced, quantitative MRI techniques such as T2, adiabatic T1ρ (aT1ρ), and adiabatic T2ρ (aT2ρ) relaxation time mappings are sensitive in detecting ischemic injury in a piglet model of LCPD [4,5]. However, the sensitivities of these techniques have not been assessed to detect the subsequent repair processes. The objective of this study was to evaluate if T2, aT1ρ, and aT2ρ are sensitive in detecting reparative changes following ischemic injury to the femoral head in a piglet model of LCPD.

Methods: We retrospectively evaluated MRI images from studies of piglet models of LCPD that had histological evidence of femoral head repair following ischemic injury. Specifically, we included femoral head data sets for which: (i) we acquired an MRI protocol consisting of a high-resolution, morphological 3D DESS image, quantitative 3D SPACE T2, aT1ρ, and aT2ρ relaxation time maps, and 3D subtracted CE-MRI; and (ii) there were both viable (i.e., control) and affected (i.e., necrotic, reduced cellularity, and/or fibrovascular repair) regions identified histologically. In total, we identified seven femoral heads (from four piglets) that met these criteria. Three of the piglets (6-10 weeks old) were imaged 1 week following surgical induction of bilateral femoral head ischemia using an intravascular embolization approach. One piglet (6 weeks old) was imaged 1 week following surgical induction of unilateral femoral head ischemia using a conventional ligation approach [5]. The piglet model studies were approved by our local IACUC. All piglets were imaged *in vivo* at 3T MRI and euthanized following the exam to allow the harvesting of the femoral heads for histological processing. Femoral head specimens were bisected, fixed in 10% NBF, decalcified in 10% EDTA, and routinely processed for H&E staining. A board-certified veterinary pathologist annotated the H&E-stained photomicrographs at 0.5X magnification to demarcate regions of the epiphyseal bone that were: (i) viable; (ii) necrotic; (iii) reduced in bone marrow cellularity (but without overt necrosis); and (iv) undergoing repair (fibrovascular tissue). For each femoral head, the 0.5X photomicrograph and its annotations were spatially co-registered to the 3D DESS image, as illustrated in Figure 1. The 3D relaxation time maps and 3D subtracted CE-MRI image were also spatially co-registered to the 3D DESS image. Annotations were used to define regions of interest (ROIs), and the median T2, aT1ρ, and aT2ρ relaxation times and contrast-enhancement ratio (CER; the ratio of CE-MRI signals between the affected and viable ROIs) were measured for each ROI. The percent change in the measured values of the affected ROIs were also calculated relative to the values in the viable ROI for each femoral head.

Results: In total, 20 affected ROIs between all 7 femoral heads were identified histologically: 3 necrotic, 12 reduced cellularity, and 5 fibrovascular repair. All femoral heads also had 1 viable ROI. On average, all three relaxation times (T2, aT1ρ, and aT2ρ) were increased in the affected vs. viable ROIs (Figure 2). However, there was an overall decrease in the relaxation times between the reduced cellularity and the fibrovascular repair ROIs. On average, the CER was decreased in the necrotic ROIs and increased in the reduced cellularity and fibrovascular repair ROIs. Figure 3 shows a representative example of a femoral head with regions of reduced cellularity with corresponding increases in aT2ρ relaxation times and CER.

Discussion: Our findings suggest that T2, aT1ρ, and aT2ρ relaxation times, which are known to increase in the femoral head with ischemic injury [4,5], are decreased as the injured regions undergo repair. This is potentially significant since relaxation time mapping may provide a means to non-invasively assess the stages and progression of LCPD through the bone repair process. In particular, the relaxation times may normalize as the bone heals. The primary clinical utility of CE-MRI is to distinguish ischemic vs. perfused regions of the femoral head (which is reflected in the decreased vs. increased CER in the necrotic vs. reduced cellularity and fibrovascular ROIs). Interestingly, we found that CER was greatest in the reduced cellularity ROIs, which may relate to neovascularization and/or hemorrhage in these regions. Limitations of this retrospective study include a lack of longitudinal data and heterogeneity of the histological findings. In conclusion, T2, aT1ρ, and aT2ρ relaxation time mapping are potentially sensitive in detecting early repair (i.e., infiltration of fibrovascular tissue) of the ischemically injured bone of the femoral head.

Clinical Relevance: Quantitative T2, aT1ρ, and aT2ρ mappings are non-invasive, non-contrast-enhanced techniques that may be sensitive in detecting ischemic injury and subsequent repair to the femoral head. These techniques may be clinically useful to monitor progression and inform treatment of LCPD.

References: **[1]** Kim HKW. *JBJS* 2012; 94(7):659-69. **[2]** Laine JC, et al. *J Am Acad Ortho Surg* 2018; 26(15):526-536. **[3]** Gulani V, et al. *Lancet Neurol* 2017; 16:564-570. **[4]** Johnson CP, et al. *Radiology* 2018; 289(2):386-395. **[5]** Johnson CP, et al. *J Orthop Res* 2022; 40(2):484-494.

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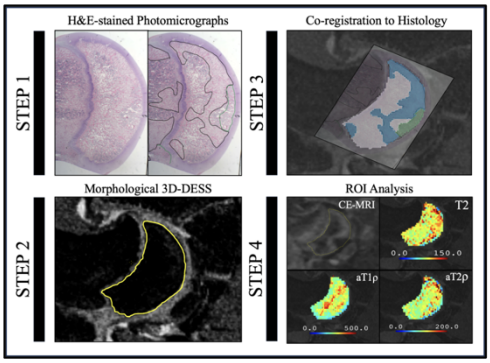

Figure 1: Histology-MRI co-registration process. Annotated histological sections were overlaid on a matching 3D DESS slice. The T2, aT1ρ, and aT2ρ maps and CE-MRI images were also co-registered to the 3D DESS image. Median relaxation times and contrast-enhancement ratio were then calculated for each of the annotated regions.

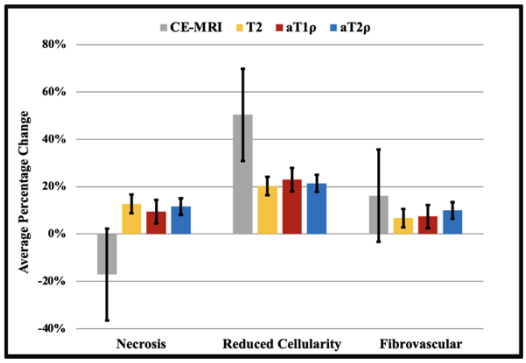

Figure 2: Average percentage change (±standard error) in contrast-enhancement ratio (CER) and T2, aT1ρ, and aT2ρ relaxation times in each affected ROI compared to the viable ROI within each femoral head.

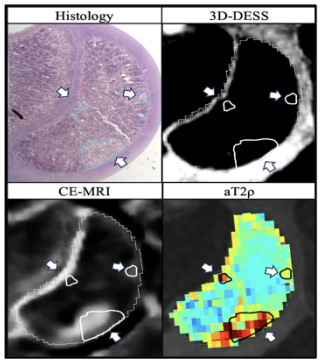

Figure 3: Example images for one femoral head illustrating the correlation of reduced cellularity ROIs across histology, 3D DESS, CE-MRI, and aT2ρ. White arrows indicate segmented ROIs for independent analysis.