Sensitivity of IVIM in Detecting Acute Femoral Head Ischemia: An In Vivo Piglet Model Study

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INTRODUCTION: Legg-Calvé-Perthes disease (LCPD) is a childhood hip disorder characterized by interruption of the blood supply to the developing femoral head, which without early intervention can lead to joint deformation and premature osteoarthritis [1]. Detection of LCPD in the early, avascular stage involves the assessment of perfusion changes in the developing femoral head which cannot be detected by conventional radiographs and morphological magnetic resonance imaging (MRI). Thus, gadolinium-based contrast-enhanced MRI (CE-MRI) is utilized to identify a lack of perfusion (ischemia) in the femoral head by a lack of signal enhancement [2]. However, concerns about the risk of gadolinium deposition in the brain have limited CE-MRI use in children [3], prompting a need for alternative, non-contrast-enhanced approaches to detect and monitor LCPD [2]. Recently, IntraVoxel Incoherent Motion (IVIM), a technique that utilizes a series of diffusion-weighted images (DWI) to measure both tissue perfusion and diffusion [4], has been proposed as a potential non-contrast-enhanced alternative to CE-MRI to assess LCPD [5]. Specifically, in a prior study, IVIM perfusion fraction (f) decreased while IVIM diffusion (Ds) increased in the secondary ossification center (SOC; i.e., the bone and bone marrow of the femoral epiphysis) one week following surgical induction of global femoral head ischemia in a piglet model of LCPD [5]. However, this technique was only assessed at one-time point (one week post-operatively) with only the contralateral, unoperated femoral head as a perfused control. The purpose of our current study was to determine whether IVIM is sensitive to acutely induced femoral head ischemia in the piglet model between 0 to 14 days post-operatively by comparing IVIM parameters between pre- and post-operative scans in the ischemic and control femoral heads. We hypothesized that the IVIM perfusion fraction (f) will decrease in the ischemic femoral heads immediately following the onset of ischemia and remain decreased over two weeks, whereas Ds will gradually increase with injury.

METHODS: Our local IACUC approved this study. Twenty-two six-week-old piglets received a pre-operative, bilateral 3T MRI of their hips followed by a unilateral operation to induce complete femoral head ischemia that included placement of a ligature around the femoral neck and transecting the ligamentum teres [6]. The contralateral, unoperated femoral head served as a perfused control. The piglets were then imaged a second time, using the same MRI protocol, at either 0 (n=4), 1 (n =4), 2 (n=4), 4 (n=4), 7 (n=3), and 14 (n =3) days post-operatively. The MRI protocol included: (i) IVIM using a RESOLVE DWI sequence with 12 b-values (0, 20, 30, 40, 50, 60, 70, 80, 90, 100, 300, 500 s/mm^2), TR/TE1/TE2 = 2500/68/122 ms, EPI factor = 94, readout segments = 5, spatial resolution = 1.1x1.1 mm^2, slice thickness = 2.0 mm, GRAPPA=2, and fat sat; and (ii) subtraction CE-MRI to confirm the complete femoral head ischemia. Quantitative IVIM parameters (f and Ds) were calculated on a pixel-by-pixel basis using an Analytical Segmented approach (AS) [7]. A region of interest (ROI) constituting the secondary ossification center (SOC) of the femoral head was drawn manually using b=0 diffusion-weighted images at a single middle slice. Median f and Ds values were measured in each ROI, and the values were compared between the pre- and post-operative scans in the ischemic and control femoral heads using paired *t*-tests (p<0.025 was considered statistically significant after Bonferroni correction for two comparisons).

RESULTS: CE-MRI confirmed the absence of femoral head perfusion in the operated femoral head in all 22 piglets post-operatively (Figure 1). Pre-operatively, f and Ds values in the SOC were similar between the left and right femoral heads (Figure 2). Post-operatively, f values were significantly decreased in the SOC of the ischemic femoral head (p = 0.0006) as well as compared to the control femoral head (p < 0.0001) (Figures 1 and 2). On average, f values in the ischemic vs. control femoral heads were 0.06±0.03 vs. 0.14±0.06 (Figure 2). Interestingly, the f values significantly increased in control femoral head between the pre- and post-operative scans (p = 0.008) (Figure 2). The f values were consistently lower in the operated vs. control femoral heads from 1 to 14 days post-surgery (Figure 3). Conversely, Ds values were significantly increased on average following surgery in the ischemic femoral heads (p = 0.0102) and between the ischemic vs. control femoral heads (p=0.0022) (Figures 1 and 2). However, the increase in Ds values was preceded by an initial decrease in the ischemic vs. control femoral heads immediately after surgery, before gradually increasing (Figure 3).

DISCUSSION: Our findings demonstrate that the IVIM parameters f and D are sensitive in detecting acute ischemia and subsequent injury to the femoral head without need for a contrast agent. IVIM perfusion fraction (f) was consistently decreased in the ischemic femoral heads, strongly supporting its ability to provide a non-contrast alternative to assess ischemia and perfusion changes in bone. The changes in Ds, with an initial decrease immediately following onset of ischemia followed by a gradual increase with ischemic injury to the SOC, agree with prior studies of ADC changes in the piglet model [8, 9] as well as diffusion changes in the brain parenchyma following stroke [10]. The current understanding is that the initial reduction in ADC (and Ds) is due to cytotoxic edema (i.e., uptake of water into bone marrow cells) [8, 10], and the subsequent increase in ADC (and Ds) is a result of gradual necrosis and destruction of the bone marrow cells [9, 10]. In conclusion, IVIM perfusion fraction (f) can provide a non-contrast-enhanced alternative to CE-MRI to detect acute ischemia and monitor perfusion changes in the femoral head, which may be clinically useful in assessing early-stage LCPD.

SIGNIFICANCE/CLINICAL RELEVANCE: IVIM techniques may serve as a non-contrast-enhanced alternative to CE-MRI to non-invasively measure femoral head ischemia and perfusion changes for the detection, staging, and monitoring LCPD and other forms of osteonecrosis of the femoral head.

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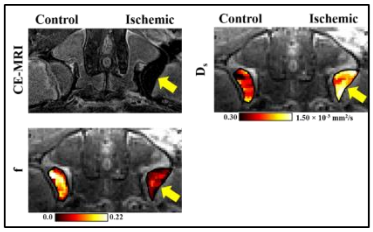

Figure 1. Subtracted CE-MRI and IVIM f and Ds maps of the femoral heads of a representative piglet at 4 days post-surgery. CE-MRI confirmed global induction of ischemia in the operated femoral head (yellow arrow). f decreased while Ds increased in the SOC of the ischemic (yellow arrow) vs. control femoral head.

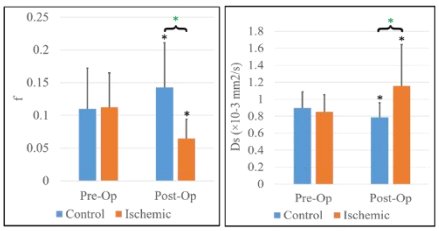

Figure 2. Average values of the IVIM f and Ds parameters within the SOC of the ischemic and control femoral heads pre- and post-surgery (n=22 pairs). Overall, f decreased in the ischemic and increased in control femoral heads while Ds increased in ischemic and decreased in the control femoral heads. Error bars indicate the standard deviation. * p<0.025 for pre-op vs. post-op. * p<0.025 for ischemic vs. control.

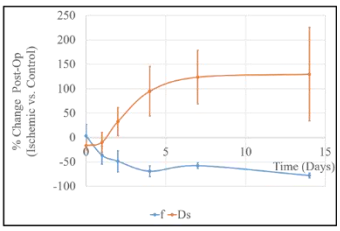

Figure 3. Average percentage change in IVIM parameters f and Ds within the SOC of the ischemic vs. control femoral heads 0 to 14 days following surgery. f decreased in the ischemic vs. control femoral heads one day following surgery and remained decreased over the 14 day interval. Ds initially decreased and then increased in the ischemic vs. control femoral heads. Error bars indicate the standard deviation.