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LGE Patterns in Pulmonary Hypertension Do Not Impact Overall Mortality

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ABSTRACT

OBJECTIVES The goal of this study was to determine the prognostic value of late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) features in patients with pulmonary hypertension.

BACKGROUND The prognostic significance of LGE in the clinical assessment of patients with pulmonary hypertension remains uncertain.

METHODS Consecutive patients with suspected pulmonary hypertension seen at a specialist pulmonary hypertension referral center who underwent right heart catheterization and CMR with LGE imaging within 48 h were identified. Short-axis late-enhancement imaging was performed using a 3-dimensional gradient spoiled echocardiography sequence on a 1.5-T scanner. Three groups were identified: 1) no late enhancement of the myocardium; 2) late enhancement at the right ventricular insertion points (LGE-IP); and 3) late enhancement involving the right ventricular insertion points and the interventricular septum (LGE-S).

RESULTS Of 194 patients, 162 had pulmonary hypertension. LGE was identified in 135 of 162 (83%) patients with pulmonary hypertension, and 47 (29%) of patients demonstrated LGE-S. Patients with LGE-S had significantly higher right ventricular end-diastolic volume index ($p = 0.013$) and lower mixed venous oxygen saturation ($p = 0.045$) than patients with LGE-IP alone. The presence of LGE-S ($p = 0.022$), but not LGE-IP alone, right ventricular end-systolic volume ($p = 0.045$), right ventricular ejection fraction ($p = 0.034$), mixed venous oxygen saturation ($p = 0.021$), mean right atrial pressure (0.027), and male sex ($p = 0.002$) predicted mortality. At multivariate analysis, male sex was the only significant predictor of mortality independent of covariate predictors ($p = 0.027$).

CONCLUSIONS The presence of LGE at the right ventricular insertion points is suggestive of the presence of pulmonary hypertension. LGE may also be more extensive, involving the septum; however, after multivariable analysis including other factors associated with pulmonary hypertension, septal LGE was not associated with an increase in overall mortality. (J Am Coll Cardiol Img 2014;7:1209–17) © 2014 by the American College of Cardiology Foundation.

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at right heart catheterization. Pulmonary hypertension is classified into 5 groups: 1) pulmonary arterial hypertension (PAH); 2) pulmonary hypertension because of left-sided heart disease; 3) pulmonary hypertension associated with lung disease and/or hypoxemia; 4) pulmonary hypertension that is due to chronic thromboembolic disease (CTEPH); and 5) a miscellaneous group (1). Given the

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

CMR = cardiac magnetic resonance

CTEPH = chronic thromboembolic disease

LGE = late gadolinium enhancement

LGE-IP = late gadolinium enhancement at the right ventricular insertion points

LGE-S = late gadolinium enhancement at the interventricular septum

LVEDV = left ventricular end-diastolic volume

LVESV = left ventricular end-systolic volume

mPAP = mean pulmonary artery pressure

PAH = pulmonary arterial hypertension

PVR = pulmonary vascular resistance

RVEDM = right ventricular end-diastolic mass

RVEDV = right ventricular end-diastolic volume

RVEF = right ventricular ejection fraction

RVESV = right ventricular end-systolic volume

SV = stroke volume

VMI = ventricular mass index

WHO = World Health Organization

nonspecific nature of the symptoms of pulmonary hypertension, there is increasing interest in improving noninvasive approaches to diagnosis. Specific treatments are available for PAH and CTEPH where severe elevation of pulmonary vascular resistance (PVR) usually occurs (2). The optimal treatment strategy is not clear, but there is a general consensus that patients with more severe disease should have intensive therapy. Consequently, there is increasing interest in the role of various modalities in risk stratification.

Right ventricular failure occurs as a result of prolonged elevation of mPAP and PVR, and is considered the key determinant of adverse outcome in patients with PAH and CTEPH (3–6). Improving our understanding of the nature of right ventricular failure in pulmonary hypertension is, therefore, of value. Cardiac magnetic resonance (CMR) is a noninvasive, nonionizing, and reproducible method of assessing right ventricular morphology and function (7–11). The addition of LGE CMR allows evaluation of the health of the myocardium through the accumulation of gadolinium. Several patterns of myocardial LGE have been described in ischemic and nonischemic pathologies (12–14), and studies have assessed LGE in patients with pulmonary hypertension (5,15–18).

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The clinical significance of LGE as a clinical marker in the context of pulmonary hypertension remains uncertain. Two typical patterns of LGE exist in pulmonary hypertension: involvement of the right ventricular insertion points alone and LGE of the interventricular septum and the insertion points. The prognostic significance of these 2 subphenotypes and the clinical value of LGE in relation to CMR right ventricular indexes and invasive metrics measured at right heart catheterization remain uncertain. The aim of this study was to evaluate the prognostic value of LGE, CMR, and invasive hemodynamics in patients with suspected pulmonary hypertension.

METHODS

PATIENTS. Consecutive treatment-naive patients undergoing right heart catheterization and CMR for suspected pulmonary hypertension were identified at a high-volume, nationally designated pulmonary hypertension referral center. Patients with suspected pulmonary hypertension attending the Sheffield Pulmonary Vascular Disease Unit routinely undergo CMR as part of their diagnostic work-up. Inclusion criteria required the patients' right heart catheter and CMR imaging to be performed within 48 h. Exclusion criteria were as per standard criteria for patients undergoing CMR. Approval for retrospective analysis of imaging techniques was granted by the local research ethics committee.

CMR IMAGE ACQUISITION. CMR imaging was performed on a 1.5-T whole-body scanner GE HDx (GE Healthcare, Milwaukee, Wisconsin), using an 8-channel cardiac coil. Four-chamber and short-axis cine images were acquired using a cardiac gated multislice balanced steady-state free precession sequence (20 frames per cardiac cycle, slice thickness 8 mm, FOV 48, matrix 256 × 256, BW 125 KHz/pixel, TR/TE 3.7/1.6 ms). A stack of images in the short-axis plane with slice thickness of 8 mm (2-mm interslice gap) were acquired fully covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave-triggered acquisition.

Ten minutes following gadolinium contrast injection (0.1 mmol/kg of gadolinium-DTPA; Gadovist, Bayer, Germany), late-enhancement imaging was performed using a 2-dimensional inversion-recovery prepped fast gradient echocardiography sequence (repetition time 7.1 ms, echo time 3.4 ms, slice thickness 8 mm, FOV 45 × 40.5, matrix 256 × 224). Effective myocardial nulling was achieved with TI, typically ranging from 100 to 160 ms, with the inversion-recovery sequence triggered on each R-R interval with triggering on each heartbeat. A selective 180° inversion-recovery triggered to end-diastole was acquired in the short axis, obtaining limited 3 to 5 slices through the ventricles. Studies were performed with patients in the supine position with a surface coil and with retrospective electrocardiogram gating.

IMAGE ANALYSIS. Image analysis was performed on a GE Advantage Workstation 4.1, by a radiologist experienced in CMR, who was blinded to the patient's clinical information and cardiac catheter parameters. A second observer experienced in CMR analyzed the LGE images blinded to the clinical data and blinded to the first observer's results. The scans were defined as nondiagnostic when image quality significantly affected cardiac measurements or volumetric analysis could not be accurately performed.

Right and left ventricular volumes. Endocardial surfaces were manually traced from the stack of short-axis cine images, using our MR workstation software (GE Advantage Workstation ReportCard) to obtain

right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV). The RVEF was calculated as: RVEF = (RVEDV − RVESV)/RVEDV × 100). Right ventricular stroke volume (SV) was calculated: as RVEDV − RVESV. Right ventricular volume measurements were indexed for body surface area (BSA) where appropriate, for example, RVEDV indexed for BSA is represented as RVEDVI. Left ventricular ejection fraction was defined as: LVEDV − LVESV/LVEDV × 100 and left ventricular SV as LVEDV − LVESV.

Right ventricular mass and ventricular mass index. The right ventricular epicardial and endocardial borders on each end-diastolic short-axis slice image were outlined. The interventricular septum was considered as part of the left ventricle. The myocardial volume for each slice was calculated by multiplying the area of the right ventricular wall by the slice thickness. The product of the sum total of the myocardial slice volumes for each ventricle and the density of myocardium (1.05 g/cm^3) was used to estimate right ventricular end-diastolic mass (RVEDM) (10). RVEDM index was defined as RVEDM/BSA measured in g/m^2. The left ventricular epicardial and endocardial borders on each end-diastolic short axis slice were outlined, left ventricular end diastolic mass was thus derived. Ventricular mass index (VMI) was defined as RVEDM divided by left ventricular end-diastolic mass.

Late gadolinium enhancement. Late gadolinium-enhanced images were qualitatively assessed for hyperintensity at the interventricular insertion points or along the interventricular septum. The presence or absence of delayed enhancement was also recorded. We scored images as no LGE, LGE involving the right ventricular insertion points (LGE-IP), and LGE involving both the right ventricular insertion points and the interventricular septum (LGE-S), as previously described (15) (**Figure 1**).

RIGHT HEART CATHETERIZATION AND CLINICAL EVALUATION. Right heart catheterization was performed using a balloon-tipped 7.5-F thermodilution catheter (Becton-Dickinson, Franklin Lakes, New Jersey). Patients referred for the investigation of suspected pulmonary hypertension also underwent detailed clinical evaluation including blood

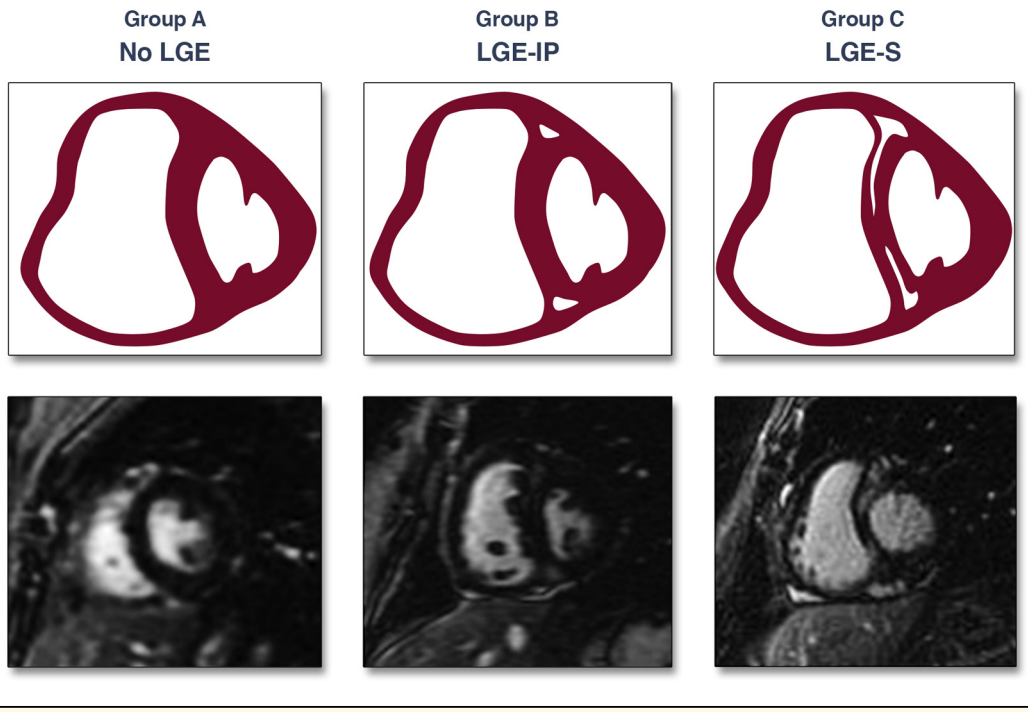

FIGURE 1 Subgroups Divided According to LGE Features

Group A = no late gadolinium enhancement (LGE), Group B = LGE at the insertion points (IP), and Group C = LGE at the interventricular septum (LGE-S).

TABLE 1 Demographic, Invasive Hemodynamic, and CMR Indexes in Patients With Pulmonary Hypertension, and Control Patients (mPAP <25 mm Hg)

	Controls (n = 32)	Pulmonary Hypertension (n = 162)	p Value
Demographics			
Age, yrs	59 ± 15	61 ± 15	0.356
Female, %	56	59	0.943
WHO functional class, n*	I (3), II (13), III (16)	I (3), II (33), III (112), IV (14)	0.002
Catheter measurements			
mRAP, mm Hg	6 ± 3	11 ± 5	<0.0001
mPAP, mm Hg	19 ± 3	46 ± 13	<0.0001
sPAP, mm Hg	30 ± 6	75 ± 23	<0.0001
dPAP, mm Hg	11 ± 3	28 ± 10	<0.0001
PCWP, mm Hg	10 ± 3	12 ± 6	0.036
CI, l/min/m^2	3.7 ± 0.8	2.7 ± 0.8	<0.0001
PVR, dyne/s/cm^5	120 ± 82	630 ± 416	<0.0001
Svo_2, %	73 ± 6.0	63.6 ± 8.8	<0.0001
MR indexes			
RVEDVI, ml/m^2	72 ± 16	99 ± 39	<0.0001
RVESVI, ml/m^2	42 ± 13	75 ± 37	<0.0001
RVEF, %	40 ± 14	26 ± 15	<0.0001
RVSVI, ml/m^2	29 ± 13	24 ± 16	0.108
LVEDVI, ml/m^2	58 ± 16	47 ± 14	0.001
LVESVI, ml/m^2	19 ± 10	17 ± 8	0.222
LVEF, %	67 ± 11	64 ± 12	0.294
LVSVI, ml/m^2	38 ± 11	30 ± 11	0.001
VMI, ratio	0.25 ± 0.1	0.80 ± 0.4	<0.0001
LGE			
Absent	29 (91)	27 (17)	
LGE-IP	3 (9)	88 (54)	
LGE-S	0 (0)	47 (29)	

Values are mean ± SD, %, n, or n (%). *Comparison of WHO functional class groups I and II versus groups III and IV.

CI = cardiac index; CMR = cardiac magnetic resonance; dPAP = diastolic pulmonary artery pressure; LGE = late gadolinium enhancement; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVSVI = left ventricular stroke volume index; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index; sPAP = systolic pulmonary artery pressure; Svo_2 = mixed venous oxygen saturations; VMI = ventricular mass index; WHO = World Health Organization.

testing, echocardiography, computed tomography scanning, lung function testing, exercise testing, and perfusion lung imaging as appropriate. Patients with mPAP ≥ 25 mm Hg were classified as having pulmonary hypertension, with patients with mPAP < 25 mm Hg classified as having no pulmonary hypertension. Diagnostic classification of the form of pulmonary hypertension was by standard criteria following multidisciplinary assessment. PVR was determined as follows: PVR in dynes = 80 × (mPAP − pulmonary capillary wedge pressure/cardiac output). Data are also provided for the mixed venous oxygen saturation sampled from the pulmonary artery.

STATISTICS. Comparisons of CMR measurements between patients with "no pulmonary hypertension" and patients with pulmonary hypertension were analyzed using the independent Student *t* test for continuous data and the chi-square for categorical data. World Health Organization (WHO) functional class was dichotomized into groups I and II versus groups II and IV. The Fisher exact test was used to determine the diagnostic strength of the presence of LGE, and the sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratios were calculated. Kaplan-Meier analysis assessed the prognostic value of LGE imaging in patients with pulmonary hypertension. Groups were compared by means of the log-rank test. The interval from completion of evaluation with CMR and right heart catheterization until all-cause death, transplantation, or census was regarded as the overall follow-up period. The prognostic value of LGE, CMR and right heart catheter data, and patient age and sex were assessed using univariate Cox proportional hazards regression analysis in patients with pulmonary hypertension. Variables significant at $p < 0.05$ were entered into a multivariate Cox proportional hazards model. Stepwise backwards elimination was used to determine independent prognostic significance. To perform and display the statistics, SPSS version 18 (SPSS, Chicago, Illinois) and GraphPad Prism version 5.03 (GraphPad Software, San Diego, California) software were used. A p value <0.05 was considered statistically significant.

RESULTS

A total of 198 patients with suspected pulmonary hypertension who underwent CMR including LGE imaging were identified. Four patients had studies that were excluded because of suboptimal scans, leaving 194 patients. One hundred sixty-two patients were diagnosed with pulmonary hypertension, and 32 patients with no pulmonary hypertension. Of the patients with pulmonary hypertension, 81 had PAH (36 idiopathic PAH, 35 PAH-connective tissue disease, 7 PAH-congenital heart disease, 3 PAH-portal), 20 had pulmonary hypertension because of left heart disease, 17 had pulmonary hypertension associated with lung disease and/or hypoxemia (PH-lung), and 44 had CTEPH.

GROUP COMPARISONS. Table 1 presents demographic, invasive hemodynamic, and CMR indexes in patients with pulmonary hypertension, and those with no pulmonary hypertension. The presence of LGE was identified in 135 of 162 (83%) patients with

pulmonary hypertension, and LGE was present in 3 of 32 (9%) patients with no pulmonary hypertension. Thus, the presence of LGE had high diagnostic accuracy for the detection of pulmonary hypertension, but could not confidently exclude the presence of disease, with sensitivity 83% (77% to 89%), specificity 90% (75% to 98%), positive predictive value 98% (94% to 100%), and negative predictive value 52% (38% to 65%). Table 2 details the demographic, hemodynamic, and CMR indexes in individual subgroups of pulmonary hypertension.

Eighty-eight of 162 (54%) had LGE-IP alone, and 47 (29%) demonstrated LGE-S. Patients with LGE-S had significantly higher RVEDV ($p = 0.019$) than patients with LGE-IP alone. LVEDV and SV were significantly lower in patients with PH when compared with controls ($p = 0.001$ and $p = 0.001$, respectively); however, there was no significant difference in LVESV, LVEDV, left ventricular ejection fraction, or LVSV between patients with LGE-IP versus LGE-S ($p = 0.282$ to 0.907). The mixed venous oxygen saturation of blood sampled from the pulmonary artery was also lower in patients with LGE-S compared with those with LGE-IP alone ($p = 0.045$) (Table 3). No significant differences in mPAP, mean right atrial pressure, PVR, cardiac index, and VMI were identified between LGE-S and LGE-IP groups.

SURVIVAL ANALYSIS. The median time between baseline measurements to the end of the study was 36 months (interquartile range: 12 to 48 months);

TABLE 2 Demographic, Hemodynamic, and CMR Indexes in Individual Subgroups of Pulmonary Hypertension

	IPAH (n = 36)	PAH-CTD (n = 35)	PH-LHD (n = 20)	PH-Lung (n = 17)	CTEPH (n = 44)
Demographics					
Age, yrs	54 ± 17	64 ± 12	74 ± 9	64 ± 15	62 ± 13
Female, %	58	71	20	24	45
WHO functional class, n					
I	-	1	1	-	1
II	7	8	8	3	5
III	25	24	6	10	34
IV	4	2	-	4	4
Catheter measurements					
mRAP, mm Hg	10 ± 5	8 ± 4	14 ± 6	10 ± 4	12 ± 5
mPAP, mm Hg	57 ± 11	38 ± 15	33 ± 6	43 ± 8	49 ± 10
sPAP, mm Hg	90 ± 18	63 ± 27	54 ± 16	66 ± 14	83 ± 19
dPAP, mm Hg	37 ± 10	22 ± 9	21 ± 5	29 ± 7	29 ± 8
PCWP, mm Hg	10 ± 3	10 ± 3	22 ± 5	11 ± 3	9 ± 4
CI, l/min/m^2	2.4 ± 0.7	3.0 ± 0.7	3.3 ± 0.9	2.9 ± 0.9	2.4 ± 0.7
PVR, dyne/s/cm^5	855 ± 366	464 ± 362	156 ± 55	526 ± 328	813 ± 397
Svo_2, %	62 ± 7	67 ± 8	68 ± 6	65 ± 11	60 ± 8
MRI					
RVEDVI, ml/m^2	121 ± 45	82 ± 25	75 ± 26	103 ± 36	108 ± 11
RVESVI, ml/m^2	85 ± 38	55 ± 22	51 ± 18	82 ± 36	90 ± 40
RVEF, %	25 ± 16	32 ± 13	31 ± 9	22 ± 12	20 ± 12
RVSVI, ml/m^2	28 ± 23	24 ± 11	24 ± 10	21 ± 12	20 ± 12
LVEDVI, ml/m^2	42 ± 14	46 ± 15	53 ± 16	49 ± 10	45 ± 12
LVESVI, ml/m^2	15 ± 5	14 ± 7	19 ± 15	19 ± 8	18 ± 7
LVEF, %	63 ± 9	70 ± 10	66 ± 15	61 ± 13	60 ± 11
LVSVI, ml/m^2	27 ± 11	32 ± 11	34 ± 9	30 ± 11	28 ± 10
VMI, ratio	1.0 ± 0.3	0.6 ± 0.4	0.4 ± 0.1	0.6 ± 0.2	0.9 ± 0.3
LGE					
Absent	1 (3)	9 (26)	10 (45)	1 (6)	4 (9)
LGE-IP	23 (64)	18 (51)	8 (36)	9 (53)	26 (59)
LGE-S	12 (33)	8 (23)	2 (19)	7 (41)	14 (32)

Values are mean ± SD, %, n, or n (%).

CTEPH = chronic thromboembolic disease; IPAH = idiopathic pulmonary arterial hypertension; LGE-IP = late gadolinium enhancement of the right ventricular insertion points; LGE-S = late gadolinium enhancement of the interventricular septum; PAH-CTD = pulmonary arterial hypertension with connective tissue disease; PH-LHD = pulmonary hypertension because of left heart disease; PH-Lung = pulmonary hypertension associated with lung disease and/or hypoxemia; other abbreviations as in Table 1.

TABLE 3 Comparison of Demographics, Hemodynamics, and CMR Measurements in Patients With LGE-IP and Patients With LGE-S

	LGE-IP (n = 88)	LGE-S (n = 47)	p Value
Demographics			
Age, yrs	61 ± 15	62 ± 15	0.746
Female, %	55	47	0.509
WHO functional class, n	I (2), II (16), III (61), IV (8)	II (10), III (31), IV (6)	0.613
Invasive catheter measurements			
mRAP, mm Hg	11 ± 5	12 ± 6	0.218
mPAP, mm Hg	47 ± 12	50 ± 13	0.221
sPAP, mm Hg	77 ± 22	82 ± 22	0.239
dPAP, mm Hg	29 ± 9	31 ± 12	0.259
PCWP, mm Hg	11 ± 5	10 ± 5	0.414
CI, l/min/m^2	2.6 ± 0.8	2.6 ± 0.8	0.769
PVR, dyne/s/cm^5	667 ± 397	761 ± 442	0.254
Svo_2, %	63.7 ± 8.1	60.2 ± 10.2	0.045
CMR metrics			
RVEDVI, ml/m^2	98 ± 35	117 ± 42	0.013
RVESVI, ml/m^2	75 ± 31	92 ± 42	0.014
RVEF, %	25 ± 13	23 ± 14	0.537
RVSVI, ml/m^2	24 ± 17	25 ± 19	0.641
LVEDVI, ml/m^2	45 ± 14	45 ± 14	0.907
LVESVI, ml/m^2	16 ± 7	18 ± 11	0.282
LVEF, %	64 ± 11	62 ± 14	0.376
LVSVI, ml/m^2	29 ± 11	28 ± 11	0.535
VMI, ratio	0.9 ± 0.4	0.8 ± 3.3	0.411

Values are mean ± SD, %, or n.
Abbreviations as in Tables 1 and 2.

during the follow-up period, 39 patients with pulmonary hypertension died. As shown in Figure 2, at Kaplan-Meier analysis, patients with LGE-S had worse outcome than those patients with LGE-IP (p = 0.026). LGE-S (p = 0.022) was associated with adverse outcome at Cox proportional hazards analysis (Table 4), whereas the presence of LGE-IP alone was not associated with adverse outcome (p = 0.773). RVEF and RVESV were also significant CMR predictors of mortality (p = 0.034 and p = 0.045, respectively). VMI was not a predictor of adverse outcome (p = 0.384). Nonsurvivors with pulmonary hypertension had higher mean right atrial pressure (p = 0.027), higher WHO functional class (p = 0.029), and lower mixed venous oxygen saturation (p = 0.021) than survivors. Male sex was also associated with worse outcome (p = 0.002) at univariate analysis and was the only significant predictor of outcome at multivariate analysis (p = 0.027); of particular note, LGE-S was not predictive of mortality at multivariate analysis.

INTEROBSERVER AGREEMENT FOR LGE. There was good interobserver agreement for grading the LGE appearances (K = 0.81).

DISCUSSION

The results of this study demonstrate that the presence of LGE-IP is a characteristic feature of pulmonary hypertension, but the presence of LGE in these insertion points does not forecast mortality. Subsets of patients with pulmonary hypertension exhibit more extensive LGE that occurs throughout the interventricular septum. Importantly, after considering other factors associated with the severity of pulmonary hypertension, the presence of LGE-S does not forecast an additional increase in mortality risk.

The prevalence of LGE in this study is similar to that previously found by Blyth et al. (15) (23 of 25 patients with pulmonary hypertension) and Sanz et al. (16) (41 of 42 patients with pulmonary hypertension), supporting the hypothesis that LGE in pulmonary hypertension is characteristic. It has recently been suggested by Freed et al. (5) that the presence of LGE at the right ventricular insertion points is a feature of poor outcome in patients with pulmonary hypertension. In our study, LGE of the right ventricular insertion points alone was not associated with adverse outcome; these patients had a similar outcome to the pulmonary hypertension patients without visible LGE. By contrast, patients identified with LGE involving the interventricular septum in addition to the insertion points had a worse outcome. We postulate that simple enhancement at the right ventricular insertion points is a diagnostic metric, with clinical utility for screening for pulmonary hypertension. Whereas the severity of the enhancement, in particular extension of the LGE into the interventricular septum in our study, is a feature associated with poor outcome, we note however that LGE of the septum was not an independent marker of adverse outcome.

CMR measurements of RVEDV, RVEF (19), mass (20,21), pulsatility (22–24), and flow (25,26) have proven to be of clinical value in the assessment of patients with pulmonary hypertension, and recent studies have identified the prognostic value of volumetric and functional CMR measurements in the baseline and serial assessment of patients with PAH (3,4,27). van Wolferen et al. (4) studied the prognostic value of CMR measurements in 64 patients with idiopathic PAH. They found, a large RVEDV, low LVEDV, and low SV to be associated adverse outcome, and changes in these metrics at follow-up were predictive of mortality. More recently from the same group, van de Veerdonk et al. (3) showed that progressive reduction in RVEF at follow-up predicts mortality independent of pulmonary

vascular resistance. In our study, RVEF like LGE involving the interventricular septum predicted mortality at univariate analysis but was not found to be independent of sex. Shehata et al. (28) studied LGE in pulmonary hypertension patients. They found the mass of LGE correlated with invasive hemodynamics, reduced RVEF, increased right ventricular mass, and reduced eccentricity index (28). We note that low LVEDV (3) and SV have previously been identified as prognostic markers in patients with PAH and in selected idiopathic PAH cohorts (29); however, LVEDV, LVESV, and LVEF and SV were not found to be significantly predictive in this mixed cohort of patients with pulmonary hypertension.

Measuring the severity of LGE CMR is challenging, Blyth et al. (15) measured the mass of late gadolinium-enhanced myocardium, which correlated well with right ventricular volume, mass, RVEF, and mPAP. The authors also qualitatively assessed the severity of LGE by dividing patients into with and without septal enhancement, as in our study. Patients with paradoxical septal motion evident in early diastole

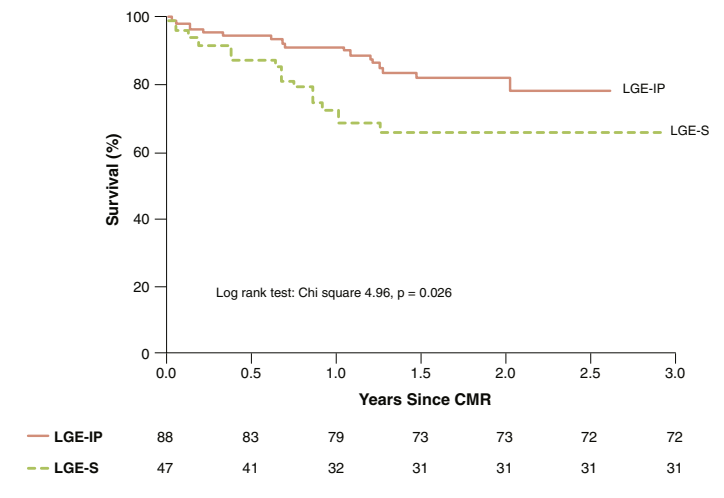

FIGURE 2 Kaplan-Meier Plot Analysis: Outcome Comparison for Patients With LGE-IP Versus LGE-S

The values below signify numbers at risk at 6-month intervals. CMR = cardiac magnetic resonance; LGE-IP = late gadolinium enhancement of the right ventricular insertion points; LGE-S = late gadolinium enhancement of the insertion points in addition to the septum.

TABLE 4 Demographic, Right Heart Catheter, and CMR Metrics as Predictors of Adverse Outcome Using Cox Proportional Hazards Regression Analysis

Overall Mortality	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value
Demographics				
Age, yrs	1.017 (0.993–1.042)	0.164		
Sex, female %	0.334 (0.167–0.666)	0.002	0.414 (0.190–0.906)	0.027
WHO functional class	2.253 (0.795–6.387)	0.126		
Invasive catheter measurements				
sPAP, mm Hg	0.994 (0.980–1.008)	0.396		
dPAP, mm Hg	0.998 (0.969–1.031)	0.988		
mPAP, mm Hg	0.993 (0.969–1.018)	0.599		
mRAP, mm Hg	1.069 (1.008–1.135)	0.027	1.060 (0.983–1.129)	0.093
PCWP, mm Hg	1.005 (0.946–1.068)	0.867		
Svo_2, %	0.954 (0.917–0.993)	0.021	0.987 (0.936–1.042)	0.645
CI, $l.min^{-1}.m^{-2}$	0.773 (0.489–1.221)	0.269		
PVR, $dyn.s.cm^{-5}$	1.000 (1.000–1.001)	0.298		
MR indexes				
RVEDVI, ml/m^2	1.004 (0.996–1.012)	0.367		
RVESVI, ml/m^2	1.009 (1.000–1.017)	0.045	0.997 (0.982–1.012)	0.686
RVEF, %	0.970 (0.944–0.999)	0.034	0.987 (0.956–1.019)	0.413
RVSVI, ml/m^2	0.972 (0.942–1.003)	0.073		
LVEDVI, ml/m^2	0.995 (0.964–1.028)	0.995		
LVESVI, ml/m^2	1.013 (0.947–1.062)	0.577		
LVEF, %	0.983 (0.950–1.016)	0.308		
LVSVI, ml/m^2	0.981 (0.940–1.026)	0.412		
VMI, ratio	0.606 (0.196–1.872)	0.384		
LGE present or absent	1.138 (0.474–2.728)	0.773		
LGE-S	2.139 (1.115–4.103)	0.022	1.598 (0.722–3.540)	0.248

CI = confidence interval; other abbreviations as in Tables 1 and 2.

characteristically demonstrated late septal gadolinium enhancement, suggesting that late enhancement is related to strain at interventricular insertion points. When these 2 groups were compared, patients with LGE-S had significantly larger right ventricular volume and lower mixed venous oxygen saturation than those with LGE-IP.

MECHANISM OF LGE IN PULMONARY HYPERTENSION. The underlying mechanism of LGE in pulmonary hypertension is not fully understood. Myocardial fibrosis as a result of mechanical stress on the myocardium at the right ventricular insertion points in pulmonary hypertension is believed to be an etiological factor leading to LGE. In a study by McCann et al. (17), histology was obtained in 2 patients with PAH who died and underwent autopsy. Fibrosis was present at the right ventricular insertion points. However, there was also evidence of interstitial space expansion, which may result in accumulation of gadolinium and resultant hyperenhancement. Unfortunately, no direct correlation with LGE imaging was possible because the 2 patients did not undergo CMR. Bradlow et al. (30) undertook a pathological correlation of insertion-region enhancement in PAH with LGE images in a patient who died from idiopathic PAH. Microscopy of myocardium from the insertion point revealed myocardial disarray and increased collagen and fat between fiber bundles, but no evidence of replacement fibrosis. The authors suggest that LGE in PAH may not directly infer underlying myocardial fibrosis. The mechanism leading to myocardial LGE and changes in the LGE appearance over time in patients with pulmonary hypertension warrants further investigation. Methods such as native T1 mapping, extracellular volume imaging, and T2 mapping may allow for quantitation of the myocardial changes in pulmonary hypertension, and may better characterize the presence and extent of changes such as edema, fibrosis, and disarray.

CONCLUSIONS

The presence of LGE of the myocardium is a common feature of pulmonary hypertension. Characteristically, the right ventricular insertion points are involved with frequent extension of LGE into the interventricular septum. Whereas the presence of LGE at the right ventricular insertion points is of diagnostic value, the presence of LGE at the interventricular septum is associated with more right ventricular dilation despite a similar afterload. Importantly, however, after multivariable analyses considering other factors associated with pulmonary hypertension, the presence of septal LGE confers no additional increase in mortality.

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