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Prognostic Significance of Left Ventricular Fibrosis in Patients with Congenital Bicuspid Aortic Valve

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Abstract

This study sought to evaluate the prognostic value of left ventricular (LV) fibrosis assessed by late gadolinium enhancement (LGE) of the myocardium during cardiac magnetic resonance (CMR) imaging in patients with bicuspid aortic valve (BAV), which is associated with early aortic valve fibrosis and calcification. To what degree the LV myocardial wall is affected by fibrosis and its prognostic value is currently unknown. This is a retrospective, single center study evaluating all adult patients with BAV who had CMR and followed from March 2002 to March 2016. CMR and transthoracic echocardiogram images were reviewed. Clinical data were abstracted from the electronic medical record. A total of 29 patients were included in the study, of which 11 (38%) had CMR studies that demonstrated the presence of LGE. Patients with LGE had significantly higher aortic valve mean gradients by echocardiography when compared to LGE negative patients (30.3 ± 7.2 mmHg vs 14.7 ± 3.6 mmHg, p = 0.049). They were also more likely to have LV hypertrophy. Patients with LGE were ten times more likely to need aortic valve replacement (AVR) within one year of the CMR study than did patients without LGE (55% vs 5.5%, P = 0.0028). In conclusion, evaluation of LGE by CMR as a marker of LV myocardial fibrosis can have additional prognostic value when evaluating patients with aortic stenosis secondary to BAV.

Keywords

Bicuspid aortic valve; Cardiac magnetic resonance; Late gadolinium enhancement; Aortic valve replacement

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Little is known about the prevalence of myocardial fibrosis in patients with BAV. Since its first description in 2001 [1], myocardial late gadolinium enhancement (LGE) has become a routine component of many cardiac magnetic resonance imaging (CMR) protocols. LGE imaging has been used to identify the presence, pattern, and size of fibrosis and has been proven of prognostic capacity [2]. For instance, the presence and amount of LGE has been linked to left ventricular recovery in patients after an MI [3]. It has also been shown to have strong prognostic value in patients with NICM [4] as well as HCM [5]. However, there is a paucity of data on the prognostic impact of the presence or absence of LGE in patients with BAV. Hence, in this study we attempted to evaluate the prevalence and clinical significance of left ventricular myocardial LGE in adult patients with BAV.

Methods

We conducted a retrospective study of adult patients (>18 years old) with BAV followed at UCLA Medical Center from March 2002 to March 2016. All patients who had a diagnosis of BAV and had undergone CMR imaging were initially screened for the study. Patients with CMR studies which did not include sequences to detect LGE were excluded from the study. In addition, patients with prior cardiac surgery were excluded from the study since patients may have acquired LGE as a consequence of the cardiac surgery alone [6]. Clinical information was obtained from the electronic medical record and the data were de-identified before being used for analysis. The study protocol was approved by the institutional review board of Ronald Reagan Medical Center and the study was conducted in accordance with the protocol.

Cardiac MR images were performed at UCLA Medical Center on a Siemens Avanto 1.5T MR scanner (Siemens USA, Malvern, PA). The image acquisition protocol included breath-held, multi-planar segmented SSFP cine imaging, in addition to flow quantification sequences across the aortic valve. Supplemental multiplanar inversion recovery images were obtained at 10 minutes following administration of a gadolinium based, extracellular contrast agent (GBCA); either Magnevist (gadopentetate dimeglumine, Bayer Pharma) or Multihance (gadobenate dimeglumine, Bracco Diagnostics) at a dose of 0.15–0.2 mmol/kg to assess for delayed myocardial hyper-enhancement. All images were reviewed on a Mac OsiriX workstation by one observer (PR) who was unaware of the subjects' clinical information. Transthoracic echocardiograms were obtained with use of a Philips iE33 ultrasound machine (Philips USA, Andover, MA). The severity of aortic valve stenosis and regurgitation as well as left ventricular function was evaluated by using the established American Society of Echocardiography criteria [7]. Diastolic dysfunction was defined as described in the American Society of Echocardiography guidelines [8]

Patient data were collected retrospectively from electronic medical record. Continuous variables were reported as mean ± standard error. The unpaired t-test was used to compare the means of continuous variables, the chi-squared test was used to analyze categorical variables (reported as %), and Kaplan-Meier analysis was used for time to event data. A p-value of < 0.05 was considered statistically significant. All data were analyzed using GraphPad Prism 6 (La Jolla, CA).

Results

A total of 254 patients with BAV who had at least one CMR study performed at our institution were evaluated for inclusion in our analysis (March 2002 to March 2016), of which 68 patients had LGE sequences performed. Patients who had previously had cardiac surgery were excluded from the study, as prior surgery is a potential cause of LGE on CMR (Figure 1). Thus, a total of 29 patients were included in the study. 18 patients had no evidence of LGE (Figure 2, A), while 11 patients did have LGE on CMR (Figure 2, B arrow).

Baseline demographic, clinical, and echocardiographic characteristics of the 2 groups are presented in Table 1. There was no difference in the left ventricular ejection fraction (LVEF) or the size of ascending aorta. Interestingly, the mean gradient across the BAV was significantly higher in the LGE positive (30.3 ± 7.2 mmHg) group when compared to the LGE negative group (14.7 ± 3.6 mmHg, p = 0.049). Furthermore, there was more left ventricular hypertrophy in the LGE positive group (10.3 ± 0.9 mm) when compared to the LGE negative group (7.6 ± 0.3 mm, p = 0.01), as measured by the LV posterior wall thickness on end-diastole. A similar pattern was seen in the interventricular septum (IVS) thickness. Global longitudinal strain was calculated whenever possible and such data were available only in a minority of patients (5 patients in the LGE− and 4 patients in the LGE+) showing no difference (−18.0 ± 1.7 for LGE− vs. −16.4 ± 2.1, p = 0.57).

We next examined the association between the presence of LV fibrosis and the need for surgical replacement of the bicuspid aortic valve. Patients with positive LGE were ten times more likely to undergo aortic valve replacement (AVR) within 1 year of the CMR study (55%) when compared to patients with a CMR negative for LGE (5.5%, p = 0.0028) (Figure 3), and Kaplan-Meier analysis showed that freedom form AVR was significantly lower at 5 years at 5.1% in the LGE positive group when compared to the 92.8% in the LGE negative group (p < 0.0001) (Figure 4). There was no difference in mortality at 5 years between these two groups. When adjusted for age, gender, NYHA class, left ventricular function, and aortic stenosis severity, the presence of LGE+ with hazards ratio of 2.84 did not reach statistical significance (p = 0.09), by cox proportional-hazard analysis.

Discussion

The findings of our study suggest that the presence of LGE on CMR examinations is associated with greater severity of the disease. Patients with left ventricular myocardial LGE by CMR have increased severity of stenosis across the aortic valve in addition to increased left ventricular hypertrophy. Most importantly, the presence of LGE in patients with BAV appears to be associated with a significantly higher likelihood of needing AVR within 1 year of the CMR examination, and only a 5.1% freedom from AVR in the following 5 years after CMR. These findings are consistent with other observations that demonstrate increased morbidity and worse outcomes with fibrosis in other pathological cardiac conditions such as ischemic, hypertrophic, dilated, and nonischemic [5,9–11].

Despite the fact that BAV is the most common congenital heart disease in adults and a significant cause of AVR surgeries, to the best of our knowledge there are no prior data that evaluate the prognostic utility of LGE in patients with BAV. Although calcification and stenosis occur prematurely in patients with BAV, the rate of progression of disease varies amongst individual patients. Currently there are no clinical criteria to determine patients who would benefit from closer follow up or who may develop accelerated calcification of the bicuspid valve. Our data suggests that the presence of left ventricular fibrosis on CMR may identify patients with more severe disease, who will require valve replacement surgeries sooner. The reasons behind increased cardiac fibrosis in these patients are unclear. We show that patients with LGE have greater transvalvular gradients and the presence of ventricular fibrosis could reflect increased hemodynamic strain on the left ventricle. Alternatively, altered signaling pathways (e.g Notch) that contribute to the development of BAV could perhaps independently contribute to the development of fibrosis [12].

To date, there are no medical treatments for advanced aortic valve disease and surgical, or more recently transcatheter AVR are the only treatments available for these patients. Timing of such interventions remains an area of great clinical importance. In the absence of symptoms, timing of AVR for severe aortic valve stenosis can be challenging and not straightforward and currently based on the assessment of cardiac function and/or transvalvular gradients. Our observations suggest that the assessment of cardiac fibrosis by LGE should be investigated in future prospective studies as an independent prognostic indicator of outcomes of patients newly diagnosed with BAV.

Our data also sheds insight into the development of LV fibrosis in patients with BAV. Although our cohort was small, the population studied is fairly representative of patients with BAV disease. LGE was present on more than a third of patients (38% of patients) at initial diagnosis suggesting that it is not rare but perhaps commonly found in BAV disease. LGE positive patients observed in our cohort were more likely to have both significant aortic stenosis and left ventricular hypertrophy and were ten times more likely to need AVR within 1 year when compared to patients with LGE negative CMR examinations. There was no difference in the prevalence and severity of aortic regurgitation or diastolic dysfunction. Absence of LGE on CMR had an excellent negative predictive value for AVR with only 5% of the patients needing AVR within 1 year and 92.8% of the patients free from AVR at 5 years. These findings suggest that CMR with LGE imaging included in the examination protocol may be a powerful prognostic tool in the clinical assessment and risk stratification of patients with BAV and significant aortic stenosis.

One of the major limitations of our study is its sample size, which is not uncommon for a single-center retrospective study. These findings are intriguing and could add to prognostic factors that identify patients who are at high risk of developing accelerated BAV disease, however such findings will need to be confirmed in a larger prospective study.

In conclusion, our study suggests that left ventricular myocardial LGE on CMR in patients with BAV is associated with significant aortic stenosis, left ventricular hypertrophy and a high probability of needing AVR in the near future. Furthermore, the absence of LGE had a high negative predictive value of not needing AVR within the next 5 years, suggestive of a

less rapid progression of disease. Thus, CMR with LGE imaging holds potential promise as a prognostic tool in the follow up and long-term management strategy for patients with aortic valve stenosis in the setting of BAV. Larger prospective multi-center studies would be needed to further assess LGE on CMR as a marker in identifying high-risk BAV patients.

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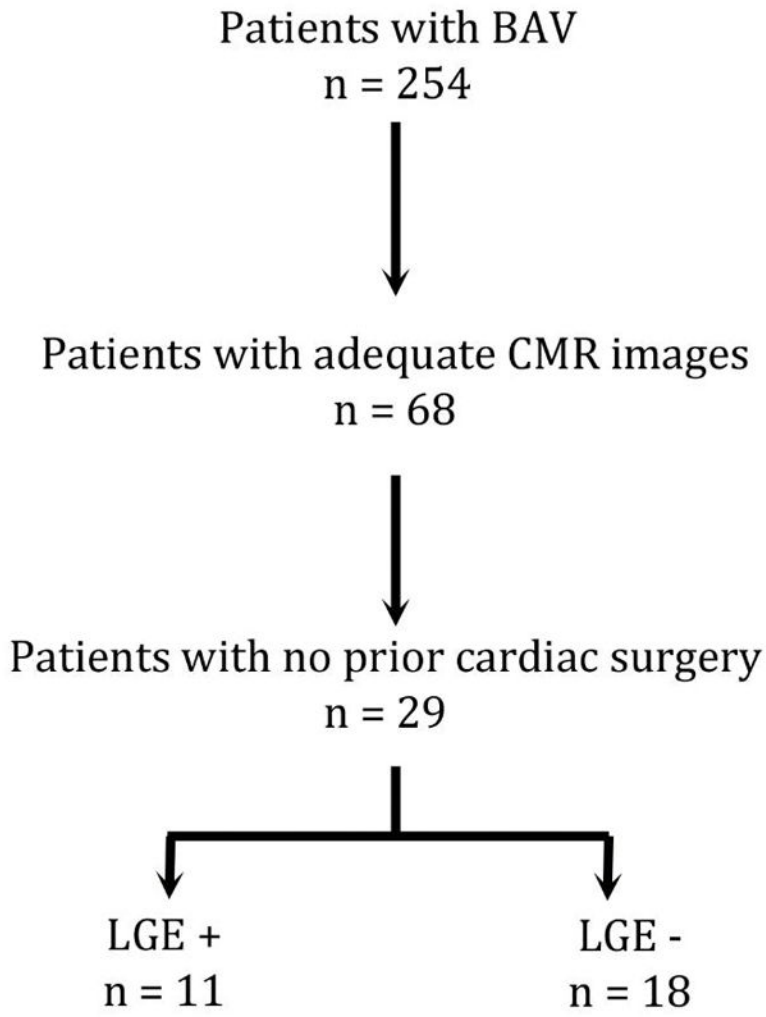

Figure 1. Patient selection in the study of LGE by CMR in the setting of BAV

There are 11 patients with LGE+ and 18 patients with LGE− included in the study. *BAV = bicuspid aortic valve; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement.*

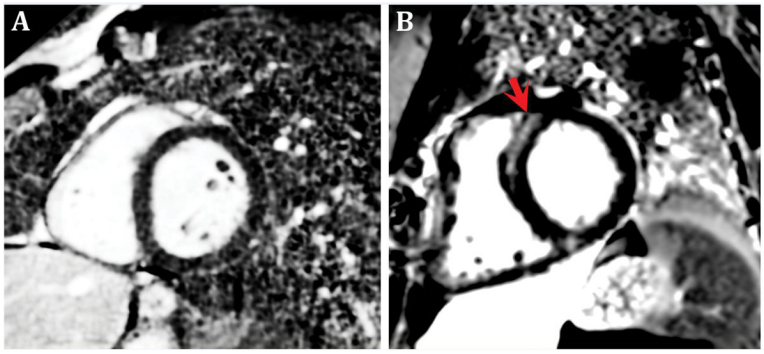

Figure 2. Assessment of LGE by CMR in patients with BAV

Panel A showing LGE − images and B showing LGE (red arrow) in the LV wall. *LGE = late gadolinium enhancement; CMR = cardiac magnetic resonance; BAV = bicuspid aortic valve; LV = left ventricle.*

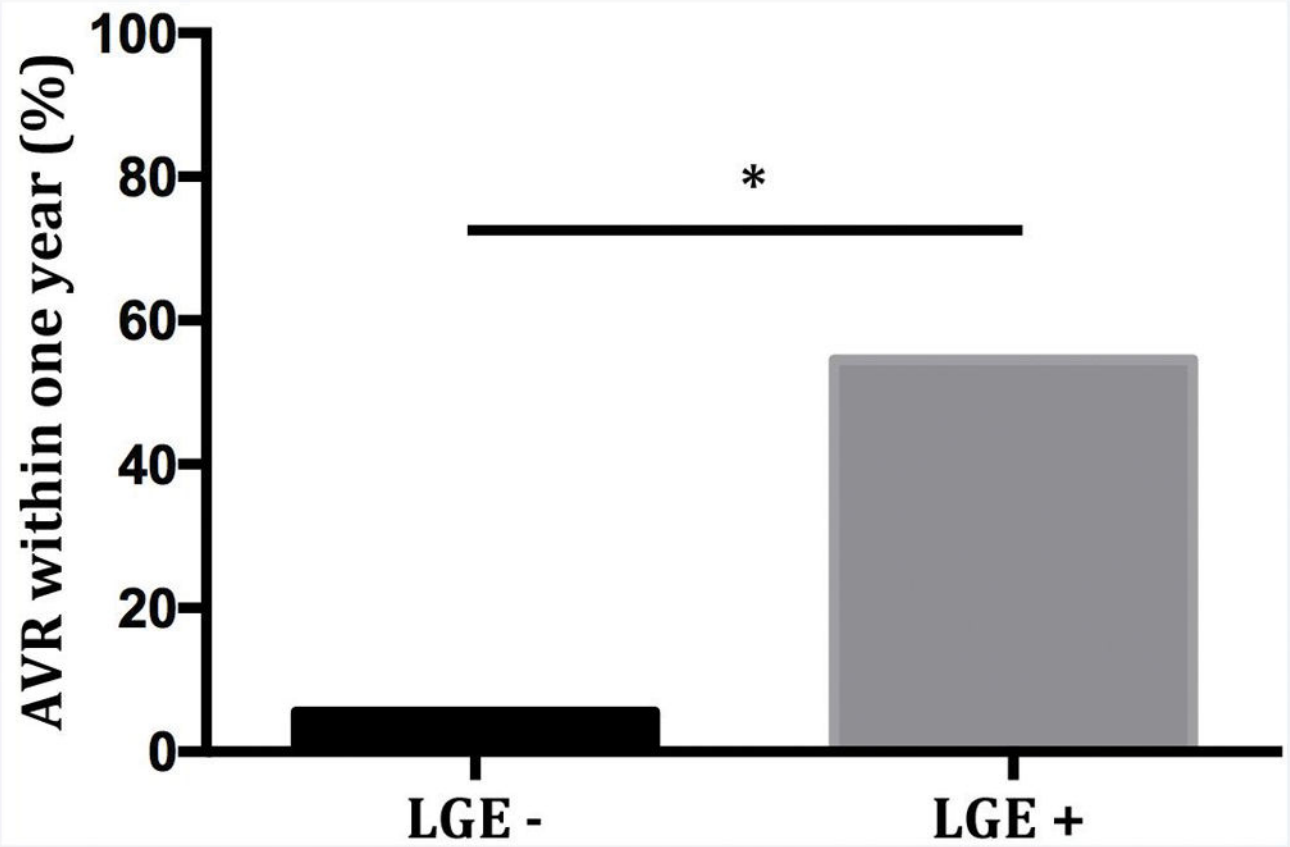

Figure 3. Presence of LGE and AVR

Patients with LGE + had a 55% chance of needing aortic valve surgery within 1 year and LGE − patients had only a 5.5% chance during the same time. *LGE = late gadolinium enhancement; AVR =aortic valve replacement; P = 0.0028.*

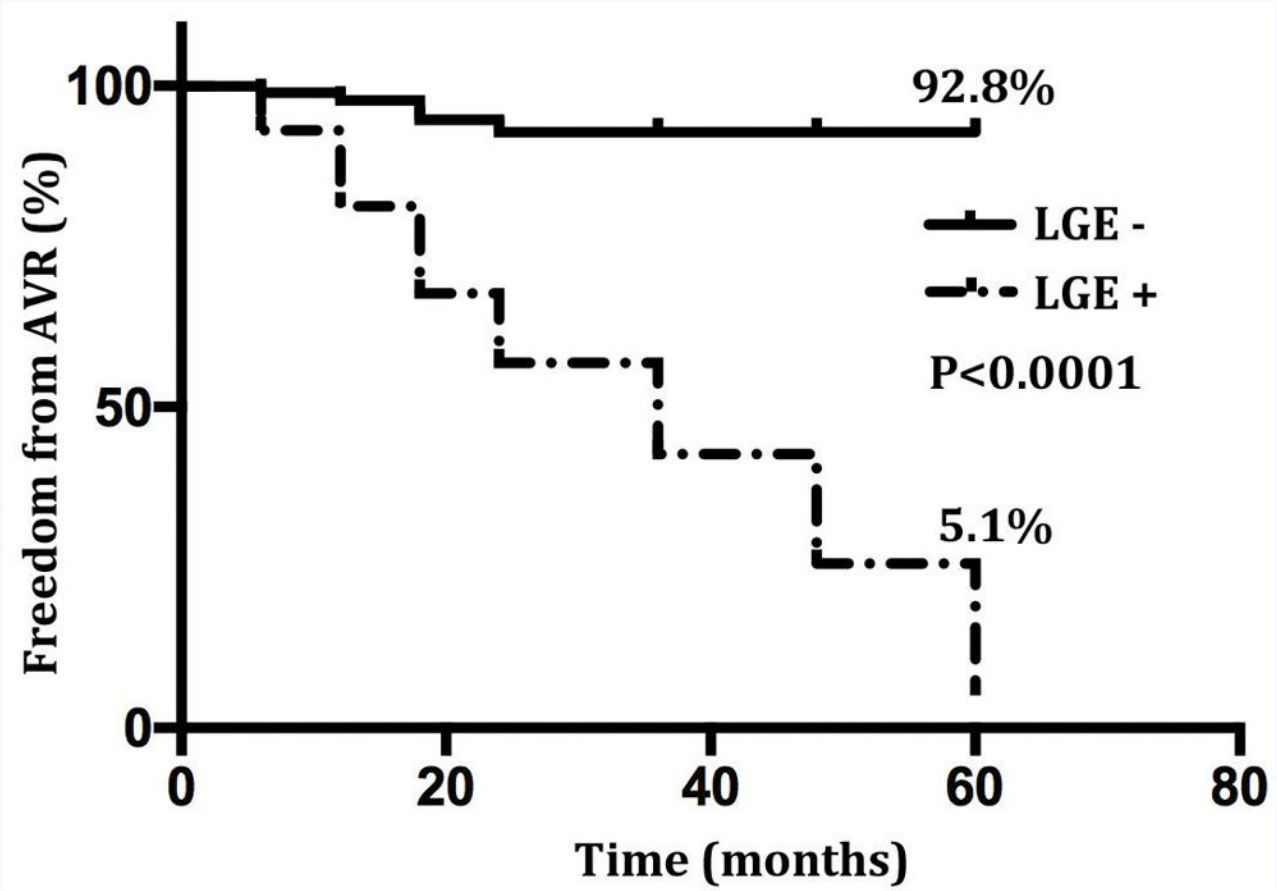

Figure 4. Freedom from AVR at 5 years for both groups

Kaplan-Meier analysis showing that at 5 years from CMR, freedom from AVR is 5.1% for patients with LGE+ and 92.8% for patients with LGE−. *AVR = aortic valve replacement; LGE = late gadolinium enhancement; CMR = cardiac magnetic resonance; P<0.0001.*

Table 1

Baseline characteristics of the two study groups

Variable	LGE − (n=18)	LGE + (n=11)	P Value
Age (years)	39.7 ± 3.1	44.2 ± 4.1	0.39
Men	12 (67%)	7 (64%)	0.86
Hypertension	11 (61%)	6 (55%)	0.73
Hyperlipidemia	4 (22%)	3 (27%)	0.76
Diabetes mellitus	0 (0%)	1 (9%)	0.19
Beta blocker	8 (44%)	5 (45%)	0.96
ACE/ARB	5 (28%)	5 (45%)	0.33
Presence of coarctation	4 (22%)	2 (18%)	0.79
History of valvuloplasty	1 (6%)	0 (0%)	0.43
Mean duration (years)	4.6 ± 0.9	4.5 ± 1.1	0.97
LVEF (%)	64.6 ± 2.3	62.4 ± 1.7	0.53
Ascending aorta (cm)	3.6 ± 0.16	4.0 ± 0.29	0.19
Mean gradient across AV (mmHg)	14.7 ± 3.6	30.3 ± 7.2	**0.049**
LV posterior wall thickness (mm)	7.6 ± 0.3	10.3 ± 0.9	**0.01**
IVS wall thickness (mm)	10.0 ± 0.5	12.1 ± 0.9	**0.03**
Severe aortic regurgitation	1 (2%)	0 (0%)	0.43
Moderate aortic regurgitation	7 (39%)	6 (55%)	0.41
Diastolic dysfunction	3 (17%)	2 (18%)	0.92

LGE = late gadolinium enhancement; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CMR = cardiac magnetic resonance; LVEF = left ventricular ejection fraction; AV = aortic valve; IVS = interventricular septum; Diastolic dysfunction as defined in the American Society of Echocardiography guidelines (Nagueh et al. 2016).