Original Article

Relationship between right and left ventricular function in candidates for implantable cardioverter defibrillator with low left ventricular ejection fraction

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ABSTRACT

Background: Indications for the primary prevention of sudden death using an implantable cardioverter defibrillator (ICD) are based predominantly on left ventricular ejection fraction (LVEF). However, right ventricular ejection fraction (RVEF) is also a known prognostic factor in a variety of structural heart diseases that predispose to sudden cardiac death. We sought to investigate the relationship between right and left ventricular parameters (function and volume) measured by cardiovascular magnetic resonance (CMR) among a broad spectrum of patients considered for an ICD.
Methods: In this retrospective, single tertiary-care center study, consecutive patients considered for ICD implantation who were referred for LVEF assessment by CMR were included. Right and left ventricular function and volumes were measured.
Results: In total, 102 patients (age 62 ± 14 years; 23% women) had a mean LVEF of $28 \pm 11\%$ and RVEF of $44 \pm 12\%$. The left ventricular and right ventricular end diastolic volume index was 140 ± 42 mL/m^2 and 81 ± 27 mL/m^2, respectively. Eighty-six (84%) patients had a LVEF $< 35\%$, and 63 (62%) patients had right ventricular systolic dysfunction. Although there was a significant and moderate correlation between LVEF and RVEF ($r=0.40$, $p < 0.001$), 32 of 86 patients (37%) with LVEF $< 35\%$ had preserved RVEF, while 9 of 16 patients (56%) with LVEF $\geq 35\%$ had right ventricular systolic dysfunction (Kappa=0.041).
Conclusions: Among patients being considered for an ICD, there is a positive but moderate correlation between LVEF and RVEF. A considerable proportion of patients who qualify for an ICD based on low LVEF have preserved RVEF, and vice versa.
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1. Introduction

An implantable cardioverter defibrillator (ICD) is an effective treatment to reduce mortality in patients with advanced heart failure with left ventricular ejection fraction (LVEF) $< 30\%$ [1–3]. The decision to implant an ICD for primary prevention is complex, but largely depends on a LVEF < 30–35%, which is a major inclusion criterion in the landmark ICD trials [2–8].

Prediction of ICD treatment benefit in individual patients remains difficult and a large proportion of patients with an ICD never receive an appropriate shock. Conversely, some patients with relatively preserved LVEF suffer sudden cardiac death. Therefore, additional and more refined risk assessments are needed to improve patient selection for ICD implantation [3].

Right ventricular ejection fraction (RVEF) is an independent predictor of survival in patients with heart failure [9–11]. Previous studies suggest that the RVEF may have a prognostic value in post-myocardial infarction patients [10–12], and a poor right ventricular

function may be an independent predictor of life-threatening arrhythmia [12,13]. In addition, there are other conditions in which right ventricular systolic dysfunction (RVSD) may have an important prognostic value. For example, in patients with arrhythmogenic right ventricular dysplasia, RVSD is a major diagnostic criterion [13,14]. In patients with pulmonary arterial hypertension and congenital conditions such as tetralogy of Fallot, a poor RVEF is a predictor of poor outcome, and this affects patient management [14,15]. However, other ventricular parameters such as RVEF and ventricular volumes in patients receiving ICD have not been well studied.

Cardiovascular magnetic resonance imaging (CMR) is recognized as a versatile, safe, and reproducible technique, allowing for accurate structural and functional assessment of the heart. CMR is the gold standard for ejection fraction measurement [15–17]. Considering the technical limitations of other imaging modalities such as 2D echocardiography, this method is particularly useful to measure RVEF [13,16,17].

The purpose of this study is to assess the relationship between RVEF and LVEF, as measured by CMR in patients referred for ICD implantation. We also evaluated the relationship between LVEF, RVEF, and right and left ventricular volumes. This is clinically relevant because if there is no strong correlation between left ventricular (LV) and right ventricular (RV) parameters, there is a potential for the RV assessment to offer an incremental value in ICD stratification.

2. Materials and methods

2.1. Study design and patient population

This retrospective, single-center study was approved by the institutional research ethics board. We included consecutive patients considered for ICD implantation (primary prevention) who underwent CMR between March 2007 and October 2009, identified from a clinical database. Patients with incomplete imaging datasets were excluded, but there were no other exclusion criteria so as to reflect a "real world" cohort of patients.

2.2. Cardiovascular magnetic resonance imaging

CMR studies were performed on a commercially available 1.5 T whole body scanner (Achieva, Philips, Medical Systems, Best, Netherlands). The standard CMR protocol included ECG gated steady-state free precession imaging in short axis orientation, perpendicular to the left ventricular long axis. Ten to 12 contiguous slices were obtained during 10–20 s of breath holds (slice thickness 8 mm, with no inter-slice gap, in plane resolution 1.6×1.6 mm). Late gadolinium enhancement images were acquired approximately 10 minutes after intravenous administration of 0.1–0.2 mmol/kg of gadolinium (gadopentate dimeglumine) with the inversion time adjusted to optimally null the normal myocardium. All CMR data were obtained by a single experienced reader blinded to other clinical data, using a commercially available workstation (Extended Workstation, Philips Medical Systems). Measurement of right and left ventricular volumes (end-diastolic and end-systolic volumes), stroke volumes, and ejection fraction were obtained in short axis orientation, according to the standard criteria [13,18]. To assess inter-observer reliability, a second experienced CMR reader independently measured the RVEF in 20 randomly selected cases.

LVEF $< 35\%$, which is a commonly used threshold for ICD implantation [2,18,19], was used as a cut-off value for moderate to severe LV dysfunction. We defined RVSD as abnormal RVEF $< 47\%$ for men or $< 53\%$ for women [2,19,20]. We defined dilated left ventricle as left ventricular end-diastolic indexed volume > 108 mL/m^2 (male) or 102 mL/m^2 (female) and dilated RV as right

ventricular end-diastolic indexed volume > 126 mL/m^2 (male) or 118 mL/m^2 (female) [20].

We evaluated the presence of chronic right ventricular myocardial infarction in the late gadolinium enhancement images.

2.3. Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (for normally distributed data) and categorical variables as number and percentage. The relationship between continuous variables (RVEF and LVEF) was assessed by the non-parametric Spearman's correlation coefficient (r). The chi-square test (or Fisher's exact test, where appropriate) was used for comparisons of categorical variables. We used Cohen's kappa statistic to measure the agreement between LV and RV dysfunction. The intraclass correlation coefficient (ICC) was calculated to assess inter-observer agreement. A p-value of 0.05 (2-tailed) was defined as statistically significant. Statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, New York, USA).

3. Results

3.1. Baseline clinical characteristics

A total of 102 patients were identified, among whom 63 (62%) had RVSD and 39 (38%) had normal RVEF. The baseline clinical characteristics did not differ between patients who had RVSD and normal RVEF (Table 1). CMR data are summarized in Table 2. There was good inter-observer reliability in RVEF measurements between the 2 CMR readers (ICC=0.80, $p < 0.001$).

3.2. Relationship between RV and LV systolic function

Fig. 1 is a scatterplot showing the relationship between the RVEF and LVEF. There was a positive but moderate correlation between LVEF and RVEF ($r = 0.40$, $p < 0.001$). Approximately half of patients had both an LVEF $< 35\%$ and RVSD ($n = 54$, 53%), but 32 of 86 patients (37%) with LVEF $< 35\%$ had preserved RVEF, while 9 of 16 patients (56%) with LVEF $\geq 35\%$ had RVSD. Table 3 demonstrates the correlation between LVEF and RVEF values.

Table 1
Baseline clinical characteristics of the study population according to right ventricular function.

	Total	RVEF $< 47\%$ (M) or $< 53\%$ (F)	RVEF $\geq 47\%$ (M) or $\geq 53\%$ (F)	*p*-value
n	102	63 (62%)	39 (38%)	–
Age, years	62 ± 14	61 ± 12	62 ± 16	0.64
Gender (female)	23 (23%)	17 (27%)	33 (85%)	0.25
Hypertension	62 (61%)	40 (63%)	22 (56%)	0.53
Dyslipidemia	69 (68%)	40 (53%)	29 (74%)	0.28
History of smoking	49 (48%)	27 (43%)	22 (56%)	0.98
Current smoker	7 (7%)	6 (10%)	1 (3%)	
Diabetes	41 (40%)	25 (40%)	16 (41%)	1.00
Prior MI	61 (60 %)	36 (57%)	25 (64%)	0.54
LGE RCA territory	25 (24%)	25 (100%)	0	
Prior heart failure	53 (52%)	28 (44%)	25 (64%)	0.07
Prior PCI	37 (36%)	22 (35%)	15 (40%)	0.83
Prior CABG	23 (23%)	13 (21%)	10 (26%)	0.63

Data are presented as mean $\pm$ standard deviation or number and percentage. CABG, coronary artery bypass grafting; F, female; LGE, late gadolinium enhancement; M, male; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVEF, right ventricular ejection fraction

Table 2
Left and right ventricular volume and ejection fraction.

Value	Mean $\pm$ SD
LVEDV, mL	267 ± 85
LVEDVi, mL/m^2	140 ± 42
LVESV, mL	197 ± 80
LVESVi, mL/m^2	103 ± 40
LVEF, %	28 ± 11
RVEDV, mL	156 ± 56
RVEDVi, mL/m^2	81 ± 27
RVESV, mL	90 ± 44
RVESVi, mL/m^2	47 ± 22
RVEF, %	44 ± 12

LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic indexed volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic indexed volume; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular enddiastolic indexed volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVESVi, right ventricular end-systolic indexed volume
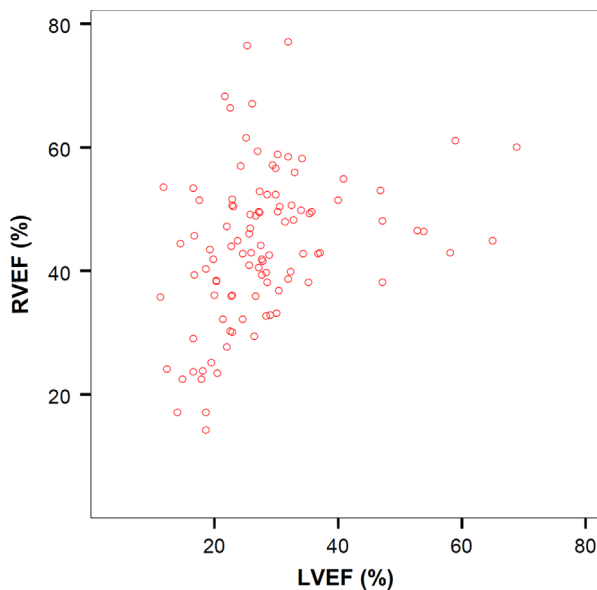

Fig. 1. Relationship between right and left ventricular function. Scatterplot demonstrates a positive but only moderate correlation between the right and the left ventricular ejection fraction (Spearman $r = 0.40$, $p < 0.001$). LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.

Table 3
Relationship between LVEF and RVEF.

	RVEF $\geq 47\%$ (M) or $\geq 53\%$ (F)	RVEF $< 47\%$ (M) or $< 53\%$ (F)	Total
LVEF $\geq 35\%$	7	9	16
LVEF $< 35\%$	32	54	86
Total	39	63	102

F, female; LVEF, left ventricular ejection fraction; M, male; RVEF, right ventricular ejection fraction.

3.3. Relationship between RV and LV systolic function and volume

We examined the relationship of RVEF and LVEF with other ventricular parameters, including right and left end-diastolic ventricular indexed volumes. Among the 63 patients with RVSD, the majority had a normal RV size ($n = 56$, 88%) but a dilated left ventricle ($n = 44$, 70%). Of the 86 patients with LVEF $< 35\%$, 14 (54%) patients had a normal LV volume, whereas 7 (8%) patients had a dilated RV (Table 4).

Table 4
a. Relationship of RV size and LV and RV systolic function.

	LVEF		RVEF	
RV size	$< 35\%$	$> 35\%$	$< 47\%$ (M)/ $< 53\%$ (F)	$\geq 47\%$ (M)/ $\geq 53\%$ (F)
Dilated	7	0	5	2
Normal	77	16	56	37
Kappa	0.028		0.025	

b. Relationship of LV size and LV and RV systolic function

	LVEF		RVEF	
LV size	$< 35\%$	$> 35\%$	$< 47\%$ (M)/ $< 53\%$ (F)	$\geq 47\%$ (M)/ $\geq 53\%$ (F)
Dilated	71	4	44	30
Normal	14	12	17	9
Kappa	0.467		-0.051	

F, female; LV, left ventricle; LVEF, left ventricular ejection fraction; M, male; RV, right ventricle; RVEF, right ventricular ejection fraction.

3.4. Chronic RV myocardial infarction

We evaluated the presence of chronic right myocardial infarction in the late gadolinium enhancement images. Twenty-five (24%) patients had positive late gadolinium enhancement in the RV consistent with chronic myocardial infarction in the RV territory. All these patients also had RVSD.

4. Discussion

In this single-center study, we observed a positive but only moderate correlation between RVEF and LVEF in patients considered for ICD implantation. More than half of the patients with LVEF $< 35\%$–which is the most commonly accepted threshold value for ICD implantation–had also RVSD. The majority of patients with RVSD had a normal RV size and dilated LV, whereas the majority of patients with LVEF $< 35\%$ had a dilated LV but normal RV size. Since there is positive but only moderate correlation between RV and LV structural and functional parameters in patients referred for potential ICD implantation, RV assessment may offer valuable information for risk stratification of ICD candidates.

Since the largest ICD clinical trials included patients with a moderately to severely reduced LVEF [2,4,6–8,20], this is also the main criterion in current evidence-based guidelines for ICD implantation [2,4,6,7,21]. However, there is increasing evidence of substantial variability and underutilization of ICD, as well as inappropriate shocks and implant complications [22]. Therefore, there is a need for more accurate risk stratification that enhances the selection of patients who will derive the greatest benefit from ICD therapy, with the ultimate goal to improve patient care and health outcomes in a cost-effective manner.

RVSD is as an independent predictor of mortality in patients with heart failure and adverse outcomes after myocardial infarction [10,12,23]. In patients with idiopathic dilated cardiomyopathy, RVEF has also been shown to be an independent predictor of survival [12,24,25], and biventricular involvement represents a typical feature of this disease. In a case control study of 57 ICD patients, Malasana and colleagues identified a higher prevalence of RVSD in the group with ICD shocks than in those who did not have ICD shocks. However, this study included only a small number of patients, and the relationship between the LV and RV was not analyzed [13]. Our study, building on previous work, is the first to analyze the relationship between the LVEF and RVEF in a cohort with a wider range of LVEF values who were considered for ICD implantation. Tabereaux and colleagues demonstrated that

RVSD represents a strong predictor of lack of clinical response to cardiac resynchronization therapy (CRT) in patients with heart failure due to left ventricular dysfunction, and should be considered when prescribing CRT [26]. However, this remains unexplored in the ICD population. In arrhythmogenic right ventricular dysplasia [22], RVSD is a major diagnostic criterion, and ICD is an important therapeutic option; however, current guidelines do not contemplate the inclusion of morphologic or functional RV parameters in the decision of ICD implantation [14,27]. A multicenter study of patients with tetralogy of Fallot [23,27] suggested the importance of ICD therapy in preventing sudden death in high-risk patients. In these patients, RV deterioration is an important prognostic indicator. Although in these specific diseases, the RV may be the origin of life-threatening arrhythmia, it is not known whether RV structural and functional parameters may afford additional guidance for ICD placement in the majority of patients who have LV dysfunction.

In our patient cohort, there was a positive but moderate correlation between RVEF and LVEF in patients being considered for ICD implantation. These results raise the potential value of RVEF in the risk stratification of patients being considered for ICD implantation, independent of the LVEF. It is important to note that, if there is a very strong correlation between RVEF and LVEF, then RVEF could not provide any additional prognostic value.

Our study follows previous efforts to investigate the use of CMR in patients considered for ICD implantation. Joshi and colleagues demonstrated the contribution of CMR in the risk stratification of patients receiving an ICD [28]. About 20% of patients considered for ICD implantation were reclassified when studied by CMR as compared with echocardiography. More recently, the extent and heterogeneity of the scar in late gadolinium CMR imaging may predict the outcome [29,30], and have been proposed as additional promising markers to stratify risk in ICD patients [31]. CMR provides more accurate and reproducible measurements of RV volumes and function as compared with 2D echo or nuclear imaging. Our study suggests that RVEF assessment might be another useful parameter in assessing risk stratification of ICD candidates.

The present study has a number of limitations. It is a retrospective, single-center study, which could limit its external validity, although the lack of strict inclusion and exclusion criteria enhances the generalizability of our findings. We did not have detailed clinical information that could help in the definition of the etiology of the RV dysfunction, so in our population, we cannot exclude any additional cause of RV dysfunction. Furthermore, outcome data were not available in this study. Therefore, long-term follow-up studies to evaluate the relationship between RV function and ICD outcomes are warranted, and may help further risk-stratify patients with RV dysfunction. This will be the focus of our future research efforts.

5. Conclusion

There is a positive but only moderate relationship between RVEF and LVEF in patients being considered for ICD implantation. A considerable proportion of patients who qualify for ICD based on low LVEF have preserved RVEF, and vice versa. Given its prognostic value, RVEF assessment by CMR may have the potential to refine risk stratification beyond LVEF. Our findings support the need for long-term studies to determine whether RVEF independently predicts ICD benefit and should be incorporated into ICD management decisions.

Disclosures

None.

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Conflict of interest

All authors declare no conflict of interest related to this study.

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