Abnormalities of Vascular Structure and Function in Children With Perthes Disease

WHAT’S KNOWN ON THIS SUBJECT: The causes of Perthes disease are unknown. There is considerable evidence that the disease has a vascular mechanism, although the nature of this is unknown. There is some suggestion that affected individuals may have a heightened cardiovascular risk in adulthood.

WHAT THIS STUDY ADDS: Children with Perthes disease have reduced vascular caliber, which is independent of body height, and abnormal functional vascular measures. These findings may be important in the mechanism of disease and may have implications on long-term vascular morbidity.

abstract

BACKGROUND AND OBJECTIVES: Perthes disease is a childhood precipitant to osteoarthritis of the hip, for which the etiology and mechanism are unknown. There is mounting evidence to suggest a vascular insult is responsible for disease, and it is suggested that this may have long-term implications for the vascular health of affected individuals. This study sought to use ultrasound measures to investigate vascular structure and function in children affected by Perthes disease.

METHODS: This case control study encompassed 149 cases and 146 controls, frequency matched for age and gender. Endothelial function was measured by using the technique of flow-mediated dilation of the brachial artery, and alterations in arterial flow were recorded in response to an ischemic stimulus.

RESULTS: There was a significant structural alteration in the vasculature among individuals with Perthes disease (resting brachial artery diameter (cases 2.97 mm versus controls 3.11 mm; \( P = .01 \)), which remained even after adjusting for height. In addition, there was a notable reduction in blood velocity (cases 33.84 cm/s versus controls 37.83 cm/s; \( P = .01 \)) and blood flow (cases 149.82 mL/min versus controls 184.67 mL/min; \( P = .001 \)), which was independent of baseline arterial size. There was no evidence to suggest that flow-mediated dilation of the brachial artery was impaired among affected individuals (\( P = .71 \)).

CONCLUSIONS: Children with Perthes disease exhibit small artery caliber and reduced function, which is independent of body composition. These data imply that that Perthes disease may reflect a wider vascular phenomenon that could have long-term implications for the vascular health of affected individuals. Pediatrics 2012;130:1–6
Perthes disease (juvenile idiopathic osteonecrosis of the femoral head) affects ~1 in 850 children in Northern Europe and the United States. The disease manifests through hip pain with limited movements and presents a marked physical and psychological burden in childhood. The disease often alters the shape of the hip, which may accelerate osteoarthritic changes, and is a common precipitant for joint replacement in early adult life.

The mechanism by which the avascular necrosis develops is unknown. It is hypothesized that there is diminished blood supply via the lateral ascending vessel to the epiphysis. Many observers have suggested that this may arise through a thrombophilic process, but a systematic review of coagulopathies among 475 cases concluded that there were no significant differences in antithrombin activity, protein S or C activity, or antiphospholipid antibodies. The relationship with the Factor V Leiden mutation is uncertain; however, it appears unlikely that there is a major thrombophilic association.

More recently, it has been suggested that abnormalities in vascular structure and function may be the mechanism by which the disease develops, with particular interest focused toward the possibility of endothelial dysfunction. The endothelium forms a large endocrine organ, the function of which is to regulate vascular tone, platelet aggregation, coagulation, and fibrinolysis. Endothelial dysfunction may precipitate inflammation, thrombosis, vasoconstriction, and atherosclerotic plaque formation. Endothelial dysfunction in children and young adults has been demonstrated in relation to passive smoking, short stature, and low birth weight. Each of these has similarly been associated with Perthes disease.

The dilator response of a conduit artery to increased flow after a period of imposed distal limb ischemia is a common measure of endothelial function, which is termed flow-mediated dilation (FMD). FMD is a noninvasive and widely accepted measure that is commonly used in research as an independent predictor of cardiovascular events. Adults who were affected by Perthes disease in childhood are demonstrated to have a greater risk of premature cardiovascular disease in adulthood, therefore adding support to an abnormality of vascular function. Recently, it has been proposed that hyperemic blood flow responses to a period of ischemia also predict cardiovascular outcomes. These responses reflect small-artery dilator function, rather than that of the larger conduit arteries.

Despite previous suggestions that the mechanism responsible for Perthes disease may be related to vascular dysfunction, no previous study has investigated large- or small-artery functional responses in children with Perthes disease. We hypothesized that FMD and hyperemic responses to an ischemic stimulus would be abnormal in children with Perthes disease.

METHODS

Participants
A case-control study was undertaken at Alder Hey Children’s Hospital, Liverpool. Cases comprised patients drawn from the Merseyside Perthes register and recruited at a routine hospital attendance. All patients were aged 5 to 16 years with a confirmed diagnosis of Perthes disease. In each case the diagnosis was verified by a consultant pediatric radiologist and consultant pediatric orthopedic surgeon based upon the radiographic appearance and clinical features. Bilateral synchronous disease necessitated a skeletal survey to exclude a multiple epiphyseal dysplasia (MED). Cases of MED, cerebral palsy, and developmental hip dysplasia were excluded owing to their known independent association with avascular necrosis of the hip. No cases were actively immobilized, and all were at least 4 months after the last surgical intervention.

Controls were an age- and gender-stratified sample of the orthopedic outpatient population, frequency matched on a 1:1 basis. Age matching occurred within 2 groups: 5 to 10 years old, 11 to 16 years old. Controls were similarly attending Alder Hey Hospital and were drawn from a number of children’s orthopedic outpatient clinics. The clinics sampled were knee clinic, general orthopedic clinic, normal variants clinic, and trauma clinic. Any controls with a restriction in hip movement, unless a clear alternative diagnosis was apparent, were excluded. On each sampling day, all eligible controls were approached for inclusion. Controls with MED, cerebral palsy, and developmental hip dysplasia were excluded, as were patients actively immobilized (irrespective of site of pathology) and those within 4 months of surgery.

Research Design
Parents and children were invited to attend a research clinic, at which vascular parameters and basic anthropometrics (height/weight) were measured and demographic details recorded. Endothelial function was measured by using the technique of FMD. This is a noninvasive measure of endothelial function that sonographically measures the degree of brachial artery dilation in response to a shear stimulus. The technique has widespread acceptance throughout the literature and is increasingly being used in childhood epidemiologic studies.

Measurement Procedures
FMD was recorded by using a standardized technique. All scans were recorded by a single trained observer
Diameter measurements, with use of this semiautomated software, are considerably more repeatable (coefficient of variation = 6.7%) than manual methods and are associated with less observer error.\textsuperscript{25} The resultant graphical output automatically calculates the FMD, after indicating the point of cuff deflation whereby the arterial flow and shear rise rapidly.

**Statistical Analysis**

Analysis was conducted by using univariate and bivariate analyses, and then a multivariate model. Logistic regression was conducted universally adjusting for age (continuous variable) and gender (categorical variable). Additional adjustments were made for each of the confounding variables that arose, and confounders were retained within the model if their inclusion produced a 10% measured change in effect size. All analyses were conducted by using Stata 10.0 (StataCorp, College Station, TX). \( P \) values of < .05 were considered significant.

**RESULTS**

One hundred forty-nine patients and 146 controls were recruited to take part. Thirty-two children (17 patients and 15 controls) were unable to tolerate the examination or scans were of insufficient quality to allow vascular measures to be made. The demographic details of patients and controls are listed in Table 1. There was no difference in the age or gender of either group.

Bivariate analyses revealed that the mean height of individuals with Perthes disease was 5 cm less than controls (\( P \) = .02), although weight and BMI were not different between groups (Table 1). The vascular parameters demonstrated a reduced brachial diameter (cases 2.97 mm versus controls 3.11 mm; \( P \) = .01), reduced blood velocity (cases 33.84 cm/s versus controls 37.83 cm/s; \( P \) = .01) and reduced blood flow (cases 149.82 mL/min versus controls 184.67 mL/min; \( P \) = .001). There was no difference in the FMD response (\( P \) = .71). After adjusting for age and gender, each of these associations remained (Table 2, adjustment 1).

FMD was negatively correlated with age, height, and resting brachial artery diameter. Blood flow was positively correlated with age, height, weight, BMI, and resting brachial diameter. Blood velocity was positively correlated with age and height. Adjusting for each of the confounding variables revealed that only the adjustment for height had any notable effect on any of the vascular predictor variables (Table 2, adjustment 2). Even after adjusting for resting brachial artery size, a reduction in velocity and flow persisted (Table 3).

### Table 1 Anthropometric and Vascular Measures in the Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Value (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n = 149)</td>
<td>Controls (n = 146)</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height, m</td>
<td>1.41 (1.36–1.43)</td>
<td>1.46 (1.45–1.49)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>43.3 (39.6–46.9)</td>
<td>45.0 (41.9–48.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>20.4 (19.6–21.2)</td>
<td>20.3 (19.6–21.0)</td>
</tr>
<tr>
<td>Vascular parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting vessel diameter, mm</td>
<td>2.97 (2.88–3.04)</td>
<td>3.11 (3.05–3.19)</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>7.26 (6.78–7.73)</td>
<td>7.40 (6.82–7.98)</td>
</tr>
<tr>
<td>Average velocity, cm/s</td>
<td>33.84 (31.95–35.72)</td>
<td>37.83 (35.60–40.07)</td>
</tr>
<tr>
<td>Integral minimum flow, mL/min</td>
<td>149.82 (137.94–161.70)</td>
<td>184.67 (167.55–201.80)</td>
</tr>
<tr>
<td>Integral minimum shear rate, AU</td>
<td>27 438 (25 739–29 157)</td>
<td>29 470 (27 488–31 453)</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>67.46 (62.50–72.42)</td>
<td>63.94 (57.88–70.00)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

* Vascular measures available in 132 cases and 129 controls.
This is the first study that has examined arterial function in children with Perthes disease. It has been suggested that the mechanism for Perthes disease is vascular in origin, based upon pathologic and clinical evidence, along with the unusual anatomy of the vasculature to the infant femoral epiphysis.\(^3,27\) It has been demonstrated that between 3 and 7 years, the blood supply to the epiphysis is almost universally dependent on a single artery, the lateral ascending artery.\(^3,27\) Pathologic studies of femoral heads affected by Perthes disease have demonstrated changes that are consistent with an avascular process.\(^28–30\) Likewise, the clinical appearance of disease supports a vascular mechanism, because the anterior aspect of the head, which is the furthest point from the vascular origin, is universally affected.\(^31\) Our findings support this mechanism by demonstrating decreased vasodilator capacity in small arteries that control blood flow responses, after a period of ischemia. Such arteries are likely to be of similar caliber to those implicated in Perthes disease.

The primary objective of this study was to assess FMD responses and investigate the hypothesis that endothelial dysfunction may be apparent in subjects with Perthes disease. Previous researchers have suggested abnormalities in endothelial function based on the presence of biochemical parameters and risk factors in Perthes disease that are known to impair endothelial function.\(^5–17\) Yet no studies to date have sought to assess endothelial function directly. Our finding, that blood flow was impaired, despite normal conduit artery dilator function, suggests that vascular dysfunction in smaller arteries may precede that in larger vessels. This abnormality of the distal vascular bed increases peripheral resistance and thus reduces blood velocity and flow. This is the first study, to our knowledge, to demonstrate decreased arterial caliber and reduced blood flow in Perthes disease.

We acknowledge that the findings of the current study require cautious interpretation; nevertheless, our findings raise the hypothesis that Perthes disease may reflect a wider vascular phenomenon that may manifest as cardiovascular disease in later life. In support of our findings, a recent study using the common animal model of Perthes disease (the stroke-prone spontaneously hypertensive rate) has demonstrated arterial narrowing, and artherosclerotic-like hypertrophy of the vasculature to the immature hip among these rats.\(^32\) The stroke prone spontaneously hypertensive rate rat is also a common animal model of arteriosclerosis, hypertension, and cerebrovascular disease and is known to develop spontaneous femoral head ischemia in infancy in ~50% of cases.\(^35\) Furthermore, abnormal hyperemic responses, such as those observed in the current study, have recently been shown to be associated with cardiovascular disease in adults.\(^19,20\) Likewise, reduced arterial size is believed to be a key factor contributing to the higher cardiovascular risk in individuals of short stature.\(^34\) Long-term cardiovascular consequences of Perthes disease have been identified by 1 study that demonstrated greater

### Discussion

The principal findings of this study are that children with Perthes disease exhibit smaller conduit arterial caliber and impaired hyperemic responses to an ischemic stimulus, a surrogate marker of small-artery function, in comparison with controls. Furthermore, we observed no apparent difference in the conduit artery FMD response. It is well established that a growth abnormality exists in Perthes disease, with well-established small-artery function, in response to an ischemic stimulus, a surrogate marker of small-artery function, in addition to any phenomena pertaining to arterial size.

### Table 2: Multivariable Adjustment of Each of the Parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjustment 1a</th>
<th>P</th>
<th>Adjustment 2b</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometrics</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Height, cm</td>
<td>0.95 (0.92–0.98)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.00 (0.98–1.02)</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.02 (0.97–1.08)</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular parameters</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Flow-mediated dilation (%)</td>
<td>0.98 (0.91–1.06)</td>
<td>0.65</td>
<td>0.97 (0.89–1.05)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Resting vessel diameter (mm)</td>
<td>0.30 (0.14–0.66)</td>
<td>0.003</td>
<td>0.38 (0.17–0.86)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Flow (per 100 mL/min)</td>
<td>0.51 (0.34–0.76)</td>
<td>0.001</td>
<td>0.53 (0.35–0.81)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Velocity (per 10 cm/s)</td>
<td>0.72 (0.57–0.91)</td>
<td>0.005</td>
<td>0.71 (0.56–0.90)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.
a Adjustment 1: adjusted for age and gender.
b Adjustment 2: adjusted for age, gender, and height.
c Vascular measures available in 132 cases and 129 controls.

### Table 3: Vascular Parameters Adjusted for Arterial Size

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjustmenta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow (per 100 mL/min)</td>
<td>0.60 (0.36–0.99)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Velocity (per 10 cm/s)</td>
<td>0.72 (0.57–0.92)</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.
a Adjusted for age, gender, height, and resting vessel diameter (millimeters).
cardiovascular risk in adults who had Perthes disease in infancy. This study, based on the Swedish inpatient register, demonstrated a higher frequency of ischemic heart disease (hazard ratio 2.69 [95% confidence interval 1.20–6.03]) and hypertension (hazard ratio 2.97 [95% confidence interval 1.87–4.72]), after adjusting for socioeconomic deprivation. The study, published in 2010, recruited individuals diagnosed between 1965 and 2005, and, therefore, the majority of individuals are relatively young to consider cardiovascular disease. There are no studies to date that detail the cause of death in individuals with Perthes disease; however, if an appropriate historic cohort were identified additional research in this area would be invaluable.

In the current study the control group was formed from a hospital population. The advantage of this group was that it overcomes selection bias related to access to health care. Yet, at the same time, it introduces the assumption that a group of hospital patients are representative of the population at large. To help overcome this, a number of hospital clinics formed the control group, therefore attempting to prevent overrepresentation of individuals with diseases associated with the exposure variable. Any bias attributable to hospital populations would be likely to move the odds ratio toward the null; therefore, the observed differences may be underestimates.

In summary, the novel finding of this study was the reduction in small artery caliber and function in children with Perthes disease, which appeared independent of body size. This may be an important finding both in terms of the etiology of Perthes disease and may have long term consequences for vascular health.

REFERENCES


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