Late gadolinium enhancement in aortic stenosis: Is it an indication for surgical treatment in asymptomatic patients?

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Editorial
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ABSTRACT

Background: It remains a challenge to determine the best time to refer asymptomatic patients for aortic valve replacement (AVR).

Aims: We aimed to determine whether late gadolinium enhancement (LGE) in patients with asymptomatic aortic stenosis (AS) has an independent prognostic significance for adverse postoperative cardiovascular events and changes in left ventricular (LV) hypertrophy (LVH) and LV ejection fraction (LVEF).

Methods: Consecutive patients with severe asymptomatic AS were prospectively enrolled in the study. All patients underwent cardiovascular magnetic resonance with LGE assessment. Patients were followed up every 6 months, and immediately after the onset of symptoms, they were referred for AVR. Early outcomes, as well as LVH and LVEF in the follow-up after AVR, were compared between patients with and without LGE.

Results: Ninety-one patients (34 females, 57 males, median [interquartile range] age: 59.2 [56.9–61.6] years) were evaluated, and 68 persons (75%) were treated with AVR. LGE patients (LGE+) developed symptoms earlier than patients without LGE (LGE–, median [interquartile range]: 18 [7–34] months vs. 28 [14–47] months; $P = 0.01$), but there were no differences in early complications ($P = 0.14$) and LVEF ($P = 0.47$) post-AVR between the groups. One year after AVR, no differences were observed between LGE+ and LGE– patients with regard to LV posterior wall thickness ($P = 0.26$), interventricular septum thickness ($P = 0.16$), and LVEF ($P = 0.9$).

Conclusions: The outcome for patients with asymptomatic AS but with LGE was similar to this observed in the non-LGE group. Watchful waiting in this group, with referral to AVR immediately after symptom onset, is associated with comparable results as in LGE– patients.

Key words: asymptomatic aortic stenosis, cardiac magnetic resonance, early marker, late gadolinium enhancement

WHAT'S NEW?

We found that the presence of late gadolinium enhancement on cardiac magnetic resonance (CMR) was associated with earlier progression from asymptomatic to symptomatic disease but did not predict worse clinical outcomes after aortic valve replacement (AVR). In our study, there were no significant differences in post-AVR left ventricular function and dimensions between patients with and without late gadolinium enhancement on CMR. We concluded that watchful waiting of this group and early referral for AVR immediately after the onset of symptoms determines good postoperative outcomes regardless of the presence of myocardial fibrosis.

INTRODUCTION

Aortic stenosis (AS) is the most common primary valve disease requiring invasive treatment [1]. Progressive aortic valve stenosis causes adaptive left ventricular changes, which may be detected both as a left ventricular (LV) hypertrophy (LVH) and microscopic changes characterized by myocardial fibrosis [2, 3]. Myocardial fibrosis in AS is a complex process of extensive collagen volume expansion involving at least 3 major changes: endocardial thickening, subendocardial micro scars, and diffuse interstitial fibrosis [4]. An established tool for non-invasive assessment of fibrosis is cardiovascular magnetic resonance (CMR) [5]. There are two approaches to imaging fibrosis with CMR: late gadolinium enhancement (LGE) [6], which allows quantification of focal interstitial expansion, and extracellular volume fraction (ECV), which assesses the diffuse interstitial expansion of fibrosis [5]. The severity of myocardial fibrosis correlates significantly with heart diastolic dysfunction, and the myocardial fibrosis assessment may provide valuable data about the pathophysiology of the disease and therapeutic response [7].

The indications for surgical treatment of symptomatic AS are well-established and supported by numerous studies [1]. However, it is still a challenge to determine the best time to refer asymptomatic patients for aortic valve replacement (AVR) [1, 5, 8].

In this study, we explored whether LGE-CMR combined with transthoracic echocardiography (TTE) measurement has an independent prognostic significance for adverse postoperative cardiovascular events, such as early postoperative complications. Additionally, we assessed changes in LVH and LV ejection fraction (LVEF) in patients with and without LGE.

MATERIAL AND METHODS

Ninety-seven consecutive patients (36 women [37%] and 61 men [73%]) with severe asymptomatic AS who were admitted to our Institute were prospectively enrolled in the study (Figure 1). AS was diagnosed based on medical history, physical examination, and TTE. Exclusion criteria included symptomatic AS, predominant aortic regurgitation or more than mild mitral and tricuspid regurgitation or stenosis, and a history of coronary artery disease (myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention). The absence of the symptoms was confirmed by exercise testing [9]. Clinical progression of AS

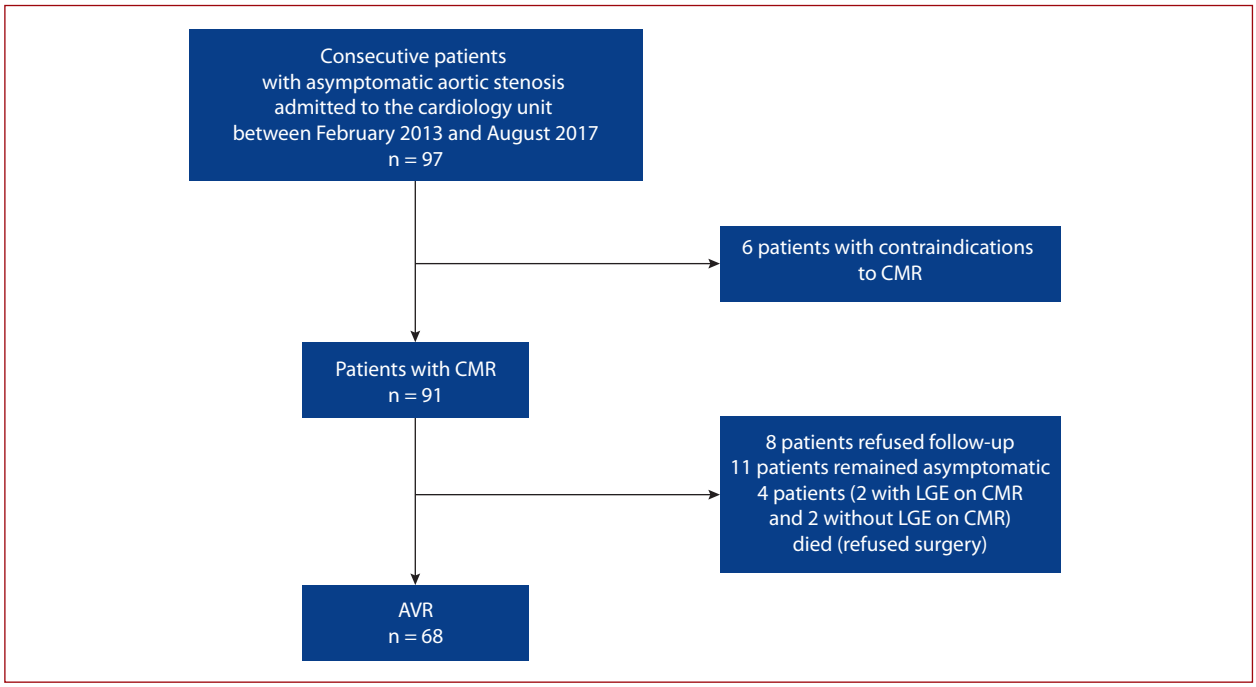


Figure 1. Flowchart of study design for inclusion and exclusion criteria

was assessed every 6 months. Patients were referred for AVR at the onset of symptoms such as dyspnea, angina, dizziness during exertion, or syncope. CMR was performed, and LGE was assessed at baseline (91 patients) and at the time of referral for AVR (36 patients).

Data on patient comorbidities, e.g., hypertension, coronary artery disease, diabetes mellitus, hypercholesterolemia, and renal insufficiency were collected.

The study was conducted in accordance with the World Medical Association's 1975 Declaration of Helsinki. The protocol for the study was reviewed and approved by the Ethics Committee. Written informed consent was obtained from all participants.

Echocardiography

Standard comprehensive TTE was carried out on each patient at baseline, at the onset of symptoms, and after AVR. Vivid S70 and E9 machines (General Electric Medical Systems, Milwaukee, WI, US) were used. Echocardiographic measurements were performed by qualified echocardiographers experienced in assessing valvular heart diseases and prosthesis function.

According to the latest guidelines of the European Society of Cardiology [1], severe AS was defined by the aortic valve area ≤1.0 cm^2, mean aortic gradient ≥40 mm Hg, or aortic jet velocity ≥4.0 m/sec.

The following TTE data were assessed: LV end-diastolic diameter, LV end-systolic diameter, interventricular septum (IVS) diameter at the end-diastole, end-diastolic posterior wall thickness (PW), and LVEF. All measurements were made in the parasternal long-axis view.

Cardiac magnetic resonance

CMR was performed on a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany). The imaging protocol was based on the recommendations of the Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols [10, 11] and included electrocardiogram-gated, breath-hold, steady-state free precession cine as well as LGE images acquired in long- and short-axis planes. The LGE acquisitions were performed 10–15 minutes after the intravenous administration of 0.1 mmol/kg of gadobutrol. The images were analyzed by an experienced radiologist and a cardiologist using a dedicated system (Leonardo workstation, Siemens, Forchheim, Germany) (Figure 2). Further detailed volumetric and functional assessments were performed using commercially available software (MASS 6.2.1, Medis, Leiden, the Netherlands). The analyzed LV parameters included end-diastolic volume, end-systolic volume, LV mass (LVM), stroke volume (SV), and EF. The end-diastolic volume, end-systolic volume, SV, and LVM were indexed for the body surface area (BSA). All scans were verified by a radiologist and a cardiologist experienced in heart CMR assessment. Based on the presence of LGE on CMR, patients were allocated to two groups: patients with LGE on CMR (LGE+) and patients without LGE on CMR (LGE–). In patients undergoing a second CMR, LGE progression was defined as new LGE *loci* appearing on the second CMR.

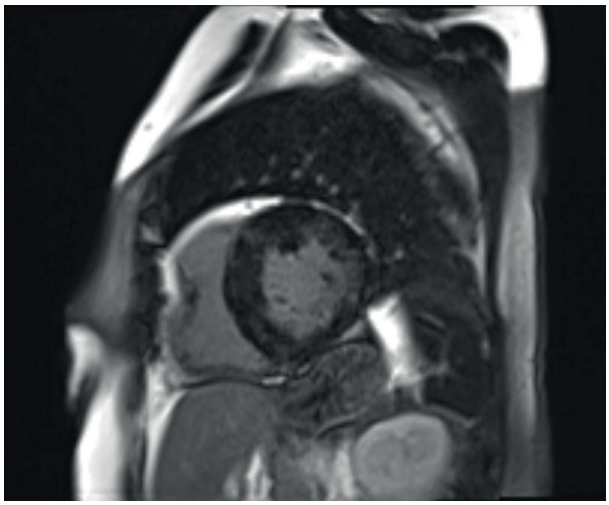


Figure 2. Late gadolinium enhancement on cardiac magnetic resonance. Short axis

Outcomes

The decision on the AVR method (transcatheter vs. surgical) was made by the Heart Team's consensus. The following data of the early outcomes were assessed: hospitalization time after AVR, the length of hospitalization in the intensive care unit after AVR, the need for extracorporeal membrane oxygenation or continuous renal replacement therapy, episodes of new atrial fibrillation and postpericardiotomy syndrome occurrence. In all patients, TTE was performed after AVR and before discharge. All patients were followed up for 12 and 24 months after the procedure (TTE with LVH and LVEF assessment).

Statistical analysis

All statistical analyses were performed using the SAS 9.4. The data distribution was verified by the Kolmogorov–Smirnov test. Unless otherwise stated, continuous data were presented as means (standard deviations) for normal distribution or medians (interquartile ranges [IQR]: 25^{th} percentile–75^{th} percentile) for non-Gaussian distribution. Categorical variables were presented as counts and percentages. The T-test in the case of continuous data and the χ^2 test or Fisher's exact test in the case of categorical variables were performed to compare clinical characteristics. Echocardiographic and CMR measurements from patients with LGE and those without LGE on CMR were compared between the groups using analysis of variance (normal distribution data) or robust analysis of variance based on M-estimation (non-Gaussian distribution) with age and sex as covariance [12]. To examine differences between the early outcomes after AVR in patients with and without LGE, the Mann–Whitney test and the χ^2 test or Fisher's exact test were performed, as appropriate.

Table 1. Baseline clinical characteristics of patients

Characteristics	All n = 91	LGE+ n = 53	LGE– n = 38	P-value
Age, years, median (IQR)	61 (55–66)	62 (57–70)	60 (49–64)	0.01
BMI, kg/m^2, median (IQR)	26.0 (24.5–28.6)	26.0 (24.5–28.2)	25.6 (23.9–29.5)	0.87
Female, n (%)	34 (37.4)	13 (24.5)	21 (55.3)	0.003
Hypertension, n (%)	62 (68.1)	39 (73.6)	23 (60.5)	0.19
CAD, n (%)	10 (11)	7 (13.2)	3 (7.9)	0.51
DM, n (%)	9 (9.9)	6 (11.3)	3 (7.9)	0.73
RI, n (%)	4 (4.4)	3 (5.7)	1 (2.6)	0.64

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; RI, renal insufficiency

Table 2. Comparison of cardiovascular magnetic resonance measures and the echocardiographic data from patients with and without late gadolinium enhancement (LGE). Classical measures (means) are expected marginal means, and positional measures (medians) represent estimated responses. The models included the main effect (LGE) and two confounding variables: age and sex

Parameter	n = 91	LGE– n = 38	LGE + n = 53	*P*-value
Cardiovascular magnetic resonance				
EDV, ml, mean (95% CI)	168.1 (159.0–177.3)	152.1 (141.0–163.3)	169.0 (158.7–179.2)	0.038
ESV, ml, mean (95% CI)	58.6 (53.9–63.3)	52.2 (45.8–58.5)	58.2 (52.4–64.1)	0.18
SV, ml, mean (95% CI)	109.5 (103.9–115.2)	99.9 (92.5–107.4)	110.7 (103.8–117.5)	0.047
LVM, g, median (IQR)	135 (99–184)	111 (84–139)	163 (147–174)	<0.001
EDV/BSA, ml/m^2, mean (95% CI)	87.8 (84.0–91.6)	81.2 (75.8–86.6)	89.7 (84.7–94.6)	0.03
ESV/BSA, ml/m^2, mean (95% CI)	30.3 (28.1–32.5)	27.5 (24.2–30.7)	30.7 (27.7–33.7)	0.17
SV/BSA, ml/m^2, mean (95% CI)	57.2 (54.8–59.6)	53.6 (50.0–57.2)	58.8 (55.4–62.1)	0.047
LVM/BSA, g/m^2, median (IQR)	74.5 (57.0–90.5)	61.4 (52.1–71.6)	83.5 (78.2–87.0)	<0.001
LA, cm^2, mean (95% CI)	25.3 (23.9–26.7)	24.9 (22.8–27.1)	25.1 (23.1–27.2)	0.90
RA, cm^2, median (IQR)	22.6 (21.5–23.8)	20.8 (20.6–25.9)	23.4 (22.9–23.5)	0.02
Echocardiography				
LVEDd, mm, mean (95% CI)	45.6 (44.3–46.8)	44.2 (42.6–45.8)	45.3 (43.8–46.8)	0.36
LVEDs, mm, mean (95% CI)	27.8 (26.7–28.9)	26.6 (25.1–28.1)	27.8 (26.4–29.2)	0.29
IVS, mm, mean (95% CI)	14.1 (13.6–14.7)	13.2 (12.5–14.0)	14.4 (13.7–15.0)	0.04
LVPW, mm, mean (95% CI)	11.1 (10.7–11.6)	10.8 (10.1–11.5)	11.1 (10.5–11.8)	0.50
LVEF, %	67.7 (66.7–68.9)	68.7 (67.1–70.2)	67.2 (65.8–70.2)	0.19
LAA, cm^2, mean (95% CI)	20.9 (19.6–22.1)	19.8 (17.7–21.9)	20.9 (19.0–22.8)	0.45
RAA, cm^2, mean (95% CI)	16.7 (15.7–17.7)	15.5 (14.0–16.9)	16.2 (14.7–17.6)	0.51
AVA, cm^2, median (IQR)	0.85 (0.7–1.0)	0.75 (0.7–0.9)	0.9 (0.87–0.92)	0.85
GA, mm Hg, median (IQR)	47.0 (38–56)	45.4 [41.7–47.6]	48.1 (47.2–49.3)	0.11
LVOT, mm, mean (95% CI)	22.3 (21.6–22.9)	20.9 (20.0–21.8)	22.4 (21.7–23.2)	0.01
AA, mm, mean (95% CI)	39.1 (38.8–40.3)	37.6 (35.8–39.4)	39.4 (37.7–41.1)	0.16

Abbreviations: AA, aortic annulus perimeter; AVA, aortic valve area; BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; GA, mean transvalvular gradient; IQR, interquartile range; IVS, interventricular septal thickness; LA, left atrium; LAA, left atrial area; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular muscle mass; LVOT, left ventricular outflow tract perimeter; LVPW, left ventricular posterior wall thickness; RA, right atrium; RAA, right atrial area; SV, stroke volume

A two-way repeated-measures ANOVA with *post hoc* NIR testing was used to compare changes in IVS PWD and LVEF over follow-up. All *P*-values were two-sided, and a *P* value <0.05 was considered statistically significant.

RESULTS

In all patients, surgical AVR was performed since every patient fulfilled the criteria for the low-risk group. The baseline clinical characteristics of patients are summarized in Table 1. Apart from higher age and lower proportion of females in the LGE+ group, there were no differences in the baseline characteristics. We admitted 97 consecutive patients with asymptomatic AS to our center during the analyzed period. Six patients with contraindications to CMR (metal elements, claustrophobia, renal failure) or lack of consent were excluded. CMR and TTE were performed on 91 patients (34 females [37%] and 57 males 73%]) with asymptomatic AS. LGE was present in 53 patients (58%). During follow-up, 68 persons (75%) were treated with AVR due to clinical progression of AS.

In 36 patients, a second CMR study was performed at the moment of symptom occurrence. Early complications and follow-up of LVH and LVEF (12 and 24 months after the procedure) were reported.

Echocardiographic and CMR data from patients with and without LGE

A comparison of the CMR measures and the TTE data between patients with and without LGE adjusted for age and sex is displayed in Table 2. In particular, there were no

Table 3. Baseline characteristics of patients treated with aortic valve replacement

Characteristics	LGE+ n = 42	LGE– n = 26	*P*-value
Age, years, median (IQR)	61 (56 – 67)	58.5 (49 – 65.0)	0.07
BMI, kg/m^2, median (IQR)	25.9 (24.5–28.2)	25.9 (24.5–29.4)	0.98
Female, n (%)	14 (25.9)	21 (51.2)	0.01
Hypertension, n (%)	40 (74.15)	24 (58.5)	0.11
Diabetes mellitus, n (%)	3 (7.3)	6 (11.1)	0.53
Hypercholesterolemia, n (%)	44 (81.5)	30 (73.2)	0.33
Coronary artery disease, n (%)	7 (13.7)	3 (8.1)	0.41
EuroSCORE II, %, median (IQR)	0.97 (0.91–1.34)	1.16 (0.77–1.28)	0.99
Creatinine clearance, ml/min, median (IQR)	84 (73–103)	96 (68–113)	0.76
N-terminal pro-B-type natriuretic peptide, pg/ml, median (IQR)	420 (154–856)	167 (98–532)	0.07

Abbreviations: see Tables 1 and 2

Table 4. Comparison of early outcomes and post-aortic valve replacement complication in patients with and without late gadolinium enhancement (LGE) on cardiac magnetic resonance

	n = 68	LGE+ n = 42	LGE- n = 26	*P*–value
Median hospitalization time after SAVR, days (IQR)	8 (7–10)	8 (7–10)	8 (7–10)	0.66
Median hospitalization time in ICU, days (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.19
1 day, n (%)	23 (33.8)	12 (28.6)	11 (42.3)	0.25
>1 day, n (%)	45 (66.2)	30 (71.4)	15 (57.7)	
ECMO, n (%)	0 (0)	0 (0)	0 (0)	1.00
CRRT, n (%)	0 (0)	0 (0)	0 (0)	1.00
Death, n (%)	0 (0)	0 (0)	0 (0)	1.00
Post-pericardiotomy syndrome, n (%)	10 (14.7)	7 (16.7)	3 (11.5)	0.73
Atrial fibrillation, n (%)	15 (22.1)	12 (28.6)	3 (11.5)	0.10
The need for prolonged catecholamines, n (%)	1 (1.5)	1 (2.4)	0 (0)	1.00
Composite outcomes (death, need for ECMO, CRRT and prolonged catecholamines use, post pericardiotomy syndrome or new atrial fibrillation), n (%)	23 (33.8)	17 (40.5)	6 (23.1)	0.14

Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SAVR, surgical aortic valve replacement; other — see Table 2

differences in AS severity (measured as the aortic valve area [P = 0.85] and mean aortic gradient [P = 0.11]) between patients with and without LGE. Patients with LGE had significantly greater hypertrophy of IVS on TTE compared to patients without LGE (P = 0.04). What is more, on CMR, end-diastolic LV volume, LV mass, and SV, both absolute and BSA-indexed values, were substantially higher in LGE patients than in those without (Table 2).

Outcomes for patients undergoing surgical aortic valve replacement with and without LGE

AVR was performed after 24 (median, IQR 11–38) months of follow-up from baseline CMR. Patients with LGE on CMR developed symptoms earlier than patients without LGE (median [IQR] 18 [7–34] months vs. 28 [14–47] months after baseline assessment; *P* = 0.01). There were no significant correlations between the time of follow-up to the symptom onset and CMR measurements while adjusting for age and BSA.

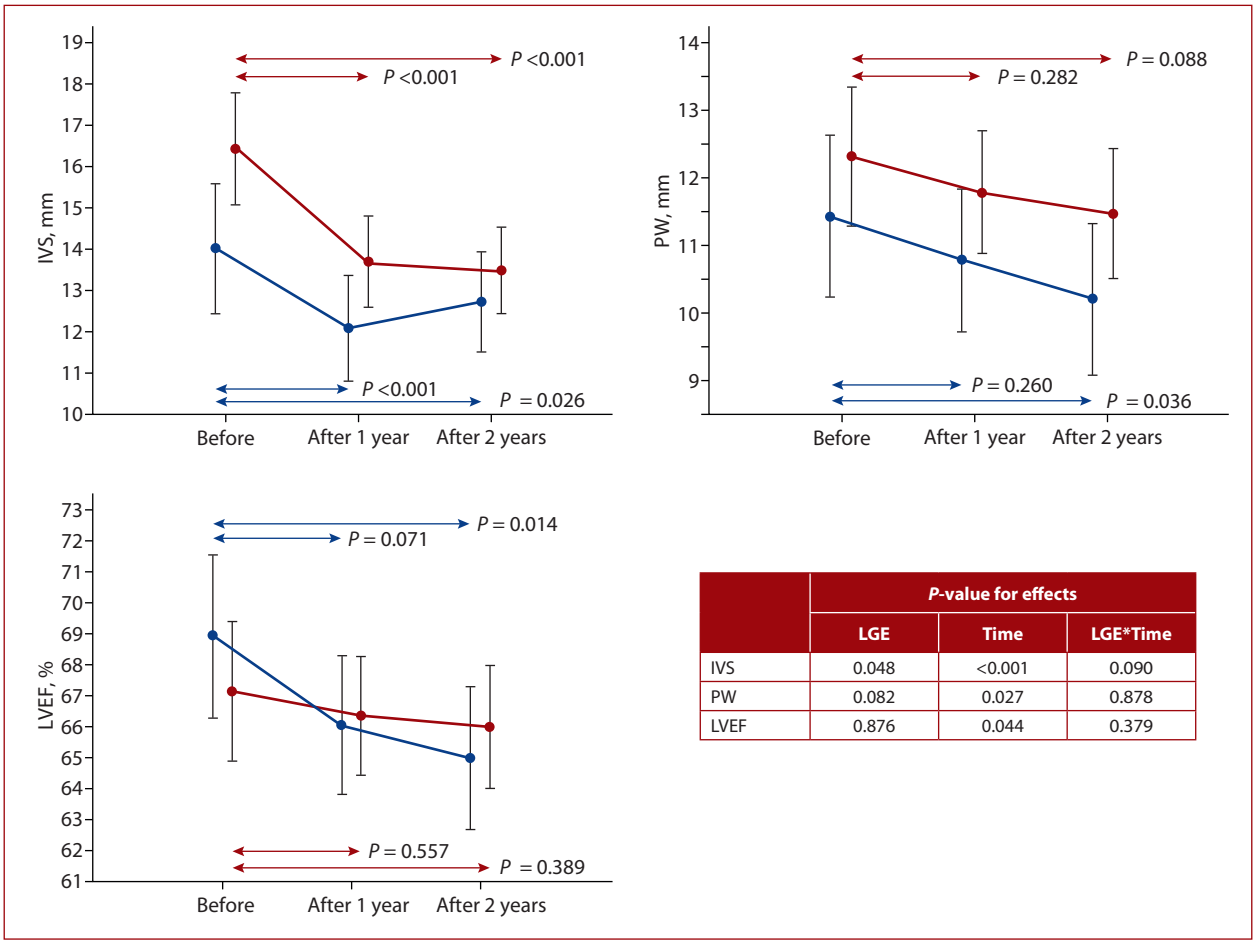
Table 3 shows the clinical characteristics of patients who underwent AVR. There was a tendency towards higher B-type natriuretic peptide levels in LGE patients at the time of symptom onset (median [IQR] 420 [154–856] pg/ml vs. 167 [98–532] pg/ml; P = 0.07). No significant differences were observed in the post-AVR LVEF between patients with and without LGE on CMR (63.6 [5.5] % vs. 64.6 [5.2]%; P = 0.47). Table 4 shows hospitalization time and early post-AVR complications comparison. None of the patients needed extracorporeal membrane oxygenation or continuous renal replacement therapy after AVR. The median time of hospitalization and median time of stay in the intensive care unit were similar between groups. Moreover, there were no differences in early complications post-AVR between patients with and without LGE progression on the second CMR (Table 5).

In the follow-up, one year after AVR, no differences were observed between LGE+ and LGE– patients in the univariate analysis with regards to PW thickness (11.3 [1.7] mm vs. 10.6 [1.9] mm; *P* = 0.26), IVS thickness (13.2 [1.9] mm vs. 12.2 [2.4] mm; *P* = 0.16), and LVEF (65.7 [5.4]% vs. 65.9 [3.3]%; *P* = 0.9). However, when comparing pre-AVR and post-AVR results, LGE+ patients had greater reduction in IVS thickness (16.1 [2.3] mm vs. 13.2 [1.9] mm; *P* <0.001) and PW dimension (12.4 [2.0] mm vs. 11.3 [1.7] mm; *P* = 0.047) vs. LGE- patients (IVS: 14.1 [3.4] mm vs. 12.2 [2.4] mm; *P* = 0.005; PW: 11.4 [1.4] mm vs. 10.6 [1.9] mm; *P* = 0.20).

Table 5. Comparison of early outcomes and post-aortic valve replacement complications in patients with and without late gadolinium enhancement (LGE) progression on second cardiac magnetic resonance

	Without LGE progression n = 31	With LGE progression n = 5	*P*-value
Median hospitalization time after SAVR, days (IQR)	8 (7–10)	8 (8–10)	0.50
Median hospitalization time in ICU, days (IQR)	2 (1–2)	2 (1–2)	0.85
1 day, n (%)	12 (38.1)	2 (40.0)	1.00
>1 day, n (%)	19 (61.3)	3 (60.0)	
ECMO, n (%)	0 (0)	0 (0)	1.00
CRRT, n (%)	0 (0)	0 (0)	1.00
Death, n (%)	0 (0)	0 (0)	1.00
Post-pericardiotomy syndrome, n (%)	6 (19.4)	1 (20.0)	1.00
Atrial fibrillation, n (%)	6 (19.3)	1 (20.0)	1.00
The need for prolonged catecholamines, n (%)	1 (3.2)	0 (0)	1.00

Abbreviations: see Tables 2 and 4



	P-value for effects		
	LGE	Time	LGE*Time
IVS	0.048	<0.001	0.090
PW	0.082	0.027	0.878
LVEF	0.876	0.044	0.379

Figure 3. Changes in selected morphological parameters and functions of the left ventricle during follow-up as a function of late gadolinium enhancement (LGE) on magnetic resonance imaging. Two-way repeated ANOVA with *post hoc* comparisons NIR test results

Abbreviations: IVS, interventricular septum; LVEF, left ventricular ejection fraction; PW, posterior wall thickness

The results of the multivariate analysis are presented in Figure 3. Notably, in LGE patients, we observed a reduction in LVEF after 2 years (68.3 [3.4]% vs. 64.4 [4.0]%; $P = 0.01$). This contrasts with LGE+ patients in whom no such a reduction was observed (67.7 [4.7]% vs. 65.0 [5.3]%; $P = 0.39$). LVEF was not significantly different between these groups (64.4 [4.0]% vs. 65.0 [5.3]%; $P = 0.7$).

DISCUSSION

In this prospective study, we found that patients with LGE on CMR developed symptoms earlier than patients without LGE, but there were no differences in the post-AVR LVEF and outcomes between patients with and without LGE on CMR. In addition, patients with LGE had higher N-terminal pro-B-type natriuretic peptide levels at the time of symptom

onset. Two years after AVR, no differences were observed between patients with and without LGE in the univariate analysis with regards to PW and IVS thickness and LVEF. However, when comparing pre-AVR and post-AVR results, LGE+ patients had a greater reduction in IVS and PW thickness versus LGE– patients. Moreover, LGE patients had significantly greater hypertrophy of IVS on TTE compared to patients without LGE. What is more, on CMR, end-diastolic LV volume, LV mass, and SV, both absolute and BSA-indexed values, were substantially higher in LGE patients than in those without. However, there were no differences in the severity of aortic stenosis between those two groups. Notably, in LGE– patients, we observed a reduction in LVEF after 2 years, whereas in LGE+ patients, no such a reduction was observed. This observation is intriguing and requires further investigation.

In our study, women were less likely to have LGE on CMR. The effect of sex on mortality has been studied previously, and female sex was not associated with higher in-hospital and late mortality rates compared with men [13].

Aortic stenosis relies on progressive narrowing of the aortic valve and may be considered the paradigm for LV pressure overload. LVH is a compensatory response to overload, which can help maintain systolic function. Although initially, this change restores wall stress [14], finally, it proves maladaptive and predicts adverse prognosis [15]. Recent data have suggested that in isolated AS, increased LVM predicts the presence of systolic dysfunction and heart failure independent of the severity of valvular obstruction [16]. Our observation is partially consistent with the findings of several previous studies. Dweck et al. [17] showed that on CMR, the magnitude of LVH varied widely but was unrelated to the severity of aortic stenosis. However, they did not assess LGE presence. Also, a small sample size study [18] showed that the AS subjects with LGE had higher LV end-diastolic volumes than those without. Midwall LGE on CMR is a frequent feature of left ventricular hypertrophy, regardless of its cause, and depends on the severity of LV remodeling [18]. However, in the study by Rudolph et al. [18], only 21 patients with AS were included. To the best of our knowledge, our study is one of the largest comparing LV dimensions between asymptomatic AS with and without LGE on CMR.

LGE reflects focal replacement fibrosis, which is irreversible and occurs in the later stages of AS [19]. It is known that focal fibrosis has been associated with diastolic dysfunction [7]. Previous studies showed that LGE does not resolve after AVR, but diffuse fibrosis and myocardial cellular hypertrophy regressed [2]. These changes are accompanied by structural and functional improvements [2]. The usefulness of LGE assessment on CMR as a predictor of outcomes in AS patients is widely discussed. LGE is considered a powerful prognostic marker of all-cause mortality in AS patients [6]. What is more, the presence, type, localization, and extent of LGE play an important role in identifying the etiology of heart failure [20].

A prospective 2-center study showed that in a multivariate Cox regression analysis adjusting for age, sex, aortic valve area, AVR, and LVEF, the presence of LGE and LGE volume were not associated with clinical outcomes [19]. However, they also enrolled patients with moderate AS, 88% of patients underwent AVR within the median time between CMR and AVR of 3 days (IQR 1 to 26 days), and they did not compare outcomes in patients with and without LGE.

In the first studies from the Indian subcontinent [21], they enrolled 109 AS patients who underwent CMR and found that LGE was detected by CMR in 43% of patients with severe AS and was a predictor of recurrent heart failure, hospitalization for cardiovascular causes and decrease in LVEF.

However, in multivariate analysis, age >62 years and a higher class in the New York Heart Association classification were the only predictors of the primary outcome (composite of mortality, LVEF decline >20%, new-onset heart failure or hospitalization for cardiovascular causes, and new-onset arrhythmia). In the study, only 38 patients (34.9%) were referred for aortic valve replacement, while the remaining 71 patients (65.1%) were managed conservatively. Contrary to our study, Dweck et al. [17] assessed the prognostic significance of LGE in AS and found that midwall fibrosis and LVEF were independent predictors of all-cause mortality by multivariate analysis. However, the study enrolled patients not only with severe but also with moderate AS. Moreover, only 50% of enrolled patients underwent AVR, and there was no comparison of post-AVR outcomes between patients with and without LGE. Interestingly, the mortality rate in patients with LGE who underwent AVR was 4-fold lower than those who did not.

Chin et al. [22] used the total extracellular volume of the myocardium indexed to body surface area (iECV) and LGE to categorize patients with normal myocardium, extracellular expansion, and replacement fibrosis. They found that there were significant differences in all-cause mortality between these groups. However, it should be noted that both healthy volunteers (n = 37 [18.2%]) and patients with aortic stenosis (mild n = 34 [16.7%], moderate n = 45 [22.2%] and severe n = 87 [42.9%]) were enrolled and there were significant differences in the incidence of ECV and LGE between these groups.

The study by Barone-Rochette et al. [23] showed that the presence of LGE is an independent predictor of mortality in patients with AS undergoing AVR. However, it is worth emphasizing that patients with midwall fibrosis had initially reduced LVEF compared to patients without fibrosis. Also, a meta-analysis [24] showed that LGE, native T1, and ECV measured by CMR can help stratify risk in AS. Currently, available data suggest that the presence of myocardial fibrosis plays a key role in the selection of

candidates for AVR [25], but further studies in a subset of asymptomatic stenosis patients are needed. The largest study (n = 523 patients) involving data from 6 UK cardiothoracic centers [26] showed that LGE in patients with severe AS was independently associated with mortality, and its presence was associated with a 2-fold higher late mortality. Importantly, all patients were symptomatic at the moment of the CMR imaging, enrolled patients were older than our study group, and fewer than 60% of study groups were listed as surgical AVR. In our study, a good outcome in terms of LV function and hypertrophy after AVR, regardless of the presence of LGE, may have been caused by asymptomatic SA in observed patients who were referred to surgical AVR immediately after the onset of first symptoms.

Limitations

Our results represent a single-center experience. In this study, we used only LGE to assess myocardial fibrosis, whereas earlier studies also used extracellular volume as a measure of diffuse myocardial fibrosis. On TTE, we assessed systolic function of the left ventricle only by LVEF; we did not assess the global longitudinal strain. The small sample size of the subgroup ruled out some comparisons. Due to the short period between enrollment in the study and the onset of symptoms, a second CMR was performed on only 36 (52.9%) of the 68 patients who underwent AVR.

CONCLUSIONS

The outcome of patients with asymptomatic AS but with LGE was similar to this observed in the non-LGE group. Watchful waiting in this group, with referral to AVR immediately after the onset of symptoms, is associated with comparable results as in patients without LGE.

Article information

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