Repeatability of a transcatheter arterial embolization approach to induce partial femoral head ischemia in a porcine model of Legg-Calvé-Perthes Disease

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INTRODUCTION: Legg-Calvé-Perthes disease (LCPD) is a pediatric orthopedic disorder that often results in permanent deformity of the femoral head. Though the exact etiology of LCPD is incompletely understood, disruption of the vascular supply to the femoral head plays a critical role in its pathogenesis. Ischemia of epiphyseal cartilage, bone, and marrow leads to osteonecrosis, subsequent remodeling, and, oftentimes, to formation of an incongruent hip joint. The established animal model of LCPD uses an encircling ligature placed around the femoral neck to occlude the vascular supply [1]. While this approach is effective in creating global ischemia, the procedure is surgically invasive, and the resultant total necrosis of the femoral head does not reflect the partial and heterogeneous epiphyseal involvement commonly seen in LCPD patients [2]. A recent study demonstrated a minimally invasive, transcatheter arterial embolization (TAE) approach to induce partial femoral head ischemia in juvenile pigs by targeted delivery if embolic material to better capture the natural pathogenesis of LCPD [3]. The purpose of the current study was to refine and test the repeatability of this approach to induce sustained partial femoral head ischemia at 7 days post-embolization in a series of juvenile pigs.

METHODS: This study was approved by the Institutional Animal Care and Use Committee. TAE was performed unilaterally in domestic pigs aged 10 (n=2) and 16 (n=3) weeks old; one additional 10-week-old pig was excluded due to small vessel size interfering with completion of the procedure. The contralateral femoral head served as untreated control. Only male pigs were used because clinically affected patients are disproportionally male at a 4:1 ratio. Pigs were anesthetized and the right carotid artery was accessed. A guide catheter was advanced to the deep femoral artery and contrast angiography was performed to identify vessels corresponding to the medial and lateral femoral circumflex arteries (MFCA and LFCA) in children. With guidewire assistance, a selective microcatheter was advanced into these target vessels, followed by delivery of embolic microspheres and gelatin slurry (n=4) or embolic microspheres alone (n=1). 16-week-old pigs were embolized in both the MFCA and LFCA. One each of the two 10-week-old pigs was treated in the MFCA or LFCA only. Animals were recovered from the procedure and were imaged using contrast-enhanced MRI (CE-MRI) 7 days post-embolization to determine the presence of femoral head ischemia. Immediately following the MRI exam, pigs were euthanized, their femoral heads were harvested, fixed in formalin, and decalcified for histologic evaluation.

RESULTS: TAE of the MFCA and/or LFCA was confirmed in all pigs intraoperatively based on stasis and/or reflux of contrast media in the targeted vessel(s). CE-MRI obtained 7 days after TAE of both the MFCA and LFCA in the 16-week-old pigs demonstrated persistent ischemia of the femoral head, with the peripheral region more severely affected than the central region (Figure 1). Embolization of the MFCA alone in a 10-week-old pig resulted in persistent partial ischemia of the femoral head at 7 days postoperatively. The other 10-week-old pig undergoing TAE of the LFCA alone had no apparent perfusion deficits on CE-MRI. Histologic results are pending for two of three 16-week-old pigs. H&E-stained histological sections available for a 10- and a 16-week-old pig with persistent ischemia at 7-days on MRI demonstrated heterogeneous lesions with regions of epiphyseal osteonecrosis and marrow necrosis involving up to 50% of epiphysis, often overlapping areas of hemorrhage. Variably well-demarcated adjacent regions of viable bone, mild fibroplasia, and increased osteoblast activity were also noted (Figure 1D). Despite the lack of persistent ischemia in one of the 10-week-old pigs on CE-MRI, histological injury was still apparent, although limited to a thin band of reduced cellularity along the epiphyseal side of the growth plate.

DISCUSSION: CE-MRI findings indicate that TAE can induce persistent, partial ischemia of the femoral head of at least 7 days duration. Histologically, changes consistent with mild to moderate ischemic injury of the femoral head were present in both age groups, demonstrating successful induction of some degree of ischemia in all pigs. It is noteworthy that after embolization of the two primary vessels believed to supply the femoral head in pigs [4], lesions were more severe at the periphery of the epiphysis. This finding is not unexpected considering the high metabolic activity in this region due to active conversion of cartilage to bone, through the process of endochondral ossification [5]. This regional nature of ischemia also suggests that, while the MFCA and LFCA are accepted as the primary vascular supply to the femoral head, other vessels may also supply this region through either natural anastomoses, collateralization, or via increased flow through dormant/resolving embryologic vasculature (e.g., the artery of the ligament teres). Further implementation of this model will allow determination how injury to individual vessels and varying degrees of femoral head ischemia determines the course of LCPD.

SIGNIFICANCE/CLINICAL RELEVANCE: This minimally invasive, repeatable TAE model of LCPD offers an alternative to existing models by capturing the natural pathogenesis of the disease to induce clinically relevant partial femoral head ischemia in young pigs. Through generating heterogeneous lesion sizes and locations, it better reflects the spectrum of LCPD seen in children and provides a platform for studying disease pathogenesis and testing therapies.

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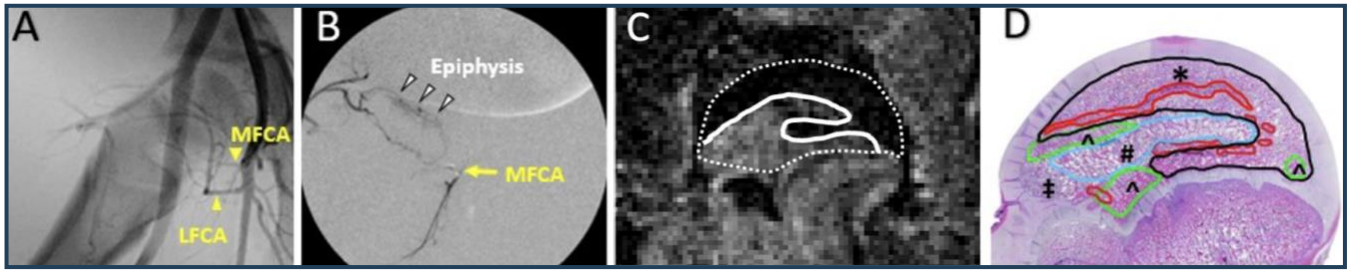

FIGURE 1: Selected images of TAE and its effects in a 16-week-old pig. (A) Fluoroscopic image of vessels corresponding with the MFCA and LFCA arising from the deep femoral artery. (B) A subtracted fluoroscopic image showing the circumferential perfusion of contrast media around the femoral epiphysis. (C) Subtracted CE-MRI of the femoral head (dotted line) 7 days after embolization (white line separates the perfused and ischemic portions) and (D) corresponding H&E-stained histological section showing necrosis (*, black outline) in 50% of the femoral head that had persistent ischemia, as well as regions of reduced cellular density (#, blue outline), hemorrhage (red outlines), and early repair (^, green outlines). There was a small region of unaffected bone and marrow (‡).