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Prognostic impact of late gadolinium enhancement in the risk stratification of heart transplant patients

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Aims The aim of the present study was to assess the association of the presence and amount of late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) with cardiovascular adverse events in patients with orthotopic heart transplantation (HTx).

Methods and results We enrolled 48 patients (mean age, 54.7 ± 14.6 years; 37 men) at various stages after HTx. All patients underwent standard CMR at 1.5 T, to characterize both cardiac anatomy and LGE. Late gadolinium enhancement was detected in 26 patients (54%). All-cause and cardiovascular mortalities, and a composite of major adverse cardiovascular events (MACE) recurrence were evaluated during the follow-up period for a median of 5.16 years. Ten patients (21%) died and 26 (54%) were readmitted because of MACE. Multivariate Cox analysis identified as independent predictors of MACE a diagnosis of cardiac allograft vasculopathy (CAV) (HR 3.63; 1.5–8.7 95% CI; $P = 0.0039$), left ventricular end systolic volume index (HR 1.04; 95% CI 1.01–1.079; $P = 0.008$), LGE mass (HR 1.04; 1.01–1.06 95% CI; $P = 0.0007$), LGE % of left ventricular mass (HR 1.083; 1.03–1.13 95% CI; $P = 0.0002$). Independent predictors of all-cause death were CAV (HR 6.33; 95% CI 1.33–30.03; $P = 0.0201$), LGE mass (HR 1.04; 1.01–1.07 95% CI; $P = 0.005$), LGE % of left ventricular mass (HR 1.075; 1.02–1.13 95% CI; $P = 0.007$). Patients with CAV had a risk of MACE by 5 years of 67% (95% CI 0.309–0.851%); the addition of 7.9 LGE % to the risk model increased the predicted risk to 88% (95% CI 0.572–0.967%).

Conclusions The current study demonstrated that the presence of CAV and the total amount of LGE have a significant independent association with MACE and mortality in HTx patients.

Keywords cardiovascular magnetic resonance • late gadolinium enhancement • heart transplant • coronary allograft vasculopathy

Introduction

Survival after heart transplantation (HTx) has improved over the last two decades with a median life expectancy of 14 years for those surviving the first year after HTx.[1] Nevertheless, cardiac allograft vasculopathy (CAV) remains one of the leading causes of death,[2] with a survival rate of about 50% at 10 years.[3,4] CAV affects the entire coronary artery vasculature of the graft and even mild non-obstructive lesions are related to major adverse cardiac events.[5]

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However, cardiac adverse events can occur with patent epicardial arteries and there is no association between abnormalities of the intima and media of small intramyocardial microcirculation and epicardial vessels.[6–8] Intramyocardial vessels may be totally occluded before the large epicardial arteries become critically stenosed[7]; a finding confirmed in endomyocardial biopsies, where patchy microscopic ischaemic injuries, interstitial, perivascular, replacement fibrosis and chronic inflammation have been described.[7,9] Recently a 50% prevalence of infarct-atypical intramyocardial late gadolinium enhancement (LGE) not related to epicardial coronary arteries CAV has been reported in HTx patients.[10,11] Braggion Santos *et al.* failed to find a correlation with the presence or severity of lesions in epicardial arteries detected by IVUS in HTx patients with both the infarct-typical LGE or the infarct-atypical intramyocardial LGE.[12] At present limited prognostic data are available for presence of LGE in HTx patients; only recently Butler and coworkers reported that the presence of LGE is an independent predictor of all-cause mortality and 5-year adverse outcome in HTx recipients.[13,14]

We hypothesized that the extent of LGE could independently predict adverse CV outcomes in HTx recipients in addition to CAV detection and represent a marker of cardiac allograft condition.

Methods

This is a single-centre prospective cohort study carried out at Niguarda-Ca' Granda hospital between January 2006 and June 2014. The study was performed in accordance with the declaration of Helsinki and informed consent was obtained from each patient.

Patients underwent post-transplant surveillance according to ISHLT Guidelines.[1] Angiographic diagnosis of CAV was based on the detection of localized luminal narrowing $\geq$50%, distal pruning, or progressive tapering of the epicardial coronary arteries. After the first post-operative year, EMB surveillance for both antibody and cell mediated rejection was performed only in HTX recipients at higher risk for late acute rejection (AMR). The immunoperoxidase staining for C4d and C3d was carried out only if a suspect of AMR arose, according to Kobashigawa *et al.*[15] At the time of CMR, the majority of patients in our cohort were stable and did not show clinical signs of rejection such as worsening exercise tolerance, jugular venous distension, decrease of systolic blood pressure, or rise in heart rate $>$15% in the previous 3 months. Clinical assessment was carried out every 6 months including stress test ECG. Survival and time to adverse events were calculated from the time of cardiac magnetic resonance (CMR) scan until the date of last visit. Adult HTX recipients (median 9.88 years from transplant) were eligible; exclusion criteria were contraindication to CMR and gadolinium contrast, calculated glomerular filtration rate $<$30 mL/min/1.73 m^2, active infection, clinical and histological signs of acute rejection in the previous 3 months.[1,7]

CMR protocol and data analysis

Patients underwent scans on a 1.5T scanner (Siemens Avanto©, Erlangen, Germany) (Supplementary data online, Methods, for details).

Clinical follow-up started at the time of CMR from February 2006 to January 2010, the observation period was closed on 30 June 2014, and no patients were lost to follow up (FU). The primary endpoint was a composite of first occurrence of major adverse cardiovascular events (MACE) which required hospitalization: CV death, congestive heart failure, redo transplant, arrhythmias requiring hospitalization (high degree A-V block, sustained supraventricular tachyarrhythmias, sustained ventricular tachycardia, bradycardia requiring pace-maker implantation), coronary revascularization, the secondary endpoints were all-cause death and cardiovascular death.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD and tested for normality using Kolmogorov–Smirnov test. Categorical data are presented as percentages or frequencies with differences assessed by χ^2 or Fisher's exact test. Demographic and clinical variables were compared using Student's *t*, Mann–Whitney *U* or Wilcoxon rank sum tests where appropriate. Correlations were assessed by Spearman's coefficients. Survival of patients was estimated by Kaplan–Meier analysis, with *P*-values calculated by log-rank statistics.

A univariable Cox regression model was used to test the association between the end points and baseline covariates. Only those variables which were significantly different between patients with and without index events were entered in the model. The proportional hazard assumption was tested for each covariate. Results are presented as hazard ratios (HRs) with 95% confidence intervals. For each end point three multivariate models were constructed. Each model included one of the LGE variables (presence or absence of LGE, LGE mass or total LGE% LV mass) and all the covariates which were significantly associated in the univariable Cox model. Stepwise selection (entered and retained in model if $P < 0.05$) was used to identify predictive variables. The predicted risk of the end points was estimated from a proportional hazard model that contain CAV and LGE% LVmass using the formula $P(5) = 1 - S_0(5) \times e^{\text{risk score}}$ where $S_0(5)$ is the baseline survival function at 5 years, and risk score was the product of individual parameter and corresponding Cox coefficient.

Receiver operating curve (ROC) and their area under the curve (AUC) were used to compare discrimination in predicting the endpoints. The Youden index was used to select a cut-off for each variable. Sensitivity and specificity were also calculated. Two sided *P*-values $<$0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of SAS version 9.4.

Results

CMR-derived parameters

Baseline clinical characteristics of the study population according to presence (LGE pos) or absence (LGE neg) of LGE are summarized in *Table 1*. Myocardial LGE was detected in 26 patients (54%) with a median amount of 9.16 g (IQR 3.01–21.21) corresponding to 6.4% (IQR 2.3–13.25) of LV mass. Patients in the LGE neg group were older and mostly females, and had a higher prevalence of hypertension and a trend to a lower prevalence of CAV. Time elapsed after transplant, allograft ischaemic time, donor's age, number of rejections treated with steroids, immunosuppressive therapy protocols, and standard of care cardiovascular therapy were not significantly different between the two groups.

LGE neg patients showed significant differences in CMR variables in comparison with LGE pos (*Table 2*); these latter patients had lower LVEF and RVEF, paralleled by increased LV volumes and mass. Myocardial LGE% showed a significant inverse correlation with

Table 1 Patients characteristics

	LGE positive N = 26	LGE negative N = 22	P
Male gender	24	13	0.016
Age (years)	47 ± 2.1	57 ± 10.6	0.011
Years after HTX at CMR	9.2 ± 5.9	9 ± 3.8	0.632
Cold ischaemic time	178 ± 59	171 ± 33	0.610
Donor age	34 ± 15	32 ± 13	0.738
Sex mismatch	23.1% (5 M_R/F_D 1 F_R/M_D)	13.6% (1 M_R/F_D 3 F_R/M_D)	0.639
Number of treated rejections	1.2 ± 1.5	1.8 ± 2.35	0.321
CAV	53.8%	22.7%	0.057
CAV			
0	12 (46.2%)	17 (77.3%)	0.0645
1	4 (15.3%)	3 (13.5%)	
2	8 (30.8%)	1 (4.6%)	
3	7 (7.7%)	1 (4.6%)	
Pulmonary hypertension pre-transplant	34.6%	22.7%	0.558
Diabetes	23%	0	0.490
Hypertension	26%	68%	0.011
Hypercholesterolemia	17%	14%	0.949
Chronic renal failure	69.2%	68.2%	0.806
Statins	61.5%	73%	0.592
ASA/Clopidogrel	77%	59%	0.304
Adrenergic-blockers	50%	59%	0.739
Ca-antagonists	11%	13%	0.815
ACE & ARB	65%	50%	0.449
Diuretics	31%	36%	0.953

MR/FD, male recipient/female donor; FR/MD, female recipient/male donor.

LVEF (Spearman's $\rho = -0.54$, $P = 0.0001$) and RVEF (Spearman's $\rho = -0.37$, $P = 0.01$).

A subendocardial infarct-typical pattern was observed in 8 out of 26 LGE pos patients, 4 of these patients had also infarct-atypical LGE (*Figure 1* and *Table 2*).

Table 2 CMR cardiac parameters

	LGE positive N = 26	LGE negative N = 22	P
LV EF (%)	58 ± 13	68 ± 9	0.005
RV EF (%)	57 ± 11	65 ± 7	0.009
LV Mass (g)	146 ± 30	118 ± 25	0.001
LV Mass index (g/m^2)	78 ± 15	65 ± 13	0.005
LVEDV (mL)	127 ± 24	99 ± 20	0.001
LV EDV index (mL/m^2)	67 ± 17	54 ± 12	0.006
LV ESV (mL)	54 ± 24	32 ± 12	0.001
LV ESV index (mL/m^2)	29 ± 13	17 ± 6	0.001
RV EDV (mL)	116 ± 31	98 ± 28	0.04
RV EDV index (mL/m^2)	60 ± 15	54 ± 14	0.149
RV ESV (mL)	52 ± 27	35 ± 14	0.012
RV ESV index (mL/m^2)	27.2 ± 1	18.9 ± 1.4	0.012
Infarct atypical patterns	Diffuse: 9 (40.9%) Intramural: 3 (13.64%) RV insertion: 8 (36.3%) Epicardial: 2 (9.1%)		0.081

LV, left ventricle; RV, right ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LGE, late gadolinium enhancement.

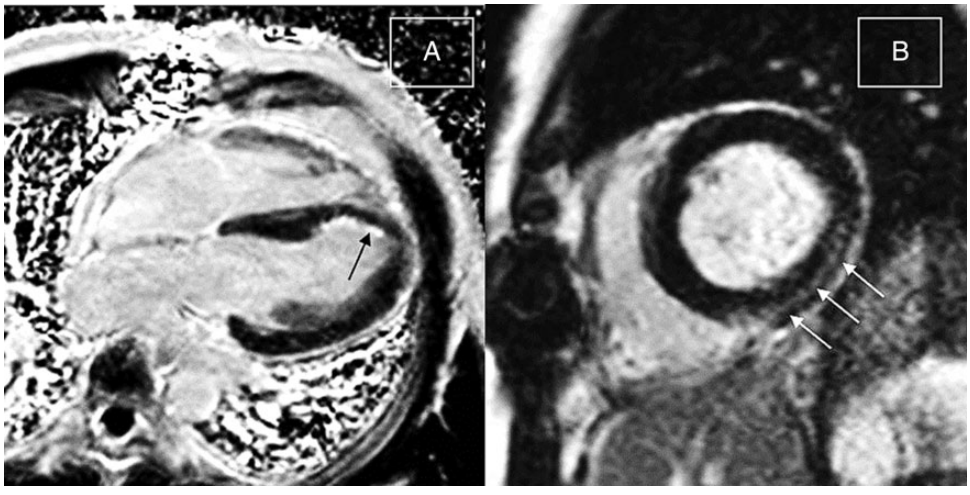

Figure 1 Post gadolinium contrast images. (*A*) Infarct-typical pattern: four-chamber view, subendocardial enhancement of the apical septum (arrows). (*B*) Infarct-atypical pattern: short axis view, subepicardial enhancement of the inferior and inferolateral wall (arrows).

Primary end-point

Median follow-up after CMR was 5.16 years (IQR 4.33–6.52). In total 26 MACE occurred (10 congestive heart failure; 1 redo transplant, 7 arrhythmias, 7 coronary revascularization, 1 CV death). Out of 19 patients with CAV 7 patients underwent revascularization and stent implantation during the observation period; in these patients ischaemia was detected by means of stress test ECG and confirmed by SPECT myocardial perfusion imaging. The majority of patients with MACE were LGE pos ($P = 0.0043$), and had a significantly higher bi-ventricular ESV, LGE mass, and LGE%. The comparison of patients with and without index events is reported in Supplementary data online, *Table S1*.

LGE presence at CMR was associated with an increased risk of sustaining an index event during follow-up, as demonstrated by the Kaplan–Meier survival curves shown in *Figure 2* (log-rank test: $P = 0.003$).

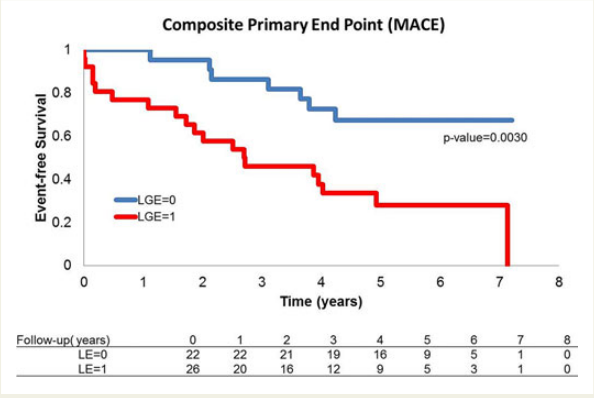

Figure 2 Kaplan–Meier event-free survival curve for the occurrence of MACE in patients, grouped by presence or absence of late gadolinium enhancement (LGE).

The unadjusted univariable clinical and CMR predictors of MACE are listed in *Table 3*. The presence of CAV, LVESVi, LVEF, LGE presence, LGE mass, and LGE% were all significant predictors of MACE.

Presence of CAV, LGE mass, and LGE% were the only variables retained as independent predictors. The presence of CAV was associated with a three-fold increase of risk of MACE in our population. For each 1 g increment of LGE mass or 1% in LGE% the hazard of MACE increased by 4.2 and 8.3% respectively (*Table 3*).

In the subset of LGE pos patients, ROC of continuous (LVESVi, LVEF, LVMi, LGE mass, LGE%) and categorical (CAV) variables were analysed to determine the optimal cut-off values and assess the diagnostic performance as predictors of events during follow-up. Both LGE mass and LGE% showed good sensitivity and excellent specificity (*Table 4*).

Patients with CAV had a risk of MACE by 5 years of 67% (95% CI 0.309–0.851%); the addition of 7.9 LGE % (cut-off value, *Table 4*) to the risk model increased the predicted risk to 88% (95% CI 0.572–0.967%). In patients without any angiographic evidence of CAV an amount of 7.9 LGE% purported a risk of MACE by 5 years of 43% (95% CI 0.171–0.614%).

Secondary end-points

A total of 10 deaths (8 cardiovascular deaths, 1 due to malignancy and 1 due to infection) were recorded and 9 out of 10 patients were LGEpos. The characteristics of these patients compared with survivors are reported in Supplementary data online, *Table S2*. Participants who died had lower LVEF, greater prevalence of CAV, greater LGE mass and LGE%. There was no association between all-cause mortality and recipient age, time from transplant, renal failure or cardiovascular risk factors.

Table 3 Univariable and multivariable Cox proportional hazards analysis for the time to occurrence of an index composite cardiac event

Variable	Univariable analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender (M vs. F)	3.352 (1.000–11.234)	0.0500						
CAV (categorical)	4.471 (1.933–10.339)	0.0005	3.164 (1.302–7.688)	0.0110	3.633 (1.511–8.731)	0.0039	3.752 (1.574–8.946)	0.0029
LV ESV index (mL/m^2)	1.056 (1.026–1.087)	0.0002	1.045 (1.011–1.079)	0.0084				
LV EDV index (mL/m^2)	1.017 (0.995–1.041)	0.1360						
LVEF (%)	0.951 (0.924–0.978)	0.0005						
LV mass index (g/m^2)	1.022 (0.996–1.049)	0.1014						
LGE (categorical)	3.450 (1.445–8.238)	0.0053						
LGE mass (g)	1.048 (1.025–1.072)	<0.0001			1.042 (1.018–1.067)	0.0007		
LGE% LV mass	1.090 (1.047–1.133)	<0.0001					1.083 (1.038–1.130)	0.0002

Model 1: Gender, CAV, LV ESV index, LVEF and LGE (categorical).
Model 2: Gender, CAV, LV ESV index, LVEF and LGE mass (g).
Model 3: Gender, CAV, LV ESV index, LVEF and LGE% LV mass.
LV, left ventricle; RV, right ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LGE, late gadolinium enhancement.

Table 4 Diagnostic performance of clinical and CMR parameters to predict MACE

	AUC	95% CI	P	P vs. LGEmass	P vs. LGE% LV mass	Cut-off value	Sensitivity	Specificity
CAV (categorical)	0.591	(0.362–0.821)	0.4355	0.01	0.02	Yes	61	57
LV ESV index (mL/m^2)	0.778	(0.541–1)	0.0214	0.15	0.29	23	83	86
LVEF (%)	0.786	(0.582–0.99)	0.0061	0.10	0.25	59.5	72	86
LV mass index (g/m^2)	0.79	(0.528–1)	0.03	0.23	0.41	71	83	86
LGE mass (g)	0.929	(0.827–1)	<0.0001	–	–	10.8	72	100
LGE% LV mass	0.897	(0.769–1)	<0.0001	–	–	7.9	72	100

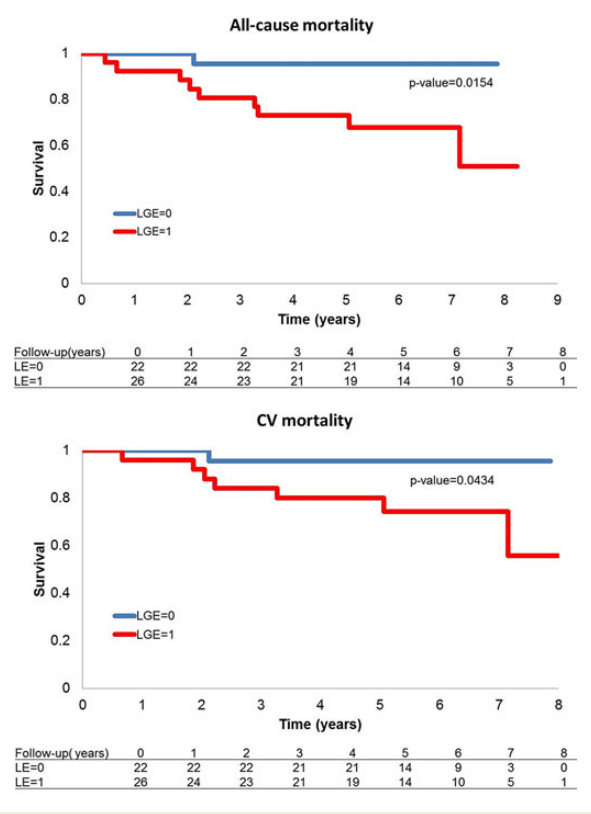

Figure 3 Kaplan–Meier survival curves for the occurrence of death from all-cause (upper panel) or cardiovascular (CV) death (lower panel) in patients, grouped by presence or absence of late gadolinium enhancement (LGE).

At univariable analysis the presence of CAV, LVEF, LVMi LGE presence, LGE mass, and LGE% were all significant predictors of death. Late gadolinium enhancement presence was associated with an increased risk of death during follow-up as shown by Kaplan–Meier survival curves (*Figure 3*, upper panel) (log-rank test: $P = 0.0154$).

The eight patients who suffered a CV death had higher prevalence of CAV, larger LV volumes, and absolute and relative amount of LGE (Supplementary data online, *Table S3*). Also in this subset of patients LGE presence predicted a significantly worse outcome (log-rank test: $P = 0.0434$) (*Figure 3*, lower panel).

The unadjusted variables associated with all-cause death or CV death analysis are reported in *Table 5*. Cardiac allograft vasculopathy, LGE mass, and LGE% were the only variables retained as independent predictors of all-cause mortality in multivariable Cox proportional hazard models (*Table 5*, upper panel). Cardiac allograft vasculopathy was associated with a six-fold increase of risk, whereas for each 1 g increment of LGE mass or 1% in LGE% death hazard increased by 4.1% ($P = 0.0053$) and 7.5% ($P = 0.0073$) respectively.

We applied the same model to assess independent predictors of CV death (*Table 5*, lower panel); as expected, the presence of CAV remained a powerful predictor of increased risk. In these patients the absolute LGE mass predicted a 4.6% increase of risk. LGE% fell short of significance to predict CV mortality.

Receiver operating curve analysis in patients LGE pos for prediction of all-cause and CV mortality by clinical and CMR parameters is shown in *Table 6*. Receiver operating curves for LGE mass and LGE% showed a fair discrimination for all-cause death, not significantly different from other variables. For CV death the discrimination of survivors from non-survivors was significant for CAV, LVEF, LGE mass, and LGE%, the areas under the curve were marginally higher for LGE mass and LGE%; however, the difference did not reach statistical significance compared with the other parameters. The addition of LGEmass or LGE% did not modify the risk of death at 5 years that was determined only by CAV 28% (95% CI 0.046–0.452%).

Discussion

Our data indicate that the presence and amount of LGE at CMR in patients at various times after HTx portend a worse prognosis. The present study builds on previous work from Butler *et al.* who first emphasized the prognostic relevance of the presence of LGE in HTx patients.[14] LGE is a common finding in HTx patients and in our cohort the infarct-atypical intramyocardial patterns are more prevalent, in keeping with previous findings.[10,12,16,17] Even small amounts of LGE have been proven predictive of major adverse events[18–20] in different cardiomyopathies such as ischaemic,[21] hypertrophic,[22] and dilated.[19,20] We found an independent association between angiographic CAV, LVESVi, LGE mass, LGE%, and adverse cardiovascular outcomes. However, in our population, at variance with Butler *et al.*[14] we did not find any association between LGE and previous treated allograft rejections, RVEDV or graft age. Indeed, in our study, these variables were not different between

Table 5 Univariable and multivariable Cox proportional hazards analysis for the time to occurrence of all-cause and cardiovascular death

			Multivariable analysis all-cause death					
	Univariable analysis		Model 1		Model 2		Model 3	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender (M vs. F)	2.976 (0.377–23.510)	0.3010						
CAV (categorical)	6.336 (1.336–30.039)	0.0201	6.336 (1.336–30.039)	0.0201				
LV ESV index (mL/m^2)	1.032 (0.989–1.077)	0.1432						
LV EDV index (mL/m^2)	0.993 (0.957–1.031)	0.7091						
LVEF (%)	0.96 (0.926–0.996)	0.0282						
LV Mass index (g/m^2)	1.046 (1.005–1.089)	0.0289						
LGE (categorical)	8.411 (1.065–66.443)	0.0434						
LGE mass (g)	1.041 (1.012–1.07)	0.0053			1.041 (1.012–1.07)	0.0053		
LGE% LV mass	1.075 (1.020–1.133)	0.0073					1.075 (1.020–1.133)	0.0073
			Multivariable analysis CV death					
	Univariable analysis		Model 1		Model 2		Model 3	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Gender (M vs. F)	2.352 (0.289–19.142)	0.4240						
CAV (categorical)	10.825 (1.324–88.534)	0.0263	10.825 (1.324–88.534)	0.0263			10.825 (1.324–88.534)	0.0263
LV ESV index (mL/m^2)	1.053 (1.007–1.101)	0.0232						
LV EDV index (mL/m^2)	0.997 (0.958–1.038)	0.8903						
LVEF (%)	0.948 (0.913–0.984)	0.0049						
LV mass index (g/m^2)	1.054 (1.007–1.104)	0.0227						
LGE (categorical)	6.519 (0.801–53.035)	0.0796						
LGE mass (g)	1.046 (1.015–1.078)	0.0037			1.046 (1.015–1.078)	0.0037		
LGE% LV mass	1.084 (1.024–1.148)	0.0057						

Model 1: Gender, CAV, LVESV index, LVEF, LV mass index and LGE (categorical).
Model 2: Gender, CAV, LVESV index, LVEF, LV mass index and LGE mass (g).
Model 3: Gender, CAV, LVESV index, LVEF, LV mass index and LGE% LV mass.
LV, left ventricle; RV, right ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LGE, late gadolinium enhancement.

patients with and without the index events. Possible explanations are the different timing of CMR scans which, in their study, was concomitant with endomyocardial biopsies performed to prove active rejection and a lower mean graft age, 3.5 $\pm$ 4 years vs. 10 $\pm$ 6 in our cohort.

Patients who suffered from MACE had a higher LGE amount that could possibly be determined by a number of interacting factors such as previous graft rejections, immunosuppressive treatment, hypertension, and systemic inflammation,[7] but in our study none of these variables was associated with cardiovascular adverse events or death in long-term survivors. Late gadolinium enhancement had a stronger prognostic significance when assessed as a continuous variable, suggesting that the total burden of fibrosis can be an important determinant of outcome.

Overall, patient with LGE in the LV wall had initial signs of remodelling showing a worse LV and RV function and a higher LVMi even though the values were still within normal CMR limits. LV and RV function were inversely correlated with LGE% suggesting that higher amounts of fibrosis could be responsible for the impaired ventricular function. At univariable analysis a higher LVEF was associated with a better prognosis and a survival advantage but was not subsequently retained in multivariable model as an independent predictor of outcome, thus lending support to the superior prognostic impact of allograft vasculopathy and fibrosis.

The ROC curve analysis determined the optimal cut-off of 7.9 LGE% which showed a 100% specificity in risk stratification for MACE. Our data are in line with the findings of Assomull *et al.* who reported, in patients with dilated cardiomyopathy, that the association between a >4.8 LGE% and outcome was better than for conventional prognostic parameters.[23]

The elusive link between fibrosis and CAV

Invasive conventional angiography and IVUS have a Class1 recommendation[1] for the detection and surveillance of CAV, but the evaluation of distal lesions of intramural small arteries and arterioles can only be achieved by means of indirect methods evaluating the

Table 6 Diagnostic performance of clinical and CMR parameters to predict death

	AUC	95% CI	P	P vs. LGE mass	P vs. LGE% LV mass	Cut-off	Sensitivity	Specificity
Death from all causes								
CAV (categorical)	0.67	0.479–0.861	0.0809	0.47	0.59	Yes	78	56
LV ESV index (mL/m^2)	0.542	0.261–0.823	0.7712	0.06	0.12	32	56	69
LVEF (%)	0.674	0.428–0.919	0.1655	0.50	0.60	54.6	67	75
LV mass index (g/m^2)	0.684	0.407–0.961	0.1927	0.51	0.69	91	67	88
LGE mass (g)	0.764	0.568–0.959	0.0082	–	–	10.8	78	62
LGE% LV mass	0.743	0.54–0.946	0.0189	–	–	7.9	78	63
CV death								
CAV (categorical)	0.706	0.523–0.89	0.0272	0.44	0.54	Yes	86	56
LV ESV index (mL/m^2)	0.73	0.498–0.962	0.0519	0.45	0.59	32	71	72
LVEF (%)	0.825	0.651–0.999	0.0002	0.95	0.86	54.6	86	78
LV mass index (g/m^2)	0.758	0.498–1	0.052	0.61	0.77	91	71	83
LGE mass (g)	0.818	0.62–1	0.0016	–	–	10.8	85	61
LGE% LV mass	0.802	0.589–1	0.0055	–	–	10	86	72

coronary flow reserve.[11,24] Symptoms associated with ischaemia are often not perceived because of the denervation of the transplanted heart; as a consequence, the presence of CAV is revealed clinically at a late stage as heart failure, ventricular arrhythmias, or sudden death. In our study the presence of CAV purports a risk three times higher for MACE and ten times higher for cardiovascular death. Conversely, the presence of LGE is independent of the occurrence and degree of CAV severity at angiography[10,12] thus suggesting the possibility that other mechanisms could contribute to the pattern that we have observed.[7,9]

In five patients with angiographic CAV we could not detect any LGE, and only 50% of patients with detectable LGE were diagnosed with CAV, confirming the lack of correlation between epicardial lesions and LGE.[6,11] According to previous studies infarct-atypical LGE was prevalent in patients who reached primary or secondary endpoints.[12,16] It has long been recognized that lesions resulting from focal or diffuse ischaemia caused by small vessel obstructions at optical microscopy are manifested as myocyte vacuolization or microfocal infarction,[25] myocytolysis and interstitial fibrosis[7] which appear as spotty areas in the LV wall at CMR.[17,26] Ischaemic injury, however, is only one part of the picture and when compounded by ongoing inflammation, subclinical antibody mediated rejection or infections,[7] it aggravates the damage to the endothelium, promotes vascular smooth muscle proliferation and causes loss of myocytes resulting in focal replacement fibrosis.[7] In addition, rejection has no link with CAV, but it can result in replacement fibrosis and LGE at CMR. What we can infer by means of CMR is that LGE is the algebraic sum of all these pathogenetic mechanisms which, in the long term, can cause adverse remodelling of the graft and its eventual failure.[27]

Study limitations

Our sample size is limited as it is a common feature of single-centre studies in HTx patients. The population enrolled has an inherent heterogeneity depending on the date of HTx that spanned from 1988 to 2009 involving different cold ischaemic times, surgical techniques, immunosuppressive therapies, clinical care, and anti-microbial prophylaxis, total number of rejections, concomitant therapies to reduce the atherosclerotic burden, all factors which might have had a different impact on LGE. The study design has an internal selection bias for outcome because only patients who could undergo CMR were evaluated whilst patients with more severe chronic kidney disease or other contraindications to CMR were excluded.

We have quantified only coarse replacement fibrosis. More recent techniques, such as T1 mapping, allow the quantification of interstitial fibrosis. We did not carry out a repeat scan to monitor LGE pattern, amount, and distribution over time. Finally, the presence of CAV was entered as a categorical dichotomous variable; we did not assess arterial wall lesions with IVUS or measure coronary flow reserve.

Conclusions

The extension of LGE at CMR identifies a group of HTx patients with higher risk of MACE and CV death, compared to HTx patients without LGE. A cut-off value of LGE content of 7.9% of LV mass shows an excellent performance to predict major adverse cardiac events. Cardiac magnetic resonance represents a non-invasive diagnostic tool to monitor graft health that can complement coronary angiography.

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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