MRI Relaxation Times Detect Changes in the Metaphysis Following Ischemic Injury to the Femoral Head: An In Vivo Piglet Model Study

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INTRODUCTION: Legg-Calvé-Perthes disease (LCPD) is a childhood idiopathic form of osteonecrosis of the femoral head that occurs when the blood supply to the developing femoral head is interrupted, which may interfere with the normal hip development and function and can lead to permanent deformity and premature onset of osteoarthritis [1]. In early-stage LCPD, femoral head changes are mostly seen in the secondary ossification center (SOC; i.e., the bone and bone marrow of the femoral epiphysis that is proximal to the growth plate), but changes in the growth plate and metaphysis (i.e., the bone and bone marrow distal to the growth plate) have also been reported [2-5]. Studies have shown that quantitative mappings of T1ρ, T2, adiabatic T1ρ (aT1ρ), and adiabatic T2ρ (aT2ρ) relaxation times are sensitive to injury following femoral head ischemia, with increased values in the SOC as early as 48 hours after surgical induction of global femoral head ischemia in a piglet model [6-8]. These studies reported that the relaxation times remained unchanged in the metaphysis [5-7]. However, sub-regions of the metaphysis, such as primary spongiosa (PS: a region of thin trabeculae made up of bone-covered calcified cartilage) and secondary spongiosa (SS: a region distal to the PS and composed of bone with small amounts of calcified cartilage), which are adjacent to the growth plate and metabolically active, require a closer investigation for a complete understanding of the injury caused by LCPD. Furthermore, a recent histological study has shown that the PS is thinned one week following induction of ischemia in this LCPD piglet model [5]. Our current study aimed to determine whether T1ρ, T2, aT1ρ, and aT2ρ relaxation times are sensitive to changes that occur in the PS and SS due to ischemic injury to the developing femoral head. We hypothesized that the relaxation times are sensitive to changes in the SS and thinning of the PS.

METHODS: This study was approved by our institution's IACUC. Eleven piglets at the age of 6 weeks underwent surgery to induce global ischemia in one of the femoral heads by placing a ligature around the femoral neck and transecting the ligamentum teres [2]. The contralateral femoral head was unoperated and served as a control. One week after surgery, the bilateral hips of each piglet were imaged *in vivo* at 3T MRI using: (i) T1ρ, T2, aT1ρ, and aT2ρ mapping using a magnetization-prepared 2D TSE sequence; and (ii) subtraction CE-MRI to confirm complete ischemia induction in the operated femoral heads. For quantitative MRI analysis, line profiles were used to trace the changes in relaxation times within the metaphysis. The regions of interest (ROIs) were drawn using T2-weighting MRI images where the start of the line profiles was traced along the boundary of the growth plate facing the epiphysis and extending about 10 mm into the metaphysis (Figure1a). Variation of each relaxation time for every line profile was then measured (Figure 1b), and the Gaussian mean at each location was taken to represent the overall relaxation values at that distance (Figure 1c). The first minima point from the physis was taken as the relaxation time value and the location of the PS (Figure 1c, green arrows), and the first maxima following the PS represented the relaxation time value and location of the SS (Figure 1c, yellow arrows). The distance between the locations of the PS and SS represented the "spongiosa separation" (Figure 1c, blue lines). The percent changes in the median relaxation times and spongiosa separation in the ischemic vs. control femoral heads were calculated and statistically compared using paired *t*-tests ($p<0.05$). We also assessed their respective effect sizes (Cohen's d). Two of the 10 piglets were euthanized immediately following the MRI exam, and the femoral heads were harvested for histological analysis.

RESULTS: CE-MRI confirmed global femoral head ischemia in the operated femoral heads of 10/11 piglets by lack of signal enhancement (Figure 1d). One piglet was partially ischemic and was excluded from the analysis. In the PS, T2 relaxation times had a marginal increase in the ischemic vs. control femoral heads (Figure 2), increasing on average 13±17% (p=0.058; d=0.69). In the SS, all relaxation times were significantly decreased in the ischemic vs. control femoral heads, with the greatest percentage changes occurring in T1ρ and aT2ρ (Figure 2). T1ρ, T2, aT1ρ, and aT2ρ decreased on average 21±14% (p=0.0016; d=1.41), 14±8% (p=0.0015; d=1.43), 13±13% (p=0.0095; d=1.04) and 20±10% (p = 0.0003; d=1.83), respectively. There were no significant changes in relaxation times in the greater metaphysis (GM) of the ischemic vs. control femoral heads (Figure 2). The spongiosa separation was significantly decreased for all relaxation times in the ischemic vs. control femoral heads (Figure 2), with T1ρ, T2, aT1ρ, and aT2ρ decreasing on average 24±11% (p=0.0004; d=1.71), 29±16% (p=0.0016; d=1.47), 28±11% (p=0.0002; d=1.86), and 27±15% (p = 0.0007; d=1.60, respectively. Histological analysis identified evidence of thinning of the PS in the ischemic vs. control femoral heads (Figure 3).

DISCUSSION: Our findings demonstrate that T1ρ, T2, aT1ρ, and aT2ρ relaxation time mapping are sensitive to metaphyseal changes as a result of ischemic injury to the femoral head. We conjecture that the decrease in SS relaxation times are due to the conversion of SS into a more mature bone of the metaphysis (which is less vascularized and has reduced marrow cellularity). The reduction in spongiosa separation following ischemia in the femoral epiphysis suggests (i) the slowing down of PS production and the conversion of PS into SS and/or (ii) higher conversion rate of a highly metabolically active layer of the SS into a more mature metaphyseal bone as compared to the rate of conversion of PS into SS.

SIGNIFICANCE/CLINICAL RELEVANCE: Relaxation time mapping may provide a non-contrast-enhanced approach to detect and characterize the severity of damage caused in the metaphysis due to ischemic injury to the epiphysis of the femoral head. This study motivates clinical translation of relaxation time mapping to assess femoral head growth disturbances in LCPD.

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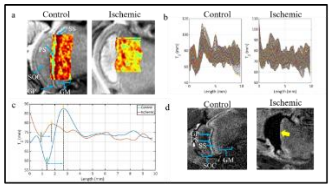

Figure 1: Metaphyseal relaxation time and spongiosa definitions. (a) T2 map within the ROI overlaid on a T2-weighted image. (b) T2 line profiles within the ROI from left to right (i.e., from physis into metaphysis). (c) Mean T2 line profile values within the ROI from left to right. The first minima represents primary spongiosa (green arrow), the first maxima following the primary spongiosa represents secondary spongiosa (yellow arrow), and the distance between the primary and secondary spongiosa represents spongiosa separation (blue arrows). (d) CE-MRI confirming the presence of ischemia (yellow arrow). SOC = Secondary Ossification Center, GP = Growth Plate, PS = Primary Spongiosa, SS = Secondary Spongiosa, GM = Greater Metaphysis.

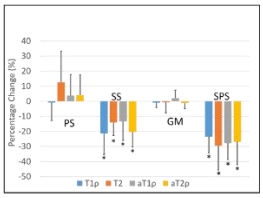

Figure 2: Average percentage change in relaxation times in the primary (PS) and secondary (SS) metaphyseal spongiosa, greater metaphysis (GM), and spongiosa separation (SPS) of the ischemic vs. control femoral heads (n=10 pairs). All relaxation times decreased in the SS and all had decreased spongiosa separation in the ischemic vs. control femoral head. * $p<0.05$

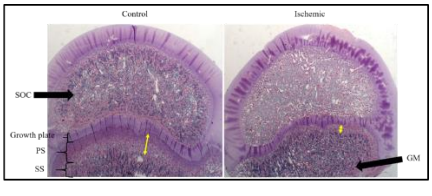

Figure 3: Photomicrographs (0.5x, H&E) of a pair of control and ischemic femoral heads showing the growth plate and adjacent epiphyseal and metaphyseal bone and marrow. The extent of the primary metaphyseal spongiosa is indicated by the yellow lines. Thinning of the primary spongiosa is apparent in the ischemic femoral head.). SOC = Secondary Ossification Center, PS = Primary Spongiosa, SS = Secondary Spongiosa, GM = Greater Metaphysis