INTRODUCTION
Epiphyseal ischemia is a common pathway for a number of disorders that result in disability in childhood and predispose to premature osteoarthritis in adulthood. These include Legg-Calvé-Perthes disease and avascular necrosis resulting from therapy for hip dysplasia. Decreased epiphyseal or metaphyseal signal enhancement can be seen on dynamic Gadolinium-enhanced images. Lack of blood flow, however, is not an indication of the severity of damage. The only way to determine whether ischemia has resulted in lasting damage has been to wait for radiographic abnormalities to manifest months or years later. There may be, however, an earlier window of opportunity to institute therapy. If diagnostic techniques could detect whether permanent damage has occurred, it would be possible to intervene to restore flow, or, if cartilage is no longer viable, to minimize long-term disability.

In animal models of injury, MRI can demonstrate normal and deranged growth cartilage vascularity [1]. Diffusion MRI can show early changes in epiphyseal ischemia [2]. Similar findings can be found in children with ischemic growth disorders [3]. Here, we focus on diffusion MRI in the evaluation of ischemia in growth cartilage. We hypothesize that diffusion imaging can (1) detect evolving ischemia, and (2) differentiate early from late ischemia leading to sequelae.

METHODS
We have imaged three piglets with diffusion tensor MRI (DTI). One femoral neck of each piglet was surgically ligated at 3 weeks of age in order to induce ischemia; the other head served as a control. In two piglets the ligamentum teres was also severed. These two piglets were imaged 24 hours, 1 week, 2 weeks, 4 weeks and 8 weeks after surgery, and the third was imaged during the first 2 weeks only. During these 8 weeks, the piglets were allowed to move freely. After 8 weeks, the piglets were sacrificed, the hips removed and sectioned for histological analysis. In addition, CT imaging was used to assess the degree of degeneration in this model of prolonged ischemia.

We used a segmented echo planar imaging (EPI) sequence with TR/TE = 3000/70 ms and b=0 and 700 mm/s, with 6-8 2 mm thick slices covering each joint (in plane resolution = 200 μm). Images were acquired at 3T (Trio, Siemens, Erlangen). We present scalar data of the magnitude of the diffusion tensor (trace apparent diffusion coefficient, or, ADC). We measured ADC in the epiphyseal cartilage, physeis, metaphysis and secondary ossification center for the operated and control hips. T1 weighted images post-Gadolinium (ProHance, Bracco, Princeton, NJ) were also measured to assess perfusion.

RESULTS
In two piglets, femoral neck ligature led to markedly decreased enhancement of the femoral head, followed by partial reperfusion that began 1 week later and lasted throughout the experiment (Fig 1). There was increasing epiphyseal flattening and progressive premature closure of the physeis (Fig 2). ADC increased by 30% after 24h of ischemia in the operated epiphysis relative to the control, consistent with our earlier work studying short-term ischemia [2], and subsequently increased by 27% and 16% after 1 and 2 weeks (Fig 3). Although initial imaging revealed marked decrease in enhancement in the operated hip, by 1 week some amount of revascularization occurred (Fig 1), which persisted until 4 weeks when the values in the operated hip were no longer substantially different from control. The ADC was also increased in the secondary ossification center by 3% 24h post surgery and 63% and 97% 1 and 2 weeks post surgery (presumably indicating active revascularization) before returning to control values after 4 weeks. No significant difference was observed in ADC value between operated and control physes and metaphyses. These both showed downward trends in ADC value with increasing time, suggesting age-related changes. The third piglet failed to show epiphyseal ischemia and was sacrificed at 2 weeks, as there were no epiphyseal changes on perfusion or diffusion imaging.

Despite the return to control values in ADC after 4 weeks, we observed gross morphological changes in the operated hips, consisting of broadening of the epiphysis, flattening of the femoral head, premature closure of the physeis and shortening of the femoral neck. These changes were visible on the MR images, on CT, and grossly, after sacrifice.

DISCUSSION
In acute stroke, DTI demonstrates a biphasic response to ischemia related to the duration of the insult and presumably to the severity of tissue damage. Prior to our work, diffusion changes had not been studied in detail in skeletal ischemia. Our preliminary data suggests that early ischemia leads to increased diffusion in the cartilage and marrow, perhaps related to vasogenic edema or active revascularization, but more lasting ischemia results in a normalization of values. The window of reversibility of ischemia has yet to be defined. In ischemia leading to permanent damage, imaging currently plays a role in detecting reperfusion. Although gadolinium enhancement was restored, tissue damage showed by abnormal diffusion resulted in lasting deformity. A more important goal, therefore, is to determine whether ischemia will lead to epiphyseal deformity and growth arrest. Both the piglet without epiphyseal changes and the control femurs showed no changes in diffusion. Since DTI is sensitive to changes in tissue structure, the increase in ADC seen in the epiphyseal structures may reflect the breakdown of the marrow of the epiphyseal ossification center and the surrounding epiphyseal cartilage.

Our data suggest that diffusion imaging is an indicator of lasting tissue damage in epiphyseal ischemia.

FIGURES

Figure 1: Images obtained 24 hr and 1 wk after femoral neck ligation. Top row: T1-weighted images post-Gadolinium. Bottom row: ADC maps (Scale is in units of 10^−3 mm^2/s, range: 0.5-2.00). A. Control femoral head 24 hours post surgery, showing normal perfusion. B. Operated femoral head 24 hours post surgery. The entire head is dark, indicating complete loss of blood flow. The ADC is slightly increased. C. Control femoral head 1 wk post surgery, showing no change. D. Operated femoral head 1 wk post surgery. Portions of the head now appear bright, indicating some revascularization has occurred. ADC has continued to increase in the epiphyseal cartilage and secondary ossification center.

Figure 2: CT with 3-D surface rendering of the femoral heads 8 weeks after surgery. The operated femur (arrow) is shorter and has a flattened epiphysis and a shorter femoral neck. The control is on the right.

Figure 3: ADC (10^−3 mm^2/s) vs. Time (8 hours) post surgery for A. Epiphyseal cartilage. B. Secondary ossification center. Mean ± SD is shown for operated (filled markers, n=2) vs. control (unfilled markers, n=2).

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