Right Ventricular Ejection Fraction Is Incremental to Left Ventricular Ejection Fraction for the Prediction of Future Arrhythmic Events in Patients With Systolic Dysfunction

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Background—Left ventricular ejection fraction remains the primary risk stratification tool used in the selection of patients for implantable cardioverter defibrillator therapy. However, this solitary marker fails to identify a substantial portion of patients experiencing sudden cardiac arrest. In this study, we examined the incremental value of considering right ventricular ejection fraction for the prediction of future arrhythmic events in patients with systolic dysfunction using the gold standard of cardiovascular magnetic resonance.

Methods and Results—Three hundred fourteen consecutive patients with ischemic cardiomyopathy or nonischemic dilated cardiomyopathy undergoing cardiovascular magnetic resonance were followed for the primary outcome of sudden cardiac arrest or appropriate implantable cardioverter defibrillator therapy. Blinded quantification of left ventricular and right ventricular (RV) volumes was performed from standard cine imaging. Quantification of fibrosis from late gadolinium enhancement imaging was incrementally performed. RV dysfunction was defined as right ventricular ejection fraction ≤45%. Among all patients (164 ischemic cardiomyopathy, 150 nonischemic dilated cardiomyopathy), the mean left ventricular ejection fraction was 32±12% (range, 6–54%) with mean right ventricular ejection fraction of 48±15% (range, 7–78%). At a median of 773 days, 49 patients (15.6%) experienced the primary outcome (9 sudden cardiac arrest, 40 appropriate implantable cardioverter defibrillator therapies). RV dysfunction was independently predictive of the primary outcome (hazard ratio=2.98; *P*=0.002). Among those with a left ventricular ejection fraction >35% (N=121; mean left ventricular ejection fraction, 45±6%), RV dysfunction provided an adjusted hazard ratio of 4.2 (*P*=0.02).

Conclusions—RV dysfunction is a strong, independent predictor of arrhythmic events. Among patients with mild to moderate LV dysfunction, a cohort greatly contributing to global sudden cardiac arrest burden, this marker provides robust discrimination of high- versus low-risk subjects. **(*Circ Arrhythm Electrophysiol*. 2017;10:e004067. DOI: 10.1161/CIRCEP.116.004067.)**

Key Words: arrhythmias, cardiac ■ death, sudden, cardiac ■ magnetic resonance imaging ■ prognosis ■ ventricular dysfunction, right

Current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend the use of left ventricular ejection fraction (LVEF) to inform therapeutic decision making about implantable cardioverter defibrillator (ICD) therapy.[1] However, of patients receiving devices in accordance with published LVEF-based thresholds, only a minority (21–35%) receive appropriate therapy over a 3- to 4-year period of clinical follow-up[2,3] and 18% will experience inappropriate shocks associated with mortality risk.[4] More importantly, the majority of patients experiencing sudden cardiac arrest (SCA) have been shown to have an LVEF that exceeds current guideline-based thresholds for prophylactic ICD implantation.[5] Accordingly, the contemporary use of LVEF as a solitary risk prediction tool is suboptimal and highlights an immediate need for incremental markers predictive of future arrhythmic events.

In response to clinical need, a host of noninvasive markers are currently being explored to improve the stratification of patients at risk of arrhythmic death.[6–9] However, the role of right ventricular (RV) ejection fraction (RVEF), a simple measure akin to LVEF, to provide incremental utility in this setting has not yet been explored. Although RVEF by cardiovascular magnetic resonance (CMR) imaging, the reference standard for its volumetric quantification, was recently shown to be

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WHAT IS KNOWN

- Left ventricular ejection fraction has been used as the primary risk stratification tool in the selection of patients for implantable cardioverter defibrillator therapy; however, this risk marker fails to identify substantial portion of patients experiencing sudden cardiac arrest.
- Cardiovascular magnetic resonance offers the capacity to quantify right ventricular (RV) function with high intra- and interobserver reproducibility. RV dysfunction quantified by cardiovascular magnetic resonance has been shown as a prognostic marker for heart failure–related outcomes in patients with nonischemic dilated cardiomyopathy.

WHAT THE STUDY ADDS

- In patients with ischemic cardiomyopathy and nonischemic dilated cardiomyopathy with a mean left ventricular ejection fraction of 32±12%, RV dysfunction defined as RV ejection fraction ≤45% was an independent predictor of the arrhythmic outcome of sudden cardiac arrest or appropriate implantable cardioverter defibrillator therapy with a hazard ratio of 2.98.
- Among those with left ventricular ejection fraction >35%, RV dysfunction provided an adjusted hazard ratio of 4.2.
- RV dysfunction, determined by cardiovascular magnetic resonance, is an independent predictor of sudden cardiac arrest or appropriate implantable cardioverter defibrillator discharge in patients with mild to moderate LV dysfunction.

independently associated with nonarrhythmic events among patients with nonischemic dilated cardiomyopathy (NIDCM),[10] no study has examined its capacity to predict arrhythmic events among patients with systolic dysfunction. Given expanding clinical use of CMR and ease of reporting the RVEF from routine images, demonstration of independent prognostic value of this marker could provide a significant impact on clinical practice. In this study, we examined the incremental value of RVEF beyond LVEF alone for the prediction of future SCA or appropriate ICD therapy in patients with systolic dysfunction.

Methods

Study Population

Consecutive patients referred for CMR imaging with a clinical diagnosis of either ischemic cardiomyopathy (ICM) or NIDCM were studied. All patients confirmed to have an LVEF of ≤54% by cine CMR quantitative image analysis were included in the study cohort. ICM was defined as any of the following; (1) previous history of myocardial infarction, (2) coronary imaging confirming ≥70% stenosis in ≥1 vessel, or (3) late gadolinium enhancement (LGE) imaging showing a dominant ischemic (subendocardial-based) pattern of fibrosis based on expert visual scoring. Patients not meeting any of these criteria and having no identified cause for their cardiomyopathy (ie, sarcoidosis, amyloidosis, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy) were considered to have NIDCM.

Patients were referred for the following reasons: the staging of disease severity in consideration of possible device therapy (75%), to establish the cause of symptomatic heart failure (22%), or to investigate the cause of ventricular arrhythmia (3%). All patients with previous ventricular arrhythmia (sustained ventricular tachycardia in 23, SCA in 6) were identified by detailed chart review and adjusted for by multivariable analysis. Patients with standard contraindications to contrast-enhanced CMR were excluded from this cohort study, inclusive of a glomerular filtration rate of ≤30 mL/min/1.73 m^2. Patients with existing implanted cardiac devices were not studied.

All patients agreed to participate in the study by giving both verbal and written informed consent. The Institution's Research Ethics Board approved this study.

CMR Imaging Protocol

CMR imaging was performed using a 3T MRI scanner (Siemens, Erlangen, Germany) equipped with a 32-channel cardiac coil. Standard SSFP-based cine images were obtained in sequential short-axis views at 10-mm intervals from the atrioventricular annulus to apex. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, echo time 1.3 ms, flip angle 10 degrees, matrix 256×205, iPAT 2, and temporal resolution 28 to 38 ms. Ten minutes after the intravenous administration of gadolinium contrast agent (0.15–0.2 mmol/kg Gadovist; Bayer, Inc, Quebec, Canada), LGE imaging was performed using a standard, segmented inversion-recovery gradient echo pulse sequence. Typical imaging parameters were slice thickness 8 mm, gap 2 mm, echo time 1.93 ms, flip angle 20 degrees, matrix 256×205, segments 13 to 21, and iPAT 2. The inversion time was optimized to null normal myocardium.

CMR Image Analysis

All images were deidentified and analyzed in a random order. Two experienced CMR interpreters blinded to all baseline and clinical outcome variables first performed qualitative image interpretation. Using consensus scoring, the presence of any LGE and the corresponding LGE pattern was recorded and categorized as ischemic (subendocardial-based) or nonischemic (midwall, RV insertion point, subepicardial, or diffuse). In the case of disagreement, a third blinded reader was used to reach consensus.

Quantitative image analysis was performed by blinded core laboratory personnel using commercially available software (cvi[42]; Circle Cardiovascular Inc, Calgary, Alberta, Canada). As shown in Figure 1, sequential short-axis cine images underwent contour tracing to obtain the LV and RV end-diastolic volume, end-systolic volume, and ejection fraction. For the RV, contour tracing was performed from standard short-axis images from the pulmonary valve to the apex using phase-matched cross-referencing to available long-axis views. LV mass was determined at end-diastole with the papillary muscles included as part of the myocardium. All volume and mass measurements were indexed to body surface area, calculated using the Mosteller formula. LGE quantification was performed using a Signal Threshold versus Reference Myocardium technique as previously described,[11] with the largest contiguous region of homogenously nulled (dark) myocardium serving as the reference region on each slice. A signal threshold of ≥5 SD above the mean signal of reference myocardium was used to define abnormal tissue (ie, fibrosis) with total LGE expressed as a percentage of the LV mass.

Two blinded investigators determined interobserver and intraobserver reproducibility for RV volume and RVEF measurements by repeating measurements in random order for 20 randomly selected patients.

Follow-Up and Clinical Events

Clinical follow-up was initiated at the time of CMR imaging. All patients were followed until they experienced the composite primary outcome, died of other causes, or had their final follow-up visit, whichever came first. A total of 165 patients underwent

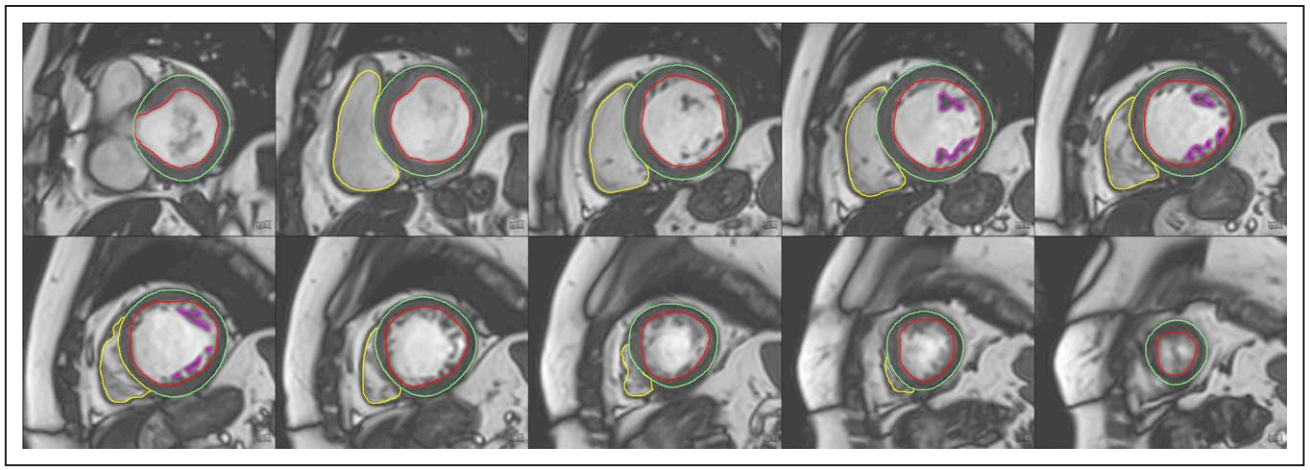

Figure 1. Examples of semiautomated contouring of the left ventricle (LV) and right ventricle (RV) for derivation of end-diastolic and end-systolic contours. Quantification was performed by contour tracing of the LV endocardial border (red lines), LV epicardial border (green line), and RV endocardial border (yellow line) for all relevant short-axis images. For the LV, the papillary muscles were included in the LV mass.

device implantation after CMR imaging, 139 for primary prevention and 26 for secondary prevention. Patients were followed for the primary composite clinical outcome of SCA or appropriate ICD therapy with all events adjudicated by a blinded electrophysiologist. Appropriate ICD therapy was defined as antitachycardia pacing and shock for fast ventricular tachycardia (R-R <320 ms) or ventricular fibrillation. ICD therapy was deemed inappropriate when provided in the setting of supraventricular tachycardia, T-wave oversensing, or for device malfunction (eg, lead fracture). SCA was defined as death occurring within 1 hour of symptom onset. Follow-up was performed by a review of all medical records, a scripted telephone interview, and blinded review of all device interrogations.

Statistical Analysis

All values were expressed as mean± SD. Clinical and CMR-based baseline characteristics were compared using independent *t* tests or the Mann-Whitney *U* test for continuous variables depending on the distribution. Categorical variables were compared using the χ^2, corrected χ^2, or Fisher exact test depending on the expected cell count. All clinical and magnetic resonance imaging–based variables were evaluated for associations with the primary outcome. Univariable associations between CMR characteristics and outcomes were performed using Cox proportional hazards regression. Multivariable Cox regression analysis was performed to assess for independent associations between RV dysfunction and the primary outcome. With 49 clinical events ≤4 covariates were considered eligible to avoid overfitting and were selected based on clinical relevance and demonstration of association (P<0.1) by univariable analysis. A threshold of 35% was selected for LVEF based on current practice guideline and a threshold of 15% was selected for LGE.[11] All models were assessed for collinearity and proportional hazards assumption. Kaplan-Meier method was used to generate survival curves for those with RVEF ≥45% and those with RVEF <45% using the Log-rank test. A priori subgroup analysis separating patients by LVEF above or below 35% was performed. An exploratory (post hoc) analysis was also performed after stratification for patients with NIDCM and an LVEF >35%. To assess for influences of death unrelated to the primary outcome on predictive utility from RV dysfunction, we performed a competing risk analysis, as previously described.[12]

We assessed interobserver and intraobserver reproducibility using the Bland-Altman analysis. All statistical analyses were performed using SPSS for Macintosh, version 21.0 (SPSS, Inc, Chicago, Illinois), Stata/SE 12.0 (StataCorp LP, College Station, Texas), and R version 3.3.

Results

A total of 314 patients (231 male) with a mean age of 59±13 years were studied. Disease pathogenesis was classified as ICM in 164 (52%) patients and NIDCM in 150 (48%) patients.

Primary Composite End Point

During a median follow-up of 773 days (interquartile range=819), 49 patients (15.6%) experienced the primary composite outcome. This included 9 patients experiencing SCA and 40 patients receiving appropriate device therapy (10 antitachycardia pacing and 30 shock).

Baseline Clinical Characteristics

Baseline clinical characteristics were not significantly associated with the primary outcomes, with the exception of previous ventricular arrhythmia and the use of digoxin and diuretics, both more prevalent in those with a primary outcome (Table 1). A nonsignificant trend toward increased arrhythmic events was observed in the ICM versus NIDCM cohort (P=0.12).

Baseline CMR Characteristics

All baseline CMR characteristics are shown in Table 2. The mean LVEF of the population was 32±12% (range, 6–54%), with a mean RVEF of 48±15% (range, 7–78%). Using the a priori definition of an RVEF ≤45%,[10] RV dysfunction was identified in 112 patients (36%) with a respective prevalence of 31% and 41% in the ICM and NIDCM subgroups (P=0.08).

Of all CMR baseline variables, the following were associated with the primary outcome: left ventricular end-diastolic volume indexed to body surface area, left ventricular end-systolic volume indexed to body surface area, LVEF, right ventricular end-systolic volume indexed to body surface area, RVEF, and total %LGE. The mean LVEF was significantly lower in patients experiencing a primary outcome (27±11 versus 33±12%; P<0.001). Similarly, the mean RVEF was significantly lower (44±15 versus 49±15%; P=0.02), the prevalence of RV dysfunction being 49% and 33% in those

Table 1. Baseline Demographics of the Cohort and the Univariable Associations With Primary Outcome

Characteristics	Total Cohort (N=314)	RVEF ≤45% (N=112)	RVEF >45% (N=202)	HR (95% CI)	*P* Value
Age, y	59±13	58±14	59±12	1.02 (0.99–1.04)	0.16
Male sex, n (%)	231 (74)	84 (75)	147 (74)	1.08 (0.55–2.12)	0.82
Hypertension, n (%)	151 (48)	48 (43)	103(51)	1.17 (0.67–2.05)	0.59
Diabetes mellitus, n (%)	70 (22)	22 (20)	48 (24)	0.86 (0.42–1.77)	0.68
Hyperlipidemia, n (%)	163 (52)	50 (45)	113 (56)	0.82 (0.47–1.43)	0.48
Smoking, n (%)	126 (40)	42 (38)	84 (42)	1.07 (0.61–1.88)	0.82
H/O coronary artery disease, n (%)	73 (23)	23 (21)	50 (25)	1.43 (0.78–2.59)	0.24
QRS interval (ms)	132±32	134±33	131±31	1.00 (0.99–1.01)	0.76
QTc (ms)	463±41	472±39	458±41	1.00 (0.99–1.00)	0.33
H/O ventricular arrhythmia, n (%)	29 (9)	4 (4)	25 (12)	4.49 (2.42–8.36)	<0.001*
NYHA class 3–4, n (%)	145 (46)	68 (61)	77(38)	1.16 (0.67–2.04)	0.59
Ischemic cardiomyopathy, n (%)	164 (52)	51(46)	113 (56)	1.58 (0.89–2.83)	0.12
Medications†					
ACE inhibitor	185 (65)	64 (65)	121 (65)	1.34 (0.70–2.57)	0.38
ARB	68 (24)	26 (27)	42 (23)	1.08 (0.56–2.09)	0.82
Amiodarone	19 (7)	6 (6)	13(7)	1.87 (0.79–4.43)	0.15
Beta-blocker	244 (86)	81 (83)	163 (88)	1.03 (0.46–2.32)	0.94
Calcium blocker	28 (10)	5 (5)	23(12)	1.29 (0.54–3.05)	0.57
Digoxin	55 (19)	25 (26)	30 (16)	2.04 (1.09–3.80)	0.03*
Diuretic	177 (62)	74 (76)	103 (55)	1.99 (1.02–3.87)	0.04*
Statin	155 (55)	48 (49)	107 (58)	0.87 (0.48–1.56)	0.63

Continuous data are expressed as mean±SD, categorical data as n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; H/O, history of; HR, hazard ratio; NYHA, New York Heart Association; and RVEF, right ventricular ejection fraction.

*P<0.05. Ischemic cardiomyopathy was defined as history of coronary artery disease and/or the presence of ischemic LGE.

†Total number of the patients for the medications data is 284.

with versus without occurrence of the primary outcome, respectively (P=0.03). Total %LGE was higher in those with a primary outcome (20±18% versus 13±15%; P=0.02). Table 3 summarizes the results of univariable and multivariable analyses and describes corresponding hazards for the primary outcome. The first multivariable model aimed to describe the predictive value of LVEF after adjustment for previous ventricular arrhythmia and total %LGE and provided a hazard ratio (HR) of 0.57 per 10% increase in LVEF (P<0.001). The second model used an identical analysis using RVEF and

Table 2. CMR Characteristics of the Cohort and the Univariable Associations With Primary Outcome

Characteristics	Total Cohort (N=314)	RVEF ≤45% (N=112)	RVEF >45% (N=202)	HR (95% CI)	*P* Value
LVEDVI, mL/m^2	115±38	126±41	108±34	1.01 (1.00–1.02)	0.002*
LVESVI, mL/m^2	80±37	96±40	71±31	1.01 (1.00–1.02)	<0.001*
LVEF, %	32±12	26±11	36±11	0.95 (0.92–0.97)	<0.001*
LVEF ≤35%, n (%)	193 (61)	90 (80)	103 (51)	2.86 (1.46–5.62)	0.002*
RVEDVI, mL/m^2	67±22	75±27	62±18	1.01 (0.997–1.02)	0.15
RVESVI, mL/m^2	36±20	53±23	26±10	1.01 (1.00–1.03)	0.03*
RVEF, %	48±15	31±10	58±8	0.98 (0.96–0.99)	0.009*
Total LGE (% of LV mass)	14±15	14±15	15±16	1.02 (1.01–1.04)	0.003*
Total LGE >15% of LV mass, n (%)	113 (36)	37 (33)	76 (38)	2.20 (1.25–3.86)	0.006*

Continuous data are expressed as mean±SD, categorical data as n (%). CI indicates confidence interval; CMR, cardiovascular magnetic resonance; EDVI, end-diastolic volume indexed to body surface area; EF, ejection fraction; ESVI, end-systolic volume indexed to body surface area; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricle; and RV, right ventricle.

*P<0.05. LGE was quantified by signal threshold versus reference mean technique using signal intensity threshold of 5SD of the remote myocardium.

Table 3. Univariable and Multivariable Associations of Clinical and CMR Characteristics With Primary Outcome (49 Events)

	Univariable				Model 1†				Model 2‡				Model 3§			
Characteristics	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value
Demographics																
Age	1.02	0.99–1.04	2.06	0.16												
Sex	1.08	0.55–2.12	0.06	0.82												
NYHA class 3 or 4	1.16	0.67–2.04	0.29	0.59												
H/O coronary artery disease	1.43	0.78–2.59	1.30	0.24												
Ischemic cardiomyopathy	1.58	0.89–2.83	2.48	0.12												
H/O ventricular arrhythmia	4.49	2.42–8.36	17.45	<0.001*	5.34	2.86–9.97	38.1	<0.001*	5.48	2.81–10.68	35.1	<0.001*	7.92	3.82–16.45	45.2	<0.001*
Amiodarone	1.87	0.79–4.43	1.75	0.15												
Digoxin	2.04	1.09–3.80	4.57	0.03*												
Coronary risk factors																
Diabetes mellitus	0.86	0.42–1.77	0.18	0.68												
Hypertension	1.17	0.67–2.05	0.30	0.59												
Hypercholesterolemia	0.82	0.47–1.43	0.49	0.48												
Smoking	1.07	0.61–1.88	0.05	0.82												
ECG																
QRS durations, ms	1.00	0.99–1.01	0.10	0.76												
QTc, ms	1.00	0.99–1.00	0.97	0.33												
CMR																
LVEDVI (per 1 mL/m^2)	1.01	1.00–1.02	8.62	0.002*												
LVESVI (per 1 mL/m^2)	1.01	1.00–1.02	12.39	<0.001*												
LVEF (per 10%)	0.58	0.45–0.76	17.31	<0.001*	0.57	0.44–0.73	38.1	<0.001*								
LVEF ≤35%	2.86	1.46–5.62	10.96	0.002*									2.36	1.16–4.79	45.2	0.017*
RVEDVI (per 1 mL/m^2)	1.01	1.00–1.02	1.94	0.15												
RVESVI (per 1 mL/m^2)	1.01	1.00–1.03	3.91	0.03*												
RVEF (per 10%)	0.79	0.67–0.94	6.49	0.009*					0.71	0.58–0.86	35.1	0.001*				
RVEF ≤45%	2.04	1.16–3.58	6.04	0.013*									2.98	1.51–5.88	45.2	0.002*
Total LGE (per 10% LV mass)	1.27	1.09–1.49	8.15	0.004*	…	…	…	N.S	1.23	1.05–1.45	35.1	0.009*				
Total LGE >15% of LV mass	2.21	1.26–3.87	7.46	0.006*									1.89	1.06–3.36	45.2	0.031*

CI indicates confidence interval; CMR, cardiovascular magnetic resonance; EDVI, end-diastolic volume indexed to body surface area; ESVI, end-systolic volume indexed to body surface area; EF, ejection fraction; H/O, history of; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricle; NYHA, New York Heart Association; and RV, right ventricle.

*P<0.05.

†Model 1 represents multivariable Cox regression model with history of ventricular arrhythmia, LVEF (per 10%), and total LGE (per 10% LV mass).

‡Model 2 represents multivariable Cox regression model with history of ventricular arrhythmia, RVEF (per 10%), and total LGE (per 10% LV mass).

§Model 3 represents multivariable Cox regression model with history of ventricular arrhythmia, LVEF ≤35%, RVEF ≤45%, and total LGE >15% of LV mass.

provided an HR of 0.71 per 10% increase (P<0.001). Finally, RV dysfunction (RVEF ≤45%) was entered as a discreet variable and shown to be independently associated with the primary outcome after adjustment for LVEF, previous ventricular arrhythmia, and total %LGE providing an HR of 2.98 (P=0.002).

Figure 2 shows a Kaplan-Meier survival analysis of the whole study cohort according to the presence or absence of RV dysfunction, showing significantly worse event-free survival among those with an RVEF ≤45% (P=0.011). The cumulative event rate was 21.4% versus 12.4%, respectively, among those with versus without RV dysfunction.

To illustrate the incremental value of RV dysfunction versus current LVEF-based risk criteria (LVEF ≤35%) for the prediction of SCA or appropriate ICD therapy, we modeled cumulative hazards for this end point based on one

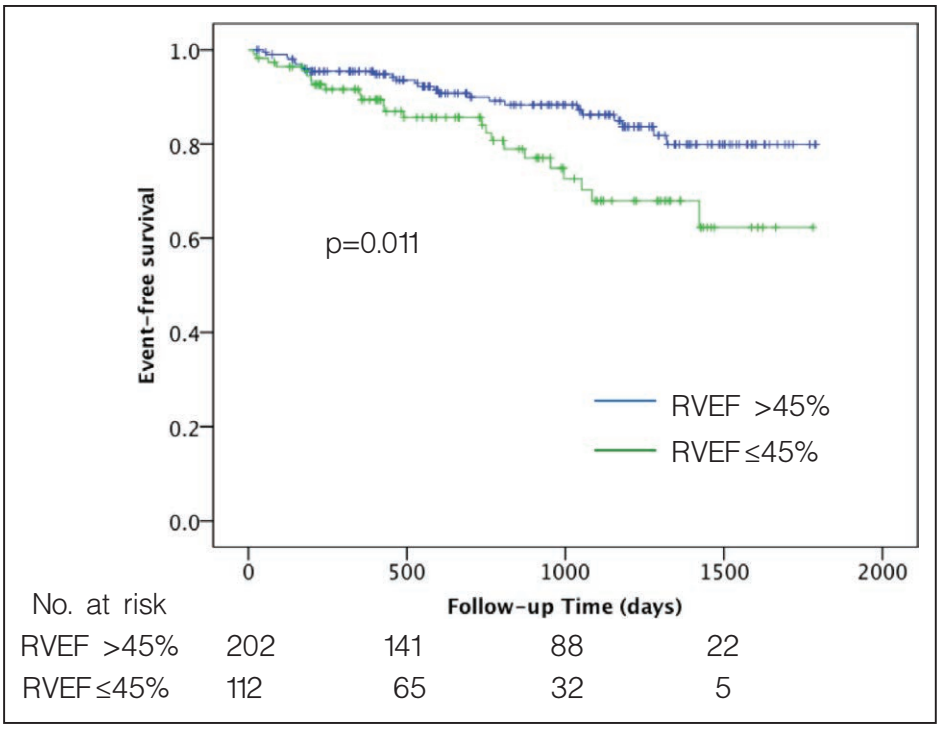

Figure 2. Kaplan-Meier curves showing event-free survival for the primary outcome for the entire cohort. Patients with right ventricular ejection fraction (RVEF) ≤45% showed a significant higher rate of events compared with those with RVEF >45%.

or both these criteria being met. As shown in Figure 3, a progressive rise in risk of the primary outcome occurred with LV dysfunction alone (HR, 3.6; confidence interval, 1.40–9.43), RV dysfunction alone (HR, 6.7; confidence interval, 1.97–22.66), or both (HR, 8.1; confidence interval, 3.01–22.05).

Subgroup Analysis

A prespecified subgroup analysis was performed to assess the incremental prognostic value of RV measures in patients with versus without an LVEF ≤35%. A total of 121 patients had an LVEF between 36% and 54% (mean 45±6%), their respective baseline and CMR clinical characteristics versus those with an LVEF ≤35% shown in Tables 4 and 5, respectively.

Among patients with an LVEF ≤35%, the only baseline CMR variable associated with the primary outcome was LVEF (*P*=0.005). In contrast, among patients with an LVEF >35%, there was no association between LVEF and the primary outcome (*P*=0.79). However, significant associations were identified for right ventricular end-diastolic volume indexed to body surface area (76±17 versus 64±19 mL/m^2; *P*=0.03), right ventricular end-systolic volume indexed to body surface area (41±15 versus 29±11 mL/m^2; *P*=0.005), RVEF (47±10 versus 55±11%; *P*=0.01), RV dysfunction (45% versus 15%; *P*=0.014), and total %LGE (19±13 versus 10±13%; *P*=0.03). Multivariable analysis showed RV dysfunction to be an independent predictor of the primary outcome after adjustment for total %LGE, demonstrating a 4.2-fold increased risk of the primary outcome (*P*=0.02; Table 6).

Figure 4 shows Kaplan-Meier survival analysis of patients with an LVEF >35% according to the presence or absence of RV dysfunction. Patients with RV dysfunction experienced significantly lower event-free survival (*P*=0.011), with a cumulative event rate of 22.7% versus 6.1%, respectively, among those with versus without RV dysfunction. Exploratory (post hoc) analysis was performed in this patient cohort (LVEF >35%) having a diagnosis of NIDCM (N=71) in recognition of RV dysfunction being more prevalent versus the ICM subgroup. Univariable analysis (Table 7) revealed RV dysfunction to be the strongest predictor of the primary outcome with an HR of 6.9 (confidence interval 1.3–37.9, *P*=0.03), with a cumulative event rate of 22% versus 3.8%, respectively, among those with versus without RV dysfunction.

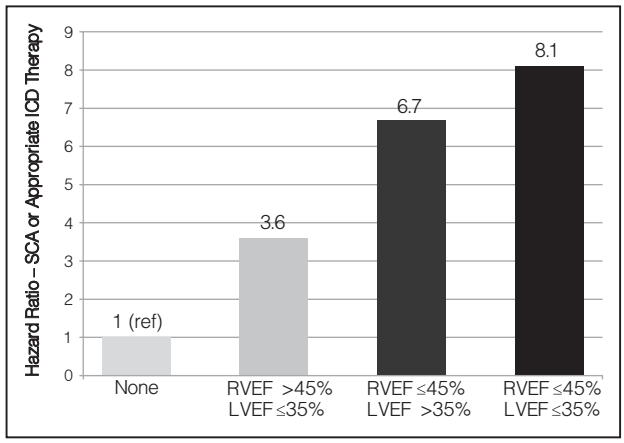

Figure 3. Cumulative event hazards for sudden cardiac arrest (SCA) or appropriate implantable cardioverter defibrillator (ICD) therapy based on right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF)–based function thresholds, presented for their respective combinations. A progressive rise in hazard is seen for those meeting none, left ventricle (LV) alone, right ventricle (RV) alone, and both risk markers.

Table 4. Univariable Associations of Clinical Baseline Characteristics With Primary Outcome for Patients With LVEF Above and Below 35%

	LVEF ≤35%				LVEF >35%			
Characteristics	Values (N=193)	HR	95% CI	*P* Value	Values (N=121)	HR	95% CI	*P* Value
Age, y	61±11	1.01	0.99–1.04	0.36	56±14	1.01	0.96–1.05	0.77
Male sex, n (%)	143 (74)	0.66	0.32–1.37	0.26	88 (73)	3.90	0.50–30.45	0.20
Hypertension, n (%)	96 (50)	1.28	0.68–2.43	0.45	55 (46)	0.70	0.20–2.40	0.57
Diabetes mellitus, n (%)	56 (29)	0.66	0.30–1.45	0.30	14 (12)	0.77	0.10–6.07	0.80
Hyperlipidemia, n (%)	108 (56)	0.89	0.47–1.68	0.72	55 (46)	0.42	0.11–1.60	0.21
Smoking, n (%)	79 (41)	0.90	0.47–1.71	0.75	47 (39)	1.40	0.43–4.58	0.58
H/O coronary artery disease, n (%)	49 (26)	1.32	0.67–2.58	0.42	24 (20)	1.36	0.36–3.83	0.65
QRS interval, ms	138±31	0.997	0.99–1.01	0.56	122±30	1.00	0.98–1.02	0.87
QTc, ms	468±40	0.99	0.99–1.00	0.20	454±42	0.99	0.97–1.00	0.30
H/O ventricular arrhythmia, n (%)	11 (6)	3.53	1.56–8.04	0.003*	18 (57)	13.67	3.91–47.84	<0.01*
NYHA class 3–4, n (%)	114 (59)	0.80	0.42–1.52	0.49	31 (26)	1.00	0.27–3.78	1.00
Ischemic cardiomyopathy	114 (59)	1.42	0.71–2.81	0.32	50 (41)	1.17	0.36–2.83	0.80
Medications†								
ACE inhibitor	127 (70)	0.84	0.42–1.69	0.63	58 (57)	5.55	0.68–45.13	0.11
ARB	51 (28)	1.09	0.55–2.19	0.80	17 (17)	0.04	0.0–99.39	0.41
Amiodarone	9 (5)	1.26	0.39–4.13	0.70	10 (10)	5.78	1.38–24.20	0.016*
Beta-blocker	154 (85)	1.13	0.47–2.73	0.78	90 (88)	1.00	0.12–8.14	1.00
Calcium blocker	14 (8)	1.24	0.44–3.53	0.68	14 (14)	2.09	0.42–10.39	0.37
Digoxin	46 (25)	1.80	0.92–3.52	0.09	9 (9)	1.23	0.15–10.10	0.84
Diuretic	136 (75)	1.60	0.70–3.67	0.26	41 (40)	0.94	0.22–3.94	0.93
Statin	107 (59)	0.80	0.42–1.55	0.51	48 (47)	1.04	0.26–4.15	0.96

Continuous data are expressed as mean±SD, categorical data as n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; H/O, history of; HR, hazard ratio; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

*P<0.05. Ischemic cardiomyopathy was defined as history of coronary artery disease and/or the presence of ischemic LGE.

†Total number of the patients for the medications data is 284 (102 for LVEF >35%).

An exploratory subgroup analysis was also performed to consider potential differences between patients experiencing appropriate ICD therapy versus those experiencing SCA (Tables I and II in the Data Supplement). Although several clinical variables showed significance, no CMR-based measure demonstrated significant differences between these subgroups.

Competing Risks Analysis

A competing risk analysis was performed to assess robustness of risk predictions related to RV dysfunction after consideration of patients experiencing death unrelated to the primary outcome. This analysis (Figure I in the Data Supplement) demonstrated maintained predictive utility with significant separation of risk estimate curves among those with versus without RV dysfunction.

Reproducibility of RVEF Measurement

Intra- and interobserver variability for RVEF produced mean difference and 95% limits of agreement of –0.5±5.5% and –0.1±6.7%, respectively. Bland-Altman analyses are shown in Figure 5.

Discussion

This study provides strong sentinel support for the incremental contributions of RVEF beyond LVEF alone in the prediction of arrhythmic events among patients with systolic dysfunction. The presence of RV dysfunction, defined as an RVEF ≤45%, was associated with a 2.98-fold higher risk of SCA or appropriate ICD therapy, a finding exaggerated among those with an LVEF >35% where this risk grew to 4.2-fold.

Expanding clinical interest can be observed for the study of RV dysfunction in systolic heart failure patients over the past 2 decades. Early studies revealed RV function by radionuclide angiography to be associated with heart failure–related outcomes, such as total cardiac mortality and urgent transplantation,[13,14] all-cause mortality and pretransplant hospitalization,[15] and a reduction in exercise capacity.[15] With technological advancements in echocardiography, these efforts were refocused on the validation of surrogate markers of global RV function obtained from the 4-chamber long-axis view where basal to mid-portions of the RV free wall are most reliably seen. These measures, inclusive

Table 5. Univariable Associations of Baseline CMR Characteristics With Primary Outcome for Patients With LVEF Above and Below 35%

	LVEF ≤35%				LVEF >35%			
Characteristics	Values (N=193)	HR	95% CI	*P* Value	Values (N=121)	HR	95% CI	*P* Value
LVEDVI, mL/m^2	131±35	1.006	0.997–1.02	0.20	89±27	1.01	0.99–1.03	0.21
LVESVI, mL/m^2	100±32	1.009	0.999–1.02	0.07	49±18	1.02	0.99–1.04	0.25
LVEF, %	25±6	0.93	0.89–0.98	0.005*	45±6	0.99	0.89–1.09	0.79
RVEDVI, mL/m^2	68±24	1.00	0.99–1.02	0.68	65±19	1.03	1.00–1.06	0.04*
RVESVI, mL/m^2	39±23	1.00	0.99–1.02	0.66	30±12	1.01	1.03–1.12	0.03*
RVEF, %	45±17	0.99	0.97–1.01	0.30	54±11	0.95	0.91–0.99	0.03*
RVEF ≤45%, n (%)	90 (47)	1.29	0.68–2.45	0.43	22 (18)	4.17	1.27–13.68	0.019*
Total LGE (% of LV mass)	16±16	1.01	0.996–1.03	0.13	11±13	1.03	1.004–1.07	0.03*
Total LGE >15% of LV mass, n (%)	79 (41)	1.60	0.84–3.02	0.15	35 (29)	3.51	1.06–11.6	0.04*

Data are expressed as mean±SD. CI indicates confidence interval; CMR, cardiovascular magnetic resonance; EDVI, end-diastolic volume indexed to body surface area; EF, ejection fraction; ESVI, end-systolic volume indexed to body surface area; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricle; and RV, right ventricle.

*P<0.05.

of fractional area change,[16] tricuspid annular plane systolic excursion,[17,18] and more recently RV peak global longitudinal strain,[19,20] have each been associated with relevant heart failure outcomes such as cardiac mortality,[21] all-cause mortality,[22] in addition to composite end points heavily weighted by mortality or transplantation.[23–25] However, no study to date has assessed the value of RV function to predict future arrhythmic events.

CMR offers the capacity to quantify RV function through unobstructed visualization of the endocardial borders throughout all phases of the cardiac cycle. Similar to the derivation of LVEF, RV end-diastolic and end-systolic volumes can be routinely obtained from the same short-axis cine images, presenting no incremental investment with respect to imaging time. This technique has been shown, both in our current study and by others,[10,26,27] to provide high intra- and interobserver reproducibility and has recently been shown to predict nonarrhythmic clinical outcomes in patients with systolic dysfunction.[10] In this study of 250 patients with NIDCM, Gulati et al[10] identified associations between RV dysfunction, similarly defined as an RVEF ≤45%, and the composite outcome of all-cause mortality or cardiac transplantation. Among the 34% of patients meeting this criterion, a 3.9-fold increase in the primary outcome was observed over a median of 6.9 years after adjustment for other baseline variables. A second study by Doesch et al[28] similarly identified RV dysfunction, defined as RVEF <38% (median value of cohort), to be associated with a 4.7-fold increase in all-cause mortality and 2.6-fold increase in heart failure hospitalization among 140 patients with NIDCM over a median follow-up of 3 years. In combination, these 2 recent studies support that among patients with NIDCM, RV dysfunction is an important prognostic marker for heart failure–related outcomes. However, to our knowledge, the capacity of RV function to predict future arrhythmic events has not been explored.

The current study identifies RV function to be an important marker of future arrhythmic events among patients with systolic dysfunction. Among those with an RVEF ≤45%, a 2.98-fold higher risk of the primary outcome was identified after adjustment for relevant and eligible covariates inclusive of LVEF. However, most noteworthy is the identification of superior predictive utility for RVEF versus LVEF in patients with mild to moderate LV dysfunction (LVEF >35%). In this subgroup, RV dysfunction (RVEF <45%) was observed more frequently among patients with versus without events (45% versus 15%; P=0.014) and portended a 4.2-fold higher risk after adjustment for baseline covariates. As such, this study introduces sentinel evidence for RVEF being incremental to current risk stratification tools among patients with mild to moderate systolic dysfunction. It is in this patient subgroup that the greatest global contribution to SCA has been reported in North America,[29] and previous studies indicating that ≈70% of patients experiencing SCA had a pre-event LVEF >35%.[5] Accordingly, noninvasive markers associated with elevated risk of ventricular arrhythmias in this patient cohort are of critical need.

A higher prevalence of RV dysfunction was observed in those with NIDCM versus ICM. In response to this finding, we performed an exploratory post hoc analysis in those with NIDCM and an LVEF >35% to estimate the predictive utility of RV dysfunction. This revealed respective event rates of 22% versus 3.8% in those with versus without RV dysfunction (HR, 6.9), suggesting strong discriminative utility in this subcohort. However, as a post hoc analysis, confirmation in a larger study population is required with sufficient power to adjust for relevant covariates. The higher prevalence of RV dysfunction in NIDCM identified in this study is supported by similar findings in previous studies.[10,29] For example, a study by La Vecchia et al[30] studied 153 patients with LVEF <45% and found a prevalence of RV dysfunction (defined as RVEF <35%) by angiography estimation of 65% in NIDCM versus 16% in patients with ICM (P<0.001). Whether such reductions in RV function reflects decompensation related to chronically elevated LV filling pressures or a primary process

Table 6. Univariable and Multivariable Associations of Clinical and CMR Characteristics With Primary Outcome for Patients With LVEF >35% (11 Events)

	Univariable				Model 1†				Model 2‡				Model 3§			
Characteristics	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value	HR	95% CI	χ^2	*P* Value
Demographics																
Age	1.01	0.96–1.05	0.09	0.77												
Sex	3.90	0.50–30.45	2.42	0.20												
NYHA class 3 or 4	1.00	0.27–3.78	0.00	1.00												
H/O coronary artery disease	1.36	0.36–3.83	0.19	0.65												
Ischemic cardiomyopathy	1.17	0.36–2.83	0.06	0.80												
H/O ventricular arrhythmia	13.67	3.91–47.84	16.62	<0.01*	27.3	6.4–116.9	26.7	<0.01*								
Amiodarone	5.78	1.38–24.20	4.58	0.016*												
Digoxin	1.23	0.15–10.10	0.04	0.84												
Coronary risk factors																
Diabetes mellitus	0.77	0.10–6.07	0.07	0.80												
Hypertension	0.70	0.20–2.40	0.33	0.57												
Hypercholesterolemia	0.42	0.11–1.60	1.78	0.21												
Smoking	1.40	0.43–4.58	0.30	0.58												
ECG																
QRS durations, ms	1.00	0.98–1.02	0.03	0.87												
QTc, ms	0.99	0.97–1.00	1.23	0.30												
CMR																
LVEDVI (per 1 mL/m^2)	1.01	0.99–1.03	1.35	0.21												
LVESVI (per 1 mL/m^2)	1.02	0.99–1.04	1.13	0.25												
LVEF (per 10%)	0.87	0.32–2.40	0.07	0.79												
RVEDVI (per 1 mL/m^2)	1.03	1.00–1.06	3.89	0.04*												
RVESVI (per 1 mL/m^2)	1.01	1.03–1.12	9.6	0.03*												
RVEF (per 10%)	0.59	0.37–0.95	4.30	0.03*					0.6	0.4–0.9	8.7	0.02*				
RVEF ≤45%	4.17	1.27–13.68	4.94	0.019*	10.4	2.5–42.7	26.7	0.001*					4.2	1.27–13.7	9.07	0.02*
Total LGE (per 10% LV mass)	1.45	1.04–2.03	3.88	0.03*					1.5	1.1–2.1	8.7	0.03*				
Total LGE >15% of LV mass	3.51	1.06–11.60	4.15	0.04*									3.5	1.06–11.8	9.07	0.04*

CI indicates confidence interval; CMR, cardiovascular magnetic resonance; EDVI, end-diastolic volume indexed to body surface area; EF, ejection fraction; ESVI, end-systolic volume indexed to body surface area; H/O, history of; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricle; NYHA, New York Heart Association; and RV, right ventricle.

*P<0.05.

†Model 1 represents multivariable Cox regression model with history of ventricular arrhythmia and RVEF ≤45%.

‡Model 2 represents multivariable Cox regression model with RVEF (per 10%) and total LGE (per 10% LV mass).

§Model 3 represents multivariable Cox regression model with RVEF ≤45% and total LGE >15% of LV mass.

of the RV myocardium remains unanswered. Accordingly, future studies aimed at serial evaluations of both imaging and serum markers in this population are required. Irrespectively, given independent associations of RV dysfunction and future arrhythmic events, this imaging marker may be of critical importance to the evaluation of heart failure patients for primary prevention ICD. This may be highly relevant for patients experiencing LV functional recovery above current ICD thresholds.

Limitations

Several limitations of the current study warrant discussion. Our study did not exclude patients with a previous history of ventricular arrhythmia, this variable being defined as any prior ventricular arrhythmia and not requiring cardiac symptoms or hemodynamic collapse to be documented, given that this information was not available in all patients. To maximize the generalizability of our findings, we therefore included this variable in multivariable analyses and demonstrated that

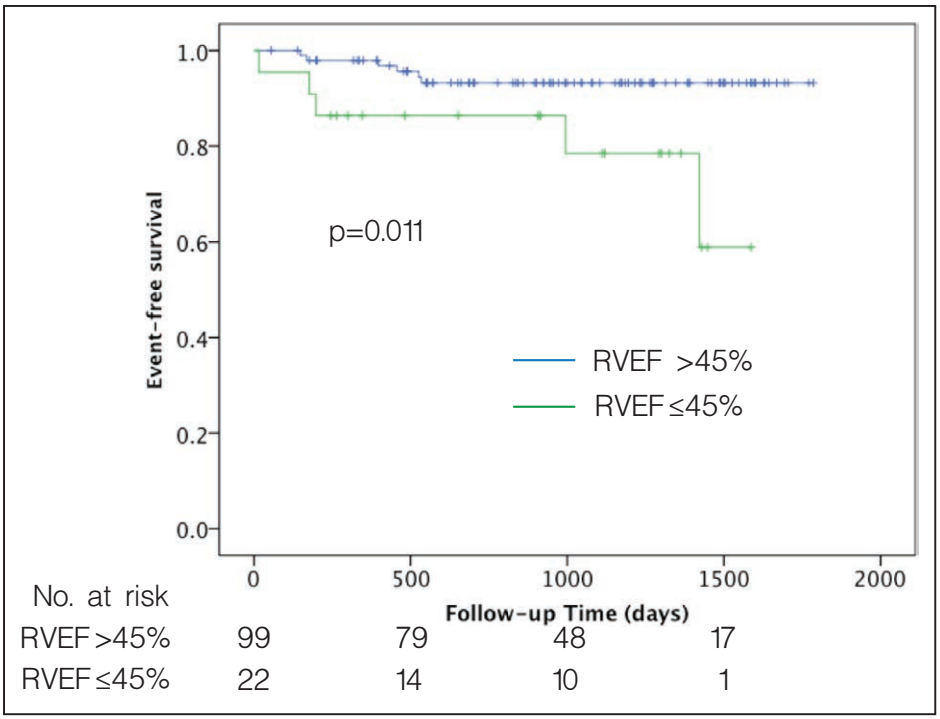

Figure 4. Kaplan-Meier curves showing event-free survival for the primary outcome in patients with left ventricular ejection fraction >35%. Patients with right ventricular ejection fraction (RVEF) ≤45% showed a significantly higher rate of events compared with those with RVEF >45%.

RV dysfunction remained a robust predictor of the primary outcome.

Our study has several limitations not addressable by statistical adjustment. First, this study was performed at a single tertiary care referral center, introducing the potential for referral bias and clinical practice bias about patient management. Generalizability to a broader heart failure population, therefore, requires confirmation of our findings within a larger, multicenter setting. Second, patients referred for CMR imaging protocols are currently restricted to those with a glomerular filtration rate of >30 mL/min/1.73 m^2 because of Food and Drug Administration–based recommendations. Accordingly, these data should not be extrapolated to patients with advanced renal impairment. Third, the primary composite outcome was inclusive of appropriate ICD therapy, which can be challenged as an imperfect surrogate of life-threatening arrhythmia. As with previous published studies including this as a composite end point, inherent limitations are recognized. Fourth, although no patients were referred with a diagnosis of pulmonary hypertension, our study did not perform noninvasive or invasive estimates of pulmonary arterial pressure. Similarly, severity of tricuspid regurgitation was not quantified using such techniques. Accordingly, we were unable to adjust for these variables in our analysis. Finally, total % LGE was included as a marker in this study because of its recognized contribution to arrhythmia risk and availability from CMR imaging. However, we did not report on the reproducibility of this marker as our group has done so in previous studies.[11]

Conclusions

RV dysfunction is a strong and independent predictor of SCA or appropriate ICD therapy in patients with systolic dysfunction. The value of this marker seems greatest among those with mild to moderate LV dysfunction, a large subcohort contributing to global SCA burden yet lacking validated risk prediction markers. Accordingly, RV dysfunction may be of equivalent clinical relevance to LV dysfunction for the risk

Table 7. Univariable Associations of CMR Characteristics With Primary Outcome for Patients With NIDCM and LVEF >35%

	Univariable			
Characteristics	HR	95% CI	χ^2	*P* Value
LVEDVI (per 1 mL/m^2)	1.03	1.00–1.07	4.39	0.04*
LVESVI (per 1 mL/m^2)	1.05	1.00–1.10	4.06	0.04*
LVEF (per 1%)	0.99	0.86–1.14	0.02	0.88
LVEF (per 10%)	0.89	0.22–3.71	0.02	0.88
RVEDVI (per 1 mL/m^2)	1.05	1.01–1.08	5.46	0.02*
RVESVI (per 1 mL/m^2)	1.11	1.04–1.18	11.84	0.001*
RVEF (per 1%)	0.92	0.86–0.99	5.57	0.02*
RVEF (per 10%)	0.44	0.22–0.88	5.57	0.02*
RVEF ≤45%	6.90	1.26–37.88	5.30	0.03*
Total LGE (per 1% LV mass)	1.04	1.00–1.08	2.17	0.08
Total LGE (per 10% LV mass)	1.43	0.96–2.13	2.17	0.08

CI indicates confidence interval; CMR, cardiovascular magnetic resonance; EDVI, end-diastolic volume indexed to body surface area; EF, ejection fraction; ESVI, end-systolic volume indexed to body surface area; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricle; NIDCM, nonischemic dilated cardiomyopathy; and RV, right ventricle.

*$P<0.05$.

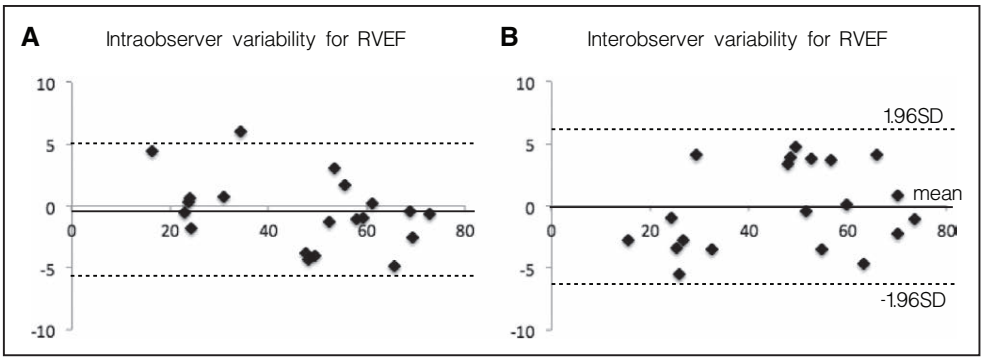

Figure 5. Bland-Altman plots of intraobserver variability (**A**) and interobserver variability (**B**) of right ventricular ejection fraction (RVEF).

stratification of patients with systolic dysfunction and warrants further investigation.

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