Perfusion MRI in Early Stage of Legg-Calvé-Perthes Disease to Predict Lateral Pillar Involvement

A Preliminary Study

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Background: Current radiographic classifications for Legg-Calvé-Perthes disease cannot be applied at the early stages of the disease. The purpose of this study was to quantify the perfusion of the femoral epiphysis in the early stages of Legg-Calvé-Perthes disease with use of perfusion magnetic resonance imaging (MRI) and to determine if the extent of epiphyseal perfusion can predict the lateral pillar involvement at the mid-fragmentation stage.

Methods: Twenty-nine patients had gadolinium-enhanced perfusion MRI at the initial stage or early fragmentation stage of Legg-Calvé-Perthes disease and were followed prospectively. The percent perfusion of the whole epiphysis and its lateral third was measured by four independent observers using image analysis software. The radiographs obtained at the mid-fragmentation stage were used for the lateral pillar classification. Intraclass correlation coefficient (ICC) and logistic regression analyses were performed.

Results: The mean age (and standard deviation) at diagnosis was 7.7 ± 1.7 years (range, 5.3 to 11.3 years). The mean interval between the MRI and the time of maximum fragmentation was 8.2 ± 5.5 months. The interobserver ICC for the percent perfusion of the lateral third of the epiphysis was 0.90 (95% confidence interval [CI]: 0.83 to 0.95). The mean percent perfusion of the lateral third of the epiphysis was 92% ± 2%, 68% ± 18%, and 46% ± 12% for the hips in which the lateral pillar was later classified as A, B, and C, respectively (p = 0.001). When the perfusion level was ≥90% in the lateral third of the epiphysis, the odds ratio of the lateral pillar being later classified as group A, as opposed to B or C, was 72.0 (CI: 3.5 to 1476). With a perfusion level of ≤55% in the lateral third of the epiphysis, the odds ratio of the lateral pillar being later classified as group C, as opposed to A or B, was 33.3 (CI: 2.8 to 392). Similar results were obtained for the whole epiphysis.

Conclusions: Perfusion MRI measurements of the total epiphysis and its lateral third obtained at the early stages of Legg-Calvé-Perthes disease were predictive of lateral pillar involvement at the mid-fragmentation stage of the disease.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Legg-Calvé-Perthes disease is a juvenile form of idiopathic osteonecrosis of the femoral head that can produce a permanent femoral head deformity and osteoarthritis.

Predicting which patients will have a good outcome and which will have a poor outcome at the early stage of the disease, before a substantial deformity develops, remains a clinical challenge.

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A commentary by Perry L. Schoenecker, MD, is linked to the online version of this article at jbjs.org.
The Catterall and lateral pillar classifications are radiographic prognosticators of outcome based on the radiographic features present in the fragmentation stage of the disease. Herring et al. observed that the extent of femoral head collapse at the lateral third of the epiphysis in the mid-fragmentation stage correlates strongly with outcome. In their lateral pillar classification, the extent of collapse of the lateral third of the affected epiphysis was originally categorized into three groups (A, B, and C). While this classification is conceptually intuitive, its clinical applicability has been hampered by the need to wait until the mid-fragmentation stage, when the maximal epiphyseal collapse has occurred, to assign the lateral pillar class and by the categorical nature of the classification, which is prone to subjectivity. The waiting period from the initial stage to the mid-fragmentation stage can range from four to eight months. This “wait-to-classify” approach has raised some concerns because the primary goal of treatment for Legg-Calvé-Perthes disease is to prevent or minimize the deformity, and a substantial amount of deformity of the femoral head can develop during this waiting period. Similar concern has been raised regarding the Catterall classification as it requires a period of observation to determine the extent of femoral head involvement, which is based on epiphyseal collapse. The limitations of these classification systems underscore the need to develop a prognostic system that can be applied at the early stage of Legg-Calvé-Perthes disease to guide treatment decisions before substantial collapse of the femoral head occurs.

Magnetic resonance imaging (MRI), a sensitive modality that permits multiplanar imaging of the femoral head, can detect Legg-Calvé-Perthes disease during the early stages of the disease. Non-contrast MRI studies have been shown to be better than radiography and pinhole scintigraphy for delineating the extent of femoral head involvement in patients with Legg-Calvé-Perthes disease. In the initial stage of Legg-Calvé-Perthes disease, however, non-contrast MRI has limited utility since it relies on signal changes from fat present in the epiphysis (lipid degradation) to detect osteonecrosis. Since it takes weeks to months for the fat signal to decrease, there have been reported cases of non-contrast MRI producing false-negative results or underestimating femoral head involvement.

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**Fig. 1**

**Fig. 1-A** A graph showing the distribution of the percent perfusion of the lateral third of the epiphysis corresponding to each lateral pillar group. **Fig. 1-B** A bar graph showing the mean percent perfusion (and standard deviation) of the lateral third of the epiphysis corresponding to each lateral pillar group. The means differed significantly among the groups. **Fig. 1-C** A graph showing the distribution of the percent perfusion of the whole epiphysis corresponding to each lateral pillar group. **Fig. 1-D** A bar graph showing the mean percent perfusion (and standard deviation) of the whole epiphysis corresponding to each lateral pillar group. The means differed significantly among the groups.
when it was performed within three to six months after the first symptoms\textsuperscript{13-16}.

In contrast, gadolinium-enhanced MRI with a subtraction technique (henceforth referred to as \textit{perfusion MRI}) provides information more specifically about the blood flow to the femoral head and has been used to detect early ischemia (hypoperfusion) in patients with Legg-Calvé-Perthes disease\textsuperscript{10,17,18}.

A recent study comparing non-contrast and contrast-enhanced MRI showed that the contrast-enhanced MRI better delineated the extent of femoral head necrosis at the initial stage of Legg-Calvé-Perthes disease\textsuperscript{19}. Another recent study demonstrated that the extent of avascularity (lack of epiphyseal perfusion) measured with use of perfusion MRI at the early stage of Legg-Calvé-Perthes disease correlated with the...
The extent of radiographic femoral head deformity at the time of a two-year follow-up was assessed.

The purpose of this study was to determine whether perfusion MRI performed in the initial or early fragmentation stage of Legg-Calvé-Perthes disease can predict the radiographic lateral pillar involvement at the maximum fragmentation stage.

**Materials and Methods**

**Patient Cohort**

The cohort consisted of the patients with Legg-Calvé-Perthes disease prospectively enrolled in an institutional review board-approved perfusion MRI study at one institution from 2008 to 2012. To be eligible, a patient had to be diagnosed with Legg-Calvé-Perthes disease between the ages of five and twelve years and had to have a gadolinium-enhanced MRI when the disease was in Waldenström stage I or IIa (i.e., the initial or the early fragmentation stage) as well as serial follow-up radiographs demonstrating maximum fragmentation of the epiphysis for assignment of the lateral pillar classification. Patients with femoral head osteonecrosis due to trauma, corticosteroids, or any other non-idiopathic causes were excluded.

**Waldenström Staging**

The Waldenström stage was verified by consensus of three reviewers. Stage I, or the initial stage, is defined as the stage in which there is increased radiodensity (sclerosis), a smaller ossific nucleus with or without subchondral fracture, and/or mild flattening of the femoral head. In stage IIa, or the early fragmentation stage, the sclerotic epiphysis has begun to fragment and one or two vertical fissures are seen on the anteroposterior or lateral view. More advanced epiphyseal fragmentation with greater flattening and resorptive changes indicates the stage of maximum fragmentation (stage IIb).

**Perfusion MRI**

Gadolinium-enhanced MRI with a subtraction technique was performed as soon as it could be scheduled following the initial clinic visit, when the disease was still in Waldenström stage I or IIa. The MRI was done with use of a 1.5-T scanner (GE Healthcare, Milwaukee, Wisconsin) with a four or eight-channel surface coil so that both hips could be imaged simultaneously. Coronal fast spin echo (FSE) T1-weighted, and chemically fat-suppressed coronal FSE T1 and T2-weighted, images were acquired prior to gadolinium administration. Sagittal pre-contrast fat-suppressed FSE T1-weighted images were also obtained. Intravenous administration of gadoteridol (0.2 mL/kg at 0.5 mmol/mL; maximum dose, 20 mL or 10 mmol) was followed by the acquisition of fat-suppressed coronal T1-weighted images of both hips and sagittal fat-suppressed images of the affected hip with 4-mm slices with no gap. The non-true dynamic post-contrast images were used to assess the femoral head perfusion by subtracting the initial pre-contrast fat-suppressed T1-weighted images from corresponding post-contrast images to produce subtraction images, which increase the conspicuity of the contrast medium in the epiphysis.

**MRI Analysis**

Perfusion of the femoral epiphysis was calculated from coronal contrast images with use of MRI analysis software called HipVasc (Texas Scottish Rite Hospital for Children, Dallas, Texas). HipVasc is a MATLAB-based software program that uses a built-in DICOM (Digital Imaging and Communications in Medicine) reader to extract details of MRIs. To obtain perfusion percentages, the entire osseous epiphysis is defined as a region of interest on fat-suppressed coronal T1-weighted images (six, seven, or eight MRIs per femoral head). On each slice, the orientation of the proximal femoral physis is marked, and this is used by the HipVasc software to define the medial, lateral, and central thirds of the epiphysis. Avascularity is defined on a subtraction image slice and is converted to a distribution of pixel intensities by the software. This distribution...
The area of interest is expanded to all slices and represented as a percentage of the region of interest (the total or the lateral third of the femoral head).

Four independent observers measured the perfusion percentages of the total epiphysis and its lateral third using the HipVasc software after two teaching sessions. The four observers consisted of an orthopaedic resident in post-graduate year 4 (PGY4), a research coordinator focusing on Legg-Calvé-Perthes disease, a second-year medical student, and an undergraduate student. All four reviewers were blinded to patient identity, age, and history and to the lateral pillar outcomes of the affected hips. Three observers participated in the intraobserver reliability testing by repeating the MRI measurements.

**Assignment of Lateral Pillar Classification**

Each patient had anteroposterior and frog-leg lateral radiographs of the pelvis obtained at presentation and at follow-up visits spaced three to four months apart until the reossification stage (Waldenström stage III) occurred. The lateral pillar classification was assigned by consensus of three observers using the radiographs obtained at the maximum fragmentation stage. The three observers consisted of two staff pediatric orthopaedic surgeons with special interest in Legg-Calvé-Perthes disease and a second-year medical student. The original lateral pillar classification system with three groups (A, B, and C) was used. We also examined the interobserver and intraobserver agreement of the three observers by having them grade the radiographs independently on two separate occasions.

**Statistical Analysis**

A one-way analysis of variance (ANOVA) was used to evaluate differences in means. The intraclass correlation coefficient (ICC) for the interobserver reliability of the perfusion MRI measurements was computed with use of the INTRACC SAS Macro (SAS, Cary, North Carolina). A two-way cross tabulation and the Fisher exact test were used to analyze the association between certain cutoff levels of percent perfusion and the lateral pillar involvement. In addition, we obtained the odds ratio (OR) and its 95% confidence interval (CI) for the probability of developing certain lateral pillar groups at specific cutoff levels of perfusion of the epiphysis. Weighted kappa statistics were utilized to assess the intraobserver and interobserver agreements of the lateral pillar classification. P < 0.05 was considered significant. SAS 9.3 and R 3.0.0 software (R development, 2013) were used for the analysis.

**Perfusion MRIs obtained at the initial disease stage showing a lack of perfusion (black area) in the central region of the epiphysis and some perfusion in the lateral aspect of the epiphysis (grey area).** Fig. 3-C Corresponding HipVasc images showing the level of perfusion in the epiphysis. (Not all MRIs analyzed are shown because of space limitation.) A color scale of the level of perfusion is shown on the right, with blue indicating absence of perfusion and red and aqua indicating perfusion. This patient had 54% perfusion of the whole epiphysis and 65% perfusion of the lateral third of the epiphysis.

**Follow-up radiograph obtained at the mid-fragmentation stage showing a lateral pillar group B hip.** This patient had healed Legg-Calve-Perthes disease on the left side, which was not included in this study.
Source of Funding
This study was funded internally by Texas Scottish Rite Hospital for Children. There was no external funding.

Results
Twenty-nine patients (twenty-nine affected hips—sixteen right and thirteen left) met the inclusion criteria and were analyzed. There were twenty-two boys and seven girls. The mean age (and standard deviation) at diagnosis was 7.7 ± 1.7 years (range, 5.3 to 11.3 years). Seventeen hips were in Waldenström stage I and twelve hips were in stage IIa at the time of the perfusion MRI. The interval from the initial clinic visit to the MRI ranged from the same day to 3.5 months, with a mean of twenty-seven days. The mean interval between the time of MRI and the time of maximum fragmentation was 8.2 ± 5.5 months. Of the twenty-nine patients included in the study, ten were treated with femoral varus osteotomy, seven were treated with Petrie casts with or without hip adductor tenotomy, five were treated with restricted weight-bearing, and seven were treated symptomatically.

The final lateral pillar classification was group A for four hips, group B for nineteen, and group C for six (Fig. 1). The weighted kappa values for intraobserver reliability were 0.80 (95% CI: 0.55 to 0.95), 0.92 (95% CI: 0.69 to 1.00), and 0.96 (95% CI: 0.71 to 1.00) for the three observers, which indicates substantial to excellent agreement. The weighted kappa value for interobserver reliability was 0.80 (95% CI: 0.51 to 0.93), which indicates substantial agreement.

Figs. 4-A through 4-D A seven-year-old boy who had a lateral pillar group C hip at the mid-fragmentation stage. Fig. 4-A Initial anteroposterior (AP) and lateral (Lat) radiographs obtained at presentation, when the disease was in Waldenström stage I.

Fig. 4-B Perfusion MRIs obtained at the initial disease stage showing a lack of perfusion (black area) in most of the epiphysis except the lateral aspect of the epiphysis shown in the right lower panel (grey area). Fig. 4-C Corresponding HipVasc images showing the level of perfusion in the epiphysis. (Not all MRIs analyzed are shown because of space limitation.) A color scale of the level of perfusion is shown on the right, with blue indicating an absence of perfusion in most of the epiphysis except the lateral aspect of the epiphysis in image 4. This patient had 40% perfusion of the whole epiphysis and 53% perfusion of the lateral third of the epiphysis.
The mean percent perfusion of the lateral third of the epiphysis was 92% ± 2%, 68% ± 18%, and 46% ± 12% in the hips in which the lateral pillar was later classified as A, B, and C, respectively (Fig. 1-B), with a significant difference among groups (ANOVA, p = 0.001). Post-hoc comparisons showed that the mean percent perfusion of the lateral third of the epiphysis in the hips with a group-A lateral pillar was greater than that of the hips with a group-B or C lateral pillar (p < 0.05 and p < 0.01, respectively). The mean percent perfusion of the lateral third in the hips later classified as lateral pillar group B was also greater than that in the hips later classified as lateral pillar group C (p < 0.03).

The mean percent perfusion of the whole epiphysis was 91% ± 5%, 56% ± 20%, and 34% ± 10% in the hips in which the lateral pillar was later classified as A, B, and C, respectively (ANOVA, p < 0.001) (Fig. 1-D). The mean percent perfusion of the whole epiphysis of the hips with group-A involvement of the lateral pillar was greater than that of the hips that developed group-B or C involvement (p < 0.05 and p < 0.01, respectively). Furthermore, the mean percent perfusion of hips that developed group-B involvement of the lateral pillar was greater than that of those with group-C involvement (p < 0.05).

The ICC of the four observers for the MRI measurements was 0.90 (95% CI: 0.83 to 0.95) for the percent perfusion of the lateral third of the epiphysis and 0.93 (95% CI: 0.87 to 0.97) for the percent perfusion of the whole epiphysis. Recalculation of the ICC after exclusion of the measurements of one observer at a time produced similar ICC values compared with the ICC of all four observers, indicating that no one observer was better or worse than the others.

Three observers participated in the intraobserver reliability testing by repeating the MRI measurements. For the MRI measurements of the whole epiphysis, the intraobserver reliability was 0.90 (95% CI: 0.80 to 0.95) for the second-year medical student, 0.90 (95% CI: 0.80 to 0.95) for the research coordinator, and 0.99 (95% CI: 0.98 to 1.00) for the PGY4 orthopaedic resident. For the MRI measurements of the lateral third of the epiphysis, the intraobserver reliability was 0.86 (95% CI: 0.72 to 0.93) for the second-year medical student, 0.91 (95% CI: 0.82 to 0.96) for the research coordinator, and 0.95 (95% CI: 0.89 to 0.98) for the PGY4 orthopaedic resident.

We obtained odds ratios for the probability of a hip developing a certain classification of lateral pillar involvement based on specific thresholds for the percent perfusion of the epiphysis. With a perfusion level of ≥90% in the lateral third of the epiphysis (Figs. 2-A through 2-D), the odds ratio of the lateral pillar later being classified as group A, as opposed to B or C, was 72.0 (CI: 3.5 to 1476). With a perfusion level of ≤55% in the lateral third of the epiphysis, the odds ratio of the lateral pillar later being classified as group C, as opposed to A or B, was 33.3 (CI: 2.8 to 392) (Figs. 3-A through 4-D). With a perfusion level of ≥290% in the whole epiphysis, the odds ratio of developing group-A involvement of the lateral pillar, as opposed to B or C, was 24.0 (95% CI: 1.5 to 395). With a perfusion level of ≤40% in the whole epiphysis, the odds ratio of developing group-C involvement of the lateral pillar, as opposed to A or B, was 23.8 (95% CI: 2.1 to 262).

**Discussion**

The lateral pillar classification has a good correlation with outcome. One major limitation of the classification is that it can be applied correctly only at the mid-fragmentation stage of Legg-Calvé-Perthes disease as it is based on the amount of the collapse of the lateral third of the epiphysis. Ideally, a prognosticator of outcome of Legg-Calvé-Perthes disease should be usable at the early stage of the disease, prior to the development of a substantial femoral head deformity, so that a treatment decision can be made to prevent or minimize the deformity. Furthermore, the prognosticator should be quantitative and reliable. In this study, we investigated the relationship between the amount of perfusion of the femoral epiphysis measured with perfusion MRI at the early stage of Legg-Calvé-Perthes disease and the involvement of the lateral pillar at the mid-fragmentation stage. We observed a significantly greater percent perfusion of the whole epiphysis and in the lateral third of the epiphysis in the femoral heads that developed group-A lateral pillar involvement compared with those that developed group-B or C involvement. When the percent perfusion of the whole epiphysis or the lateral third of the epiphysis was ≥90%, it was more likely that the lateral pillar would be characterized as group A, as opposed to B or C, at the mid-fragmentation stage. Conversely, when the percent perfusion of the whole epiphysis or the lateral third of the epiphysis was low (≤40% or ≤55%, respectively), it was more likely that the lateral pillar would be characterized as group C as opposed to A or B.
The results of this study suggest that one of the potential benefits of assessing the perfusion of the epiphysis at the early stage of Legg-Calvé-Perthes disease is its ability to differentiate between hips that will have group-A involvement of the lateral pillar from those that will have group-B or C involvement in the later stage of the disease. Clinically, this would aid in the early treatment decision-making. Currently, there is a controversy over timing of surgical intervention among the surgeons who treat Legg-Calvé-Perthes disease. Some evidence suggests that the optimal timing of containment surgery such as femoral varus osteotomy is at the early stages (Waldenström stage I or IIa) of the disease. However, the current practice for patients who present with the early stages of Legg-Calvé-Perthes disease is commonly a waiting or observational period of four to eight months until the lateral pillar or Catterall classification can be properly applied. One of the reasons for this “wait-to-classify” approach has been to distinguish the patients with a good prognosis (lateral pillar group A or Catterall group I or II) from those with a poor prognosis (lateral pillar group C or Catterall group IV). During this observation period, many patients develop a substantial femoral head deformity, which is counterproductive to the attainment of the treatment goal of preventing or minimizing deformity. The ability to distinguish, at the early stages of the disease, hips that will ultimately have group-A involvement of the lateral pillar from those that will have group-B or C involvement may help surgeons to avoid operating on patients who do not require surgical intervention (lateral pillar group A) and proactively treat patients who will benefit from surgical intervention (lateral pillar B or B/C border).

The results of this study showed a considerable overlap of perfusion MRI measurements between the hips that later received a lateral pillar B classification and those that received a C classification. Several factors may have contributed to the overlap, including the categorical nature of the lateral pillar classification, in which the distinction between B and C is relatively subjective. Furthermore, although the enrollment of the patients into this study was prospective, the treatment and the timing of intervention were left to the treating physicians, which could have influenced the lateral pillar involvement. It is important to note that previous studies have shown some variability in the outcomes of lateral pillar group-B hips, with some having a good outcome (Stulberg class I or II) and some having a poor outcome (Stulberg class III or higher). Some attempts have been made to further stratify the lateral pillar B group into subgroups or to quantify the lateral pillar height to increase the prognostic power of this classification. Since perfusion MRI measurements are quantitative, they may have a better resolution of stratifying the outcomes of the patients. In a recent study, measurements of perfusion MRI obtained at the early stages of Legg-Calvé-Perthes disease were shown to correlate with the femoral head deformity as measured with the radiographic deformity index after two years of follow-up. A lower perfusion MRI index at early stages of Legg-Calvé-Perthes disease correlated with a greater radiographic deformity. A longer-term study is needed to validate the prognostic value of perfusion MRI measurements obtained at the early stages of the disease.

One of the advantages of using a quantitative measure instead of a categorical classification is the avoidance of the subjectivity and poor to moderate interobserver agreement inherent in a categorical classification. The ICC for the interobserver reliability of the four independent observers in our study demonstrates that the quantification of perfusion MRI is reliable. The good inter-observer and intraobserver agreements obtained in this study are consistent with those reported in two previous studies in which perfusion MRI was used by two or more observers to quantify perfusion.

This study does have limitations. Although the patients were enrolled in a prospective fashion, the analysis of the medical records was performed in a retrospective fashion. Other limitations of the study include a small sample size and a short follow-up. In a separate study, however, we observed a moderate correlation between the amount of epiphyseal perfusion assessed with perfusion MRI and two-year radiographic outcomes. Given the relatively recent application of perfusion MRI in patients with Legg-Calvé-Perthes disease, long-term data are not available.

Strengths of our study include the prospectively enrolled patient population, independent assessment of the MRIs by four observers, quantitative study design, and statistical analysis. To our knowledge, this is the first study to quantitatively compare the percent perfusion of the epiphysis at the early stages of Legg-Calvé-Perthes disease with the lateral pillar involvement at the maximum fragmentation stage.

In conclusion, perfusion MRI measurements of the total epiphysis and its lateral third at the early stages of Legg-Calvé-Perthes disease were predictive of lateral pillar involvement at the maximum fragmentation stage.

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