CLINICAL SIGNIFICANCE OF LATE GADOLINIUM ENHANCEMENT AT RIGHT VENTRICULAR ATTACHMENT TO VENTRICULAR SEPTUM IN HYPERTROPHIC CARDIOMYOPATHY

Running title: *Focal LGE and Outcome in HCM*

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STRUCTURED ABSTRACT

Objectives: The aim of this study was to evaluate the prognostic significance of late gadolinium enhancement (LGE) confined to the right ventricular (RV) insertion area in hypertrophic cardiomyopathy (HCM) patients.

Background: Cardiovascular magnetic resonance (CMR) with extensive LGE is a novel marker for increased risk for sudden death (SD) in patients with HCM. Small focal areas of LGE confined to the region of right ventricular (RV) insertion to ventricular septum has emerged as a frequent and highly visible CMR imaging pattern of uncertain significance.

Methods: CMR was performed in 1293 consecutive HCM patients from 7 HCM centers, followed for 3.4 ± 1.7 years.

Results: Of 1293 patients (47 ± 14 years of age), 134 (10%) had LGE present only in the anterior and/or inferior areas of the RV insertion to ventricular septum, occupying 3.7 ± 2.9% of LV myocardium. Neither the presence nor extent of LGE in these isolated areas was a predictor of adverse HCM-related risk, including sudden death (HR_{adj} 0.82; 95% CI: 0.45-1.50; p = 0.53, and HR_{adj} 1.16/10% increase in LGE; 95% CI: 0.29-4.65; p = 0.83, respectively). Histopathology in 20 HCM hearts show the insertion areas of RV attachment to be composed of a greatly expanded extracellular space characterized predominantly by interstitial-type fibrosis and interspersed disorganized myocyte patterns and architecture.

Conclusions: LGE confined to the insertion areas of RV to ventricular septum was associated with low risk of adverse events (including sudden death), and therefore this unique LGE pattern by itself cannot be regarded as a marker to predict adverse prognosis in HCM. Gadolinium pooling in this region of the left ventricle does not reflect myocyte death and repair with replacement fibrosis or scarring.

Keywords: hypertrophic cardiomyopathy, magnetic resonance imaging, late gadolinium enhancement

CONDENSED ABSTRACT

Extensive late gadolinium enhancement (LGE) has been associated with adverse events in hypertrophic cardiomyopathy (HCM). It is unclear whether focal areas of LGE confined to the region of right ventricular (RV) insertion to ventricular septum is also associated with an adverse prognosis. In a large cohort of HCM patients, neither the presence nor extent of LGE, when confined to the RV insertion areas, was associated with an increased risk of adverse events. Furthermore, histopathology of post mortem HCM hearts demonstrated these areas to be composed of expanded extracellular space with areas of interstitial fibrosis, rather than replacement fibrosis and scarring.

ABBREVIATIONS

HCM = hypertrophic cardiomyopathy; ICD= internal cardioverter defibrillator; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricle; LVED = left ventricle end-diastolic; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; RV = right ventricle; SD = sudden death; VF = ventricular fibrillation; VT = ventricular tachycardia.

INTRODUCTION

Contrast-enhanced cardiovascular magnetic resonance (CMR) with extensive late gadolinium enhancement (LGE) has emerged as a novel marker for identifying patients with hypertrophic cardiomyopathy (HCM) at increased risk for adverse disease consequences (1-7). Utility of LGE as a risk marker is predicated on quantifying the amount of LGE relative to overall left ventricular (LV) mass, although the significance attached to specific patterns or locations of LGE remains incompletely resolved (1,8-11).

Since the initial descriptions of LGE in HCM, one contrast-enhanced pattern has been of particular note, in which LGE is confined exclusively to the insertion areas of the right ventricle (RV) into anterior and/or inferior ventricular septum (5,12). Indeed, this specific LGE pattern continues to be of interest given the increasing penetration of CMR into clinical cardiovascular practice (8,10,11). Therefore, in this substudy, we systematically assessed our large HCM-CMR database (1) to define the prevalence, clinical profile and prognostic significance of this unique LGE pattern to patients with HCM. To characterize the morphology of the LV wall at the point of RV wall insertion, histopathologic examination was performed in an independent group of hearts with HCM and in appropriate controls.

METHODS

Selection of patients

We evaluated 1669 HCM patients who were initially considered for CMR study at 7 HCM centers from November 2001 to February 2010. A total of 376 patients were excluded from the cohort based on these criteria: prior implantation of an internal cardioverter

defibrillator(ICD), or other incompatible device, history of sustained VT/VF, claustrophobia, known associated obstructive coronary artery disease (including history of myocardial infarction or acute coronary event associated with increased cardiac enzymes or Q-waves), other myocardial diseases, septal myectomy or alcohol ablation performed before CMR, and when complete follow-up could not be obtained (n = 7). Therefore, the final study group comprised 1293 patients referred and eligible for CMR (1). This substudy is specifically confined to study the significance of LGE in the areas of RV wall insertion to LV, and were selectively compared to a subgroup of patients without LGE, also taken from our large HCM-CMR database, in which other aspects related to LGE in HCM have been reported (1).

Follow-up of 3.4 ± 1.7 years was to the most recent evaluation (annual clinic visit or telephone interview) or death, as of January 2012. This study was approved by the Internal Review Board (IRB) of the respective participating institutions, with patients agreeing to the use of their medical information for research purposes. All authors had full access to, and take full responsibility for the integrity of the data and have read and agreed to the manuscript as written.

Definitions

Diagnosis of HCM was based on CMR documentation of a hypertrophied and non-dilated left ventricle (LV wall thickness ≥15 mm in adults and the equivalent relative to body surface area in children) in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy (13-16). LV outflow tract obstruction was defined as a peak systolic instantaneous outflow gradient ≥30 mmHg, assessed by continuous-wave Doppler echocardiography under resting conditions.

Adverse HCM-related events included: sudden death events defined as unexpected collapse in patients who had previously had a relatively uneventful clinical course, appropriate ICD interventions triggered by ventricular fibrillation or rapid ventricular tachycardia (rate ≥180 beats per minute), symptom progression during follow-up to New York Heart Association (NYHA) functional class III or IV, (including heart transplant recipients), or HCM-related heart failure death (18).

CMR analysis

LV volume, mass and ejection fraction were measured using standard volumetric techniques and analyzed with commercially available software (QMASS® v7.4, Medis Inc., The Netherlands). LV chamber was assessed according to American Heart Association 17 segment model (19). Maximal LV wall thickness was defined as the greatest dimension at any site within LV myocardium.

Images from all centers were transferred to a core laboratory (PERFUSE, Boston, MA) for centralized and blinded analysis (1). LGE images were first assessed visually for the presence and location of LGE by 2 experienced readers (R.H.C and E.A.), blinded to patient profiles and clinical outcome, with any disagreement adjudicated by a third expert reader (W.J.M) (1). RV insertion point LGE was defined as a focal area confined to the junction of RV wall into anterior and/or posterior septum, as identified on the LV short-axis image stack (Figure 1). Quantification of LGE in this region was performed by one expert reader (R.H.C.) by manually adjusting a grayscale threshold to define areas of visually identified LGE (1). These areas were then summed to generate a total volume of LGE, and expressed as a proportion of total LV myocardium (% LGE) (1).

Histopathology

Twenty post-mortem hearts from patients with HCM and sudden death were examined, separate from the present clinical study cohort (age 25 ± 10 years; 16 male; heart weights, 481±189 grams). In addition, 20 control hearts (age 29 ± 8 years; 10 male; heart weights, 356 ± 80 grams) from patients who died of a variety of cardiac or non-cardiac diseases were examined. Full wall thickness tissue blocks were taken from the LV at the anterior and inferior areas of anatomic attachment of RV wall to ventricular septum (Figure 2). Tissue was embedded in paraffin and sectioned at 8 μm thickness, stained with Masson's trichrome, and inspected by light microscopy. The severity of interstitial fibrosis and myocyte disarray were assessed semi-quantitatively on a scale of 0-3+.

Statistical analysis

Continuous and categorical data are expressed as mean (± SD) or n (%), respectively. Comparisons between groups were assessed with unpaired Student's *t*-test, Wilcoxon Rank Sum, chi-square test or Fisher's exact test, where appropriate. The pre-specified primary clinical end-point was a composite of adverse HCM-related events including: sudden death (including aborted cardiac arrest, or appropriate ICD discharge for VT/VF), adverse heart failure event (including symptom progression to NYHA class III/IV during the follow-up period, heart failure death, or heart transplantation).

Event-free survival curves were constructed using the Kaplan-Meier method, and differences between groups were examined using the log-rank test for equality of survivor functions. The relation between the presence or extent of LGE and the likelihood of subsequent events was further evaluated using univariate and multivariable Cox proportional hazards models. Variables entered into the multivariable model were: age, maximal LV wall thickness and ejection fraction. The proportional hazards assumption was tested graphically

and with time-dependent covariates before proceeding. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Prevalence and extent of LGE at RV insertion to LV

LGE was confined to the insertion area of RV wall and ventricular septum in 134 out of 1293 patients (10%), including 50 (4%) with LGE only at anterior septum, 36 (3%) only at posterior (inferior) septum, and 48 (3%) with LGE in both sites (Table 1 and Figure 1). Extent of LGE in these 134 patients was 3.7 ± 2.9% of LV myocardial mass.

Clinical profile

The 134 study patients were 47±14 years old (range 14 to 79); 88 (66%) were male (Table 1). At baseline, most were asymptomatic or mildly symptomatic (n = 117 [87%] in NYHA functional classes I/II). Thirty-seven patients (28%) had LV outflow tract gradients of ≥30 mmHg at rest.

Clinical outcome

Over the follow-up period, adverse disease-related events occurred in 13 patients (10%) with RV insertion area LGE, including 4 with sudden death (SD) events, 2 of whom had ≥1 conventional high-risk markers (13,16,20) (Table 1). Nine patients developed progressive heart failure symptoms to class III/IV or heart failure death (7%), including 2 with LV outflow obstruction (16) (gradients 49 and 52 mmHg, respectively) (Table 1). In comparison, of 745 patients without LGE in the overall CMR cohort, adverse disease-related events occurred in 65 (9%).

RV insertion point LGE vs. adverse HCM-related events

Kaplan-Meier analysis showed no significant difference in the risk of adverse HCM-related disease events between patients with RV insertion point LGE and those without LGE (log-rank p=0.71)(Figure 3). With multivariable analysis, after adjusting for a number of relevant demographic and disease-related variables known to influence risk in HCM (ie., age, maximal LV wall thickness and LV ejection fraction), neither the presence nor extent of RV insertion LGE was an independent predictor for HCM adverse events (HR_{adj} 0.82, 95% CI 0.45-1.50; p = 0.53 and HR_{adj} 1.16/10% LGE, 95% CI 0.29-4.65; p = 0.83, respectively). There was also no difference in risk between those patients with LGE confined to either of the 2 RV insertion areas, compared to patients with LGE present at both insertion points (HR 0.98, 95% CI 0.32-3.01; p=0.98).

Histopathologic findings

LV myocardium at the intersection of the RV wall and ventricular septum showed similar morphology in HCM and in control hearts (Figure 4). These areas were characterized by a loss of compact myocardium and markedly expanded extracellular space occupied predominantly by numerous myocytes in patterns of disarray embedded within areas of interstitial fibrosis (Figure 4). Such anatomic features were not present in compact areas of the LV wall. Semi-quantitative estimates of the degree and amount of cellular disorganization in HCM exceeded that in controls for both the anterior (2.2 ± 0.7 vs.1.1 ± 0.3, p <0.001) and posterior (2.5 ± 0.6 vs. 1.6 ± 0.5, p <0.001) RV insertion areas. Also, amounts of interstitial fibrosis were significantly greater in HCM hearts than controls for: anterior (1.5

± 6 vs. 0.5 ± 0.5; p <0.001) and inferior (1.7 ± 0.6 vs. 1.0 ± 0.6; p <0.001) RV insertion areas (Table 2).

A relatively small area of replacement fibrosis was evident in one HCM heart (in the inferior RV insertion area). Adipose tissue deposits were evident within the expanded extracellular space in both HCM (11/20) and control hearts (17/20) associated with the course of the septal perforator artery branch (Table 2; Figure 4). Abnormal intramural coronary arteries (with thickened media and narrowed lumens), characteristic of HCM (14,21,22), were absent from these areas. In 8 HCM hearts (and in 2 controls) bridging of the left anterior descending coronary artery was present.

DISCUSSION

Contrast-enhanced CMR studies in HCM patients have reported areas of LGE to be common, with extensive distribution associated with increased risk of sudden death and end-stage systolic dysfunction (1-5,7,12,23-26). However, a focal pattern of LGE in the regions of LV where the RV wall attaches to the ventricular septum anteriorly and inferiorly has been of interest to the practicing imaging community since the first study identifying LGE in HCM myocardium (12). It was initially presumed that LGE was always equivalent to replacement fibrosis, irrespective of its location. Indeed, in Choudhury et. al 100% of asymptomatic and mildly symptomatic patients (12), had LGE accumulation at the interface of RV and LV walls, which was regarded as focal scarring. Therefore, at this time, we believe it is appropriate to assess our large multicenter database of HCM patients studied with contrast-enhanced CMR for the purpose of defining the prevalence and the clinical

profile of patients with LGE specifically confined to the RV insertion areas to clarify the significance of this specific imaging marker.

Our data demonstrate that LGE, when confined to the RV insertion areas is relatively common in HCM, present in 10% of patients. However, even after adjustment for relevant disease variables, neither the presence nor extent of LGE in this region of LV proved to be a reliable predictor of adverse HCM-related events (including sudden death). Furthermore, we found no difference with respect to clinical outcome in those patients with LGE confined to either anterior, inferior or both RV insertion areas. However, we would like to underscore that this LGE pattern cannot be a source of reassurance regarding prognosis (1), without examining other clinical characteristics.

These observations also underscore a novel principle of contrast-enhanced CMR imaging in HCM, in which this specific isolated LGE pattern cannot itself serve as the basis for judging prognosis. Indeed, there is little reason to suspect that such particularly small areas of LGE (on average only 3% of LV mass) could contribute to or promote HCM-related heart failure or serve as the nidus for important ventricular tachyarrhythmias give the frequency of focal areas of LGE in the overall HCM population (2-7,16). For these reasons, it would not appear obligatory to quantify the amount of LGE when it is confined to the RV insertion point areas, for the purpose of risk stratification and decision-making.

Morphologic inspection of the RV attachment areas in an independent group of HCM and control hearts obtained at autopsy demonstrated that this anatomic region is primarily comprised of expanded extracellular space containing interstitial fibrosis (and adipose tissue) embedded with disorderly arranged myocytes, but virtually devoid of confluent scar formation representing a repair process following myocyte death. These observations are

consistent with those of Kuribayashi and Roberts (27) who demonstrated that the junctional area of ventricular septum and RV wall in HCM was morphologically similar to the hearts described here, as well as explanted hearts from patients with primary pulmonary hypertension (28).

Consequently, our clinical and morphologic observations support the principle that LGE in the RV insertion areas is the consequence of gadolinium distributed in a greatly expanded extracellular space virtually devoid of scar. Prominent in these areas is disorganized myocyte architecture created by the anatomic confluence of RV and LV walls, associated with and embedded in interstitial fibrosis (10,27,29,30,31) as well as adipocytes. Abnormal intramural small vessels, presumed to be part of the pathophysiologic pathway involving small vessel ischemia leading to cell death and replacement fibrosis, were notably absent in these areas. Probably for these reasons, LGE confined to the RV insertion areas do not convey the same clinical implications as does extensive LGE present in other areas of LV myocardium, which are thought to be largely due to replacement fibrosis (32-37), i.e. not associated with increased risk for potentially lethal ventricular tachyarrhythmias or heart failure progression.

In conclusion, the present data demonstrate that although LGE isolated to the areas of RV insertion to septum is a relatively common and highly visible pattern of contrast-enhanced CMR imaging in HCM, it nevertheless is not associated with increased risk for adverse disease-related events (including SD), and is not itself a marker for prognostic decision-making. This principle of CMR-imaging in HCM is likely related to our morphologic observation that LGE confined to the area of RV attachment onto the ventricular septum does not constitute a potentially arrhythmogenic substrate with

replacement scarring, but rather gadolinium pooling in an expanded extracellular space characterized by disorganized myocyte architecture.

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LEGENDS

Figure 1. LV short-axis contrast-enhanced CMR images in 4 HCM patients with LGE confined to the insertion area of right ventricle (RV) to ventricular septum (VS). **A.** Asymptomatic 30-year-old man with LGE in both anterior (thin arrows) and inferior (thick arrows) insertion areas; **B.** 63-year-old asymptomatic man (pathogenic mutation MYBPC3 Arg 943 Ter) and LGE in the anterior insertion area (arrow). **C.** 42-year old asymptomatic man with LGE in the inferior attachment area (arrow); **D.** Mildly symptomatic 31-year old man with LV outflow tract gradient of 100mmHg, septal thickness of 31mm, and focal areas of LGE in both the anterior (thin arrows) and inferior (thick arrows) attachment areas. LV = left ventricle.

Figure 2. Transverse cross-section of HCM heart illustrating areas from which tissue blocks were taken, at the junction of RV wall with anterior (#1) or inferior septum (#2).

Figure 3. Kaplan-Meier event free survival curves comparing 134 HCM patients with LGE confined to the RV insertion areas compared with 745 HCM patients without LGE from HCM-CMR registry (1).

Figure 4. Histopathology in the area of anatomic confluence of right ventricular (RV) wall and ventricular septum (VS). From a 28-year-old man with HCM who died suddenly (heart weight, 455 grams). **A.** Low power (original magnification x20) photomicrograph showing expanded extracellular space with interstitial fibrosis (blue stain); **B.** Higher power view

(original magnification x40) of the same anatomic area shown in **A.** shows interstitial fibrosis, disorganized myocytes, and a large deposit of adipose tissue, common in these junctional areas; **C.** High power (original magnification x100) photomicrograph of the area shown within the box in panel **B**. demonstrating a pattern of fibrosis interwoven with disorganized myocytes.

Table 1. Demographic and Clinical Characteristics of HCM Patients with CMR

Variable	RV Insertion Area LGE	Without LGE	P-Value
Number of patients	134	745	
Age, years	47±14	47±18	0.67
Male	88 (66%)	468(63%)	0.50
Body surface area, g/m^2	2.0 ± 0.2	1.9±0.3	0.07
NYHA class			0.67
I	78 (58%)	438(59%)	
II	39 (29%)	204(27%)	
III/IV	17 (13%)	103(14%)	
Atrial fibrillation	23 (17%)	72 (10%)	0.02
Basal LVOT gradient ≥ 30 mmHg	37 (28%)	182 (26%)	0.66
No. risk factors	0.6 ± 0.7	0.34±0.54	<0.0001
No conventional risk factors	63 (47%)	488 (69%)	
Nonsustained VT (ambulatory Holter)	29 (22%)	60 (9%)	
Unexplained syncope	16 (12%)	61 (9%)	
Family history of HCM-SD	30 (22%)	114 (16%)	
LV thickness ≥ 30 mm	10 (7%)	8 (1%)	
ICD implantation	24 (18%)	88 (12%)	0.09
Ejection fraction	66 ± 8	69±8%	<0.001
LV wall thickness, mm	22 ± 5	18.1±4.0	<0.001
LV mass, g	163 ± 60	147±61	0.006
LV mass index, g/m^2	82 ± 28	76±28	0.02
LVED dimension, mm	53 ± 7	54±7	0.24
LGE, g	5.7 ± 4.6	N/A	NA
% LV with LGE	3.7 ± 2.9	N/A	NA
Location of LGE		N/A	NA
RV at anterior septum only	50 (37%)		
RV at posterior septum only	36 (27%)		
RV at anterior and posterior insertion	48 (36%)		
Major clinical events in follow-up			
HCM-related SD	1 (0.8%)	6 (0.9%)	NS
Aborted cardiac arrest	2 (1.5%)	2 (0.3%)	
ICD discharge (VT/VF)	1 (0.8%)	3 (0.4%)	
Heart failure death	1 (0.8%)	0 (0%)	
Heart transplant	0	2 (0.3%)	
Progression to NYHA III/IV	8 (6%)	59 (8%)	

Abbreviations:
g = grams; HCM = hypertrophic cardiomyopathy; ICD= internal cardioverter defibrillator; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricle; LVED = left ventricle end-diastolic; LVOT = left ventricular outflow tract; N/A = not applicable; NS=not significant; NYHA = New York Heart Association; RV = right ventricle; SD = sudden death; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2. Morphologic Findings at Attachment of Right Ventricular Wall to Ventricular Septum

Variable	HCM	Controls	P value
No. hearts	20	20	
Age (years)	26±10	30±9	0.22
Male gender	16 (80%)	12 (60%)	0.21
Heart weight (grams)	481 ± 189	356 ± 80	0.14
Max.LV thickness(mm)	19.6 ± 5.09	11.9 ± 1.2	<0.001
Anterior septum			
Interstitial fibrosis*	1.5 ± 6	0.5 ± 0.5	<0.001
Myocyte disarray*	2.2 ± 7	1.1 ± 0.3	<0.001
Fat deposits	10 (50%)	9 (45%)	0.77
Confluent scar	0	0	----
Posterior septum			
Interstitial fibrosis*	1.7 ± 0.6	1.0 ± 0.6	0.003
Myocyte disarray*	2.5 ± 0.6	1.6 ± 0.5	<0.001
Fat deposits	4 (20%)	16 (80%)	<0.001
Confluent scar	1 (5%)	0	0.03
LAD myocardial bridge	8 (40%)	2 (10%)	0.033

Abbreviations:
LAD = left anterior descending coronary artery; LV = left ventricular;
Max. = maximum

Symbols:
* Scoring: semi-quantitative estimate, based on 0-3+ scale

Figure 1

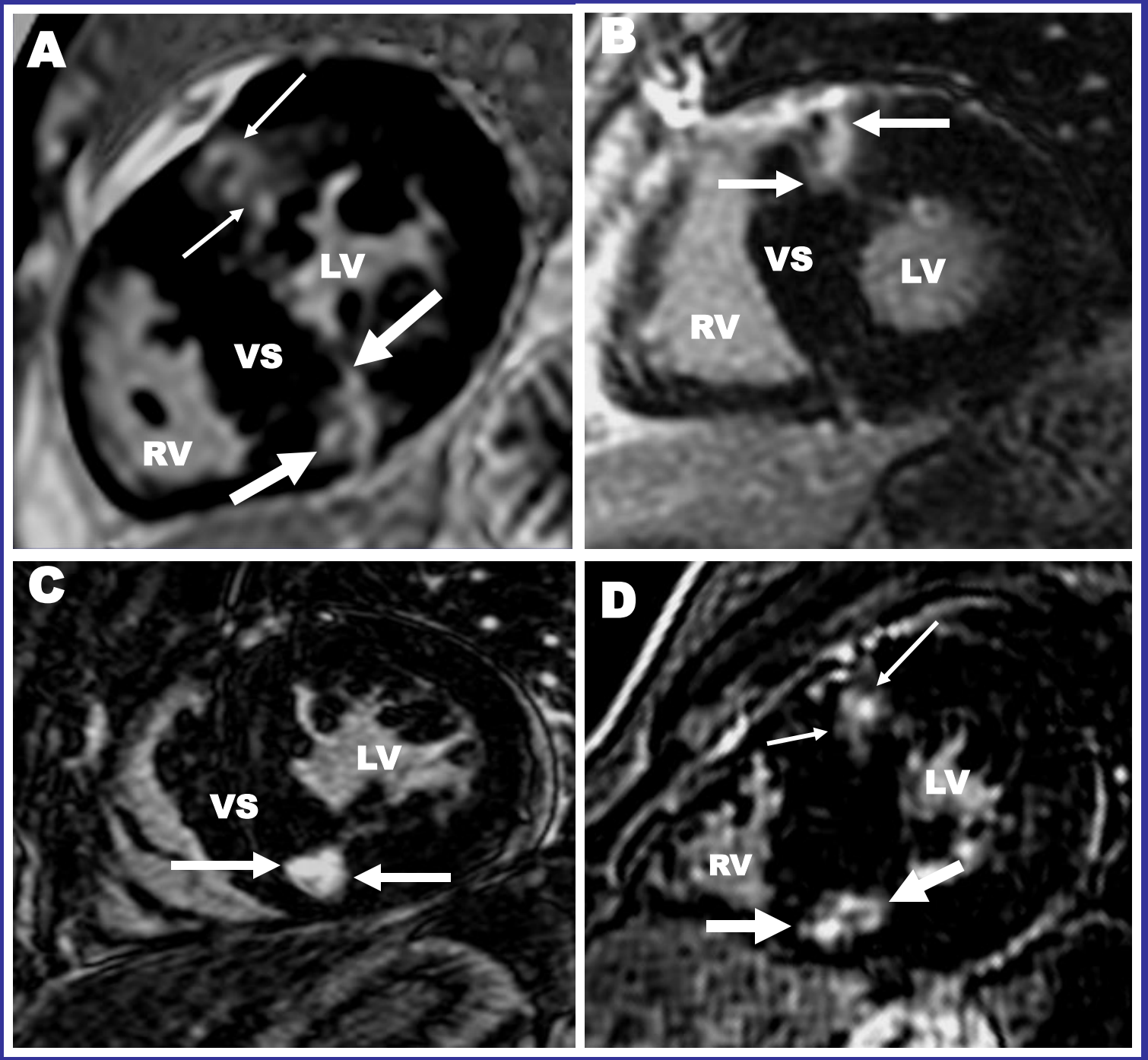

Figure 2

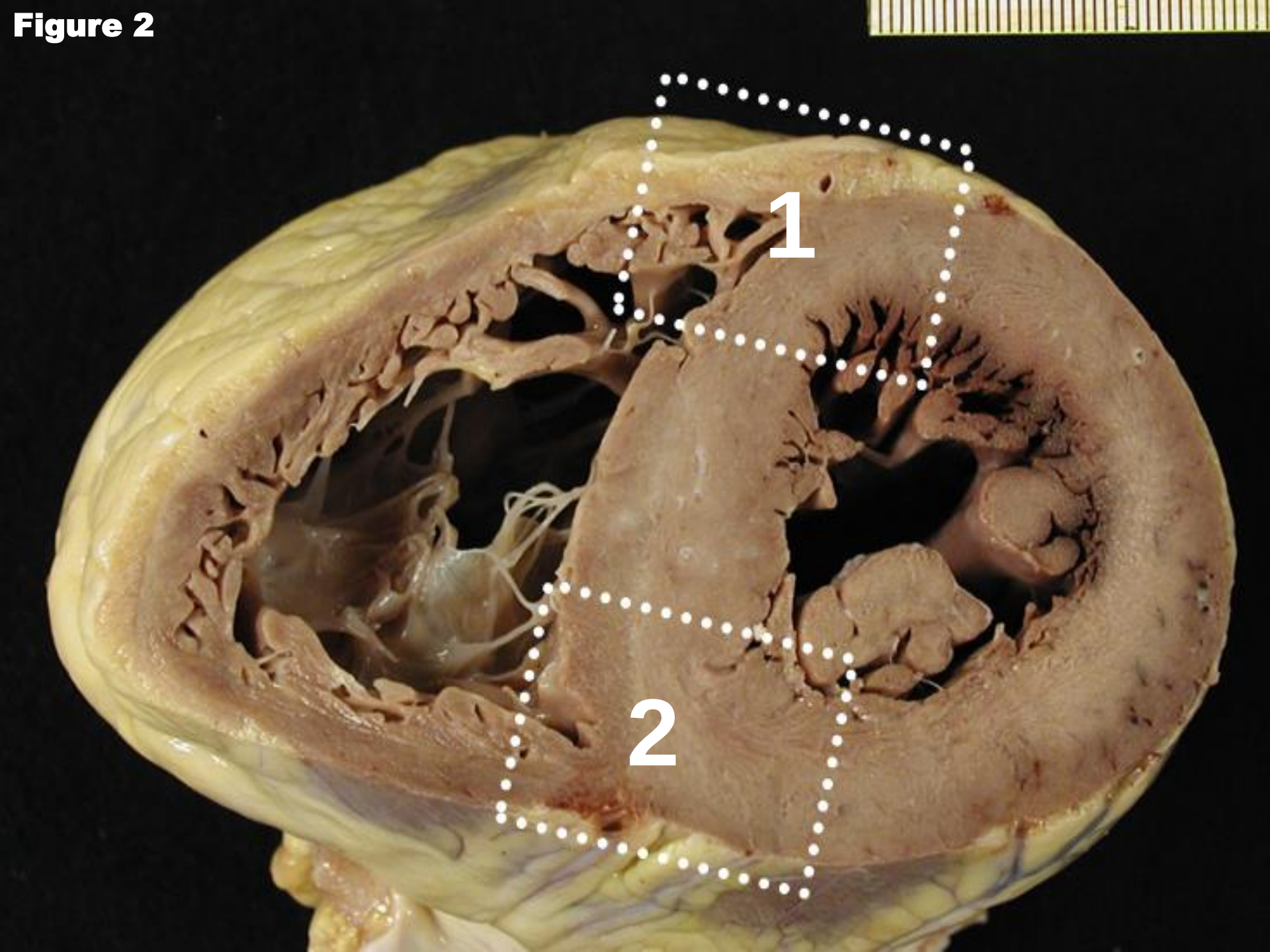

Figure 3

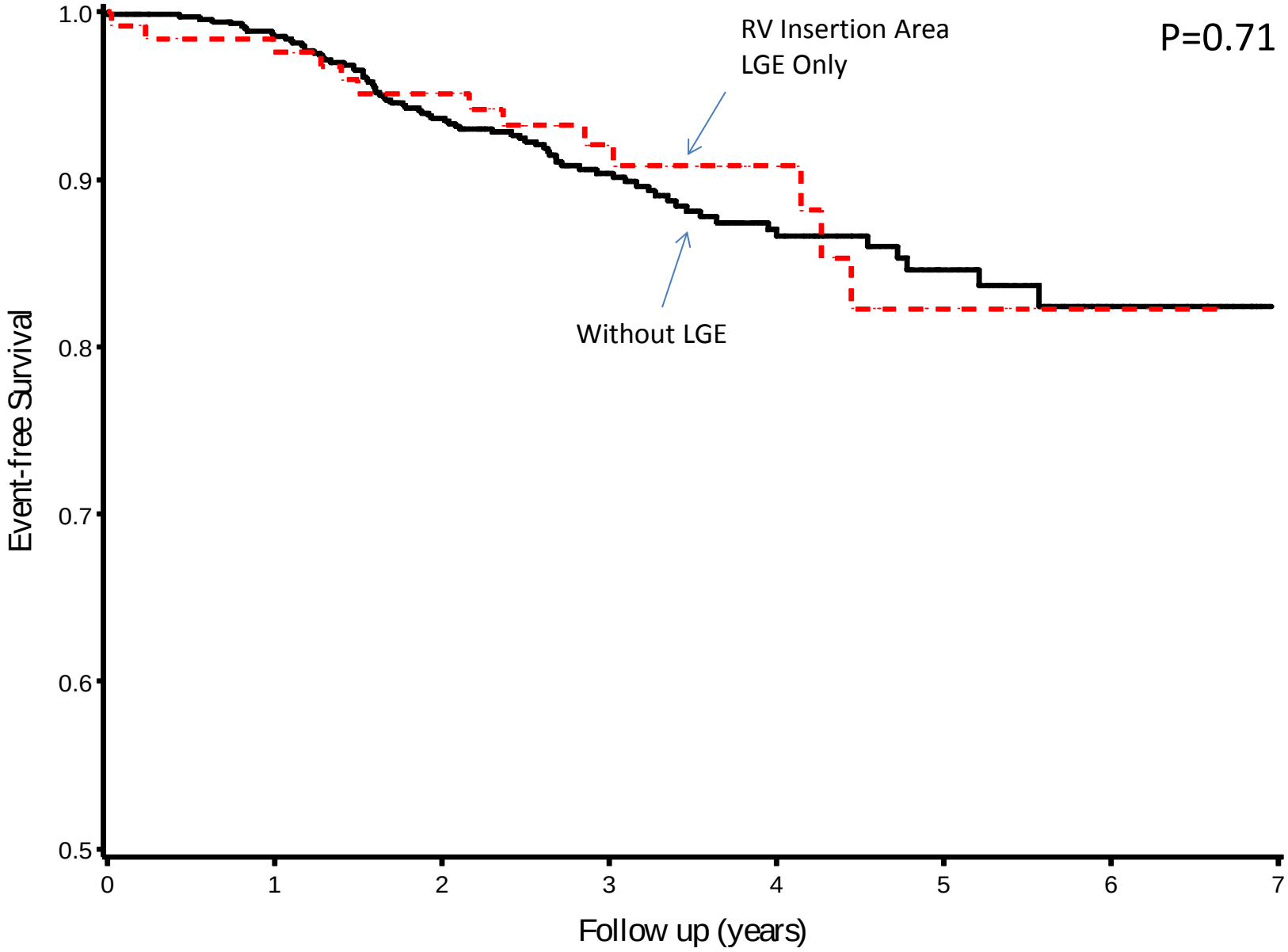
RV Insertion Area
LGE Only
P=0.71
Without LGE
Event-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0
1
2
3
4
5
6
7
Follow up (years)

Figure 4