Combined Diffusion and Perfusion MRI in Evaluating Skeletal Ischemia

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INTRODUCTION

Ischemia of the growing ends of bones leading to avascular necrosis is a common pathway for a number of disorders that result in childhood disability and a predisposition to osteoarthritis. Skeletal ischemia can be visualized via decreased signal intensity on gadolinium-enhanced images. Lack of blood flow alone, however, does not indicate the severity of damage, nor does it provide a prognosis. In current practice, determining whether ischemia has resulted in lasting damage relies on the manifestation of radiographic abnormalities, which can occur months or years after the initial insult. Surgical intervention should only be instituted when tissue destruction has subsided. If diagnostic techniques could detect whether permanent damage has occurred, it would be possible to optimally time interventions to restore flow, or, if the cartilage and bone were no longer viable, to minimize disability. Our goal is to develop MRI markers that can identify early ischemia and differentiate between early and late ischemia leading to sequelae. Here, we focus on combining diffusion and perfusion MRI to study ischemia in an animal model. We hypothesize that diffusion can detect early ischemia and differentiate between early and late injury.

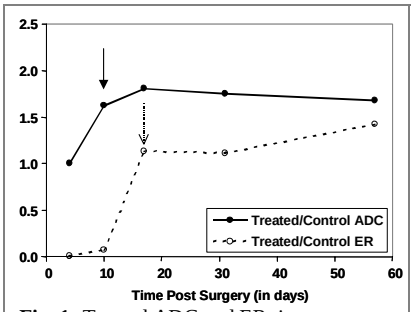

Fig. 1: Treated ADC and ER time curves for one animal. Values are normalized with respect to control. Whereas reperfusion is first observed at 2 wks (occurs between 1-2 wks), the ADC increase is first observed at 1 wk (occurs between 48 h and 1 wk).

METHODS

We studied diffusion and perfusion changes for 60 days after surgically-induced ischemia of the proximal femur in piglets (n=4). We compared the findings in the ischemic ("treated") hip with those occurring from normal maturation in the spared ("control") hip. Ischemia was induced by disrupting the arterial supply of the entire treated femoral epiphysis by ligating the femoral neck vessels and resecting the ligamentum teres. Imaging was performed at 48 hours, and 1, 2, 4, and 8 weeks following surgery, at 1.5 T. Piglets were 3 weeks old at the start of the study (corresponding to the skeletal maturity of a human child 3-5 years old). Diffusion was performed using line scan imaging [1] (TR/TE =2100/70 ms, b=0 and 700 mm^2/s, 4 mm slice thickness and 1.25 mm in-plane resolution) and quantified by calculating the apparent diffusion coefficients (ADC). Perfusion was assessed via a spoiled gradient echo sequence (TR/TE=200/2 ms, flip angle=60º, 3 mm slice thickness, and 0.625 mm in-plane resolution). Gadolinium (Prohance) at a dose of 0.2mmol/kg was injected 10 s after the start of imaging. 5 images were acquired per slice, 78 s apart. Perfusion was quantified via enhancement ratios (ERs) calculated from the signal intensity (SI): ER = (final SI – initial SI)/ final SI. Post-Gd T1-weighted images were also obtained (TR/TE=500/9 ms). After the final time point, animals were sacrificed and their hips removed. Multislice CT was used to assess bone deformity and histology was used to assess cartilaginous damage.

RESULTS

In all animals, femoral neck ligature led to markedly decreased enhancement in treated hips observed at the first time point, 48 h following surgery. ERs in the treated hip were near zero compared to the substantially higher values in the control hip (avg. treated/control ER = 9.1 ± 4.1%). Spontaneous partial reperfusion was first observed at the 2-wk time point for 3 animals and at 4 wks for the remaining animal (avg. treated/control ER = 80 ± 33% at initiation of reperfusion) and continued throughout the study. Reperfusion occurred in a spatially heterogeneous manner that varied from time point to time point as well as from animal to animal. Reperfused regions tended to have higher ERs than controls, suggesting over-compensation. Control ERs decreased over time (avg. final/initial ER = 66 ± 3.3%), suggesting age-related changes.

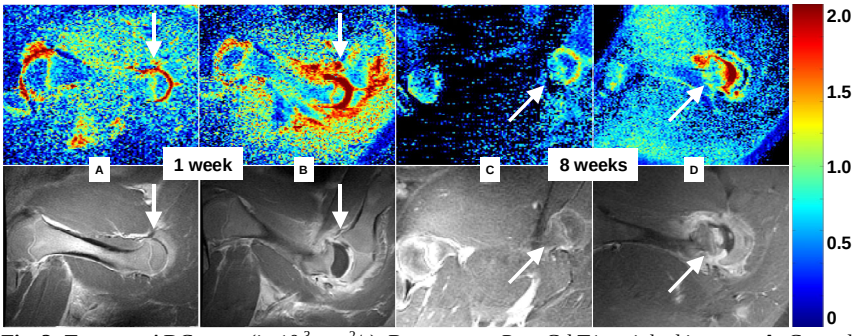

Fig. 2: Top row: ADC maps (in 10^{-3} mm^2/s). Bottom row: Post-Gd T1-weighed images. **A.** Control hip (arrow) 1 wk post surgery, showing normal perfusion. **B.** Treated hip at 1wk, showing complete loss of blood flow and increased ADC. **C.** Control hip at 8 wks. **D.** Treated hip at 8 wks. Gross morphological changes are evident (smaller, broadened head). Portions of the head now appear bright, indicating revascularization (the dark region to the right of the head is fluid, indicating an increase in joint space). ADC has remained elevated, despite the restoration of flow.

Diffusion changes following surgery appeared to follow a different time course than perfusion changes. In all animals, treated ADCs increased above control within 1 wk following surgery (by 46 ± 12% on avg.). In 2 animals, the increase was observed at the 48 h time point; in the other 2, it was observed at 1 wk. After this initial increase, treated ADCs decreased slightly and plateaued. Treated ADCs remained elevated relative to control (by 88 ± 37% on avg.). The onset of reperfusion did not abruptly change the treated ADCs. Control ADCs decreased over time (avg. final/initial ADC = 59 ± 10%), suggesting age-related changes.

The treated hips showed progressive broadening of the cartilaginous epiphysis, fragmentation and flattening of the femoral head, premature closure of the physis and shortening of the femoral neck. These changes began at the 2-wk time point and continued throughout the remainder of the study without being affected by reperfusion. The changes were visible on the MR images, on CT, and grossly, after sacrifice. Reperfusion appeared to be primarily transphyseal.

DISCUSSION

Earlier work has shown that ADC is elevated in hyperacute skeletal ischemia (24-72 h) in animals [2]. To our knowledge, this is the first study comparing the time course of diffusion and perfusion changes in an animal model of prolonged ischemia that closely parallels human disease [3]. We found that diffusion changes follow a different time course than perfusion. Treated ADCs are elevated above control shortly following surgery and before the initiation of reperfusion. No further increase occurred with reperfusion. This suggests that the ADC increase reflects damage due to the initial ischemic insult rather than reperfusion or injury caused by reperfusion. Treated ADCs remained elevated throughout reperfusion, suggesting that ADC may be a marker for lasting damage (i.e., despite the restoration of flow). The compensatory reperfusion did not avert the progressive destruction of the femoral head. ADC is therefore a better indicator of femoral head damage than gadolinium enhancement. Reperfusion was initiated too late to reverse or minimize damage and/or it contributed to the tissue destruction. We hypothesize that this may be due to the fact that reperfusion occurred spontaneously through the physis in this animal model and speculate that restoring flow through the femoral neck instead will preserve the joint. Further studies are needed to evaluate whether treated ADCs will return to control values if flow is restored through the femoral neck in a timely manner. Nevertheless, this work has shown that ADC can stay elevated despite the restoration of flow to the joint, suggesting that it may be a biomarker for irreversible damage.

REFERENCES: 1. Maier et al, AJR Am J Roentgenol 1998; 171:85. 2. Jaramillo et al, Radiology 2003; 227:825. 3. Kim et al, J Bone Joint Surg Am 2002; 84-A:1329.