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Ten-year follow-up of cardiac resynchronization therapy patients with non-ischemic dilated cardiomyopathy assessed by radionuclide angiography: a single-center cohort study

Cinzia Valzania[1] · Giulia Massaro[1] · Alberto Spadotto[1] · Lorenzo Muraglia[2] · Jessica Frisoni[1] · Cristian Martignani[1] · Matteo Ziacchi[1] · Igor Diemberger[1,3] · Stefano Fanti[2,3] · Giuseppe Boriani[4] · Mauro Biffi[1] · Nazzareno Galié[1,3]

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Abstract

Purpose Relatively few data are available on long-term survival and incidence of ventricular arrhythmias in cardiac resynchronization therapy (CRT) patients. We investigated long-term outcomes of CRT patients with non-ischemic dilated cardiomyopathy stratified as responders or non-responders according to radionuclide angiography.

Methods Fifty patients with non-ischemic dilated cardiomyopathy undergoing CRT were assessed by equilibrium Tc^{99} radionuclide angiography with bicycle exercise at baseline and after 3 months. Intra- and interventricular dyssynchrony were derived by Fourier phase analysis. Patient clinical outcome was assessed after 10 years.

Results At 3 months, 50% of patients were identified as CRT responders according to an increase in LV ejection fraction $\geq 5\%$. During a follow-up of 109 ± 48 months, 30% of patients died and 6% underwent heart transplantation. Age and history of paroxysmal atrial fibrillation were found to be predictors of all-cause mortality. CRT responders showed lower risk of death from cardiac causes than non-responders. At follow-up, 38% of patients presented at least one episode of sustained ventricular tachycardia, with a similar percentage between responders and non-responders.

Conclusion At long-term follow-up, non-ischemic CRT recipients identified as responders by radionuclide angiography were found to be at lower risk of worsening heart failure death than non-responders. Long-term risk for sustained ventricular arrhythmia was similar between CRT responders and non-responders.

Keywords Cardiac resynchronization therapy · Non-ischemic cardiomyopathy · Survival · Ventricular arrhythmia

Abbreviations

AF	Atrial fibrillation
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy device with defibrillator capabilities
ICD	Implantable cardioverter defibrillator
LV	Left ventricular
LVEF	Left ventricular ejection fraction
PER	Peak ejection rate
PFR	Peak filling rate
RV	Right ventricular
RVEF	Right ventricular ejection fraction

✉ Cinzia Valzania
cinzia.valzania@gmail.com

1 Department of Cardiology, IRCCS, Azienda Ospedaliero Universitaria Di Bologna, Policlinico Di S.Orsola, Via Massarenti 9, 40138 Bologna, Italy

2 Department of Nuclear Medicine, IRCCS, Azienda Ospedaliero Universitaria Di Bologna, Policlinico Di S.Orsola, Bologna, Italy

3 Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy

4 Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Polyclinic of Modena, Modena, Italy

Cardiac resynchronization therapy (CRT) is an effective treatment for heart failure patients with prolonged QRS duration and reduced left ventricular ejection fraction (LVEF) [1–3]. Large randomized trials have demonstrated that CRT can improve symptoms, all-cause mortality, and hospitalization rate [1–3]. However, to date, around 30% of patients do not respond to CRT, and the reasons are still not known completely [4]. Nuclear imaging can be applied reliably in CRT patients, who cannot routinely undergo cardiac magnetic resonance, and allows for a comprehensive

evaluation of biventricular function and dyssynchrony at follow-up [5].

While the beneficial effects of CRT have been widely investigated soon after CRT implant [6], relatively few data are available on very long-term clinical outcomes of CRT recipients. In a multicenter European observational study on long-term survival of ischemic and non-ischemic CRT patients, progressive heart failure was found to be the most frequent cause of death after 5 years from implant [7]. Long-term mortality data of CRT recipients according to different heart failure etiologies are still limited [8, 9]. Moreover, there are few specific data on very long-term clinical outcome of CRT responders and non-responders, respectively. In a previous study, the cumulative incidence of major adverse cardiac events at 5-year follow-up was found to be lower in super-responders than in responders and non-responders [10].

Among CRT-induced beneficial effects, a reduction in the risk for ventricular arrhythmia has been reported [11]. This may be related to several mechanisms, including reverse remodeling and changes in hemodynamics and ventricular repolarization. The incidence of ventricular arrhythmia in patients with non-ischemic dilated cardiomyopathy and the usefulness of primary prophylactic implant of an implantable cardioverter defibrillator (ICD) or CRT device with defibrillator capabilities (CRT-D) in this category of patients have long been debated [12]. However, recent data from a large remotely monitored real-world cohort of patients receiving an ICD or CRT-D device for primary prevention have shown a similar incidence of sustained ventricular arrhythmia and appropriate device therapy in non-ischemic and ischemic patients at long-term follow-up, providing support to the benefit of ICDs in patients with non-ischemic dilated cardiomyopathy [9]. Whether CRT responders exhibit lower rate of ventricular arrhythmia at follow-up is still controversial. In a previous study, echocardiographic response to CRT at mid-term follow-up did not significantly affect the rate of ventricular arrhythmia [13]. On the contrary, results from a multicenter registry have shown a lower incidence of ventricular arrhythmia and electrical storm in CRT patients identified as responders according to clinical or echocardiographic criteria compared with non-responders [14]. To our knowledge, so far, no study has analyzed the rate of ventricular arrhythmia in CRT patients defined as responders or non-responders according to nuclear imaging criteria.

In this single-center study, we aimed to investigate long-term survival and incidence of ventricular arrhythmias in a cohort of patients with non-ischemic dilated cardiomyopathy implanted with a CRT-D device and stratified as responders and non-responders according to radionuclide angiography.

1 Methods

1.1 Patient selection and study protocol

All the patients implanted with a CRT-D device at our institution between January 2007 and January 2013 were considered for inclusion and patients fulfilling the study protocol inclusion criteria were enrolled consecutively. The inclusion criteria were as follows: (i) diagnosis of non-ischemic dilated cardiomyopathy; (ii) sinus rhythm at the time of implant; and (iii) ability to perform a bicycle exercise test. For each patient, significant coronary artery disease had been ruled out by angiography before CRT implant. The initial indication for CRT was symptomatic heart failure with reduced ejection fraction (LVEF $\leq$ 35%) and QRS prolongation (QRS width $\geq$ 120 ms) [15]. LVEF was assessed before implant by transthoracic echocardiography according to biplane Simpson's method.

All patients underwent Tc^{99m} radionuclide angiography with Fourier phase analysis, at rest and during exercise, within 4 days of CRT implant (baseline) and after 3 months, as described previously [16]. CRT was switched off between implant and baseline radionuclide examination. At baseline, resting and exercise radionuclide images were recorded during spontaneous rhythm and after CRT activation; whereas at 3 months, images were recorded during CRT only. Bicycle exercise was performed at a fixed workload of 25 W to allow for adequate exercise and comprehensive image recording. Exercise radionuclide images started to be acquired when at least a 10-beat increase in heart rate had been achieved. Left ventricular (LV) function and dyssynchrony radionuclide variables were analyzed both at baseline and after 3 months.

At follow-up, all patients underwent regular CRT device interrogation and clinical evaluation at the outpatient clinic. Follow-up evaluations were usually performed every 6 months as routine clinical care. Additional CRT-D device interrogations were performed in the event of ICD shocks. The study protocol was approved by the local ethics committee, and all patients provided written informed consent for participation.

1.2 *Tc^{99m} radionuclide angiography with Fourier phase analysis*

Radionuclide angiography was performed as described previously [16]. In summary, modified *in vivo*/*in vitro* red blood cell labeling using 2–3 mg stannous pyrophosphate was performed 15 min before injection of about 925 MBq Tc^{99m}. Planar imaging was obtained in the "best septal separation" left anterior oblique view with patients in

the semi-supine position by a dual-headed gamma camera (Philips Prism 2000 XP) equipped with parallel-hole, high-resolution collimator. Data were collected in frame mode excluding extrasystolic and post-extrasystolic beats (beat length window < 10%), with 32 frames acquired at rest and 24 during exercise (in 128 × 128 matrix). Imaging acquisition ended when total counts of ≥ 6 million were recorded at rest and ≥ 4 million during exercise.

A background-corrected, time-activity curve was obtained for both ventricles by a semi-automated edge-detection method with a variable region of interest, verified visually and modified manually, if necessary. LVEF and right ventricular ejection fraction (RVEF) were computed on the basis of the relative end-diastolic and end-systolic counts [16]. LV systolic function was assessed by measuring LVEF and peak ejection rate (PER). PER was calculated from the time-activity curve as the maximum ejection rate during systole [17]. Diastolic function was assessed by measuring the peak filling rate (PFR), corresponding to the peak value of the first derivative of the diastolic portion of the time-activity curve [18].

Inter- and intraventricular dyssynchrony were evaluated by Fourier phase analysis, as described previously [16, 19]. In detail, phase images were generated from the scintigraphic data by using the Fourier phase analysis software. The Fourier phase program assigns a phase angle to each pixel of the phase image, derived from the first Fourier harmonic of time. The phase angle corresponds to the relative sequence and pattern of ventricular contraction during the cardiac cycle. Color-encoded phase images with corresponding histograms were generated for each patient. LV and right ventricular (RV) intraventricular dyssynchrony were expressed by the standard deviation of LV and RV phase histograms, respectively, while interventricular dyssynchrony was calculated as the absolute difference between LV and RV mean phase angles [16, 19].

Patients were stratified as responders and non-responders according to LVEF variations from baseline to 3-month follow-up, assessed by radionuclide angiography under rest conditions. The response to CRT was defined by an absolute increase in LVEF ≥ 5% at mid-term follow-up [16].

1.3 Long-term follow-up data collection

Clinical outcome data were collected prospectively and analyzed retrospectively by hospital record review and telephone contact. Cause-of-death data were collected by the investigators through analysis of hospital admission reports and death certificates. According to previous studies [10, 20], deaths were classified as cardiac and non-cardiac. Cardiac deaths included worsening heart failure, acute myocardial infarction, and sudden cardiac death. Non-cardiac deaths included all other deaths caused by conditions different from cardiac diseases. As in a previous study [20], patients undergoing heart transplantation were withdrawn from survival analysis at the time of transplantation. Arrhythmia episodes were collected by CRT interrogation reports collected every 6–12 months during follow-up visits and by hospital record review. Arrhythmia episodes reported on the interrogation reports were revised and classified by one of the investigators.

1.4 Statistical analysis

Data were analyzed using a commercially available statistical package SPSS Version 23.0.0 (Statistical Package for Social Sciences Inc.). Continuous variables were presented as mean and standard deviation or median and inter-quartile range. One-way analysis of variance for repeated measures and 2-sided paired *t*-test were performed for comparisons of normally distributed variables between baseline and follow-up, at rest and during exercise. The event-free survival was evaluated with the Kaplan-Meyer method. The effect of different variables on survival was investigated using the Cox proportional hazards model. Variables showing a statistically significant effect on survival in the univariate analysis were entered in a multivariate Cox proportional hazards model. *P* values < 0.05 were considered statistically significant.

2 Results

2.1 Patient characteristics

Fifty patients were included in the study. Patient characteristics at the time of CRT-D implant are presented in Table 1. Of note, 41 (82%) patients were men and had left bundle branch block on surface ECG. Patients were prevalently in NYHA functional class II–III. Four (8%) patients had a history of paroxysmal atrial fibrillation (AF). All CRT-D implants were performed for primary prevention and occurred without significant intra- or post-operatory complications. LV lead position was anterior/anterolateral in 13 (26%) patients and posterior/posterolateral in 37 (74%) patients. Immediately after CRT implant, an echocardiographic-guided optimization of the atrioventricular and interventricular delays was performed according to conventional clinical practice [21]. Median (25th–75th percentile) values of optimized atrioventricular and interventricular delays were 130 ms (110–147 ms) and − 22 ms (− 40 to 0 ms), respectively.

2.2 Radionuclide angiography evaluation

Baseline evaluation with radionuclide angiography at rest and during exercise was completed by each patient without

Table 1 Patient characteristics ($n=50$)

Age (years)	63 ± 11
Gender M/F (*n*)	41/9
Hypertension (*n*)	17 (34%)
Diabetes (*n*)	9 (18%)
Dyslipidaemia (*n*)	26 (52%)
eGFR (ml/min/1.73 m^2)	64 ± 22
COPD (*n*)	6 (12%)
History of stroke (*n*)	3 (6%)
History of paroxysmal AF (*n*)	4 (8%)
NYHA functional class (*n*)	
II	25 (50%)
III	24 (48%)
IV	1 (2%)
QRS duration (ms)	161 ± 26
QRS morphology	
LBBB	41 (82%)
RBBB	1 (2%)
IVCD	8 (16%)
LVEF (%) by echocardiography	27 ± 5
Medication (*n*)	
β-blockers	49 (98%)
ACE-inhibitors/AII-blocker	50 (100%)
Diuretics	42 (84%)
Spironolactone	32 (64%)

AII, type 2 angiotensin receptor; *ACE*, angiotensin converting enzyme; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *LBBB*, left bundle branch block; *IVCD*, intraventricular conduction delay; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *RBBB*, right bundle branch block

any complications. Three-month radionuclide examination was performed in 48 (96%) patients. One patient died for non-cardiac causes within 3 months from implant, and one patient refused to undergo radionuclide angiography at follow-up. The time- and exercise-related values of radionuclide angiography variables in the entire study population are presented in Table 2. LV systolic function, expressed by LVEF and PER, was significantly improved at rest and during exercise at 3-month follow-up ($P<0.001$ vs. spontaneous rhythm and CRT at baseline). Accordingly, an improvement in LV diastolic function, expressed by PFR, was observed at 3 months at rest as well as during exercise ($P=0.02$ vs. CRT at baseline). A CRT-induced decrease in LV intraventricular dyssynchrony occurred both at baseline ($P=0.001$ and $P=0.035$ vs. spontaneous rhythm at rest and during exercise, respectively) and after 3 months ($P<0.001$ vs. spontaneous rhythm and $P<0.01$ vs. CRT baseline, both at rest and during exercise). No variations in RVEF were observed at follow-up, but exercise RV dyssynchrony significantly decreased at 3 months ($P<0.001$ vs. spontaneous rhythm and CRT at baseline). A decrease in interventricular dyssynchrony was observed during CRT at baseline and after 3 months only under exercise conditions ($P<0.001$ vs. spontaneous rhythm and CRT at baseline).

Among the 48 patients with available 3-month radionuclide data, 24 (50%) were found to be CRT responders according to LVEF increase. In CRT responders, at mid-term follow-up, there was a significant improvement at rest in LVEF (from 26 ± 8 to 38 ± 12%, $P<0.001$), PER (from 1.59 ± 0.51 to 2.25 ± 0.69 ml/s, $P<0.001$), PFR (from 1.02 ± 0.39 to 1.47 ± 0.60 EDV/s, $P<0.001$), LV

Table 2 Radionuclide angiography variables of ventricular function and dyssynchrony at baseline and 3-month follow-up

Variable		Spontaneous rhythm	CRT	
			Baseline	3 months
LVEF (%)	Rest	26 ± 9	26 ± 9	32 ± 12*†
	Exercise	25 ± 8	27 ± 9	31 ± 12*†
Peak ejection rate (ml/s)	Rest	1.56 ± 0.50	1.68 ± 0.57*	1.96 ± 0.68*†
	Exercise	1.64 ± 0.50	1.78 ± 0.54*	1.92 ± 0.64*†
Peak filling rate (EDV/s)	Rest	1.15 ± 0.47	1.15 ± 0.39	1.30 ± 0.54†
	Exercise	1.77 ± 0.69∞	1.66 ± 0.63∞	1.90 ± 0.87†∞
LV intraventricular dyssynchrony (°)	Rest	53 ± 30	43 ± 21*	33 ± 19*†
	Exercise	53 ± 23	48 ± 21*∞	39 ± 21*†∞
RVEF (%)	Rest	41 ± 10	39 ± 8	41 ± 8
	Exercise	38 ± 10	37 ± 8	40 ± 9
RV intraventricular dyssynchrony (°)	Rest	32 ± 17	30 ± 16	26 ± 19
	Exercise	43 ± 20∞	46 ± 22∞	35 ± 21*†∞
Interventricular dyssynchrony (°)	Rest	22 ± 13	18 ± 11	18 ± 11
	Exercise	24 ± 13	16 ± 11*	15 ± 11*

CRT, cardiac resynchronization therapy; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *RV*, right ventricular; *RVEF*, right ventricular ejection fraction

*$P<0.05$ vs. spontaneous rhythm; †$P<0.05$ vs. CRT baseline; ∞$P<0.05$ vs. rest

intraventricular dyssynchrony (from 59 ± 30° to 29 ± 18°, $P < 0.001$), and RV intraventricular dyssynchrony (from 33 ± 16° to 22 ± 8°, $P < 0.01$). In non-responders, no significant changes in radionuclide variables were detected at rest between baseline and 3-month follow-up, except for a slight increase in PER (from 1.47 ± 0.51 to 1.63 ± 0.51 ml/s, $P = 0.016$).

2.3 Survival

The survival curve for all-cause mortality for the entire study population ($n = 50$) is displayed in Fig. 1. During a mean follow-up of 109 ± 48 months, 15 (30%) patients died and 3 (6%) patients underwent heart transplantation. Seven (47%) patients died of cardiac causes (6 due to worsening heart failure and 1 due to acute myocardial infarction). No sudden cardiac death occurred. The remaining 8 (53%) patients died of non-cardiac causes (5 due to cancer, 2 due to sepsis, and 1 due to worsening chronic obstructive pulmonary disease). Three (6%) patients developed permanent AF.

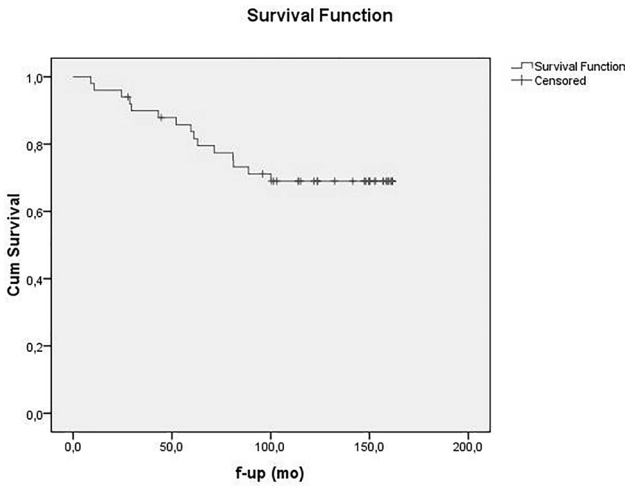

Fig. 1 Kaplan–Meier survival curve for time to all-cause mortality in the entire study population ($n = 50$)

Figure 2 shows Kaplan–Meier survival curves for time to all-cause mortality (A), time to death from cardiac causes (B), and time to death from non-cardiac causes (C) for CRT responders and non-responders, respectively. Late all-cause mortality and mortality from non-cardiac causes were not significantly different between CRT responders and non-responders ($P = 0.391$ and $P = 0.394$, respectively). However, CRT responders showed a significantly lower risk of death from cardiac causes than non-responders ($P = 0.039$). Worsening heart failure was responsible for all cardiac death among non-responders.

Clinical and radionuclide angiography predictors of all-cause mortality risk in the entire study population are presented in Table 3. Age, history of paroxysmal AF, LVEF at rest, and PER at rest and during exercise were identified as predictor variables from the univariate analysis. When predictor variables were included in the multivariate analysis, age and history of paroxysmal AF reached statistical significance as predictors of all-cause mortality.

2.4 Ventricular arrhythmias

During the follow-up, 19 (38%) patients presented at least one episode of sustained ventricular tachycardia or ventricular fibrillation, all treated efficiently by CRT-D activation. In the entire study population, the median time (25th–75th percentile) to first sustained ventricular arrhythmia was 18 (5–43) months. Fifty-four (68%) episodes of sustained ventricular arrhythmia were treated by the device with anti-tachycardia pacing and 26 (32%) with shocks. No deaths from ventricular arrhythmia were reported. Nine inappropriate CRT-D interventions (10% of all CRT-D interventions) were detected: 6 episodes in CRT responders and 3 in non-responders. The cause of inappropriate activation was AF in

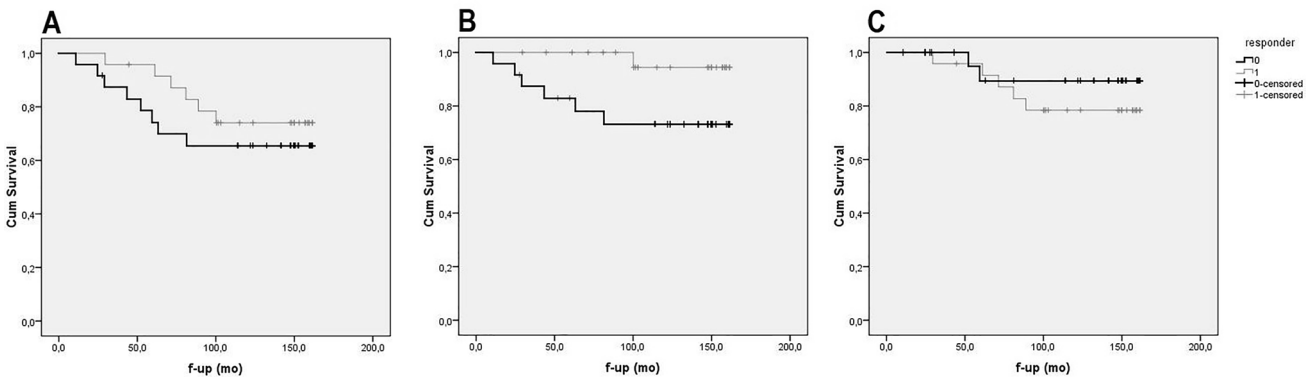

Fig. 2 Kaplan–Meier survival curves for time to all-cause mortality (**A**), time to death from cardiac causes (**B**), and time to death from non-cardiac causes (**C**) by response category. Black line refers to non-responders and gray line to responders

Table 3 Predictors of all-cause mortality risk, uni- and multivariate Cox proportional hazards models

		Univariate		Multivariate	
		HR (95% ***CI***)	*P* Value	HR (95% ***CI***)	*P* Value
Clinical variables					
Age (years)		1.07 (1.01–1.14)	0.020	1.08 (1.01–1.16)	0.029
Male gender		1.06 (0.30–3.75)	0.931		
Hypertension		0.75 (0.27–2.11)	0.588		
Diabetes		1.80 (0.57–5.65)	0.315		
Dyslipidemia		1.91 (0.65–5.59)	0.238		
eGFR (ml/min/1.73 m^2)		0.99 (0.96–1.01)	0.358		
COPD		2.08 (0.59–7.41)	0.257		
Stroke		4.21 (0.94–18.96)	0.060		
Paroxysmal atrial fibrillation		6.06 (1.67–22.03)	0.006	5.77 (1.44–23.17)	0.014
LVEF (%) by echo		1.02 (0.92–1.13)	0.697		
NYHA functional class		1.29 (0.54–3.12)	0.567		
LBBB		1.18 (0.33–4.18)	0.800		
QRS duration (ms)		1.02 (0.99–1.04)	0.093		
Radionuclide angiography variables					
LVEF (%)	Rest	0.94 (0.88–1.00)	0.052	1.02 (0.88–1.18)	0.785
	Exercise	0.94 (0.87–1.01)	0.095		
PFR (ml/s)	Rest	0.29 (0.08–1.11)	0.071		
	Exercise	0.74 (0.34–1.63)	0.454		
PER (ml/s)	Rest	0.31 (0.11–0.86)	0.024	0.30 (0.03–3.53)	0.338
	Exercise	0.24 (0.08–0.76)	0.016	0.55 (0.11–2.83)	0.473
LV IntraV dyssynchrony (°)	Rest	1.00 (0.98–1.02)	0.974		
	Exercise	1.02 (0.99–1.04)	0.111		
RVEF (%)	Rest	1.05 (0.99–1.11)	0.090		
	Exercise	1.02 (0.96–1.08)	0.638		
RV IntraV dyssynchrony (°)	Rest	0.99 (0.95–1.03)	0.605		
	Exercise	1.00 (0.97–1.02)	0.718		
InterV dyssynchrony (°)	Rest	0.98 (0.94–1.02)	0.268		
	Exercise	0.97 (0.93–1.01)	0.110		

COPD, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *LBBB*, left bundle branch block; *InterV*, interventricular; *IntraV*, intraventricular; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *PER*, peak ejection rate; *PFR*, peak filling rate; *RV*, right ventricular; *RVEF*, right ventricular ejection fraction

6 cases, lead rupture in 1 case, muscle noise in 1 case, and T-wave oversensing in 1 case.

The number of patients who presented at least one episode of sustained ventricular arrhythmia was not statistically different between CRT responders (42%) and non-responders (38%) ($P=0.77$). Figure 3 shows Kaplan–Meier curves for sustained ventricular arrhythmias for CRT responders and non-responders, respectively. As shown in the figure, no differences were found ($P=0.65$). The median time (25th–75th percentile) to first sustained ventricular arrhythmia was 20 (4–34) months and 14 (4–59) months for CRT responders and non-responders, respectively ($P=0.11$). Among CRT responders, 14 (42%) episodes of sustained ventricular arrhythmia were treated with antitachycardia pacing and 19 (58%) with shocks. In non-responders, 40 (85%) episodes of sustained ventricular arrhythmia were treated with antitachycardia pacing and 7 (15%) with shocks. The high number of shocks in CRT responders was due to the arrhythmic burden presented by one single patient who had 11 episodes of ventricular tachycardia refractory to antitachycardia pacing. From the univariate analysis, none of the analyzed clinical and radionuclide angiography parameters was identified as predictor of sustained ventricular arrhythmia in the entire study population.

3 Discussion

Both clinical outcomes and incidence of ventricular arrhythmia were investigated over a very long-term follow-up in a population of non-ischemic CRT-D recipients

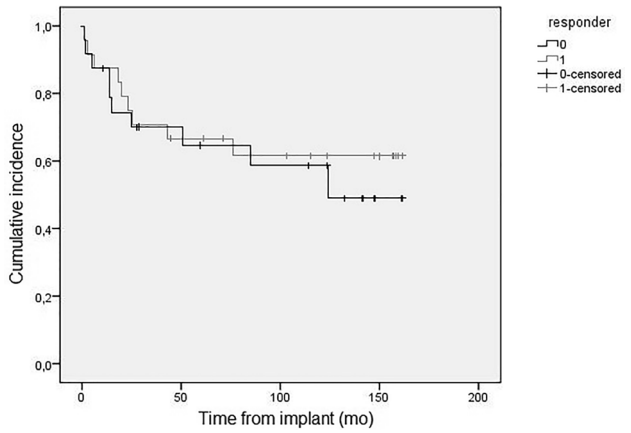

Fig. 3 Kaplan–Meier curves for appropriate sustained ventricular arrhythmia incidence by response category. Black line refers to non-responders and gray line to responders

stratified as responders or non-responders according to radionuclide angiography. Major findings were as follows: (a) during a 10-year follow-up, 30% of patients died and 6% underwent heart transplantation; (b) CRT responders showed a significantly lower risk of death from cardiac causes than non-responders; (c) age at implant and history of paroxysmal AF were found to be predictors of all-cause mortality risk; and (d) the incidence of sustained ventricular arrhythmia was not significantly different between CRT responders and non-responders.

Our findings on long-term all-cause mortality after CRT-D implant are in line with previous reports. In the study by Leyva et al. [8], over a maximum follow-up period of 16 years, total mortality was 37.2% (9.8 per 100 person-years) after CRT-D implant in a population of both ischemic and non-ischemic patients. In the same study, total mortality was found to be lower after CRT-D than after CRT-P, but the superiority of CRT-D was observed only in ischemic patients [8]. In a registry study based on real-world clinical practice, survival free of death/cardiac implant of CRT-D patients was 64% over a shorter follow-up (5 years) [22]. As in a previous European multicenter study on very long-term outcome of CRT patients [7], death due to worsening heart failure represented the main cause of cardiac mortality in our study population. Although all-cause mortality was similar between CRT responders and non-responders, CRT responders showed a significantly lower risk of death from cardiac causes. In a previous substudy of MADIT-CRT [23], CRT-induced reduction in left ventricular end-systolic volume > 35% at 1 year was associated with lower risk for long-term mortality and heart failure in patients with left bundle branch block. Taken together, these observations underline the influence of CRT-induced reverse remodeling on cardiovascular mortality and heart failure events at long-term follow-up, especially in patients with left bundle branch block.

Thus far, several predictors of long-term prognosis in patients treated with CRT have been identified [20]. Results from a large registry of ischemic and non-ischemic heart failure patients undergoing CRT showed that poor renal function, presence of AF, male gender, low functional capacity, large baseline LV end-systolic volume, and lack of LV dyssynchrony may be strongly predictive for adverse long-term outcome after CRT [20]. In a previous study on a 5-year clinical outcome of ischemic and non-ischemic patients treated with CRT [24], older age, higher NYHA class at baseline, lower LVEF before implant, and ischemic heart disease were found to be predictors of mortality. Our data from a selected population of non-ischemic CRT patients seem to confirm the role of older age and history of paroxysmal AF as predictors of all-cause mortality risk. Of note, all the patients included in our study were in sinus rhythm at implant. In a previous study [19], intraventricular dyssynchrony evaluated with phase analysis of radionuclide angiography was found to be an indepedent predictor of major cardiac events in patients with idiopathic dilated cardiomyopathy over a follow-up of 27 ± 23 months. Accordingly, previous data suggest that LV dyssynchrony by phase analysis of single-photon emission computed tomography may be predictive of cardiac death in patients with dilated cardiomyopathy [25]. In our analysis, limited to a small study population, none of the examined radionuclide angiography variables was found to be predictive of all-cause mortality or sustained ventricular arrhythmia. Further studies on larger study populations are required to evaluate the prognostic role of radionuclide angiography in CRT recipients at very long-term follow-up.

The benefit of ICD in patients with non-ischemic dilated cardiomyopathy has long been debated. In the DEFINITE trial [26], ICD implant for primary prevention in patients with severe non-ischemic dilated cardiomyopathy was associated with reduced risk of sudden cardiac death but non-significant reduction in all-cause mortality compared to standard medical therapy. More recently, in the DANISH trial, prophylactic ICD implant in patients with non-ischemic dilated cardiomyopathy was not associated with significantly lower long-term all-cause mortality compared to standard medical care [12]. However, further meta-analyses have shown a significant reduction in all-cause mortality by primary prevention ICD implant in patients with non-ischemic dilated cardiomyopathy [27, 28]. Consistently, data from a nationwide database of remote monitoring transmissions have shown a similar incidence of sustained ventricular arrhythmia in non-ischemic and ischemic ICD and CRT-D patients at long-term follow-up [9]. In our study, almost 40% of the enrolled CRT-D patients with non-ischemic dilated cardiomyopathy presented at least one episode of sustained ventricular tachycardia at long-term follow-up. Interestingly,

the number of patients who presented at least one episode of sustained ventricular arrhythmia was similar between CRT responders and non-responders. These findings highlight the overall risk for life-threatening ventricular arrhythmias even in non-ischemic patients evaluated as CRT responders at mid-term follow-up.

How improvements in cardiac function may affect risk for sudden death and mortality in heart failure patients is partially known [29, 30], and the correlation between CRT-induced reverse remodeling and risk for ventricular arrhythmia has been the object of a long debate [31]. A previous trial reported that the 5-year cumulative incidence of appropriate ICD therapy was 27% in super-responders, 34% in responders, 39% in non-responders, and 31% in negative responders, suggesting no significant association between the extent of CRT response and reduction of appropriate ICD therapy after the first year of implant [32]. Conversely, further studies have shown that LVEF recovery following CRT may be associated with reduced appropriate ICD therapy [10, 33]. Differences in the definition of CRT response and follow-up duration may perhaps account for part of the discrepancies among the reported results. Our findings on non-ischemic patients are in line with previous studies involving both ischemic and non-ischemic CRT recipients [29] and provide support to the concept that CRT responders and non-responders may have a similar risk for ventricular arrhythmia and appropriate device therapy at long-term follow-up. It should be noted that the definition of CRT response was performed in our study according to a highly reproducible imaging technique [19].

Outcome data of non-ischemic CRT-D patients from a real-world setting provide interesting clinical insights. The benefit of extending ICD therapy in patients who have improved their LVEF to > 35% under CRT treatment and who have never experienced appropriate device interventions for ventricular arrhythmias is still controversial [30]. The issue is relevant under a clinical and healthcare point of view, given the risk of complications and healthcare expenditure related to CRT replacements. Our data are in line with previous findings suggesting that even non-ischemic patients showing LVEF improvement under CRT continue to be at significant risk for ventricular arrhythmia and appropriate ICD therapy at long-term follow-up [29, 32].

3.1 Study limitations

The study has the limitations of an observational single-center analysis. The study population was small, but it included only non-ischemic CRT recipients who were able to undergo a rest and exercise radionuclide angiography examination. Moreover, a very long-term follow-up was analyzed to assess survival and incidence of ventricular arrhythmias. Long-term clinical and functional data were not collected systematically. CRT response was evaluated by radionuclide angiography in terms of LVEF increase at mid-term follow-up and not re-assessed lately. The strict criterion for CRT response definition, together with a radionuclide angiography follow-up limited to 3 months, may be responsible for a 50% CRT response rate, lower than typically reported. Moreover, heterogeneity in baseline QRS morphology and LV lead positioning may have influenced the observed response rate.

4 Conclusion

In this single-center cohort study on CRT patients with non-ischemic dilated cardiomyopathy stratified as responders or non-responders according to radionuclide angiography, we investigated both clinical outcomes and incidence of ventricular arrhythmia over a 10-year follow-up. Although late overall mortality was not significantly different between CRT responders and non-responders, CRT responders were at lower risk of death for cardiac causes. Worsening heart failure was the main cause of cardiac death in non-responders. Age at implant and history of paroxysmal AF were found to be predictors of an all-cause mortality risk. Over long-term follow-up, the number of patients who presented at least one episode of sustained ventricular arrhythmia was similar between CRT responders and non-responders. These results point out the long-term risk for ventricular arrhythmias even in non-ischemic patients evaluated as mid-term CRT responders by radionuclide angiography.

Declarations

Conflict of interest The authors declare no competing interests.

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