Detection and Grading of Coronary Allograft Vasculopathy in Children With Contrast-Enhanced Magnetic Resonance Imaging of the Coronary Vessel Wall

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Background—Coronary allograft vasculopathy is the leading cause of late death after heart transplantation in children. It is poorly detected by conventional angiography. Intravascular ultrasound is invasive and costly. This study shows that magnetic resonance imaging (MRI) late gadolinium enhancement (LGE) of the coronary vessel wall can detect and grade coronary allograft vasculopathy.

Methods and Results—Twenty-four children (10 male; age range, 9–17 years) underwent coronary angiography, intravascular ultrasound, and MRI. Maximal intimal thickness and mean intimal index were recorded. MRI included coronary magnetic resonance angiogram and LGE vessel wall imaging with 1.5 T (n=12) and 3.0 T (n=12). Ten healthy control subjects also underwent LGE MRI. Mean time posttransplantation was 5.5 years (range, 0.25–14 years). Seven patients had Stanford grade IV coronary allograft vasculopathy on intravascular ultrasound, 3 of whom had angiographic disease. Maximal intimal thickness and mean intimal index were 0.73±0.50 mm and 20.9±10.6%, respectively. On MRI, mean diameter of enhancement of vessel wall was 6.57±4.91 mm, and mean enhancement index (indexed to vessel lumen size) was 1.10±1.72. The control group showed little or no LGE. Correlation of LGE with maximal intimal thickness using the Pearson coefficient was 0.80 (P<0.001) and with mean intimal index was 0.92 (P<0.001). An MRI diameter >7.5 mm gave 86% sensitivity and 93% specificity.

Conclusions—LGE scores correlate well with traditional intravascular ultrasound measures. These promising early results encourage larger-scale clinical studies to investigate whether LGE MRI will allow closer follow-up and better prevention of coronary allograft vasculopathy in children. (Circ Cardiovasc Imaging. 2013;6:91-98.)

Key Words: coronary artery disease ◼ heart transplantation ◼ intravascular ultrasound ◼ MRI ◼ pediatrics

Coronary allograft vasculopathy (CAV) is the leading cause of late death or graft loss after heart transplantation in children.¹ It is a progressive condition thought to be caused largely by chronic immune-mediated endothelial damage.² Damaged endothelium allows cell infiltration, which is responsible for the production of cytokines, growth factors, and matrix deposition (collagen I and fibroblasts).³ This results in a progressive thickening of the intima, which is poorly detected by conventional angiography.⁴ Rapid progression is the most important predictor for all-cause death in this patient group⁵ and warrants a change in treatment. Intravascular ultrasound (IVUS) is a much more sensitive imaging modality and is therefore desirable for the early detection of CAV.⁶⁻⁸ However, it is invasive, costly, and not technically feasible in small children. This limits how closely CAV can be monitored, especially in children.

Gadolinium-based contrast agents are paramagnetic media used for magnetic resonance imaging (MRI), which are known to be deposited in diseased tissue with abundant fibrosis and extracellular matrix.⁹⁻¹¹ It is this property of gadolinium that has previously been shown to be useful for demonstrating atherosclerotic coronary vessel wall disease.¹² In this study, we examine the use of late gadolinium enhancement (LGE) for the noninvasive detection and grading of CAV. We also investigate whether this is more accurate at 3.0- or 1.5-T field strength.

Methods

Institutional review board approval was obtained before the study was begun (reference 09/H0713/53). Written informed consent was obtained accordingly. Patients >10 years of age undergoing routine IVUS after orthotopic heart transplantation were invited to take part in the study. Participants underwent cardiac MRI, followed by conventional x-ray angiography and IVUS 1 day later. In addition, 10
volunteers undergoing cardiac MRI for clinical purposes (exclusion of hereditary cardiomyopathy or for follow-up of surgically corrected congenital heart disease) also underwent coronary delayed enhancement to serve as a control group. They did not have any history of coronary disease or major risk factors (i.e., smoking, hypertension, dyslipidemia, diabetes mellitus, or family history of early disease). Volunteers were excluded if there was evidence of cardiomyopathy, reduced ventricular function, significant residual lesion, history of coarctation repair, or history of arterial switch procedure. Separate institutional review board approval and written informed consent were obtained (reference 09/H0802/078).

MRI Sequences
Cardiac MRI was performed with a 1.5-T Achieva clinical MR scanner (Philips Healthcare, Best, the Netherlands) and a 32-element cardiac phased-array receiver coil. Before imaging, 0.2 mmol/kg body weight of a gadolinium-based contrast medium (Gadovist, Bayer Schering, Berlin, Germany) was administered intravenously. Coronary MR angiography (MRA) was performed with a previously described navigator-gated free-breathing and cardiac-triggered T2-prepared 3-dimensional steady-state free precession sequence. Then, a coronary LGE sequence (navigator-gated, vector ECG-triggered, fat-suppressed T1-weighted 3-dimensional gradient-echo inversion recovery) was performed 30 to 40 minutes after the administration of gadolinium.

After an interim analysis, the final 12 patients were examined at 3.0-T field strength to investigate whether this resulted in closer correlation with conventional IVUS. This was performed with a 3.0-T Achieva clinical MR scanner (Philips Healthcare), also using a 32-element coil. A volume B1 shim was applied to use parallel radiofrequency transmit technology. Acquired in-plane image resolution was 1.25 x 1.25 mm at 1.5 T and 1 x 1 mm at 3.0 T.

MR Image Analysis
Coronary MRA images were analyzed with a semiautomatic vessel analysis tool (Soap-Bubble, release 5.0) to measure the mean coronary artery diameter and length imaged. LGE has been used to quantify atrial scar burden in the setting of atrial fibrillation. This technique, described by Oakes et al., was adapted for coronary vessel wall quantification with OsiriX version 3.9.1. LGE was defined as areas in the vessel wall with a signal intensity >2 SDs higher than normal nonenhancing vessel wall. The ascending aorta (distal-to-anastomosis site) or the descending aorta was used as the reference for normal vessel wall. With the coronary MRA used as an overlay roadmap, the volume of coronary vessel wall enhancement in the left anterior descending coronary artery was measured (Figure 1). All areas of enhancement corresponding to coronary vessel wall were included, and this was not influenced by MRA findings (e.g., presence or absence of luminal irregularity). Mean enhancement area (volume/length imaged), enhancement diameter (assuming circular area), and mean enhancement index (enhancement area/coronary mean cross-sectional area) were calculated. In addition, the position of areas of vessel wall enhancement was recorded using the distance from a major branch.

LGE measurements were repeated to calculate the intraobserver and interobserver variabilities. Two observers (G.F.G. and T.H. [both with ≥3 years of cardiovascular MRI experience]) analyzed data in an independent manner, blinded to the angiography and IVUS results.

Finally, a qualitative analysis was undertaken by means of a consensus reading for image quality scoring on all the LGE images in a blinded and random order. The 2 readers first reviewed the images independently, and any disagreement was discussed before the final grade was given. The following scoring system was used: 0 = vessel wall not visible; 1 = markedly blurred borders; 2 = moderately blurred; 3 = mildly blurred; and 4 = sharp.

Conventional X-ray Angiography and IVUS
Conventional angiography and IVUS were undertaken on the day after the MRI scan. Catheterization is normally performed under general anesthesia for children and adolescents, according to institutional protocol (n=14), but for older adolescents or young adults, performance under local anesthesia is encouraged (n=10). Catheterization and IVUS were performed only as clinically indicated. Angiograms were reported using conventional definitions.

IVUS was performed in the left anterior descending coronary artery with automated pullback at 0.5 mm/s (temporal resolution of 30 frames per second). A suitable length of vessel was imaged to allow analysis of at least 30 cross-sectional images evenly spaced (at ≈ 1.5-mm intervals in mid-diastole) over the same segment of the left anterior descending coronary artery that was analyzed at the previous annual review (identified by branch points). Maximal intimal thickness, mean intimal index, and Stanford grade were recorded. Mean intimal index is the ratio of the mean intimal area to the sum.
of the mean intimal and luminal areas. In addition, a semiautomatic interactive edge-detection software (QIVUS Clinical Edition, Medis Medical Imaging Systems) was used to improve reproducibility of measurements.20 Finally, the positions of the most affected regions (regions with thickness greater than twice the mean intimal thickness for that patient) were recorded using distance from major side branches.

Statistical Methods
First, an anatomic comparison was made between areas of enhancement on MRI and the location of prominent thickening on IVUS. Variables are then formally assessed for normality of distribution with the Kolmogorov–Smirnov test. Then, specific bivariate correlation was assessed between enhancement scores (MRI) and intimal measurements (IVUS) using the Pearson correlation coefficient.

A receiver-operating characteristic curve was constructed to choose the optimal cutoff for the sensitivity and specificity of LGE for the detection of significant CAV. Significant CAV was defined as that present on x-ray angiogram or Stanford grade IV on IVUS (Stanford score is graded for a patient according to the worst coronary lesion).

A 1-way ANOVA was used to compare enhancement measures between grades of disease as described by Stanford grading or angiography. Post hoc testing with Bonferroni correction was used for multiple comparisons between groups to identify where the significant differences lay. Stanford grade I was excluded from this analysis because there was only 1 patient in this group.

Associations with known risk factors were further explored against maximal intimal thickness by forward stepwise multivariable linear regression. The risk factors such as donor age, cytomegalovirus infection, time since transplantation, occurrence of severe or recurrent rejection, and blood pressure were assessed.1,21,22 Included variables were kept in the analysis only if they improved model fit (as defined by a significant change in the F-test statistic on residuals).

Image quality was compared between 1.5 and 3 T with a Mann–Whitney test. Interobserver agreement and intraobserver agreement for repeated MRI measurements were assessed with Bland–Altman plots. Statistical analyses were performed on SPSS version 19 (release 19.0.0, IBM Software Group, New York, NY).

Results
Twenty-four children participated (patient characteristics are given in Table 1). One was excluded from analyses because MRI at 3.0 T failed because of patient discomfort. All MRI examinations were performed free-breathing without the use of sedation or general anesthesia. Mean MRI examination time was 32 minutes (range, 20–45 minutes).

All 4 variables (maximal intimal thickness, mean intimal index, enhancement diameter, and enhancement index) were assessed visually with frequency plots and were further formally tested for normality with the Kolmogorov–Smirnov test ($P<0.05$ for all). On the basis of this assessment, all 4 variables were assumed to be normally distributed.

Patients underwent angiography and IVUS within 48 hours of the MRI procedure. One patient had IVUS delayed by 8 weeks because of initial technical failure. Seven patients had Stanford grade IV disease on IVUS, but only 3 patients had angiographic evidence of disease.

Anatomic Assessment
For the 12 patients imaged at 1.5 T, 17 regions of enhancement were identified on MRI. In 11 regions (mean intimal thickness, 0.51 mm), anatomic correlation (to within 1 mm for location from a major branch point) was observed between areas of enhancement noted in the MRI- and IVUS-depicted thickening. At 3 T, 11 of 13 enhancing lesions had exact and anatomic match (Figure 2). Detailed segmental correlation of LGE location with IVUS for each patient is given in Table 2.

Quantitative Assessment
Overall, there was excellent correlation of MRI with IVUS (Figure 3). Pearson correlation for enhancement diameter with maximal intimal thickness was 0.80 ($P<0.001$) and for enhancement index with mean intimal index was 0.92 ($P<0.001$). Correlation coefficients were 0.77 and 0.96, respectively ($P<0.05$ for both), at 3 T compared with 0.81 and 0.62 ($P<0.05$ for both) at 1.5 T.

A given patient was defined as having significant CAV if he or she had angiographic evidence of disease or Stanford grade IV disease on IVUS (This score is given for the worst coronary lesion imaged). Table 2 shows IVUS and LGE scores for each patient. The receiver-operating characteristic curve demonstrates that a cutoff of 7.5-mm mean enhancement diameter for the entire left coronary artery imaged on MRI has 86% sensitivity (95% confidence interval, 42–99) and 93% specificity (95% confidence interval, 66–99) for the detection of significant CAV. This gives a positive predictive value of 86% (95% confidence interval, 42–99), negative predictive value of 93% (95% confidence interval, 66–99), and accuracy of 91%.

Table 3 shows the enhancement scores for the control group, for different Stanford grades, and for those with angiographic disease. All those with angiographic disease had Stanford grade IV CAV. One-way ANOVA revealed that there were significant differences in enhancement scores across patient groups defined by Stanford grades and angiographic disease ($P<0.001$ for both enhancement diameter and index). Post hoc testing revealed that enhancement measures were significantly greater for grade IV with angiographic disease compared with any other grade ($P<0.01$ for all other grades, including grade IV without angiographic disease). Post hoc testing also revealed a significant difference in enhancement diameter between grade IV (without angiographic disease) and grade III disease ($P=0.016$).

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>1.5 T</th>
<th>3.0 T</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>12</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Men, n</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Age, y</td>
<td>15.1±2.2</td>
<td>15.8±1.7</td>
<td>15.5±1.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>58.9±20.9</td>
<td>57.7±10.9</td>
<td>58.4±16.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162±9</td>
<td>164±11</td>
<td>162.8±10</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>81±8</td>
<td>88±8</td>
<td>84±8</td>
</tr>
<tr>
<td>Maximal intimal thickness, mm</td>
<td>0.50±0.29</td>
<td>0.98±0.56</td>
<td>0.73±0.50</td>
</tr>
<tr>
<td>Mean intimal index, %</td>
<td>17.5±5.7</td>
<td>24.7±13.5</td>
<td>20.9±10.6</td>
</tr>
<tr>
<td>Enhancement diameter, mm</td>
<td>5.38±2.39</td>
<td>7.86±5.67</td>
<td>6.57±4.91</td>
</tr>
<tr>
<td>Enhancement index</td>
<td>0.53±0.42</td>
<td>1.72±2.35</td>
<td>1.10±1.72</td>
</tr>
<tr>
<td>Stanford grade IV disease, n</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Previous CMV infection, n</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Donor age, y</td>
<td>23±11.9</td>
<td>25.1±16.1</td>
<td>24.1±13.8</td>
</tr>
</tbody>
</table>

CMV indicates cytomegalovirus; and HR, heart rate. Patient characteristics are given as mean±SD.
Interobserver and Intraobserver Variabilities

The Bland–Altman analyses indicate that there was no significant bias between the 2 sets of repeated enhancement diameter measurements (−0.2 mm for intraobserver error \(P=0.36\) by paired \(t\) test) and −0.4 mm for interobserver error \(P=0.42\) by paired \(t\) test). Overall, intraobserver agreement was acceptable with 95% limits of agreement ranging from 1.9 to −2.3 mm. Overall, interobserver agreement was 4.2 to −4.9 mm.

Field Strength

At 1.5 T, although intraobserver agreement was acceptable with 95% limits of agreement ranging from 2.8 to −2.6, interobserver agreement was less acceptable at 4.0 to −6.5 mm. However, this was improved at 3.0 T, with 95% limits of agreement for intraobserver and interobserver agreement ranging from 1.7 to −2.3 and from 3.5 to −2.5 mm, respectively. This improvement in repeatability may be the result of an increase in LGE image quality at 3.0 T (median=3) compared with 1.5 T (median=2; \(P=0.019\) by Mann–Whitney test). Furthermore, anatomic correlation was improved at 3.0 T as detailed above.

Control Group

The control group consisted of 10 volunteers (6 male) male a mean age of 23 years 11 months imaged at 1.5 T. Although significantly older than the transplantation patients \((P<0.001\) by independent-samples \(t\) test), they were similar in age to the donors (mean donor age, 24 years 1 month; \(P=0.90\)). Volunteers had little coronary LGE. Four volunteers had no discernible LGE. The mean enhancement diameter was 0.27±0.09 mm and enhancement index was 0.02±0.03. These enhancement measurements were significantly lower than the transplant recipients \((P<0.001\) for both; Table 1).

Multivariable Analysis

In the multivariable analysis, donor age, length of time since transplantation, and MRI (enhancement diameter) were the only significant independent predictors of maximum intimal thickness on IVUS (model \(R^2=0.79, P<0.001\)). Standardized correlation coefficients were 0.69 for enhancement diameter \((P<0.001), 0.65\) for donor age \((P=0.002\), and 0.42 for time since transplantation \((P=0.048\).

Figure 2. Imaging at 3.0 vs 1.5 T for coronary allograft vasculopathy. A, Patient 1: left coronary system coronary magnetic resonance angiography (CMRA) at 3 T. B, Patient 1: late gadolinium enhancement (LGE) at 3 T (raw images formatted in same plane as A). C, Patient 2: left coronary CMRA at 1.5 T. D, Patient 2: LGE at 1.5 T (raw images formatted in same plane as C). E, Overlay of patient 1: LGE (after threshold) on CMRA at 3 T. Arrows show corresponding positions for intravascular ultrasound (IVUS; G and H). F, Overlay of patient 2: LGE (after threshold) on CMRA at 1.5 T. Arrows show corresponding positions for IVUS (I and J). G and I, IVUS images. White box illustrates intimal thickening corresponding to enhancement on overlay picture above. J and H, IVUS images. No significant intimal thickening corresponding to areas without enhancement on overlay picture above.
Table 2. Anatomic and Quantitative Information for Each Patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>T</th>
<th>LGE Location</th>
<th>IVUS Location Match</th>
<th>Location Match</th>
<th>MIT</th>
<th>MII</th>
<th>St</th>
<th>ED</th>
<th>Ei</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>LCx origin, diffuse distal segment disease</td>
<td>LCx origin, diffuse distal segment disease</td>
<td>2 of 2</td>
<td>1.30</td>
<td>25.83</td>
<td>4</td>
<td>11.53</td>
<td>1.45</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.5 cm from LCx</td>
<td>LCx origin, diffuse distal segment disease</td>
<td>0 of 1</td>
<td>0.29</td>
<td>13.24</td>
<td>2</td>
<td>5.51</td>
<td>0.63</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>20 mm distal to LCx origin, diffuse distal segment disease</td>
<td>20 mm distal to LCx origin, diffuse distal segment disease</td>
<td>2 of 2</td>
<td>0.77</td>
<td>31.11</td>
<td>4</td>
<td>7.91</td>
<td>1.05</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>Entire LM</td>
<td>LCx origin, 14 mm distal to LCx origin</td>
<td>2 of 2</td>
<td>0.35</td>
<td>13.65</td>
<td>3</td>
<td>3.94</td>
<td>0.27</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>10 mm distal to LCx origin, second Dx origin, and third Dx origin</td>
<td>LCx origin</td>
<td>1 of 1</td>
<td>0.29</td>
<td>14.01</td>
<td>2</td>
<td>3.51</td>
<td>0.17</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>LCx origin, 14 mm distal to LCx origin</td>
<td>LCx origin, 14 mm distal to LCx origin</td>
<td>2 of 2</td>
<td>0.28</td>
<td>13.86</td>
<td>3</td>
<td>3.06</td>
<td>0.10</td>
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<tr>
<td>7</td>
<td>1.5</td>
<td>2Dx, 16 mm distal to second Dx origin</td>
<td>2Dx, 16 mm distal to second Dx origin</td>
<td>2 of 2</td>
<td>0.52</td>
<td>19.17</td>
<td>3</td>
<td>4.46</td>
<td>0.38</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>LCx origin</td>
<td>LCx origin</td>
<td>1 of 1</td>
<td>0.40</td>
<td>19.24</td>
<td>3</td>
<td>4.37</td>
<td>0.31</td>
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<tr>
<td>9</td>
<td>1.5</td>
<td>Diffuse distal segment disease</td>
<td>Diffuse disease from LCx onward</td>
<td>1 of 1</td>
<td>1.52</td>
<td>46.8</td>
<td>4</td>
<td>17.44</td>
<td>6.20</td>
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<td>10</td>
<td>1.5</td>
<td>Entire left main, first Dx origin</td>
<td>Entire left main, first Dx origin</td>
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<td>13.1</td>
<td>2</td>
<td>7.08</td>
<td>1.00</td>
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<td>1.5</td>
<td>15 mm distal to LCx origin</td>
<td>15 mm distal to LCx origin</td>
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<td>0.45</td>
<td>14.32</td>
<td>3</td>
<td>3.10</td>
<td>0.13</td>
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<tr>
<td>12</td>
<td>3</td>
<td>LM 10 mm proximal to LCx origin</td>
<td>LM 10 mm proximal to LCx origin</td>
<td>1 of 1</td>
<td>0.96</td>
<td>19.24</td>
<td>3</td>
<td>9.05</td>
<td>1.13</td>
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<tr>
<td>13</td>
<td>3</td>
<td>Entire LM</td>
<td>Distal diffuse disease beginning 10 mm distal to LCx</td>
<td>1 of 1</td>
<td>1.26</td>
<td>28.36</td>
<td>4</td>
<td>11.45</td>
<td>1.61</td>
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<tr>
<td>14</td>
<td>3</td>
<td>10 mm distal to LCx origin, second Dx origin, and third Dx origin</td>
<td>Distal diffuse disease beginning 10 mm distal to LCx</td>
<td>1 of 1</td>
<td>1.50</td>
<td>29.19</td>
<td>4</td>
<td>12.34</td>
<td>3.57</td>
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<tr>
<td>15</td>
<td>3</td>
<td>First septal branch origin</td>
<td>First septal branch origin</td>
<td>1 of 1</td>
<td>0.45</td>
<td>14.83</td>
<td>3</td>
<td>1.68</td>
<td>0.03</td>
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<tr>
<td>16</td>
<td>3</td>
<td>Entire LM</td>
<td>Entire LM</td>
<td>1 of 1</td>
<td>0.40</td>
<td>19.43</td>
<td>3</td>
<td>1.39</td>
<td>0.03</td>
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<tr>
<td>17</td>
<td>3</td>
<td>Left main stem 5 mm proximal to LCx</td>
<td>Left main stem 5 mm proximal to LCx</td>
<td>1 of 1</td>
<td>0.24</td>
<td>11.13</td>
<td>1</td>
<td>1.47</td>
<td>0.04</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>37-mm length of proximal LAD</td>
<td>37.5-mm length of proximal LAD</td>
<td>1 of 1</td>
<td>1.67</td>
<td>52.2</td>
<td>4</td>
<td>19.66</td>
<td>5.70</td>
</tr>
</tbody>
</table>

CAV indicates coronary allograft vasculopathy; ED, enhancement diameter; EI, enhancement index; IVUS, intravascular ultrasound; LAD, left anterior descending; LCx, left circumflex; LGE, late gadolinium enhancement; LM, left main; MII, mean intimal index; MIT, maximum intimal thickness; and St, Stanford grade. Detailed segmental correlation of late gadolinium enhancement location with intravascular ultrasound for each patient.

Discussion

In this study, we have demonstrated the feasibility of a novel and ionizing radiation–free approach for direct noninvasive imaging of CAV. The technique not only has been successfully applied to children but also has shown preliminary validation against the gold standard for invasive CAV imaging, IVUS.

We showed that coronary LGE scores after heart transplantation were significantly raised compared with a control population. Furthermore, after heart transplantation, LGE scores correlated well with the maximal intimal thickness and mean intimal index (Pearson coefficient 0.80 [P<0.001] and 0.92 [P<0.001], respectively). An enhancement diameter >7.5 mm gave promising sensitivity and specificity values of 86% and 93%, respectively, for the detection of significant CAV.

Direct noninvasive imaging of CAV in children, with this degree of accuracy (91%), deserves further investigation and encourages a future change in practice away from invasive screening. Our findings are supported by another recent study in pediatric transplant recipients at 1.5 T showing that patients with CAV had greater signal intensity in late gadolinium coronary vessel wall images than those without CAV. However, this study used only angiography to classify the presence of CAV and therefore did not manage to demonstrate the ability of MRI to detect significant angiographically silent disease (as has been demonstrated in the study described here). Furthermore, we believe that the MRI grading system given in the Methods section gives a more accurate reflection of the affected plaque volume than the assessment of signal intensity alone.

IVUS is the most sensitive imaging modality for the detection of CAV. It has high image resolution, and measures of intimal thickness are reproducible. In addition, the prognostic significance is described above. For these reasons, many trials use IVUS as the gold standard to assess the effect of drug treatments on CAV.24,25 Despite this, the added value over angiography alone for routine clinical use remains uncertain.26 In children, there are technical limitations, and it remains an invasive technique usually requiring sedation or anesthesia. It should therefore be noted that direct noninvasive imaging of CAV has been described using multidetector computed tomography in adults. Dual-source computed tomography was shown to have a sensitivity of 85% and specificity of 84% compared with IVUS.27 Some small pediatric studies have suggested the feasibility of multidetector computed tomography in both Kawasaki disease and CAV, but issues of resolution, high heart rates, and ionizing radiation exposure...
remain important limitations.

Indirect imaging with dobutamine stress echocardiography has also been used in children to diagnose CA V. However, validation against IVUS in children is lacking. When angiography is used as the standard, dobutamine stress echocardiography shows a sensitivity of 35% to 71% for the detection of CA V in children and a specificity of 80% to 94%. Our MRI data are more robust and achieve equally good results when comparing LGE measurements against the more sensitive modality of IVUS. Furthermore, a major advantage of cardiovascular MRI is that, in addition to coronary imaging, a single examination can give information on volumes, function, wall motion, myocardial scar, and ischemia (via pharmacological stress testing). In the setting of atherosclerosis, adenosine stress perfusion MRI has shown noninferiority to single-photon emission computed tomography for the detection of myocardial ischemia, and further trials are underway. With respect to dobutamine stress, MRI has been shown to perform better than echocardiography for the detection of atherosclerotic coronary stenoses. Initial data also suggest that MRI may be able to quantitatively assess myocardial perfusion reserve. More recent data, using the robust clinical tool of myocardial LGE, showed that 84% of patients with severe CA V on angiography had typical infarct-pattern subendocardial LGE with a distribution consistent with the pattern of CA V on angiography. Despite these encouraging results, there remains a paucity of data on MRI in this setting, and no firm recommendations can be made without further comprehensive prospective trials.

For coronary LGE, as with any new technique, there will be a learning curve for acquisition, analysis, and interpretation. For example, Figure 1 shows enhancement in the area of one of the pulmonary veins as it enters the left atrium. This may represent labeling of the venous blood from the navigator, as has been previously described. Overlaying the LGE and coronary MRA images, as shown in Figure 1D, can differentiate this enhancement from coronary vessel wall enhancement. The main limitation with this study is that this new technology represents data acquisition at a single center. Diagnostic quality coronary imaging in children using MRI is not widely established across centers. Transfer of this technology across imaging platforms and reproduction of results

![Figure 3](http://circimaging.ahajournals.org/)

**Figure 3.** Two cases are shown for comparison. The first, left column, shows images from a patient with mild (Stanford grade II) coronary allograft vasculopathy (CAV). The second, right-hand column, shows a patient with severe (grade IV) CAV. A, Both patients have normal conventional angiography, showing how poorly angiography detects CAV. B, The intravascular ultrasound (IVUS) images showing a small rim of intimal thickening in the first patient compared with severe intimal thickening in the second patient. C, The segmentation of the intimal layer on the IVUS picture for clarification (bright white–rendered area). D, The quality of coronary magnetic resonance angiography (MRA) routinely achieved. E, Raw late gadolinium enhancement (LGE) images formatted in the same plane as the MRA. F, LGE image (from E) after threshold applied and overlaid onto MRA (from D). Areas of true coronary LGE are highlighted with arrows. A much greater volume of LGE (arrows) is seen in the second patient (mean enhancement diameter, 11.5 mm) than the first patient (mean enhancement diameter, 3.5 mm).

**Table 3. Summary of Magnetic Resonance Imaging Scores**

<table>
<thead>
<tr>
<th>Stanford Grade</th>
<th>n</th>
<th>Enhancement Diameter</th>
<th>Enhancement Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>10</td>
<td>0.27±0.09</td>
<td>0.02±0.03</td>
</tr>
<tr>
<td>Grade I</td>
<td>1</td>
<td>1.47</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade II</td>
<td>4</td>
<td>5.11±1.55</td>
<td>0.53±0.36</td>
</tr>
<tr>
<td>Grade III</td>
<td>11</td>
<td>4.00±2.00</td>
<td>0.30±0.30</td>
</tr>
<tr>
<td>Grade IV but no angiographic disease</td>
<td>4</td>
<td>8.93±3.20</td>
<td>1.09±0.61</td>
</tr>
<tr>
<td>Grade IV and angiographic disease</td>
<td>3</td>
<td>16.48±3.75</td>
<td>5.16±1.40</td>
</tr>
</tbody>
</table>

Summary of magnetic resonance imaging scores according to angiography and intravascular ultrasound severity.
by other institutions remain the next challenge for this technique. It should be noted that acquired image resolution, even at 3.0 T, was 1.0 mm. Coronary artery dimensions are =2 to 3 mm in diameter, and plaque size in our study varied from 0.2 to 1.3 mm in diameter and length generally >4 mm. Hence, MRI does not compare favorably with 0.1-mm resolution for IVUS or to =0.2-mm resolution for invasive coronary angiography. However, the hypothesized selective plaque uptake of gadolinium means that the imaging is more directed, aiming to image only diseased tissue. In addition, 3-dimensional MRI acquisition enables reformatting in any plane.

In addition to the quantitative assessment, we demonstrated good anatomic correlation between areas of enhancement on MRI and thickening on IVUS. However, of 17 areas showing enhancement at 1.5 T were not markedly thickened on IVUS, perhaps because of higher artifact levels caused by the reduction in signal-to-noise ratio required for high-resolution imaging. Because the signal-to-noise ratio is proportional to the static magnetic field (B0), imaging at 3.0 T should theoretically increase the signal-to-noise ratio. Furthermore, advances in parallel transmission have reduced concerns regarding off-resonance artifact levels at 3.0 T. In keeping with this, our data showed improved image quality, less observer variability in analysis, and improved anatomic correlation with IVUS at 3.0 T. However, no firm conclusions can be reached from this study about field strength because the same patients were not imaged at the 2 field strengths.

The remaining small number of cases not showing anatomic agreement (2 of 11) at 3.0 T may be congruent with an earlier study about field strength because the same patients were not imaged at the 2 field strengths.

Conclusions
This preliminary study suggests that imaging CAV with MRI may be accurate in pediatric transplant recipients. The LGE scores correlate well with traditional IVUS measures, and this observation deserves further investigation to determine the clinical use of this technique.

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Detection and Grading of Coronary Allograft Vasculopathy in Children With Contrast-Enhanced Magnetic Resonance Imaging of the Coronary Vessel Wall

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