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Midwall Fibrosis Is an Independent Predictor of Mortality in Patients With Aortic Stenosis

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Objectives	The goal of this study was to assess the prognostic significance of midwall and infarct patterns of late gadolinium enhancement (LGE) in aortic stenosis.
Background	Myocardial fibrosis occurs in aortic stenosis as part of the hypertrophic response. It can be detected by LGE, which is associated with an adverse prognosis in a range of other cardiac conditions.
Methods	Between January 2003 and October 2008, consecutive patients with moderate or severe aortic stenosis undergoing cardiovascular magnetic resonance with administration of gadolinium contrast were enrolled into a registry. Patients were categorized into absent, midwall, or infarct patterns of LGE by blinded independent observers. Patient follow-up was completed using patient questionnaires, source record data, and the National Strategic Tracing Service.
Results	A total of 143 patients (age 68 ± 14 years; 97 male) were followed up for 2.0 ± 1.4 years. Seventy-two underwent aortic valve replacement, and 27 died (24 cardiac, 3 sudden cardiac deaths). Compared with those with no LGE ($n = 49$), univariate analysis revealed that patients with midwall fibrosis ($n = 54$) had an 8-fold increase in all-cause mortality despite similar aortic stenosis severity and coronary artery disease burden. Patients with an infarct pattern ($n = 40$) had a 6-fold increase. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16 to 24.56; $p = 0.03$) and ejection fraction (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.99; $p = 0.01$) were independent predictors of all-cause mortality by multivariate analysis.
Conclusions	Midwall fibrosis was an independent predictor of mortality in patients with moderate and severe aortic stenosis. It has incremental prognostic value to ejection fraction and may provide a useful method of risk stratification. (The Prognostic Significance of Fibrosis Detection in Cardiomyopathy; NCT00930735) (J Am Coll Cardiol 2011; 58:1271-9) © 2011 by the American College of Cardiology Foundation

Aortic stenosis is a progressive condition that is characterized by a long and indolent asymptomatic phase followed by

a shorter symptomatic stage. The onset of symptoms is associated with an increased morbidity and a high mortality (1). However, there is marked heterogeneity between symptom onset and severity of valvular stenosis. There are several potential explanations for this apparent mismatch, but the hypertrophic response of the left ventricle may contribute to the development of symptoms and adverse events.

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Aortic stenosis results in increased pressure afterload and ventricular wall stress, thereby stimulating left ventricular hypertrophy (LVH). Initially, increased wall thickness maintains normal wall stress and contraction (2,3) but ultimately this becomes maladaptive. Indeed, LVH is an independent predictor of cardiac mortality, regardless of

Abbreviations and Acronyms

AVR	= aortic valve replacement
CI	= confidence interval
CMR	= cardiovascular magnetic resonance
HR	= hazard ratio
LGE	= late gadolinium enhancement
LV	= left ventricular
LVEDV	= left ventricular end-diastolic volume
LVH	= left ventricular hypertrophy

etiology (4–6). Histopathologic studies have demonstrated fibrosis in the left ventricle of patients with aortic stenosis and arterial hypertension (7,8). It has been postulated that increasing myocyte size eventually leads to myocyte apoptosis and subsequently replacement fibrosis, and that this sequence is responsible for the progression from LVH to heart failure (9). Myocardial fibrosis has also been linked to the development of arrhythmia and sudden cardiac death in a variety of conditions (10–13).

Cardiovascular magnetic resonance (CMR) is able to detect replacement myocardial fibrosis noninvasively by using late gadolinium enhancement (LGE) (14). More recent studies have demonstrated a midwall pattern of enhancement in patients with aortic stenosis in the absence of coronary artery disease (15,16). Although the use of LGE is associated with an adverse prognosis in other cardiac conditions (17–21), this technique has not been assessed in aortic stenosis. The goal of this study was to determine the prognostic implications of LGE in patients with moderate and severe forms of this disease.

Methods

Patient population. We performed a prospective, observational study of consecutive patients with aortic stenosis who attended the Royal Brompton Hospital between January 2003 and October 2008 for CMR that included gadolinium injection. All patients referred for CMR in this time period with moderate or severe aortic stenosis (based on Doppler echocardiographic demonstration of peak aortic valve pressure gradient >36 mm Hg and peak transvalvular velocity >3 m/s, according to American College of Cardiology/American Heart Association criteria [22]), were enrolled into a registry and followed up as described in the following text. In our institution, local guidelines recommend CMR for all patients with severe aortic stenosis. Other reasons for referral included diagnostic evaluation, clarification of disease severity, pre-operative evaluation, and assessment of the hypertrophic response. Exclusion criteria were disseminated malignancy; moderate or severe aortic regurgitation, mitral regurgitation, or mitral stenosis; contraindications to CMR, including pacemaker and defibrillator implantation; and an estimated glomerular filtration rate (Cockcroft-Gault equation) of <30 ml/min. The study was conducted after local research ethics committee approval in 2003 and in accordance with the Declaration of Helsinki.

Data collection. Demographic characteristics and medical history were documented from source patient record data

and patient questionnaires. The presence of coronary artery disease was defined as a prior coronary revascularization or the presence of significant coronary artery stenosis as assessed by single-photon emission computed tomography, invasive coronary angiography (>50% lumen diameter narrowing), or computed tomography coronary angiography.

Cardiovascular magnetic resonance. CMR was performed using a 1.5-T scanner (Magnetom Sonata or Avanto, Siemens, Erlangen, Germany) and a standardized protocol with stable study parameters. Steady-state free precession sequences were used for aortic valve planimetry and for the assessment of left ventricular (LV) volumes and mass. Ten to fifteen minutes after injection of 0.1 mmol/kg of gadolinium contrast agent (Gd-DTPA, Schering AG, Berlin, Germany), inversion recovery–prepared spoiled gradient echo images were acquired in standard long- and short-axis views to detect areas of LGE as described previously (18). Inversion times were optimized to null normal myocardium with images repeated in 2 separate phase-encoding directions to exclude artifact.

Image analysis. The severity of aortic stenosis was assessed using CMR-derived planimetry of the aortic valve area. This technique has been validated against echocardiographic measures of aortic stenosis severity (23). In accordance with American College of Cardiology/American Heart Association guidelines, aortic stenosis was graded using the aortic valve area as follows: mild, >1.5 cm²; moderate, 1.5 to 1.0 cm²; and severe, <1.0 cm² (22). For quantification of LV function and volumes, the endocardial and epicardial contours were semi-automatically applied in end-systole and -diastole using dedicated software (CMR-tools, Cardiovascular Imaging Solutions Ltd., London, United Kingdom). LV mass was calculated from the total end-diastolic myocardial volume multiplied by the specific gravity of the myocardium (1.05 g/ml). LV mass and volumes were indexed to body surface area, age, and sex, and were considered abnormal if they were outside the 95th percentile (24).

The presence and pattern of LGE were assessed by 2 independent observers who were blinded to the clinical data, including valve severity, coronary anatomy, and outcomes. A third blinded observer adjudicated when there was a disparity between the initial 2 observers. Patients with a mixed pattern of LGE were categorized according to the predominant pattern of fibrosis.

LGE mass was calculated semi-automatically by a single operator using MRI-MASS software (Medis, Leiden, the Netherlands). The endocardial and epicardial borders were traced for each short-axis slice. A region of interest averaging 50 mm² was defined within normal remote myocardium in an area with uniform myocardial suppression free of artifacts. A multi-pass region-growing algorithm was used to identify the fibrotic boundaries based on the “full width half maximum” technique, and fibrosis was expressed as present or absent, and its extent was quantified as a percentage of total LV mass (% LGE mass).

Clinical endpoints. The primary endpoint of the study was all-cause mortality. The secondary endpoint was cardiac mortality. Mortality data were obtained from hospital notes and the National Strategic Tracing Service, a national database for all National Health Service patients in the United Kingdom. Cause of death was established from medical notes and/or death certification records and an assessment made as to whether this represented a sudden cardiac death. Data regarding which patients had undergone aortic valve replacement (AVR) during the follow-up period were also collected.

Statistical analysis. Continuous variables were expressed as mean \pm SD and compared using one-way analysis of variance or the unpaired Student *t* test where appropriate. Categorical variables were expressed as percentages and analyzed using the chi-square test. All continuous variables were tested for normal distribution using the Shapiro-Wilk test. Variables with a skewed distribution were log transformed and the geometric mean with the 95% confidence intervals (CIs) reported. In situations in which log transformation did not normalize the data, analysis was performed using nonparametric tests (Mann-Whitney rank sum test or the Kruskal-Wallis tests, as appropriate).

Kaplan-Meier curves were used to estimate the survival distributions with regard to all-cause mortality and cardiac mortality for patients with no LGE, midwall LGE, and infarct LGE. Differences in the survival patterns of the patients in the 3 groups were assessed using the log-rank test. Univariate and multivariate survival analyses (Cox proportional hazards regression) were performed to determine independent predictors of all-cause mortality and cardiac mortality. A 2-sided *p* value <0.05 was regarded as statistically significant. All analyses were performed using Stata version 10.0 (Stata Corporation, College Station, Texas).

Results

CMR was performed on 143 consecutive patients (age 68 ± 14 years; 97 male) with a mean aortic valve area of 0.99 ± 0.31 cm². Overall, 57 patients (40%) had moderate and 86 (60%) severe aortic stenosis. CMR estimation of aortic valve severity correlated closely with echocardiographic data. Coronary artery disease was assessed in all patients (83% had invasive coronary angiography) and was present in 81 patients (57%) (Table 1).

Table 1 Baseline Characteristics of 143 Patients With Aortic Stenosis According to the Pattern of Late LGE

Characteristic	No LGE (n = 49)	Midwall LGE (n = 54)	Infarct LGE (n = 40)	p Value
Age (yrs)	64 \pm 16	70 \pm 11	70 \pm 13	0.031
Male	53	72	80	0.018
Clinical history				
AF	21	18	18	0.915
Diabetes mellitus	25	19	32	0.378
Hypertension	56	55	50	0.838
Bicuspid aortic valve	29	17	23	0.401
Documented CAD				
1-vessel	16	17	15	<0.001
2-vessel	2	6	20	
3-vessel	2	13	28	
Previous PCI	10	9	30	0.010
Previous CABG	20	8	28	0.040
Medication				
ACE inhibitor	56	48	61	0.480
Beta-blocker	56	26	49	0.007
Statins	67	60	82	0.079
Diuretic use	15	36	41	0.014
Aortic valve area by CMR (cm ²)	1.05 \pm 0.37	1.00 \pm 0.31	0.91 \pm 0.26	0.111
Peak aortic valve gradient by echo (mm Hg)	70 \pm 26	70 \pm 26	69 \pm 16	0.99
Severe aortic stenosis	53	50	65	0.353
Ejection fraction (%)	69 \pm 13	58 \pm 21	44 \pm 18	<0.001
Indexed LA volume (ml/m ²)	58.9 (53.4-64.9)	62.9 (56.2-70.3)	63.3 (57.1-70.2)	0.560
Indexed LVEDV (ml/m ²)	78.8 (72.1-86.2)	88.5 (79.4-98.6)	101.4 (92.6-111.0)	0.003
Indexed LV mass (g/m ²)	92.6 (86.0-99.6)	113.7 (104.5-123.8)	97.8 (90.9-105.2)	0.005
RVEF (%)	58 \pm 13	57 \pm 12	55 \pm 14	0.450
% LGE mass	0	5.2	7.3	—

Values are mean \pm SD, %, or geometric mean (95% confidence interval).

AF = atrial fibrillation; ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CAD = coronary artery disease; CMR = cardiac magnetic resonance; LA = left atrial; LGE = late gadolinium enhancement; % LGE mass = percentage of total left ventricular mass; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; PCI = percutaneous coronary intervention; RVEF = right ventricular ejection fraction.

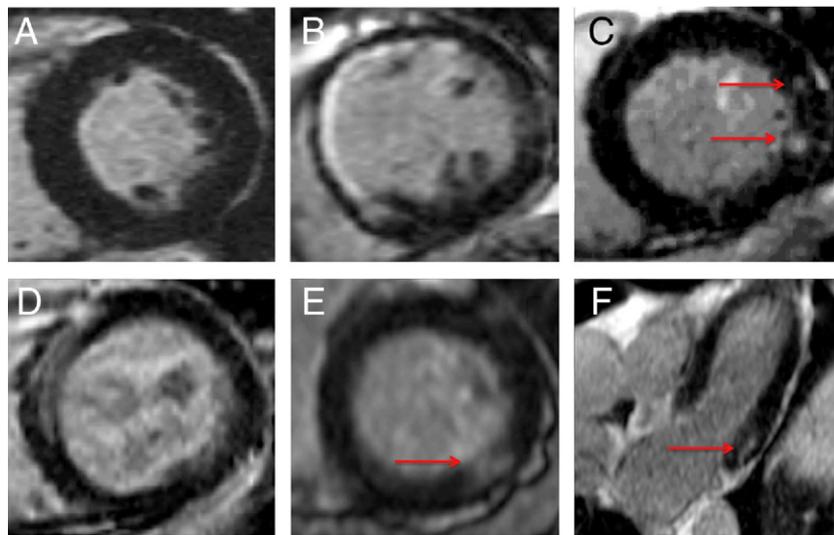


Figure 1 Patterns of LGE in Aortic Stenosis

Images showing the different patterns of late gadolinium enhancement (LGE) observed in patients with aortic stenosis. (A) No LGE. (B) Infarct LGE with a subendocardial pattern observed in the septum and anterior wall. (C) Two focal areas of midwall LGE in the lateral wall of the left ventricle (red arrows); (D) Midwall LGE in a more linear pattern affecting the septum. (E) Short- and (F) long-axis views of midwall LGE (red arrows) of the inferolateral wall in the same patient.

Patterns of LGE. Three patterns of LGE were observed: no gadolinium enhancement (no LGE group); localized enhancement consistent with prior myocardial infarction (infarct LGE group); and a midwall pattern of enhancement (midwall LGE group) (Fig. 1). Interobserver agreement in determining the pattern of LGE was very good, with a kappa value of 0.89.

LGE was absent in 49 patients (34%). There was a typical pattern of prior myocardial infarction in 40 patients (28%) and midwall fibrosis in 54 patients (38%) (Table 1). In 8 patients (6%), there was a dual pattern of both myocardial infarction and midwall fibrosis. These patients were categorized according to their predominant pattern, and the statistical analysis was performed on this basis. Seven were placed in the infarct group and 1 in the midwall group. One patient with midwall LGE who died underwent autopsy. Assessment of the macroscopic appearance of the cut surface of the heart showed myocardial fibrosis, which was confirmed histologically using Trichrome stain (Fig. 2).

Patients with no LGE were younger, more likely to be female, and less likely to be undergoing diuretic therapy. The severity of aortic stenosis and prevalence of cardiovascular risk factors were similar to the other groups. As anticipated, patients with an infarct pattern of LGE had more severe coronary artery disease, lower ejection fractions, and higher indexed LV volumes than the other groups.

Patients with midwall LGE had the highest indexed LV mass ($p = 0.005$) despite the fact that aortic stenosis severity and hypertension prevalence were similar among all 3 groups. Interestingly, ejection fraction was lower ($p = 0.007$) in patients with midwall LGE compared with those

with no LGE, even though both groups had a similar degree of coronary artery disease. Although there was an apparent trend to a correlation between ejection fraction and the midwall LGE burden (Pearson's $R = -0.26$; $p = 0.08$), this finding did not reach statistical significance. Indexed left atrial volumes were used as a marker of diastolic dysfunction (25), and there was no significant difference in this variable among the 3 groups (Table 1).

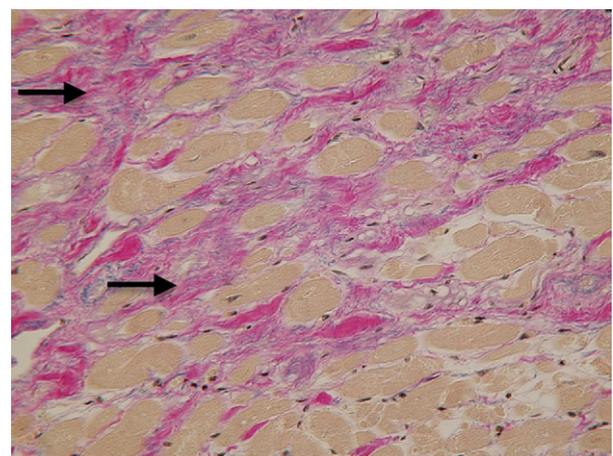


Figure 2 Histology of the Myocardium, After Trichrome Staining, in a Patient With Midwall LGE

Black arrows demonstrate increased replacement fibrosis in the midwall region of the myocardium.

Table 2 Outcome Data: Subsequent Aortic Valve Replacement, All-Cause Mortality, Cardiac Mortality, and Sudden Cardiac Deaths According to the Pattern of LGE

Variable	No LGE	Midwall LGE	Infarct LGE	p Value
Subsequent AVR, %	55	46	53	0.66
Deaths	2	16	9	0.003
Cardiac deaths	2	13	8	0.016
Sudden cardiac deaths	0	3	0	—
All-cause mortality rate*	15.7	>142.7	>173.1	—
Cardiac mortality rate*	15.7	130.2	123.2	—
All-cause mortality rate* in patients with AVR	13.7	53.8	73.6	—
All-cause mortality rate* in non-AVR patients	18.2	218.8	190.0	—

Values are the number of adverse events and the mortality rates (deaths per 1,000 patient/yr) in each group. *All-cause mortality rates are also displayed for patients who subsequently had an AVR during the period of follow-up and for those who did not (patients turned down for surgery have been excluded from this analysis [n = 2 in the midwall group, n = 4 in the infarct group]). p values for mortality rates are given in Table 3 and Figures 3 and 4. AVR = aortic valve replacement; LGE = late gadolinium enhancement.

Mortality data. Patients were followed up for a mean of 2.0 ± 1.4 years (median: 1.7 years). None of the patients were lost to follow-up and, overall, 27 patients (19%) died (Table 2). Univariate analysis revealed that compared with patients with no LGE, there was an 8-fold increase in all-cause mortality in patients with midwall fibrosis (HR: 8.59; 95% CI: 1.97 to 37.38; $p = 0.004$) and a 6-fold increase in mortality in those with myocardial infarction (HR: 6.46; 95% CI: 1.39 to 30.00; $p = 0.017$) (Table 3, Fig. 3). As fibrosis burden increased, prognosis worsened: with every 1% increase in the % LGE mass, the risk of mortality appeared to increase by 5% (HR: 1.05; 95% CI: 1.01 to 1.09; $p = 0.005$). A lower ejection fraction and an increased left ventricular end-diastolic volume (LVEDV) also predicted an increased all-cause mortality on univariate analysis.

After multivariate analysis, ejection fraction (HR: 0.96; 95% CI: 0.94 to 0.99; $p = 0.009$) and the midwall pattern

of LGE (HR: 5.35; 95% CI: 1.16 to 24.56; $p = 0.0034$) were identified as independent predictors of subsequent all-cause mortality (Table 4).

Twenty-three of the 27 deaths were from cardiac causes (Table 2). There was a 5-fold increase in cardiac mortality in the infarct group (HR: 5.44; 95% CI: 1.15 to 25.68; $p = 0.032$) and a 6-fold increase in the midwall group (HR: 6.68; 95% CI: 1.51 to 29.64; $p = 0.012$) (Fig. 4).

Three of the deaths were adjudicated as sudden cardiac deaths, and all were in the midwall group. Each of these subjects had died suddenly at home with no prior symptoms or signs of heart failure.

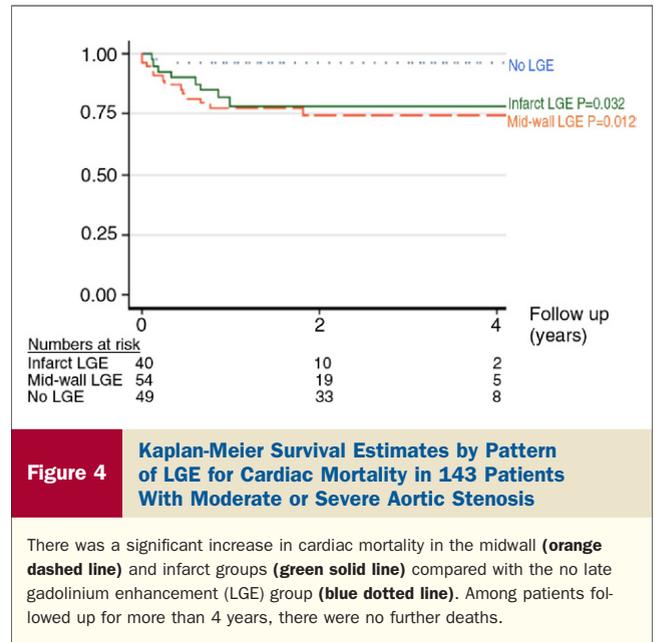
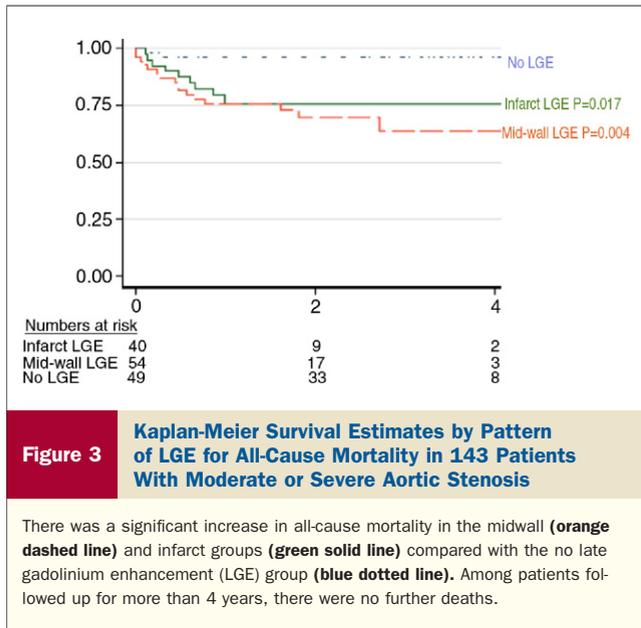
Aortic valve replacement. During follow-up, 72 patients (50%) underwent AVR (8 patients percutaneously) with no difference in rates among the 3 groups (Table 2). The occurrence of AVR was associated with an improved survival in the univariate analysis ($p = 0.01$) and multivariate analyses (HR: 0.32; 95% CI: 0.13 to 0.76; $p = 0.01$)

Table 3 Cox Proportional Hazards Model: Univariate Analysis for All-Cause Mortality

Variable	Dead (n = 27)	Alive (n = 116)	Hazard Ratio	Confidence Interval	p Value
Age (yrs)	71.5 ± 7.8	67.1 ± 14.3	1.03	0.99-1.07	0.12
Male	69.8	59.3	0.68	0.32-1.47	0.33
Subsequent AVR	25.9	55.2	0.32	0.13-0.75	0.01
Diabetes mellitus	23.1	24.8	0.94	0.38-2.35	0.90
Hypertension	53.9	54.0	1.02	0.47-2.21	0.95
Documented CAD	65.4	53.5	1.62	0.72-3.62	0.25
ACE inhibitors	53.9	54.6	0.95	0.44-2.05	0.89
Beta-blockers	42.3	43.2	1.00	0.45-2.18	1.00
Ejection fraction (%)	45.0 ± 21.6	60.6 ± 18.4	0.96	0.94-0.98	<0.001
AV area (cm ²)	0.96 ± 0.31	0.99 ± 0.31	0.68	0.19-2.40	0.55
Indexed mass (g/m ²)*	116.6 ± 34.5	103.1 ± 28.3	1.01	1.00-1.02	0.06
Indexed LVEDV (g/ml)*	99.2 (83.7-117.7)	86.0 (81.0-91.3)	3.06	1.03-9.08	0.04
LGE pattern					
No LGE	7.4	40.5	1.00	—	—
Infarct LGE	33.3	26.7	6.46	1.39-30.00	0.017
Midwall LGE	59.3	32.8	8.59	1.97-37.38	0.004
% LGE mass	12.6 ± 10.3	6.7 ± 9.1	1.05	1.01-1.09	0.005

Values are mean ± SD or %. The following were found to be significant predictors of all-cause mortality: subsequent AVR, ejection fraction, indexed LVEDV, an infarct pattern of LGE, midwall LGE, and the % LGE mass. *Natural logarithm used for analysis with proportions in the dead/alive columns presented as actual value (natural logarithm of confidence intervals).

AVR = aortic valve replacement; % LGE mass = percentage of total left ventricular mass; other abbreviations as in Table 1.



(Tables 3 and 4). In patients with midwall fibrosis, those undergoing AVR had a mortality rate of 54 per 1000 patient-years compared with 219 per 1,000 patient-years in those who did not (Table 2). The 2 groups were well matched, with no significant differences in age ($p = 0.64$), aortic valve area ($p = 0.32$), ejection fraction ($p = 0.24$), indexed LVEDV ($p = 0.29$), indexed LV mass ($p = 0.60$), documented coronary artery disease ($p = 0.77$), hypertension rates ($p = 0.10$), or diabetes mellitus ($p = 0.23$). Two patients were turned down for surgery in the midwall group, and they were excluded from this analysis.

Discussion

Aortic stenosis is the most common indication for valve replacement in Europe and North America (26). Its clinical importance continues to rise with a progressively ageing population and the expansion of percutaneous valve implantation. Here, we have investigated whether myocardial fibrosis, as assessed by using CMR, can predict prognosis in this condition. For the first time, we demonstrated that midwall fibrosis/LGE is an independent predictor of survival in aortic stenosis and seems to be of incremental prognostic value to ejection fraction.

Variable	Hazard Ratio	95% Confidence Interval	p Value
Ejection fraction	0.96	0.94-0.99	0.01
Indexed LVEDV	0.68	0.18-2.61	0.57
Midwall LGE	5.35	1.16-24.56	0.03
Infarct LGE	2.56	0.48-13.64	0.27
Subsequent AVR	0.32	0.13-0.76	0.01

Ejection fraction, midwall LGE, and subsequent AVR all emerged as independent predictors of all-cause mortality.

Abbreviations as in Table 3.

LGE has been associated with adverse clinical outcomes across a range of different cardiac conditions, including hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocardial infarction (17-20). We extend here those findings to patients with aortic stenosis. Patients with no LGE had a relatively good prognosis in contrast to those with a midwall or infarct pattern of enhancement who experienced an 8- and 6-fold increase in mortality, respectively.

The poor prognosis associated with prior myocardial infarction is well established in this and other settings (17,20) and is thought to be related to arrhythmogenicity and adverse remodeling with progression to heart failure. The findings in relation to midwall fibrosis are less expected. Although patients with prior infarction had a lower ejection fraction and more severe coronary artery disease, patients with midwall fibrosis had higher mortality. With increasing burden of midwall LGE, prognosis worsened, and in the multivariate survival analysis, midwall fibrosis emerged as an independent marker of all-cause mortality. Myocardial infarction was not independently associated, probably because of its close association with ejection fraction.

Midwall fibrosis in aortic stenosis. Fibrosis is a common pathologic alteration in patients with aortic stenosis and concurrent LVH (7). In the hypertrophied myocardium, areas of fibrosis co-localize with areas of myocyte apoptosis (27), and a pathological sequence of myocyte hypertrophy followed by apoptosis and replacement fibrosis has been described (9). Several possible triggers to this apoptotic process have been postulated, including direct mechanical forces (28,29) and angiotensin II (29,30). Ischemia has also been suggested. Increased myocardial mass and afterload lead to increased myocardial oxygen demand. The capillary bed does not expand sufficiently to increase oxygen supply, and capillary flow reserve is reduced (31,32), thereby inducing ischemia. Galiuto et al. (33) demonstrated that patients

with severe aortic stenosis and no coronary artery disease have impaired myocardial perfusion and increased cardiomyocyte apoptosis. However, the concept that midwall fibrosis is due to hypoperfusion remains unproven, and one might expect ischemia due to hypertrophy to be greatest in the subendocardium, not the midwall.

Midwall LGE is associated with an increased LV mass (15,16), being on average 11 g/m² higher in our study than in those patients without fibrosis. The explanation for this increase is not clear, given that there were no differences in the severity of aortic valve disease or rates of hypertension between the groups. Other factors are likely to be involved, including age, male sex (34-36), use of beta-blockers (37,38), and different genotypes (34,39,40).

It is unlikely that midwall fibrosis occurs secondary to coronary artery disease. Previous studies have reported that midwall LGE occurs in patients with aortic stenosis and normal coronary arteries (15,16). In our study, the presence of coronary artery disease was well characterized, with no difference in its presence between the midwall and the no-LGE groups. Furthermore, more than one-half of those with midwall LGE had unobstructed coronary arteries.

Mechanism of adverse prognosis. The adverse prognosis associated with midwall fibrosis in aortic stenosis seems to be predominantly cardiac in etiology. Midwall LGE predicted a 6-fold increase in cardiac mortality compared with no LGE, and 81% of deaths in this group were cardiac in nature.

Using CMR, we have confirmed that the ejection fraction serves as a powerful prognostic marker in aortic stenosis (41) and shown that it was impaired in the midwall group compared with the no-LGE group. Impaired LV function is therefore likely to be a major contributor to the adverse prognosis in these patients. However, on multivariate analysis, midwall fibrosis still predicted an increased mortality after adjustment for the effects of ejection fraction, which suggests the contribution of other factors.

One potential mechanism may be arrhythmogenicity. Fibrosis can serve as a structural substrate for arrhythmia (42), and its detection, using LGE, in patients with dilated cardiomyopathy or previous myocardial infarction has been linked to an increased incidence of arrhythmia and sudden cardiac death (18,43). In this study, all 3 patients with aortic stenosis who had a sudden cardiac death were in the midwall group. However, our study design was not adequately powered to examine this endpoint, and our protocol did not include routine ambulatory monitoring. In addition, other patients may have died suddenly without there being sufficient documentation to allow their identification within this study. It is therefore not possible to make any definitive assertions about the contribution of malignant arrhythmia to the adverse prognosis associated with midwall LGE in aortic stenosis. Although further work is required to evaluate this question, in our opinion the effect of midwall fibrosis on LV function is likely to represent the predominant mechanism.

Aortic valve replacement. Nearly one-half of our cohort underwent AVR during follow-up. The high rates of surgery probably underlie our observation that aortic stenosis severity was not predictive of mortality. AVR is the only available treatment capable of improving the prognosis of patients with symptomatic severe aortic stenosis and, in our study, was predictive of an improved outcome after multivariate analysis.

It is noteworthy that AVR appeared to modulate the poor prognosis associated with midwall fibrosis. After excluding patients turned down for surgery, patients with midwall LGE who had an AVR were 4 times less likely to die over the course of the follow-up than those who did not undergo AVR (Table 2). This is despite the 2 groups being well matched in terms of age, indexed LVEDV, ejection fraction, aortic valve area, indexed LV mass, hypertension, diabetes mellitus, and concomitant coronary artery disease. Furthermore, more than one-half of the patients with midwall fibrosis who died had moderate aortic stenosis and would not have been considered for AVR under conventional management practice. Myocardial fibrosis may therefore have a role in the risk stratification of patients being considered for surgery.

Interestingly, it would appear that once established, midwall fibrosis is not reversible after AVR. Weidemann et al. (44) found no change in the degree of LGE 9 months after AVR. In our study, CMR was repeated in 1 patient a year after surgery. The presence of midwall fibrosis and the % LGE mass remained unchanged (4.6% at baseline vs. 4.4% after 1 year).

In accordance, the adverse prognosis associated with midwall fibrosis also persists to a degree after AVR. The mortality rate among patients in the midwall group who underwent AVR was 53.8 per 1,000 patient-years compared with 13.7 per 1,000 patient-years in the no-LGE group.

The benefit of AVR in midwall fibrosis may instead be related to the prevention of subsequent fibrosis and the further associated increases in LV dysfunction and tendency to arrhythmia.

Study limitations. Twenty-seven patients died during the course of our study, so that fitting more than 3 variables into the multivariate analysis may be problematic. Post-hoc analysis performed using the homoscedastic adjustment inflation factor suggest that there was no evidence of overfitting in our model. Nevertheless, a multicenter study involving a larger cohort with longer follow-up is required for confirmation of our findings and definitive conclusions about differential risk based on multivariate analysis. Further attention must also be paid to the mechanisms underlying the increased mortality (including the incidence of arrhythmia, sudden cardiac death, and symptoms) and the role of AVR in modulating this risk. Ultimately, such studies may pave the way for randomized controlled trials of antifibrotic medications in the treatment of this common clinical condition.

In our institution, local guidelines recommend CMR for all patients with severe aortic stenosis. However, because patients with moderate disease were referred at the discretion of their clinician, there may have been some referral bias in this group.

Finally, established LGE techniques detect areas of replacement fibrosis within the myocardium. Diffuse interstitial fibrosis can be detected using T1 mapping techniques (45), and this has not been assessed in our study. Although this form of fibrosis predominates in aortic stenosis, T1 mapping has not been validated, whereas LGE is already established in everyday clinical practice.

Conclusions

We have shown that CMR-detected midwall fibrosis is an independent predictor of mortality in patients with moderate and severe aortic stenosis and is of incremental value in the prognostic model to ejection fraction. It may prove to be a useful method of risk stratification in patients with advanced aortic valve disease or as a future target for antifibrotic medication.

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