Late gadolinium enhancement assessed by cardiac magnetic resonance imaging in heart transplant recipients with different stages of cardiac allograft vasculopathy

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Aims
Cardiac allograft vasculopathy (CAV), which limits long-term survival after heart transplantation (HTX), is usually evaluated by coronary angiography (CA). Late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) is a non-invasive technique that can detect CAV-related myocardial infarctions. We aimed to investigate the presence of LGE infarct-typical patterns in a large sample of HTX recipients and to correlate these findings with the severity of CAV assessed by CA.

Methods and results
LGE-CMR was performed in 132 HTX patients on a 1.5-T MRI scanner (Philips, Best, the Netherlands). Infarct-typical LGE areas were identified as bright lesions with subendocardial involvement. Infarct-atypical LGE was classified as follows: (i) right ventricle (RV) insertion, (ii) intramural, (iii) epicardial, and (iv) diffuse. CA was performed for the assessment of CAV (CAV0 = no lesion, CAV1 = mild lesions, CAV2 = moderate lesions, CAV3 = severe lesions, or mild/moderate lesions with allograft dysfunction). Infarct-typical LGE patterns were detected in 29 (22%) patients distributed in all groups and they were already present in nearly every fifth CAV 0 patient, increasing significantly among CAV groups (CAV0 = 19%, CAV1 = 10%, CAV2 = 36%, and CAV3 = 71%; P < 0.01).

Conclusion
LGE-CMR was useful to identify myocardial scar possibly related to early CAV in a significant proportion of HTX recipients, otherwise classified as low-risk patients based on CA. Therefore, LGE-CMR could be helpful to intensify CAV monitoring, medical therapy, and clinical risk stratification.

Keywords
Heart transplantation • Cardiac allograft vasculopathy • Cardiac magnetic resonance • Late gadolinium enhancement

Introduction
Heart transplantation (HTX) is the definitive treatment for eligible patients with end-stage heart failure. In 1 year, more than 5000 HTX are performed worldwide.1 Cardiac allograft vasculopathy (CAV), graft failure (probably caused by undetected CAV), and malignancies are the leading causes of death in patients who survive their first year after HTX.1

CAV is usually characterized by diffuse intimal hyperplasia that may affect the epicardial vessels as well as the microcirculation in a longitudinal and concentric arteriovascular pattern.2 Although the exact aetiology of CAV is still not completely understood, diverse pathophysiological mechanisms seem to be involved, i.e. complex immunological, infectious, or inflammatory processes, as well as the traditional cardiovascular risk factors.3 Two techniques play an important role in detecting and evaluating CAV. Coronary angiography (CA) as a luminographic visualization technique is the principal screening tool in most centres, although the method is considered relatively insensitive for the detection of CAV because of the diffuse and intramural nature of the disease.4

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The second technique, intravascular ultrasound (IVUS), is able to detect occult intramural disease in angiographically normal coronary arteries and has emerged as the optimal diagnostic tool for early detection of CAV. Unfortunately, in many cases, IVUS is not employed due to high costs, limited availability, insufficient operator skills, and also to clinical time and work-flow constraints. Notably, both techniques are invasive, carrying all the risks inherent to the procedure. Because of the necessity to repeat these examinations many times after HTX, non-invasive imaging techniques to evaluate CAV have been introduced recently with promising results.

As a non-invasive technique, cardiac magnetic resonance imaging (CMR) imaging is an important diagnostic tool, since it allows excellent tissue contrast with superior image quality. In addition, after administration of gadolinium contrast agents, late gadolinium enhancement CMR (LGE-CMR) further enables high-resolution tissue characterization, as different patterns of myocardial involvement can be differentiated: (i) ischaemic or infarct-atypical pattern involving the subendocardium with various degrees of transmurality and (ii) non-ischaemic or infarct-atypical patterns, mostly omitting the subendocardium. Importantly, as has previously been published, the presence of LGE has prognostic implications for non-HTX patients in different cardiac patho-entities like ischaemic cardiomyopathies.

In HTX recipients, LGE-CMR may indirectly suggest the presence of CAV due to its ability to identify areas of late enhancement that presumably correspond to areas of silent myocardial infarctions, even in patients with CA-classified significant CAV. In this relatively large cohort of cardiac HTX recipients, we sought to investigate whether the presence of infarct-atypical pattern of LGE is related to the severity of CAV assessed by CA.

Methods

Patient population

We studied 132 adult patients at different time points after HTX between 2004 and 2011. Demographic characteristics, factors associated with the procedure, and traditional cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, obesity, and cigarette smoking) were assessed. Patients were divided into four groups according to the presence and severity of CAV (CAV0, 1, 2, 3, see below). From a clinical perspective, further analyses were performed dividing the patients into two groups: (i) non-significant CAV (CAV0–1) with no or mildly stenotic coronary lesions on CA and (ii) significant CAV (CAV2–3) with at least moderate or even more severe lesions. All subjects gave written informed consent to participate in this study. The study was approved by the local ethics committee and was conducted according to GCP.

Coronary angiography

CA is routinely performed in our centre as a surveillance method every 6–12 months after HTX in order to detect early CAV, whereupon CMR scans were carried out within 4 weeks after CA. Angiograms were obtained from multiple projections and interpreted qualitatively by two independent observers blinded to the MRI data analysis. Lesions were classified according to International Society for Heart and Lung Transplantation (ISHLT) recommendation: CAV0 = no detectable angiographic lesion, CAV1 = mild lesions without allograft dysfunction, CAV2 = moderate lesions without allograft dysfunction, and CAV3 = severe lesions or mild/moderate lesions with spatially corresponding regional allograft dysfunction.

MRI protocol

Vector-ECG-triggered LGE-CMR was performed on a 1.5-T whole body MRI scanner (Philips Medical Systems, Best, the Netherlands) employing a cardiac phased-array receiver coil. Generation of imaging planes, assessment of left ventricular (LV) function, and LGE-CMR sequences 10 minutes after contrast agent administration (0.2 mmol/kg, Magnevist, Schering, Germany) were performed in a standardized way as previously described. Three-dimensional LGE sequences were carried out in two-, four-chamber, and short-axis orientations after inversion time (TI) scout used to select the appropriate TI time to null myocardial signal, typically between 180 and 240 ms.

MRI data analysis

Two blinded observers (H.S. and S.L.) conducted image analysis at least 8 weeks after image acquisition on a commercially available CMR workstation (Philips Viewforum, Version 3.4, Best, Netherlands). The accredited AHA 17 segment model was utilized for all functional and regional descriptions. Data acquisition of end-diastolic and -systolic volumes (EDV and ESV), stroke volumes (SVs), ejection fraction (EF), and myocardial mass were generated manually as mentioned earlier.

Infarct-atypical and -atypical LGE-CMR

Images were analysed and classified according to the presence of infarct-atypical LGE, i.e. bright lesions with subendocardial involvement. Qualitative infarct size was visually assessed per segment and classified as Grade I = 25%, Grade II = 25–50%, Grade III = 51–75%, and Grade IV ≥ 75% of LV wall thickness. The presence of infarct-atypical LGE patterns, as intramural, diffuse, right-ventricular insertion (right ventricle (RV)-insertion), and epicardial, was also evaluated.

Quantitative measurement of infarct-atypical LGE-CMR

For quantitative LGE infarct size analysis, a dedicated scar measurement tool (Philips Viewforum) was utilized. Infarct size was defined as an area of delayed hyper-enhancement on multiple short-axis views. Areas of hyper-enhancement were drawn manually by delineation of hyper-enhanced vs. normally saturated dark myocardium. Mean mass of LGE-CMR volume was then normalized to mean myocardial mass and is given in percent infarcted mass per normal myocardium.

Statistical analysis

Continuous data were expressed as mean ± standard deviation, whereas discrete variables were presented as percentages. Four groups were compared using the χ² test for categorical data and the ANOVA test with logarithmic transformation when appropriate for continuous variables. If the ANOVA test was positive, a post hoc test using Tukey–Kramer’s method was performed for pairwise comparison of subgroups. Further analyses on the two groups (CAV0–1 and CAV2–3) were performed using Student’s t-test for continuous variables and χ² test for categorical data. P-values ≤ 0.05 were considered statistically significant.

Results

Patient characteristics

Based on the ISHLT classification for CAV diagnosed by CA, the majority of patients did not show significant coronary artery...
lesions \(\text{CAV}_1/\text{CAV}_2\) — 107 patients (81%), whereas in 25 patients \(\text{CAV}_2/\text{CAV}_3\) (19%) more severe lesions could be detected. Patient age (years) and gender were not statistically different. Interestingly, heart recipient cardiovascular risk factors and serum creatinine levels were also not significantly different (Table 1).

In patients with \(\text{CAV}_3\), organ age was significantly higher than in the others \((P < 0.01)\). Ischaemia time of transplanted hearts was significantly shorter in \(\text{CAV}_3\) patients when compared with \(\text{CAV}_0\) \((P = 0.02)\). An overview on baseline clinical characteristics is displayed in Table 1.

### Left ventricular parameters

When compared with the other three groups \((\text{CAV}_0, \text{CAV}_1, \text{CAV}_2)\), \(\text{CAV}_3\) patients showed a negative LV remodelling resulting in a significantly lower EF \([52.6 \pm 14 \% (\text{CAV}_3)\) vs. \(63 \pm 6.3 \% (\text{CAV}_0)\) vs. \(61.7 \pm 6.8 \% (\text{CAV}_1)\) vs. \(61.8 \pm 11.6 \% (\text{CAV}_2)\); \(P < 0.01)\], a higher ESV/body surface area \((\text{BSA})\) \([46.7 \pm 26.6 \% vs. 25.6 \pm 6.4 \% vs. 27.4 \pm 8.5 \% vs. 26.3 \pm 9.7 \text{mL/m}^2; P < 0.01)\], and a higher EDV/BSA \([94.3 \pm 32.6 \% vs. 68.9 \pm 11.8 \% vs. 7.19 \pm 15.2 \% vs. 68.4 \pm 14.4 \text{mL/m}^2; P < 0.01)\]. In contrast, baseline heart rate, wall thickness, SV, and myocardial mass were not significantly different (Table 2). The analysis of the two groups with non-insignificant \(\text{CAV}\) \((\text{CAV}_0)\) vs. the group with at least moderate angiographic lesions \((\text{CAV}_2, \text{CAV}_3)\) also demonstrated similar results: a significantly lower EF \([56.7 \pm 13.6 \% (\text{CAV}_2)\) vs. \(62.3 \pm 6.6 \% (\text{CAV}_0)\); \(P < 0.05)\], a higher ESV/BSA \([37.7 \pm 23.0 \% vs. 26.6 \pm 7.6 \text{mL/m}^2; P < 0.02)\], and a higher EDV/BSA \([82.3 \pm 28.9 \% vs. 70.5 \pm 13.8 \text{mL/m}^2; P < 0.05)\) (Table 3).

### Distribution and extent of infarct-typical LGE

Overall, infarct-typical LGE patterns were detected in 29 (22%) patients distributed among all groups and with various degrees of transmurality (Figure 1). As shown in Figure 2A, 9 cases with \(\text{CAV}_0\) (19%), 6 with \(\text{CAV}_1\) (10%), 4 with \(\text{CAV}_2\) (36%), and 10 with \(\text{CAV}_3\) (71%) had infarct-typical LGE lesions \((P < 0.01)\). Interestingly, in CAV-classified \(\text{CAV}_0\) patients without \(\text{CAV}\) detected by \(\text{CAV}\), nearly every fifth patient revealed infarct-typical LGE patterns, even more than in patients with mild coronary lesions. Transmural infarctions were present in all degrees of \(\text{CAV}\), whereas diverse distributions of infarct size were found among the groups (Figure 2B).

\(\text{CAV}_0\) patients showed the following infarct-typical transmurality patterns: (i) of 9 patients \(\text{CAV}_0\): 22.2% with \(<25\% \text{transmurality}, 22.2\% \text{with} 26–50\% \text{transmurality, 11.1\% with} 51–75\% \text{transmurality, and 44.5\% with} 76–100\% \text{transmurality}; (ii) of 6 patients \(\text{CAV}_1\): 33.3% with \(<25\% \text{transmurality, 33.3\% with} 26–50\% \text{transmurality, 0 with} 51–75\% \text{transmurality, and 33.3\% with} 76–100\% \text{transmurality; (iii) of 4 patients \(\text{CAV}_2\): 0 with <25\% transmurality, 0 with 26–50\% transmurality, 0 with 51–75\% transmurality, and 100\% with 76–100\% transmurality; (iv) of 10 patients \(\text{CAV}_3\): 10\% with <25\% transmurality, 20\% with 26–50\% transmurality, 20\% with 51–75\% transmurality, and 50\% with 76–100\% transmurality (Figure 2B).

We observed similar results after the analysis of two groups: non-significant \(\text{CAV} \text{CAV}_0\) vs. significant \(\text{CAV} \text{CAV}_3\), with 14\% of patients without significant \(\text{CAV}\) presenting infarct-typical

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### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>(\text{CAV}_0)</th>
<th>(\text{CAV}_1)</th>
<th>(\text{CAV}_2)</th>
<th>(\text{CAV}_3)</th>
<th>(P)-value</th>
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<td><strong>Heart recipients</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Number of patients (%)</td>
<td>47 (36)</td>
<td>60 (45)</td>
<td>11 (8)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.1 ± 12.1</td>
<td>51.2 ± 12.3</td>
<td>49.6 ± 12.2</td>
<td>50.8 ± 10</td>
<td>0.9</td>
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<td>Gender (% male)</td>
<td>37 (79)</td>
<td>51 (85)</td>
<td>10 (91)</td>
<td>11 (73)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 4.1</td>
<td>25.1 ± 5.4</td>
<td>27.7 ± 5.2</td>
<td>24.6 ± 4.2</td>
<td>0.4</td>
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<tr>
<td>BSA (m²)</td>
<td>1.95 ± 0.24</td>
<td>1.94 ± 0.22</td>
<td>2.1 ± 0.22</td>
<td>1.85 ± 0.2</td>
<td>(&lt;0.05)</td>
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<tr>
<td>Ischaemia time of TX heart (min)</td>
<td>202 ± 66</td>
<td>217 ± 61</td>
<td>218 ± 40</td>
<td>164 ± 36</td>
<td>0.02*</td>
</tr>
<tr>
<td>CMR years after HTX</td>
<td>4.1 ± 4.5</td>
<td>4.4 ± 5.1</td>
<td>5.1 ± 4.5</td>
<td>11 ± 5.2</td>
<td>(&lt;0.01)*</td>
</tr>
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<td><strong>Patients risk factors and symptoms</strong></td>
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<tr>
<td>Hypertension</td>
<td>27 (57)</td>
<td>40 (67)</td>
<td>8 (73)</td>
<td>9 (64)</td>
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<td>Diabetes</td>
<td>16 (34)</td>
<td>21 (35)</td>
<td>4 (36)</td>
<td>6 (43)</td>
<td>0.9</td>
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<tr>
<td>Dyslipidaemia</td>
<td>23 (49)</td>
<td>30 (50)</td>
<td>5 (45)</td>
<td>9 (64)</td>
<td>0.4</td>
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<tr>
<td>Tobacco use</td>
<td>10 (21)</td>
<td>14 (23)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.8</td>
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<td>NYHA functional class</td>
<td>1.7 ± 0.2</td>
<td>1.9 ± 0.4</td>
<td>1.8 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>0.08</td>
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<td><strong>Heart donor</strong></td>
<td></td>
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<tr>
<td>Donor age</td>
<td>34.5 ± 12.2</td>
<td>41.2 ± 14.8</td>
<td>43.1 ± 14.7</td>
<td>41 ± 12.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Donor gender (% male)</td>
<td>20 (43)</td>
<td>22 (37)</td>
<td>5 (45)</td>
<td>6 (43)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Bold P-values:** statistically significant values.

CAV\(_0\): no detectable angiographic lesion; CAV\(_1\): mild lesions without allograft dysfunction; CAV\(_2\): moderate lesions without allograft dysfunction; CAV\(_3\): severe lesions or mild/moderate lesions with allograft dysfunction; BMI: body mass index; BSA: body surface area; NYHA: New York Heart Association.

*ANOVA analysis with difference between group CAV\(_3\) vs. CAV\(_0\), CAV\(_3\) vs. CAV\(_1\), CAV\(_3\) vs. CAV\(_2\).*
Table 2  CMR—left ventricular parameters and presence of infarct-typical and atypical patterns of LGE according to the degree of CAV

<table>
<thead>
<tr>
<th></th>
<th>CAV₀</th>
<th>CAV₁</th>
<th>CAV₂</th>
<th>CAV₃</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>80 ± 11</td>
<td>76 ± 9</td>
<td>82 ± 14</td>
<td>76 ± 11</td>
<td>0.2</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>63 ± 6.3</td>
<td>61.7 ± 6.8</td>
<td>61.8 ± 11.6</td>
<td>52.6 ± 14</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>10.8 ± 1.9</td>
<td>10.5 ± 2.1</td>
<td>10.8 ± 2.6</td>
<td>10.6 ± 2.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lateral wall (mm)</td>
<td>7.3 ± 1.6</td>
<td>7 ± 1.6</td>
<td>8 ± 2.2</td>
<td>7.4 ± 2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>LV SV (mL)</td>
<td>84.1 ± 20.3</td>
<td>86.8 ± 20.4</td>
<td>87.8 ± 20.1</td>
<td>87.1 ± 21.4</td>
<td>0.9</td>
</tr>
<tr>
<td>LV EDV/BSA (mL/m²)</td>
<td>68.9 ± 11.8</td>
<td>71.9 ± 15.2</td>
<td>68.4 ± 14.4</td>
<td>94.3 ± 32.6</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>LV ESV/BSA (mL/m²)</td>
<td>25.6 ± 6.4</td>
<td>27.4 ± 8.5</td>
<td>26.3 ± 9.7</td>
<td>46.7 ± 26.6</td>
<td>&lt;0.01*</td>
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<tr>
<td>LV mass/BSA (g/m²)</td>
<td>42.7 ± 11.3</td>
<td>42 ± 9.7</td>
<td>46.2 ± 12.7</td>
<td>47.1 ± 11.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Infarct-typical LGE (patients)</td>
<td>9 (19)</td>
<td>6 (10)</td>
<td>4 (36)</td>
<td>10 (71)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Infarct-atypical LGE (patients)</td>
<td>30 (63.8)</td>
<td>37 (61.7)</td>
<td>6 (54.5)</td>
<td>8 (57.1)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Bold P-values: statistically significant values.
CAV₀, no detectable angiographic lesion; CAV₁, mild lesions without allograft dysfunction; CAV₂, moderate lesions without allograft dysfunction; CAV₃, severe lesions or mild/moderate lesions with allograft dysfunction; EF, ejection fraction; SV, stroke volume; ESV/EDV, end-systolic/end-diastolic volume; BSA, body surface area; LGE, late gadolinium enhancement.

*ANOVA analysis with difference between group CAV₃ vs. CAV₀, CAV₁, CAV₂, CAV₃ vs. CAV₀, CAV₁, CAV₂ was statistically not significant.
†ANOVA analysis with difference between group CAV₂ vs. CAV₀, CAV₁, CAV₂ vs. CAV₀, CAV₁, CAV₂ vs. CAV₀ was statistically not significant.

Figure 1: Infarct-typical LGE-CMR in HTX patients with various degrees of CAV. (A) Large lateral wall myocardial infarction in a patient with severe CAV detected by CA (CAV₃), four-chamber view; (B) small inferior scar in a patient CAV₃, two-chamber view; (C) inferior wall myocardial infarction (50% transmurality) in a patient with mild lesions (CAV₁), short-axis view; (D) small inferior scar in a patient without lesions (CAV₀), two-chamber view. The white arrows point to the LGE-CMR lesions.
Figure 2: Distribution and extent of infarct-typical LGE according to the presence and degree of CAV. (A) Comparison of the percentage of patients with infarct-typical LGE-CMR in all four groups: 9 CAV0 (19%), 6 CAV1 (10%), 4 CAV2 (36%), and 10 CAV3 (71%) patients (p < 0.01). (B and D) Various degrees of transmurality of myocardial infarction were found in all groups of patients. (C) Comparison of the percentage of patients with infarct-typical LGE-CMR in two groups: 15 CAV0–1 (14%), 14 CAV2–3 (56%) patients (p < 0.001). ANOVA analysis with difference between group CAV0 vs. CAV0, CAV0 vs. CAV1, CAV0 vs. CAV2 was statistically not significant. CAV0, no detectable angiographic lesion; CAV1, mild lesions without allograft dysfunction; CAV2, moderate lesions without allograft dysfunction; and CAV3, severe lesions or mild/moderate lesions with allograft dysfunction.

Table 3  CMR—left ventricular parameters and presence of infarct-typical and atypical patterns of LGE according to the presence of significant CAV

<table>
<thead>
<tr>
<th></th>
<th>CAV0–1 n = 107 (81%)</th>
<th>CAV2–3 n = 25 (19%)</th>
<th>P-value</th>
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<tr>
<td>Heart rate</td>
<td>78 ± 10</td>
<td>79 ± 12</td>
<td>0.8</td>
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<tr>
<td>LV EF (%)</td>
<td>62.3 ± 6.6</td>
<td>56.7 ± 13.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>10.6 ± 2.0</td>
<td>10.7 ± 2.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lateral wall (mm)</td>
<td>7.1 ± 2.6</td>
<td>7.6 ± 4.7</td>
<td>0.3</td>
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<tr>
<td>LV SV (mL)</td>
<td>86 ± 20</td>
<td>87 ± 20</td>
<td>0.7</td>
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<tr>
<td>LV EDV/BSA (mL/m²)</td>
<td>70.5 ± 13.8</td>
<td>82.3 ± 28.9</td>
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<td>LV ESV/BSA (mL/m²)</td>
<td>26.6 ± 7.6</td>
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<td>0.02</td>
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<tr>
<td>LV mass/BSA (g/m²)</td>
<td>42.3 ± 10.4</td>
<td>46.7 ± 11.6</td>
<td>0.07</td>
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<td>Infarct-typical LGE (patients)</td>
<td>15 (14)</td>
<td>14 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infarct-atypical LGE (patients)</td>
<td>67 (63)</td>
<td>14 (56)</td>
<td>0.4</td>
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</tbody>
</table>

Bold P-values: statistically significant values.
CAV0, no detectable angiographic lesion; CAV1, mild lesions without allograft dysfunction; CAV2, moderate lesions without allograft dysfunction; CAV3, severe lesions or mild/moderate lesions with allograft dysfunction; EF, ejection fraction; SV, stroke volume; ESV/EDV, end-systolic/end-diastolic volume; BSA, body surface area; LGE, late gadolinium enhancement.
LGE and >50% of patients with significant CAV presenting infarct-typical LGE. In addition, diverse distributions of infarct size were found (Figure 2C and D).

Various infarct-atypical LGE patterns were found in 81 patients distributed in all groups in similar proportions: 30 CAV0 patients (63.85%), 37 CAV1 patients (61.7%), 6 CAV2 patients (54.5%), 8 CAV3 patients (57.1%); P = 0.8. The most prevalent pattern of infarct-atypical LGE was diffuse (32 patients—39.5%), followed by the intramural (21 patients—26%), RV insertion (17 patients—21%), and epicardial patterns (11 patients—13.5%; Figures 3 and 4).

Quantitative measurement of LGE-CMR
Mean infarct-typical LGE-CMR myocardial mass was 2.6% for CAV0, 3.2% for CAV1, 4.6% for CAV2, and 7.9% for CAV3 patients (P = 0.04). There was also a significant difference in LGE-CMR size when CAV0−1 patients with no or only mild vascular disease were grouped together vs. CAV2−3 patients (P < 0.03) with more severe CAV lesions.

Discussion
Infarct-typical LGE patterns could be detected in almost one-fifth of HTX patients in the absence of detectable coronary artery lesions visualized by standard CA. Steen et al. demonstrated in 2008 that about one-fourth of 28 patients with CA-classified mild CAV also showed infarct-typical LGE. Our findings not only confirm the presence and significant prevalence of unexpected myocardial lesions detected by LGE-CMR, but, furthermore, show similar results in a larger group of HTX recipients, even in patients without any lesion detected by CA.

The lack of intraluminally protruding and, consequently, detectable angiographic lesions in patients with CMR-identified myocardial scars may be explained through the fact that CA as a luminographic technique is insensitive for the detection of primarily intramural inflammatory and atherosclerotic processes. Taking into account the different pathophysiological processes of diffuse intimal vessel wall thickening in contrast to the conventional, focal atherosclerotic plaque lesion, especially in the earlier stages of the disease, CA is likely to underdiagnose the existence, degree, or even severity of CAV. In the same line, we previously demonstrated that ~20% of patients with angiographically entirely normal coronary vessels demonstrated impaired myocardial perfusion. Moreover, we found small areas of LGE in CAV0/CAV1 patients, which are compatible with distal lesions in small arteries making the evaluation of CAV, based on conventional CA, more difficult. Interestingly, in this case, even IVUS might not be superior because of the technical limitations to assess smaller vessels such as subepicardial segments of coronary arteries. Furthermore, there might be a lack of correlation between the intimal index determined by IVUS in epicardial vessels and the small artery disease diagnosed by histological analysis. However, further studies are needed to evaluate the correlation between the existence and spatial coincidence of LGE lesions detected by CMR and CAV lesions detected by IVUS.

Apart from LGE-CMR, other non-invasive techniques for the detection of CAV are currently evaluated. Cardiac stress tests, including

Figure 3: Different infarct-atypical patterns of LGE in HTX patients. (A) Diffuse pattern, short-axis view; (B) epicardial lesion, short-axis view; (C) intramural pattern, four-chamber view; and (D) infero-septal lesion at the RV insertion, short-axis view. The white arrows point to the contrast-enhanced lesions.
dobutamine stress echocardiography and single-photon emission computed tomography, showed a high negative predictive value in screening for significant CAV. Multislice computed tomography was also employed to rule out CAV in HTX patients with promising results regarding the detection of significant coronary stenosis (≥50%).

Also, studies employing other CMR sequences rather than LGE-CMR to evaluate CAV showed interesting findings: (i) anatomical evaluation of coronary arteries through whole-heart MR CA with high specificity, positive and negative predictive values, but limited sensitivity; (ii) assessment of LV diastolic function showing a correlation between signs of diastolic dysfunction and early stage CAV, and (iii) adenosine stress perfusion demonstrating a significant reduction of myocardial perfusion reserve in HTX patients with known CAV, as previously shown by our group and others.

We found similar proportions of infarct-atypical LGE among the groups of HTX recipients. According to our results, myocardial injuries leading to these patterns of LGE are not related to CAV. In contrast to CAV, which increases over the years after HTX and reveals more patients with infarct-typical LGE patterns (71% of CAV patients had infarct-typical fibrosis after a mean time of 11 years after HTX), our group showed that infarct-atypical LGE seems to have a ‘temporal distribution’, decreasing over the years after the surgery in a pattern similar to the decremental incidence of viral myocarditis after HTX. Actually, the exact mechanisms are still unclear and could be linked to various factors that affect the tissue of the cardiac allograft, i.e. perioperative ischaemia and injuries, organ rejections, medical interventions, post-HTX infections, or donors’ characteristics.

Due to the multifactorial nature of infarct-atypical LGE, further studies are possibly warranted focusing only on these patterns of myocardial involvement in larger patient cohorts.

It is already known that perioperative injuries are related to CAV and ischaemia time may be a risk factor for infarct-atypical LGE. However, according to our results, HTX recipients with severe allograft vasculopathy (CAV3) and higher prevalence of infarct-typical LGE showed lower ischaemia times. This group of patients also had their operation about 5–6 years before patients with less severe CAV. Notably, Banner et al. showed that the median total ischaemia time in HTX increased due to an increase of organ transport and surgical implant times between 1995 and 2004. Over the years, our heart transplant centre also received organs from more distant centres and improved surgical techniques. Therefore, the conclusion that shorter ischaemia times are related to more severe CAV is premature at this juncture and, most probably, lower ischaemia times are related to ‘older surgical procedures’.

Study limitations

LGE-CMR was compared with CA instead of IVUS, which is considered the reference standard technique for the detection of early stages of CAV. However, in a clinical real-world scenario, CA remains the principal screening tool for CAV routine surveillance in most centres.

Although infarct-typical LGE is most probably related to CAV, we were not able to rule out myocardial damage already present at the donor’s heart due to procedural incompatibilities shortly before or after the HTX procedure. Also, myocardial fibrosis as a consequence of peri-procedural injuries could not be systematically precluded, since CMR could not be performed very early after the HTX operation due to the patients’ perioperative instability. Furthermore, initial episodes of cardiac rejection could affect the vascular integrity of small vessels and, therefore, could potentially result in small myocardial infarctions being detected by LGE-CMR.

In our study, we used only LGE-CMR sequences in order to assess CAV. As already mentioned, adenosine perfusion sequences and evaluation of diastolic dysfunction through CMR also showed interesting results. Whether a combined approach employing these three different techniques could be of additional value for detecting CAV non-invasively is still unknown and warrants further investigation in future studies.

![Figure 4: Distribution of different patterns of infarct-atypical LGE. (A) The most prevalent pattern of infarct-atypical LGE was diffuse (32 patients—39.5%), followed by intramural (21 patients—26%), RV insertion (7 patients—21%), and epicardial pattern (11 patients—13.5%). (B and C) Distribution of infarct-atypical patterns in all groups of patients. RV, right ventricular; CAV0, no detectable angiographic lesion; CAV1, mild lesions without allograft dysfunction; CAV2, moderate lesions without allograft dysfunction, and CAV3, severe lesions or mild/moderate lesions with allograft dysfunction.](https://academic.oup.com/ehjcimaging/article-abstract/15/10/1125/2399601)
Finally, the clinical impact of our findings on future cardiovascular risk stratification and on patient outcome has to be assessed. Unfortunately, although this is the world’s largest cardiac MRI study on HTX patients published so far, this study was still underpowered for these analyses. Nevertheless, the correlation between the presence of LGE in HTX recipients and poor cardiovascular outcomes would be of great clinical value in order to reassure the importance of LGE-CMR and, in addition to that, to help improve therapies and survival of HTX recipients.

**Conclusion**

LGE-CMR could visualize infarct-typical and -atypical contrast enhancement patterns in patients with various degrees and different stages of CAV. Interestingly, even patients without angiographically significant CAV already showed patterns of subendocardial involvement. LGE-CMR could serve as a non-invasive tool for longitudinal follow-up of HTX patients to detect subtle myocardial changes not only on a functional, but even on a myocardial tissue, level. Further studies are needed to help interpret the significance of these CMR findings and their impact on the clinical prognosis and future outcome of HTX patients with positive LGE-CMR findings.

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**References**