CHAPTER 8

Left Atrial Emptying Fraction Predicts Ventricular Arrhythmias in Patients with Implantable Cardioverter-Defibrillators

SUBMITTED

Mischa T. Rijnierse

Mehran Kamali Sadeghian

Sophie Schuurmans Stekhoven

P. Stefan Biesbroek

Anne-Lotte C.J. van der Lingen

Peter M. van de Ven

Albert C. van Rossum

Robin Nijveldt

Cornelis P. Allaart

ABSTRACT

Aims: Impaired left atrial emptying fraction (LAEF) is an important predictor of mortality in heart failure patients. As it reflects underlying left ventricular (LV) dysfunction with increased wall stress, it might be a risk marker for ventricular arrhythmia (VA) specifically. This study was aimed to evaluate the predictive value of LAEF assessed with cardiac magnetic resonance imaging (CMR) with respect to appropriate device therapy (ADT) for VA and to compare its role with CMR assessed scar size and other risk factors.

Methods and results: 229 patients (68% male, 63±10 years, 61% ischemic cardiomyopathy) with LV ejection fraction ≤35% who underwent CMR and ICD implantation for primary prevention in 2005-2012 were included. CMR was used to quantify LV volumes and function. LV scar size was quantified when late gadolinium enhancement was available (n=166). Maximum and minimum left atrial volumes (LAVmax and LAVmin), and LAEF were calculated using the biplane area-length method. The occurrence of ADT and mortality was assessed during a median follow-up of 3.9 years. In total, 62 (27%) patients received ADT. Univariable Cox analysis showed that male gender, creatinine level, LAVmin, LAEF, and total scar size were significant predictors of ADT. In multivariable Cox analysis, LAEF (HR 0.75 per 10%, P<0.01), and scar size (HR 1.03 per g, P=0.03) remained the only independent predictors of ADT. Patients with both LAEF >median and scar size <median were at low risk (13.3% ADT and 22.8% ADT or mortality at 5 years), whereas those with LAEF <median and scar size >median experienced 40.1% ADT and 53.8% ADT or mortality at 5 years (both log-rank P=0.01).

Conclusions: LAEF independently predicts ADT in patients with primary prevention ICDs. Combined assessment of LAEF and scar size identifies a group with low risk of ADT. Therefore, LAEF assessment could assist in risk stratification for VA to select patients with the highest benefit from ICD implantation.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) implantation is a first choice therapy in patients with impaired left ventricular ejection fraction (LVEF) for primary prevention of sudden cardiac death (SCD). Large clinical trials demonstrating the favorable effects of ICD therapy have resulted in current guidelines which recommend ICD implantation in patients with heart failure and LVEF ≤35%.[1] There are, however, some concerns regarding optimal patient selection for primary prevention ICD therapy. Recent large follow-up studies report an ICD discharge rate of only 9-35% after 30-36 months among patients treated with ICDs for primary prevention.[2, 3] Enhanced risk prediction of ventricular arrhythmia (VA) beyond LVEF assessment, therefore, is needed. Previous studies have demonstrated that enlarged left atrial volumes (LAV) and impaired LA function predict the risk of heart failure progression and mortality.[4-7] Recently, decreased LA emptying fraction (LAEF) was found to predict mortality independent of other markers of cardiac dysfunction in patients with heart failure.[6] As the prognosis in heart failure patients is partially driven by SCD, markers of left atrial (LA) dysfunction may also relate to VA in particular. Impaired LA function might reflect increased LV filling pressure and wall stress might contribute to the occurrence of fatal arrhythmias due to modulation of action potential duration, calcium handling, and conduction.[8-11] Data on the value of markers for LA dysfunction in predicting VA, however, are lacking. Using cardiovascular magnetic resonance imaging (CMR), LA volumes and function can be accurately evaluated. In addition, LV scar tissue which is known to be associated with the occurrence of VA, can be quantified.[12-14] This study aimed to evaluate the predictive value of LA function with respect to appropriate device therapy (ADT) for VA and to compare its role with scar size and other risk factors.

METHODS

Study population

This study retrospectively evaluated consecutive patients with ischemic and dilated cardiomyopathy (ICMP and DCMP) and LVEF ≤35% who received an ICD for primary prevention of SCD according to the ACC/AHA/ESC 2006 guidelines from January 2005 to December 2012 in VU University Medical Center.[1] This patient population has been described in a previous study.[15] For the present study, patients were included when CMR was performed within six months prior to ICD implantation. CMR was typically performed for LVEF assessment to judge the eligibility for primary prevention ICD implantation. Consequently, CMR scans were performed in clinically stable patients on optimal medical therapy, >40 days after myocardial infarction, or >3 months after revascularization according to clinical guidelines. Other reasons for performing CMR were detection of LV thrombus, guiding of LV lead placement by scar assessment in resynchronization therapy, or as part of other study protocols. Exclusion criteria were chronic atrial fibril-

lation, atrial flutter, or when no follow-up data were available. Primary prevention was defined as no history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) (>48 hours after acute myocardial infarction).

Patient characteristics prior to device implantation were collected from medical records. The local Ethics Committee of the VU University Medical Center approved the data collection and management of this study.

CMR protocol and analysis

CMR studies were performed on a 1.5-Tesla whole body scanner (Magnetom Sonata/ Avanto, Siemens, Erlangen, Germany) using a dedicated phased-array body coil as described previously. Cine imaging was performed using a retrospectively ECG-gated, steady-state free precession sequence during breath holds in mild expiration. Typical imaging parameters: slice thickness of 5 mm, slice gap 5 mm, temporal resolution <50 ms, and a voxel size of 1.3*1.6 mm. Standard long-axis slices were acquired from the 4-, 3-, and 2-chamber views. Subsequently, consecutive short-axis slices were acquired, fully covering the LV. Late gadolinium enhanced (LGE) images were acquired approximately 10-15 minutes after the administration of 0.2 mmol·kg^{-1} gadolinium-DTPA in the similar orientations as used in the cine images, using a two-dimensional segmented inversion–recovery gradient echo sequence.

Images were analysed using the dedicated software package MASS (Mass v.5.1 2010-EXP beta, Medis, Leiden, the Netherlands). Endocardial LA contours and length were drawn manually in both the apical two- and four chamber views in the frames just before mitral valve opening to obtain maximum LA volume (LAVmax) and immediately after mitral valve closure for minimum LA volume (LAVmin) (figure 1). LA length (L) was defined as the distance from the center of the mitral annulus to the posterior border of the LA area, perpendicular to the mitral annular plane. The LA appendage and pulmonary veins were excluded from the LA measurements. LA volumes were calculated using the biplane area-length LA volumes were calculated using the biplane area-lenth formula: LAV = 8(A1)(A2)/3π(L), according to the guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging, where A1 and A2 represent the planimetered LA areas in the two- and four chamber views, while for L the shortest length of both views was used.[16] LAEF was calculated LAEF was calculated as (LAVmax-LAVmin)/LAVmax x 100%. LV end-systolic and end-diastolic volumes (LVEDV and LVESV) were measured using standard methodology, and LVEF was calculated. Finally, LGE short axis images were outlined manually at the endocardial and epicardial border when available. Myocardial scar size was quantified automatically using the full-width at half-maximum method which defines scar as signal intensity ≥50% of maximum signal intensity in the hyperenhanced area. Scar size was expressed as total grams and percentages of LV mass. All CMR images were analyzed by experienced observers who were blinded to clinical follow-up data.

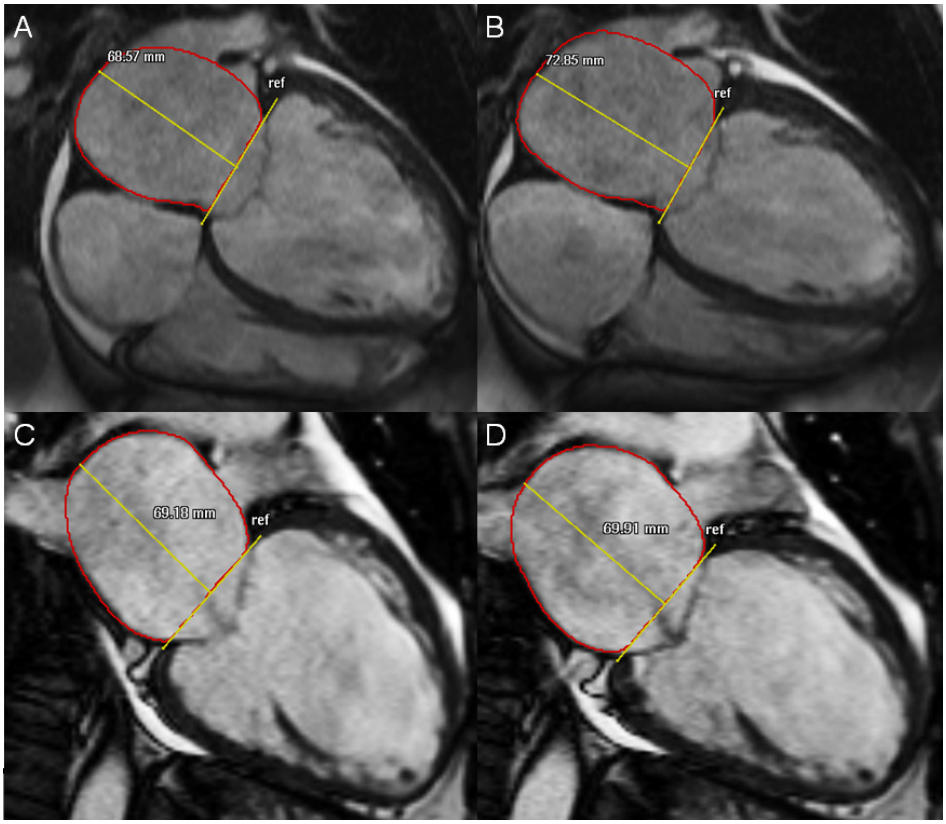


Figure 1. Example of CMR evaluation of the maximum and minimum left atrial volumes using the biplane area-length method in the apical four-chamber view (A, B) and two-chamber view (C, D). CMR, cardiovascular magnetic resonance imaging; LA, left atrium.

Follow-up

Clinical follow-up with device interrogation was routinely performed with regular intervals of six months. The ICDs were typically programmed with detection rates of > ~180 bpm (VT zone) and > ~250 bpm (VF zone), with extended detection intervals and appropriate utilization of antitachycardia pacing (ATP). Event transmissions of patients connected with home-monitoring were reviewed instantly when they occurred. All recorded events and appropriate device therapy (ADT) were reviewed by specialized cardiac technicians or by electrophysiologists. ADT was defined as an episode of ATP and/or defibrillation shock to terminate VT or VF. The primary endpoint was defined as the occurrence of first ADT. The secondary endpoint was defined as either the occurrence of ADT or all-cause mortality.

Statistical analysis

Continuous variables were expressed as mean ± standard deviations (SD). Histograms were used to determine if continuous data was normally distributed. Dichotomous and categorical data were compared using the chi-square test or, when appropriate, the Fisher's exact test. Continuous unpaired data were compared using the Student's t test or Mann-Whitney U test when appropriate. Univariable and multivariable Cox proportional hazard regression analyses were performed. Multivariable Cox proportional hazards models were performed using backward elimination with inclusion of variables with a P-value below 0.10 in univariable Cox analysis. Scar size was evaluated in a separate multivariable model (model 2) for the subgroup with LGE available (n=166). Both LAVmax index and LVESV index were not entered in multivariable analyses due to significant collinearity with LAVmin index and LVEDV index, respectively (correlation coefficients >0.90). Patients were categorized into low- and high-risk groups according to the median of LAEF (38.7%). In addition, patients with ICMP were categorized into low- and high-risk groups using the median of scar size (15.5 g), whereas DCMP patients were separately divided according to the presence or absence of scar size as the median was 0 g in this CMP group. This cutoff value was chosen as previous studies have demonstrated that among DCMP patients the presence of scar, rather than the amount of scar tissue is a significant predictor of VA.[12] Finally, patients were divided into three groups according to a combined risk factor score consisting of LAEF and scar size: 0 risk factors (both LAEF > median and scar size < median), 1 risk factor (LAEF < median or scar size > median), and 2 risk factors (both LAEF < median and scar size > median). Time to the primary and secondary endpoints were compared between risk groups using Kaplan-Meier curves and the log-rank test. A P-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS software package (version 20.0, IBM SPSS Statistics, Chicago, IL, USA).

RESULTS

Study population

In total, 240 patients were evaluated. 11 patients showed insufficient CMR image quality due to severe motion artefacts or irregularity in heart rhythm and were excluded from the analysis. Therefore, 229 patients were included in the current study. Clinical baseline characteristics are presented in table 1. Total median follow-up time was 3.9 years (IQR 2.5–5.7 years). The primary endpoint ADT was reached in 62 (27%). In 40 of 62 (65%) patients who experienced ADT, the ventricular arrhythmic event was terminated by ATP, whereas in the remaining 22 (35%) a shock was delivered. Patients who experienced ADT were more likely to be male (82% vs. 63%, P=0.005) and showed a trend towards a higher creatinine level (98 µmol/L, IQR 79-118 µmol/L vs. 88 µmol/L, IQR 73-107 µmol/L, P=0.06) when compared with patients without ADT.

Table 1. Baseline characteristics

Variable N(%), median (IQR), or mean ± SD	Study population (n=229)	Appropriate device therapy		P-value (ADT vs. no ADT)
		Yes (n=62)	No (n=167)	
Male gender	156 (68%)	51 (82%)	105 (63%)	0.005
Age (years)	63 ± 10	61 ± 10	64 ± 10	0.13
BMI (kg/m²)	26 ± 4	27 ± 4	26 ± 4	0.48
Ischemic cardiomyopathy	140 (61%)	41 (66%)	99 (59%)	0.35
PCI/CABG	112 (49%)	34 (55%)	78 (47%)	0.27
Resynchronization therapy	107 (47%)	29 (47%)	78 (47%)	0.99
NYHA class:†				0.79**
NYHA I	31 (17%)	12 (24%)	19 (15%)	
NYHA II	73 (41%)	12 (24%)	61 (47%)	
NYHA III	74 (42%)	25 (51%)	49 (38%)	
Medication:				
β Blockers	179 (78%)	46 (74%)	133 (80%)	0.38
ACE/ARB	197 (86%)	50 (81%)	147 (88%)	0.15
Diuretics	160 (70%)	42 (68%)	118 (71%)	0.67
Digoxin	6 (3%)	2 (3%)	4(2%)	0.66
Amiodarone	10 (4%)	3 (5%)	7 (4%)	1.00
Sotalol	4 (2%)	1 (2%)	3 (2%)	1.00
Statins	148 (65%)	42 (68%)	106 (64%)	0.55
Creatinine (µmol/L)	89 (75-111)	98 (79-118)	88 (73-107)	0.06*
QRS duration (ms) ǂ	128 ± 32	124 ± 29	130 ± 33	0.24

ACE, angiotensin-converting-enzyme inhibitors; ADT, appropriate device therapy; ARB, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; Diuretics include mineralocorticoid receptor antagonists; NYHA class, New York Heart Association class; PCI, percutaneous coronary intervention.
† Data available for n=178. ǂ Data available for n=218. * Compared using the Mann-Whitney U test.
** Compared using the Chi-square test for trend.

CMR results

All CMR characteristics and a comparison between patients with ADT and without ADT are presented in table 2. Median time between CMR and ICD implantation was 56 days (IQR 7.5-92). No differences were observed in (indexed) LAVmin or LAVmax between both groups. However, patients who received ADT showed significant lower LAEF (32 ± 14% vs. 38 ± 14%, P=0.003). In addition, a trend was observed towards a larger LVEDV in patients who received ADT (P=0.06), although LVEF did not differ. LGE data was available in 166 patients. Main reasons for missing LGE data were impaired renal function, LGE assessment not requested, or LGE assessment performed during a previous CMR assessment > 6 months prior to ICD implantation. Scar size was significantly larger in patients who experienced ADT (n=41) when quantified in grams (14.2 g, IQR 3.5-20.8 g vs. 6.3 g, IQR 0-16.3 g, P=0.03), whereas when expressed in percentages of LV mass, a comparable but non-significant trend was observed (12.8%, IQR 2.7-19.6% vs. 5.7%, IQR 0-16%, P=0.051).

In addition, a comparison of CMR characteristics between patients with ICMP and DCMP is provided in supplemental table S1. Mean LAEF did not differ between both CMP groups (37 ± 14% vs. 34 ± 14%, P=0.11). Patients with DCMP showed significant larger (indexed) LV volumes and lower LVEF compared with ICMP patients (all P<0.001). LGE assessment was available in 104 of 140 (74%) patients with ICMP and 62 of 89 (70%) DCMP patients (P=0.45). LGE was more often observed (97% vs. 34%, P<0.001) and of greater extent (15.5 g, IQR 8.9-21.5 g vs. 0 g, IQR 0-2.9 g, P<0.001) in patients with ICMP.

Table 2. CMR characteristics according to ADT

Variable N(%), median (IQR), or mean ± SD	Study population (n=229)	Appropriate device therapy		P-value (ADT vs. no ADT)
		Yes (n=62)	No (n=167)	
LAVmax (mL)	104 (84-132)	105 (82-135)	103 (85-130)	0.91*
LAVmax index (mL/m²)	54 (45-66)	54 (42-66)	56 (46-66)	0.61*
LAVmin (mL)	63 (48-88)	66 (51-99)	62 (47-85)	0.19*
LAVmin index (mL/ m²)	33 (25-45)	34 (25-50)	32 (25-44)	0.38*
LAEF (%)	36 ± 14	32 ± 14	38 ± 14	0.003
LVEDV (mL)	304 (253-378)	331 (270-285)	298 (249-376)	0.06*
LVEDV index (mL/m²)	162 (137-195)	170 (139-199)	159 (135-191)	0.20*
LVESV (mL)	234 (180-308)	253 (195-315)	228 (177-306)	0.11*
LVESV index (mL/m²)	124 (97-155)	131 (101-155)	123 (94-152)	0.27*
LVEF (%)	24 ± 7	24 ± 6	23 ± 8	0.79
LV mass (g)	125 ± 38	128 ± 32	124 ± 40	0.51
LV mass index (g/m²)	65 ± 18	65 ± 16	65 ± 18	0.82
LGE present (n)ǂ	122 (74%)	33 (81%)	89 (71%)	0.24
Scar size (g)ǂ	8.5 (0-17.3)	14.2 (3.5-20.8)	6.3 (0-16.3)	0.03*
Scar size (%)ǂ	7.1 (0-16.1)	12.8 (2.7-19.6)	5.7 (0-16.0)	0.051*

ADT, appropriate device therapy, CMR, cardiovascular magnetic resonance; DCMP, dilated cardiomyopathy; ICMP, ischemic cardiomyopathy; LAEF, left atrial emptying fraction; LAVmax, maximum left atrial volume; LAVmin, minimum left atrial volume; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume. ǂ Data available for n=166. * Compared using the Mann-Whitney U test. ** Compared using the Chi-square test for trend.

Supplemental table S1. CMR characteristics according to cardiomyopathy etiology

Variable N(%), median (IQR), or mean ± SD	ICMP (n=140)	DCMP (n=89)	P-value (ICMP vs. DCMP)
LAVmax (mL)	104 (84-130)	103 (84-137)	0.62*
LAVmax index (mL/m²)	54 (44-66)	56 (46-69)	0.47*
LAVmin (mL)	62 (47-87)	66 (50-92)	0.23*
LAVmin index (mL/ m²)	32 (24-44)	34 (26-48)	0.19*
LAEF (%)	37 ± 14	34 ± 14	0.11
LVEDV (mL)	290 (249-352)	345 (267-430)	<0.001*
LVEDV index (mL/m²)	155 (132-175)	181 (150-214)	<0.001*
LVESV (mL)	213 (177-270)	275 (199-343)	<0.001*
LVESV index (mL/m²)	112 (91-138)	138 (114-174)	<0.001*
LVEF (%)	25 ± 7	21 ± 8	<0.001
LV mass (g)	122 ± 34	130 ± 43	0.20
LV mass index (g/m²)	64 ± 17	67 ± 19	0.20
LGE present (n)ǂ	101 (97%)	21 (34%)	<0.001
Scar size (g)ǂ	15.5 (8.9-21.5)	0 (0-2.9)	<0.001*
Scar size (%)ǂ	14.8 (7.4-19.6)	0 (0-2.1)	<0.001*

CMR, cardiovascular magnetic resonance; DCMP, dilated cardiomyopathy; ICMP, ischemic cardiomyopathy; LAEF, left atrial emptying fraction; LAV, left atrial volume; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume. ǂ Data available for n=166. * Compared using the Mann-Whitney U test.

Predictors of ADT

The cumulative 5-year incidence rate of ADT was 26.7% for the total study population and did not differ between patients with ICMP or DCMP (log-rank P=0.55, 5-year incidence of 26.6% vs. 27.0%, respectively). Parameters that were significantly associated with the occurrence of ADT in univariable Cox analyses included male gender, creatinine level, LAVmin index, LAEF, and scar size (table 3). The multivariable Cox model for the total study population (model 1, excluding scar size) revealed that male gender (HR 2.14, 95% CI 1.10-4.13, P=0.03) and LAEF (HR 0.77 per 10%, 95% CI 0.64-0.93, P=0.006) were the only independent significant predictors of ADT, whereas for creatinine level a trend was observed (P=0.052). When adding scar size to the multivariable Cox analysis (model 2), LAEF (HR 0.75 per 10%, 95% CI 0.60-0.93, P=0.008) and scar size (HR 1.03 per g, 95% CI 1.00-1.05, P=0.03) were the only independent predictors of ADT (table 3). As demonstrated in figure 2A, patients with LAEF <median were at significantly higher risk of experiencing ADT compared with patients having LAEF >median (log-rank P<0.01) with cumulative incidences at 5 years being 34.1% versus 19.6%, respectively. Furthermore, patients with scar size >median showed a higher incidence of ADT as compared with patients having scar size <median (log-rank P=0.03) with cumulative incidence rates at 5 years of 32.4% versus 18.8%, respectively (figure 2C). A combined risk score using LAEF and scar size identified a low-risk group (13.3% ADT at 5 years), an intermediate-risk group (24.2% ADT at 5 years), and a high-risk group (40.1% ADT at 5 years) (figure 3A). The corresponding HRs for ADT in the high- and intermediate-risk group were 3.89 (95% CI 1.51-9.97, P=0.005) and 2.18 (95% CI 0.87-5.46, P=0.10), respectively, when compared with the low-risk group.

Table 3. Univariable and multivariable Cox regression analysis for predicting ADT

	Univariable analysis		Multivariable model 1: Total study population		Multivariable model 2: Subgroup with LGE available	
Parameter	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Male gender	2.55 (1.33-4.90)	0.005	2.13 (1.10-4.13)	0.03	-	-
Age (per year)	0.99 (0.96-1.01)	0.36				
Ischemic cardiomyopathy	1.17 (0.69-1.99)	0.55				
Resynchronization therapy	1.01 (0.61-1.66)	0.98				
NYHA class†	0.97 (0.65-1.44)	0.88				
β Blockers	0.75 (0.43-1.33)	0.33				
ACE/ARB	0.65 (0.35-1.22)	0.18				
Creatinine (per 10 µmol/L)	1.07 (1.02-1.11)	0.002	1.04 (1.00-1.09)	0.052	-	-
QRS duration (per 10 ms)	0.96 (0.88-1.04)	0.27				
LAVmax index (per 10 mL/m²)	1.03 (0.90-1.19)	0.64				
LAVmin index (per 10 mL/m²)	1.15 (1.01-1.31)	0.03	-	-	-	-
LAEF (per 10%)	0.73 (0.61-0.87)	0.001	0.77 (0.64-0.93)	0.006	0.75 (0.60-0.93)	0.008
LVEDV index (per 10 mL/m²)	1.03 (0.97-1.08)	0.34				
LVESV index (per 10 mL/m²)	1.02 (0.97-1.08)	0.50				
LVEF (per %)	1.00 (0.96-1.03)	0.76				
LGE present‡	1.44 (0.66-3.12)	0.36				
Scar size (per g)‡	1.03 (1.01-1.06)	0.01			1.03 (1.00-1.05)	0.03
Scar size (per %)‡	1.02 (0.99-1.06)	0.16				

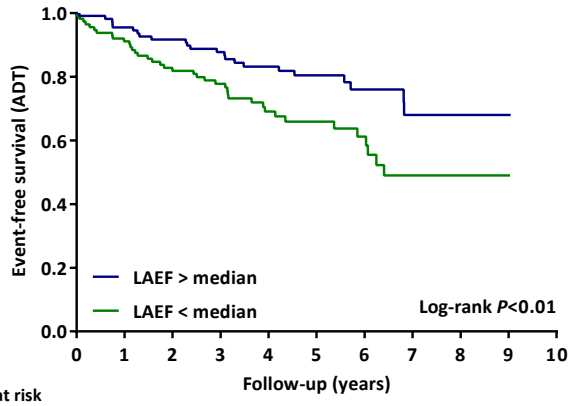
CI, confidence interval; HR, hazard ratio; other abbreviations are listed in tables 1 and 2. † Data available for n=178. ‡ Data available for n=166. Model 1: excluding scar size (total study population). Model 2: including scar size (subgroup with LGE available).

Supplemental table S2. Uni- and multivariable analyses for predicting ADT or mortality

	Univariable analysis		Multivariable model 1: Total study population		Multivariable model 2: Subgroup with LGE available	
Parameter	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Male gender	2.00 (1.23-3.25)	0.005	1.54 (0.94-2.54)	0.09	-	-
Age (per year)	1.01 (0.99-1.03)	0.34				
Ischemic cardiomyopathy	1.01 (0.67-1.53)	0.96				
Resynchronization therapy	1.34 (0.90-2.00)	0.15				
NYHA class†	1.05 (0.75-1.46)	0.78				
β Blockers	0.90 (0.56-1.44)	0.65				
ACE/ARB	0.68 (0.41-1.13)	0.14				
Creatinine (per 10 µmol/L)	1.08 (1.04-1.11)	<0.001	1.07 (1.04-1.11)	<0.001	-	-
QRS duration (per 10 ms)	0.99 (0.93-1.06)	0.84				
LAVmax index (per 10 mL/m²)	1.11 (1.00-1.23)	0.06				
LAVmin index (per 10 mL/m²)	1.20 (1.09-1.32)	<0.001	-	-	-	-
LAEF (per 10%)	0.74 (0.64-0.85)	<0.001	0.82 (0.71-0.96)	0.01	0.79 (0.65-0.95)	0.01
LVEDV index (per 10 mL/m²)	1.07 (1.03-1.11)	0.001	1.06 (1.02-1.11)	0.004	1.07 (1.01-1.13)	0.02
LVESV index (per 10 mL/m²)	1.07 (1.03-1.11)	0.001				
LVEF (per %)	0.70 (0.54-0.91)	0.009	-	-	-	-
LGE present ǂ	0.99 (0.56-1.75)	0.97				
Scar size (per g)ǂ	1.02 (0.99-1.04)	0.16			1.02 (1.00-1.04)	0.07
Scar size (per %)ǂ	1.00 (0.98-1.03)	0.89				

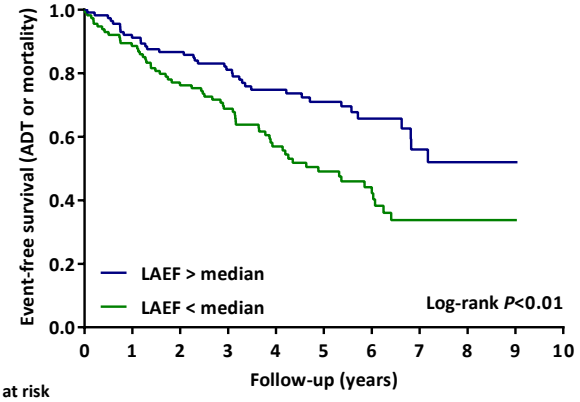
Abbreviations are listed in tables 1 and 2. † Data available for n=178. ǂ Data available for n=166. Model 1: excluding scar size (total study population). Model 2: including scar size (subgroup with LGE available).

A



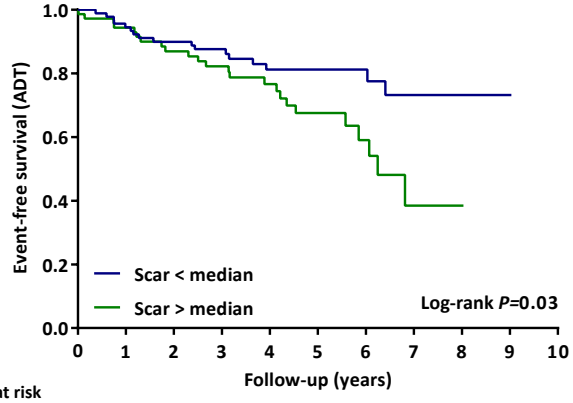
Patients at risk										
LAEF > median	114	102	96	81	64	52	27	16	6	1
LAEF < median	115	101	85	68	47	35	22	18	6	0

B



Patients at risk										
LAEF > median	114	102	96	81	64	52	27	16	6	1
LAEF < median	115	101	85	68	47	35	22	18	6	0

C



Patients at risk										
Scar < median	93	84	77	59	45	33	22	11	4	1
Scar > median	73	65	56	49	36	25	12	5	1	

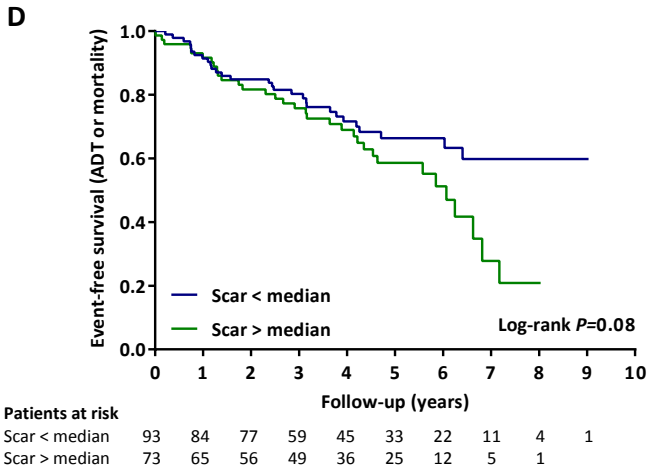


Figure 2. Kaplan-Meier curve analyses of the event free survival of ADT (A and C) and ADT or mortality (B and D), compared between patients with LAEF <median and LAEF >median (A and B) and between scar <median and scar >median (C and D). ADT, appropriate device therapy; LAEF, left atrial emptying fraction.

Predictors of ADT or mortality

The secondary endpoint of ADT or mortality occurred in 97 of 229 (42%) patients, with a cumulative incidence of 39.9% at 5 years. Univariable Cox regression analyses revealed that male gender, creatinine level, LAVmin index, LAEF, LVEDV index, LVESV index, and LVEF were significantly related to the occurrence of ADT or mortality (supplemental table S2). In multivariable analysis (model 1), LAEF (HR 0.82 per 10%, 95% CI 0.71-0.96, P=0.01), creatinine level (HR 1.07 per 10 µmol/L, 95% CI 1.04-1.11, P<0.001), and LVEDV index (HR 1.06 per 10 mL/m^2, 95% CI 1.02-1.11, P=0.004) were independently significant for predicting ADT or mortality. When adding scar size to the multivariable model (model 2), LAEF and LVEDV index remained the only independent predictors of ADT or mortality (HR 0.79 per 10%, 95% CI 0.65-0.95, P=0.01 and HR 1.07 per 10 mL/m^2, 95% CI 1.01-1.13, P=0.02, respectively), whereas for scar size only a trend was observed (HR 1.02 per g, 95% CI 1.00-1.04, P=0.07). Kaplan-Meier curve analysis for LAEF showed similar results for the secondary endpoint when stratified according to the median of LAEF (figure 2B). Patients with scar size >median, however, only showed a trend towards a higher incidence of ADT or mortality as compared with patients having scar size <median (log-rank P=0.08, figure 2D). Nonetheless, the combined risk score of LAEF and scar size could identify comparable low risk, intermediate risk, and high risk groups with a significant different time to ADT or mortality (log-rank P<0.01) with cumulative incidences at 5 years of 22.8%, 37.0%, and 53.8%, respectively (figure 3B).

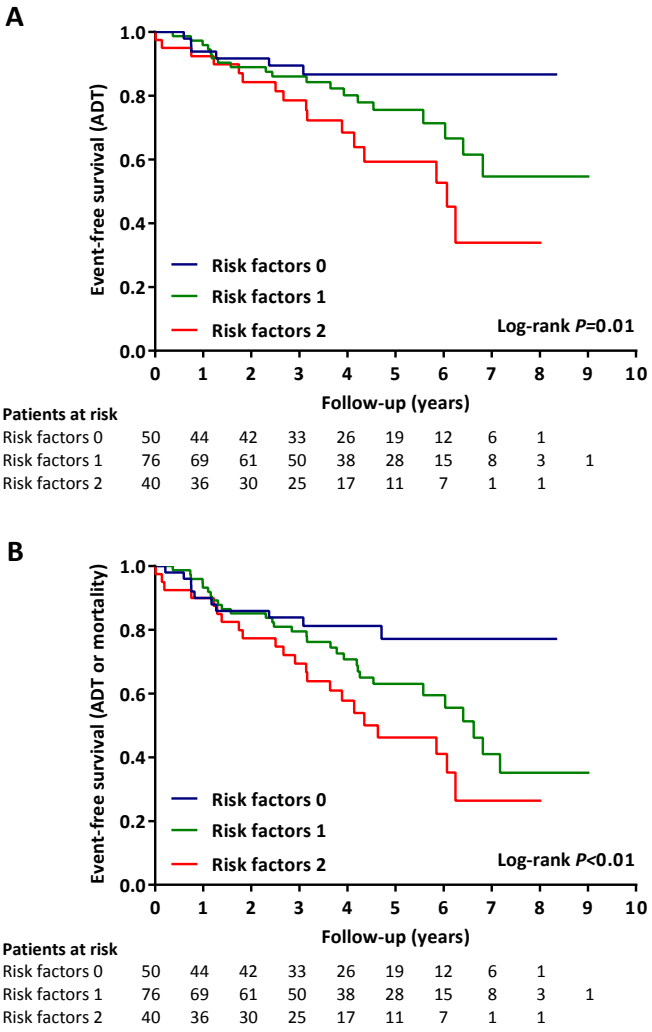


Figure 3. Kaplan-Meier curve analyses of the time to ADT (A) and ADT or mortality (B), compared between patients at low risk (0 risk factors), intermediate risk (1 risk factor), and high risk (2 risk factors) according to combined LAEF and scar size assessment. ADT, appropriate device therapy; LAEF, left atrial emptying fraction.

DISCUSSION

The current study demonstrated that both impaired LAEF and scar size were independent predictors of appropriate ICD therapy for VA. Furthermore, combined assessment of LAEF and scar size further stratified the patient cohort into high-, intermediate-, and low-risk groups for receiving ADT. Comparable results were obtained for predicting ADT or mortality.

LA function

The hemodynamics of the LV and LA are continuously intertwined and LA function is related to LV volumes, filling pressure, and wall stress.[10] For this reason, a renewed interest has emerged in the assessment of LA size and function for risk stratification in patients with various degrees of LV dysfunction and heart failure. While the LAVmax mainly reflects increased atrial pressure and volume, the LAVmin is more closely related to the diastolic LV filling pressure (atrial afterload).[17] Furthermore, total LAEF can be divided in active LAEF and passive LAEF. In a study by Posina et al. total LAEF was found to be the strongest predictor of increased LV end-diastolic pressure, whereas active LAEF and passive LAEF were of less significance.[18] The present study therefore evaluated total LAEF. Median LA volumes and LAEF as observed in the current study were comparable with the study by Pellicori et al.[6] who found a CMR assessed median LAEF of 42% in patients with heart failure. In the general population, Gupta et al.[5] found a median indexed LAVmax of 37 and 36 mL/m^2 for men and women, respectively, with corresponding LAEFs of 52 and 55% as assessed with a similar CMR evaluation.

LA and outcome

The association of LA volumes or function and mortality or heart failure progression in ICMP and DCMP has been well established by multiple studies.[4, 6, 7] The current study is the first to show that impaired LAEF is an independent predictor of ADT for VA in patients with implanted ICDs for primary prevention of SCD. In a small retrospective study by Kaplan et al.[19], LAVmax assessed by 2D-echocardiography was related to the occurrence of VA within the preceding year in 32 patients with ICDs implanted. In addition, Koilpillai et al.[20] found a correlation between LA width and non-sustained VA frequency on holter monitoring. Conversely, the current study found that LAEF and, to a lesser extent, LAVmin were related to VA, whereas LAVmax was not. The superior value of LAEF over LAVmax in predicting mortality was also demonstrated in more recent studies using CMR.[5, 6] Pellicori et al.[6] showed that although both LA volumes and LAEF were associated with heart failure hospitalization and mortality among 664 patients with heart failure, only LAEF remained predictive in multivariable analyses. Impaired LAEF was also found to be an independent predictor of mortality in the general population in a large study performed by Gupta et al.[5] The current study confirms that impaired LAEF is an

important marker of poor prognosis and suggests that this might be partly explained by the occurrence of life-threatening arrhythmias.

The exact pathophysiological link between impaired LAEF and VA remains uncertain. Impaired LAEF may reflect high diastolic LV filling pressure and increased wall stress. Previous studies have shown that increased LV filling pressure and wall stress have pro-arrhythmogenic effects on a cellular level including modulation of refractoriness, calcium handling, and conduction resulting in increased susceptibility of VA.[8, 9, 11] This hypothesis is underlined by studies that have evaluated the relation of VA and the level of B-type natriuretic peptide (BNP), which is released in response to increased LV wall stress and pressure overload. They consistently demonstrate that increased BNP is an independent predictor of ventricular arrhythmia or SCD in patients with impaired LVEF.[21, 22] Although BNP level and LAEF are intertwined and may reflect comparable pathophysiological substrates, Pellicori et al.[6] showed that LAEF was a more powerful predictor of mortality in patients with heart failure as compared with the level of BNP.

Combined LGE and LAEF

In addition to LAEF, this study identified total scar burden as an independent predictor of ADT for VA. These results are consistent with previous studies that also demonstrated the relation of scar size and VA in patients with ICMP and DCMP.[12-14] Combined assessment of LAEF and scar size using CMR resulted in an improved stratification of receiving ADT, suggesting that the combination of a large anatomical substrate with increased wall stress may in particular increase vulnerability to VA. This notion is supported by an experimental study performed in chronically infarcted canine hearts by Calkins et al.[11] which revealed that increased ventricular loading, in particular at sites of extensive fibrosis, resulted in exaggerated shortening of refractoriness and increased inducibility of VA. More recently, the value of LGE assessed scar size combined with a different marker of increased LV wall stress, NT-proBNP, in risk stratification for VA has been evaluated by Mordi and colleagues.[21] They found that patients in the lowest risk group showed 3% per year appropriate ICD therapy or mortality during follow-up, whereas the incidence in high-risk patients was 10% per year.

Limitations

Several limitations of the present study should be acknowledged. First, this study should be regarded as hypothesis-generating due to its retrospective character. Consequently, the acquired CMR images in the current study were not intended for LA evaluation specifically and 3-dimensional LA volume assessment was not possible. However, the biplane area-length method is an accurate and reproducible method which is easily and rapidly obtained from the standard long-axis views. It has been utilized in the majority of large studies that used CMR evaluation of the LA for risk stratification, which allowed comparisons with the results of the current study.[4-6z] Second, the occurrence of ADT for VA is a

surrogate endpoint and does not equal the incidence of SCD. Finally, the included patient population with both LGE and LAEF assessment available was relatively small, therefore adequate subgroup analyses could not be performed. Further prospective studies are needed to confirm the results of this study and define optimal cut-off values of LAEF and scar size in different cardiomyopathy etiologies for predicting ventricular arrhythmia.

Conclusion

Impaired LAEF independently predicts appropriate ICD therapy for ventricular arrhythmia in patients with primary prevention ICDs. Combined assessment of LAEF and scar size identifies a group with low risk of ADT and ADT or mortality. Therefore, LAEF assessment might assist in risk stratification for ventricular arrhythmia to select patients with the highest benefit from ICD implantation.

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