Heart Failure Is Common and Under-Recognized in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

BACKGROUND: Heart failure (HF) prevalence in arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) varies depending on study cohort and is not well characterized. This study sought to determine prevalence and predictors of HF in ARVC/D.

METHODS AND RESULTS: Clinical HF, defined as at least 1 HF sign or symptom, was retrospectively adjudicated for 289 patients meeting ARVC/D Task Force Criteria. HF was present in 142 patients (49%): 113 had isolated RV involvement and 29 had evidence of LV dysfunction. Average age of HF onset was 40±14 years. Most commonly reported symptoms were exertional dyspnea (78%) and fatigue (73%). Only 40% (n=57/142) had signs of volume overload. Left-sided HF signs were rare. Patients with clinical HF before ARVC/D diagnosis (n=31) were older (*P*=0.005) and met fewer Task Force Criteria (*P*=0.013) than those who developed HF after ARVC/D presentation. Female sex (odds ratio, 2.2; 95% confidence interval, 1.21–4.01; *P*=0.01) and lateral precordial T-wave inversions (odds ratio, 9.87; 95% confidence interval, 1.07–91.1; *P*=0.043) were associated with increased odds of HF. Additionally, patients with symptomatic LV dysfunction had higher odds of lateral precordial T-wave inversions (odds ratio, 18.4; 95% confidence interval, 2.92–116.18; *P*=0.002). Patients with HF were more likely to undergo heart transplantation (15/142 versus 1/147; *P*<0.001) or die during study follow-up period (7 versus 0; *P*=0.007).

CONCLUSIONS: HF symptoms, especially exertional dyspnea, are common in ARVC/D; yet, classic left-sided signs are typically absent and less than half have evidence of volume overload. Given the unique predominately right-sided phenotype, a large portion of patients with HF may be under-recognized.

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WHAT IS NEW?

- Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by fibro-fatty replacement of the myocardium, right ventricular dysfunction, and ventricular arrhythmia.
- With defibrillator therapy, patients with ARVC/D are living longer and develop other progressive manifestations of this disease. This study further describes epidemiology of heart failure in a single-center registry of ARVC/D.
- We found that heart failure symptoms/signs occurred in 49% of our ARVC/D cohort, most commonly isolated right ventricular failure. Only 40% had signs of volume overload, and left-sided heart failure signs were present in 20%.
- Female sex and lateral T-wave changes were associated with development of HF. Precordial lead T-wave changes were particularly common in patients with LV involvement.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Along with continued arrhythmia management, asymptomatic patients with ARVC/D should be considered patients with stage B HF and monitored for development of HF symptoms. HF risk factor management is also appropriate.
- In patients with reduced LV function, angiotensin-converting enzyme-inhibitor/angiotensin receptor blocker and guideline-directed β-blocker should be added as tolerated. Additionally, aldosterone antagonists can be added in those patients with New York Heart Association class II–IV symptoms.
- Referral for heart transplantation is appropriate in the setting of severe right or biventricular failure or refractory ventricular arrhythmia.
- There is much to learn about appropriate management of the predominantly right-sided heart failure in this unique patient population.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited cardiomyopathy characterized by fibro-fatty replacement of the ventricular myocardium, right ventricular (RV) dysfunction, and life-threatening ventricular arrhythmias.[1,2] Refinement of the ARVC/D diagnostic criteria[3] coupled with better understanding of the pathogenesis and clinical manifestations has led to both improved recognition and appropriate use of therapies to prevent sudden death in this population.[4]

However, the heterogeneous manifestations of heart failure (HF) in ARVC/D are less well known and HF is not a component of the 2010 Task Force Criteria (TFC). In previous studies, the prevalence of HF has ranged from 4% to 11%[5–8] although these studies were performed before either the revised diagnostic criteria were available or the widespread availability of genetic testing. In addition, several studies included at-risk family members, who are known to have a lower a priori risk of HF and prevalence numbers in these studies may not be extrapolated to the overall ARVC/D population. Of note, the development of structural heart disease in ARVC/D seems to be a slowly progressive process and therefore the onset may be subtle.[9]

We hypothesized that given the improved awareness and recognition of ARVC/D and subsequent prevention of sudden cardiac death with implantable cardiac defibrillators (ICD), HF is becoming more prevalent among patients with ARVC/D. Additionally, we hypothesized that the predominant RV involvement and lower prevalence of left-sided HF symptoms may result in under-recognition of HF symptoms in this population. The purpose of this study was to describe the prevalence, manifestations, and predictors of HF in a large US ARVC/D cohort, as well as the outcomes of those patients with ARVC/D who develop HF.

METHODS

Patient Selection

We reviewed the Johns Hopkins ARVC/D Program Registry, which was established in 1998 and prospectively enrolls patients with ARVC/D and their family members. Registry patients were included if they (1) met the 2010 Revised (TFC) for ARVC/D by last follow-up,[3] (2) had undergone screening for desmosomal mutations, and (3) had both clinical assessment for HF (either via clinic encounter or questionnaire) and evaluation of cardiac structure and function within the 2 years preceding date of last Registry follow-up. The Johns Hopkins Institutional Review Board approved the study protocol. Written, informed consent was obtained from each patient.

Clinical Data Collection

Baseline demographics and details of ARVC/D diagnosis including presentation, symptoms, medication use, comorbidities, noninvasive and invasive studies, and arrhythmia occurrence were obtained retrospectively from the ARVC/D Registry data set, accessed on September 5, 2014. The data set includes medical records and patient questionnaires on information about major clinical events, which are updated prospectively at yearly intervals after patient enrollment. As part of the Registry, detailed family history by an ARVC/D genetic counselor, as well as comprehensive (for probands) or directed (for family members) mutation testing, is performed. ECGs were read and scored according to the revised 2010 TFC. The most recent imaging study was used of each type (transthoracic echocardiogram and cardiac magnetic resonance imaging [MRI]). Composite arrhythmic outcome was defined as per our previous studies as first event of life-threatening arrhythmia, including spontaneous sustained ventricular tachycardia (VT), appropriate ICD intervention, sudden cardiac arrest, or sudden cardiac death. VT storm was defined as ≥3 sustained episodes of VT/ventricular fibrillation

separated by at least 5 minutes during 24 hours. Composite long-term outcome was defined as all-cause death or heart transplantation during study time period.

HF Adjudication

The presence of HF was determined by 2 independent HF cardiologists after retrospective review of the medical chart, including clinical assessment for HF based on review of annual follow-up documentation and imaging study reports. Patients met the definition of clinical HF if they had at least 1 HF sign or symptom in the setting of ARVC/D structural abnormalities. HF signs and symptoms included shortness of breath at rest, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema, abdominal swelling/ascites, fatigue, S3 summation gallop, jugular venous distention, and rales. If HF was considered present, patients were further categorized based on the presence or absence of structural heart disease on imaging (evidence of RV or left ventricular [LV] dilatation or dysfunction on transthoracic echocardiogram or MRI reports). RV dilatation and dysfunction were quantitatively assessed and categorized as normal, mild, moderate, or severe based on transthoracic echocardiogram or cardiac MRI report. Patients fulfilling the major structural abnormality criteria of the ARVC/D Revised Task Force Criteria were considered to have severe RV abnormality.[3] Estimated RV systolic pressure was determined by echocardiography data. Additionally, RV ejection fraction (EF), stroke volume, end-diastolic volume, and cardiac output were determined from cardiac MRI data when available. LV systolic dysfunction was defined as LVEF <45% as assessed on transthoracic echocardiogram or cardiac MRI. The subset of patients with HF was further analyzed based on the presence or absence of LV dysfunction.

Statistical Analysis

All continuous data were presented as mean±SD and categorical variables as numbers (percentages). Continuous variables were compared using the independent Student *t* test or Mann–Whitney *U* test and categorical data using χ^2 or Fisher exact tests. The cumulative freedom from death or transplant was estimated by Kaplan–Meier method. In patients with multiple end points, the first event was considered the outcome event. Differences in survival were evaluated with a log-rank test. Univariate and multivariable logistic regressions were used to identify clinical predictors of HF and LV dysfunction. A $P<0.05$ was considered significant. Statistical calculations were performed using STATA 13.1 (Stata Corp, College Station, TX). Additional sensitivity analyses were performed with (1) reclassification of those patients with fatigue as the only HF sign/symptom as not having HF and (2) exclusion of 40 patients who had ARVC/D but no structural changes to meet HF definition.

RESULTS

Study Population

All 289 patients in the study met the ARVC/D 2010 Revised Task Force Criteria. Mean age of presentation for ARVC/D was 34±14 years (Table 1). The majority had an ICD (n=247, 85%) and were on a β-blocker (n=225, 78%). Other medical comorbidities were rare.

HF Presentation and Predictors

Baseline characteristics of the study cohort (n=289) are shown in Table 1, with comparison between those with (n=142) and without (n=147) clinical HF. No significant difference was seen in sex or race between the groups with or without HF. The presence of a genetic mutation for ARVC/D did not correlate with HF; however, all 8 patients with multiple genetic mutations had symptomatic HF. Although comorbidities were rare, patients with HF were more likely to have hypertension (19/138 versus 8/145; $P=0.018$). Additionally, they were more likely to be taking a loop diuretic (24/141 versus 1/146; $P<0.001$) or aldosterone antagonist (14/141 versus 2/146; $P=0.002$; Table 1). Of the patients with HF, 113 (80%) had isolated RV involvement and the remaining 29 (20%) had biventricular involvement. The average age of HF onset was 40±14 years.

As shown in Table 2, of the 142 patients with at least 1 sign or symptom of HF, 84 had ≥2 signs or symptoms of HF (59% of HF group and 30% of total cohort) and 38 had ≥3 (27% of HF group and 13% of total cohort). The most common symptoms were dyspnea on exertion (n=108; 78%) and fatigue (n=94; 73%; Table 2). Volume overload, defined as evidence of edema or ascites, was present in 57 patients (40% of HF patients, 20% of overall ARVC/D cohort). Left-sided signs/symptoms including orthopnea (9%), paroxysmal nocturnal dyspnea (6%), and pulmonary rales (2%) were rare. Of those with HF, 85 of 142 patients met TFC for major RV structural changes; however, the presence of major TFC for RV structural changes was not more common in patients with HF than in non-HF patients (Table 3). Patients with HF had lower RV stroke volume (72.9±21.6 versus 81.7±25.7 mL; $P=0.032$), stroke volume index (40.6±12.5 versus 45.2±12.3 mL; $P=0.024$), cardiac output (4.4±1.4 versus 5.0±1.3 L/min; $P=0.006$), and cardiac index (2.49±0.75 versus 2.84±0.70 L/min per meter square; $P=0.003$) as measured by MRI, as compared with those without HF. Among the subgroup of patients with RV stroke volume data available (N=149), there was no difference in RVEF or end-diastolic volume by MRI (Table 3). Patients with HF did have more severe RV dysfunction on echocardiography (Figure 1). There was no significant difference in echocardiographically estimated RV systolic pressure measurements between those with and without HF (27.3±6 versus 26.6±6 mm Hg; $P=0.43$) or those with or without the composite arrhythmic outcome (27.2±5.9 versus 26.4±6 mm Hg; $P=0.41$).

Patients with HF had notably different ECG profiles from those without HF (Table 1). They were more likely to have right bundle branch block with negative T waves in V_1 through V_4 (20/142 versus 8/147; $P=0.026$)

Table 1. Characteristics of Patients With ARVC/D With and Without HF

	Without HF n=147	With HF n=142	Total n=289	*P* Value
Men (%)	82 (56)	65 (46)	147 (51)	0.089*
Proband (%)	105 (71)	108 (76)	213 (74)	0.37
Pathogenic mutation, any	88 (60)	85 (60)	173 (60)	0.99
Type of mutation†, n (%)				0.055
PKP2	72 (49)	64 (45)	136 (47)	
DSP	5 (3)	4 (3)	9 (3)	
DSG2	5 (3)	4 (3)	9 (3)	
DSC2	3 (2)	1 (1)	4 (1)	
JUP	2 (1)	0 (0)	2 (1)	
TMEM43	0 (0)	1 (1)	1 (0.4)	
PLN	0 (0)	2 (1)	2 (1)	
CHI/HO/DG	0 (0)	8 (6)	8 (3)	
Age at ARVC/D presentation, mean±SD	33.5±14	34±14	34±14	0.95
No. of TFC, mean±SD	6±1.6	6±1.6	6±1.6	0.12
ARVC/D presentation (%)				0.25
Sudden cardiac arrest	6 (4)	6 (4)	12 (4)	
Symptomatic	102 (69)	110 (77)	212 (73)	
Asymptomatic	39 (26)	26 (18)	65 (22)	
Comorbidities (%)				
Hypertension	8/145 (6)	19/138 (14)	27/282 (10)	0.018
Dyslipidemia	21/145 (14)	21/137 (15)	42/282 (15)	0.84
Stroke	1/145 (1)	5/137 (4)	6/282 (2)	0.085
Coronary artery disease	4/145 (3)	3/137 (2)	7/282 (2)	0.76
Medications (%)				
Loop diuretic	1/146 (1)	24/141 (17)	25/287 (8)	<0.001
ACE-inhibitor	36/146 (25)	43/141 (31)	79/287 (28)	0.27
Angiotensin receptor blocker	5/146 (3)	9/141 (6)	14/287 (5)	0.25
Aldosterone antagonist	2/146 (1)	14/141 (10)	16/287 (6)	0.002
β-blocker	111/146 (76)	114/141 (81)	225/287 (78)	0.32
Antiarrhythmic	50 (34)	66 (47)	116 (41)	0.026
ECG findings (%)				
Negative T wave in leads V_1 through V_3	116 (79)	112 (79)	228 (79)	0.59
RBBB with negative T in V_1 through V_4	8 (5)	20 (14)	28 (10)	0.026
Negative T wave in leads V_4 through V_6	1 (1)	9 (6)	10 (3)	0.018*
No. of precordial leads with T inversion, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.13
Epsilon wave in one of leads V_1 through V_3	13 (9)	16 (11)	29 (10)	0.16
TAD>55 ms in one of leads V_1 through V_3	51 (35)	52 (37)	103 (36)	0.18
Holter ectopy, median (IQR)	1645 (5175)	2624 (6595)	2489 (5410)	0.12

ACE indicates angiotensin-converting enzyme; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; HF, heart failure; IQR, interquartile range; RBBB, right bundle branch block; TAD, terminal activation duration; and TFC, Task Force Criteria.

*Significant on multivariable logistic regression model.

†One patient had a MYH7 mutation and 1 patient had a SCN5a+LMNA mutation.

and isolated T-wave inversions in precordial leads V_4 through V_6 (9/142 versus 1/147; *P*=0.018).

On multivariable logistic regression, patients with HF had a higher odds of being female (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.21–4.01; *P*=0.01), having more severe RV dysfunction on echocardiogram (OR, 4.65; 95% CI, 1.36–15.9; *P*=0.014), having hypertension (OR, 7.43; 95% CI, 1.91–28.8; *P*=0.004), and negative T waves in precordial leads V_4 through V_6 (OR, 9.87; 95% CI, 1.07–91.1; *P*=0.043; Table 4).

Table 2. Frequency, n (%), of Heart Failure Symptoms/Signs in 142 Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and Heart Failure

Frequency of signs/symptoms	
Dyspnea on exertion	108/138 (78)
Fatigue	94/129 (73)
Abdominal swelling/ascites	36/118 (31)
Lower extremity swelling	38/136 (28)
Shortness of breath at rest	17/137 (12)
Jugular venous distention	12/118 (10)
Orthopnea	12/132 (9)
Paroxysmal nocturnal dyspnea	8/132 (6)
S3 summation gallop	6/120 (5)
Hepatomegaly	1/115 (3)
Rales	2/122 (2)
Volume overload	57/142 (40)
Frequency of total number signs/symptoms per patient	
Only 1	58 (41)
≥2	84 (59)
≥3	38 (27)
≥4	17 (12)
5	12 (8)
6	6 (4)
7	3 (2)

There were 29 patients who had LV dysfunction and HF. These patients had a mean LVEF of 38±16 versus 57±7% (*P*<0.001) and LV diastolic dimension of 5.5±1.1 versus 4.6±0.5 cm (*P*<0.001) compared with those without LV involvement (Table I in the Data Supplement). Aside from lower extremity edema, there were no other signs or symptoms that were significantly more prominent in patients with biventricular dysfunction (12/28 versus 26/108; *P*=0.048). Among the 142 patients with HF, those with LV dysfunction more frequently had a history of coronary artery disease (2/28 versus 1/109; *P*=0.045) and were on an angiotensin-converting enzyme (ACE)-inhibitor (17/28 versus 26/113; *P*<0.001). Among patients with HF and a positive genotype, a higher proportion of those with LV dysfunction were carriers of a *DSP* mutation (3/15, 20% versus 1/70, 1.4%; *P*=0.016). They also had more frequent T wave-inversions isolated to precordial leads V_4 through V_6 (7/28 versus 2/113; *P*<0.001) and were less likely to meet TFC major repolarization criteria (negative T waves in leads V_1 through V_3; 16/28 versus 96/113; *P*=0.001) when compared with those without LV dysfunction. Additional characteristics and clinical events based on the presence or absence of LV dysfunction are described in Tables I and II in the Data Supplement. The only independent predictor of LV dysfunction among patients with HF on multivariable analysis was the presence of lateral precordial T-wave inversions (OR, 18.4; 95% CI, 2.92–116.18; *P*=0.002; Table III in the Data Supplement).

Timing of HF Onset

The youngest patient developed HF signs/symptoms at the age of 12 years and the oldest at 72 years, with a median age of onset of 41 years (interquartile range, 29–52 years). Of the 129 patients with known timing of HF onset, 31 had HF onset before ARVD presentation. Ten of the 31 patients were family members rather than probands. These 31 patients had less of an arrhythmic burden compared with those who developed HF after ARVC/D diagnosis: they were less likely to be on antiarrhythmic medications (9/31, 29% versus 53/97, 55%; *P*=0.013) or have had an electrophysiology study 15/31 versus 82/98; *P*<0.001 (and tended to have less VT ablation). These patients also had fewer TFC (5.7±0.3 versus 6.5±0.2; *P*=0.013) and presented with ARVC/D at an older age (40.5±2.5 versus 32.1±1.4 years; *P*=0.005). In the 245 patients without HF symptoms before ARVC/D presentation, 36% developed HF at 10 years of follow-up.

Arrhythmia

Table 5 shows outcomes among patients with ARVC/D stratified by the presence of HF. The composite arrhythmic outcome was common in the overall ARVC/D cohort (195/289); however, there was no significant difference based on the presence of HF. There were additionally no significant differences in the frequency of ICD therapy or VT ablation. Patients with HF were more likely to have had VT storm (36/142 versus 21/147; *P*=0.034; Table 5).

Long-Term Outcomes

Twenty patients met the composite outcome of all-cause death (n=4) or heart transplant (n=16) during the study period (Table IV in the Data Supplement). All patients who were transplanted met criteria for HF, except for 1 patient who was transplanted for refractory VT. Of these 20 patients, 16 met TFC for major RV structural changes and average LVEF was 43±20%. Nineteen patients experienced the composite arrhythmic outcome, and all 17 patients with an ICD received ICD therapy. Average age of death or transplant was 42.4±16.1 years. Death and transplant-free survival curves are depicted in Figure 2.

Patients with HF were more likely to undergo heart transplantation (15/142 versus 1/147; *P*<0.001). Patients with symptomatic LV dysfunction were more likely to undergo heart transplantation compared

Table 3. Structural Changes on Imaging in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia With and Without HF

	Without HF n=147	With HF n=142	Total n=289	*P* Value
Task force criteria for structural changes				
Minor abnormality	29 (20)	13 (9)	42 (14.5)	0.055
Major abnormality	75 (51)	85 (60)	160 (55.5)	0.055
Echocardiogram, n (%)				
RV dysfunction				0.001*
Mild	31/121 (26)	37/129 (29)	68/250 (27)	
Moderate	15/121 (12)	27/129 (21)	42/250 (17)	
Severe	5/121 (4)	19/129 (15)	24/250 (10)	
LVEF, %, mean±SD	56±9 (N=133)	53±12 (N=135)	55±11 (N=268)	0.03
LVEDD, cm, mean±SD	4.8±0.6 (N=117)	4.8±0.7 (N=122)	4.8±0.6 (N=239)	0.72
RVSP, mm Hg	26.6±6 (N=95)	27.3±6 (N=101)	26.9±6 (N=196)	0.43
Magnetic resonance imaging, mean±SD				
RVSV, mL	81.7±25.7 (N=90)	72.9±21.6 (N=59)	78.2±24.5 (N=149)	0.032
RVSVI, mL/m^2	45.2±12.3 (N=83)	40.6±12.5 (N=52)	43.4±12.5 (N=135)	0.024
RVEF, %†	42.1±11.5 (N=90)	40.8±10 (N=59)	41.5±10.9 (N=149)	0.48
RVEDV, mL†	203±55 (N=90)	192±56 (N=59)	199±62 (N=149)	0.38
RV cardiac output, L/min	5.0±1.4 (N=67)	4.4±1.4 (N=45)	4.8±1.4 (N=112	0.006
RV cardiac index, L/min per m^2	2.8±0.7 (N=63)	2.5±0.7 (N=40)	2.7±0.7 (N=103)	0.003

HF indicates heart failure; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; RV, right ventricle; RVEF, RV ejection fraction; RVEDV, RV end-diastolic volume; RVSP, right ventricular systolic pressure; RVSV, RV stroke volume; and RVSVI, RV stroke volume index.

*Significant on multivariable logistic regression model.

†Data presented for those patients with right ventricular stroke volume data available.

with those with HF but without LV involvement (7/29 versus 8/113; *P*=0.008). One patient underwent ventricular assist device placement before heart transplantation. Patients with HF were also more likely to die during study follow-up period (7/142 versus 0/147; *P*=0.007), with those patients with LV dysfunction at highest risk (4/29 versus 3/113, *P*=0.013). Three of the 7 deaths were because of post-transplant complications, 1 because of complications during epicardial ablation, 2 because of sudden cardiac death in the setting of longstanding cardiomyopathy, and 1 a noncardiac death.

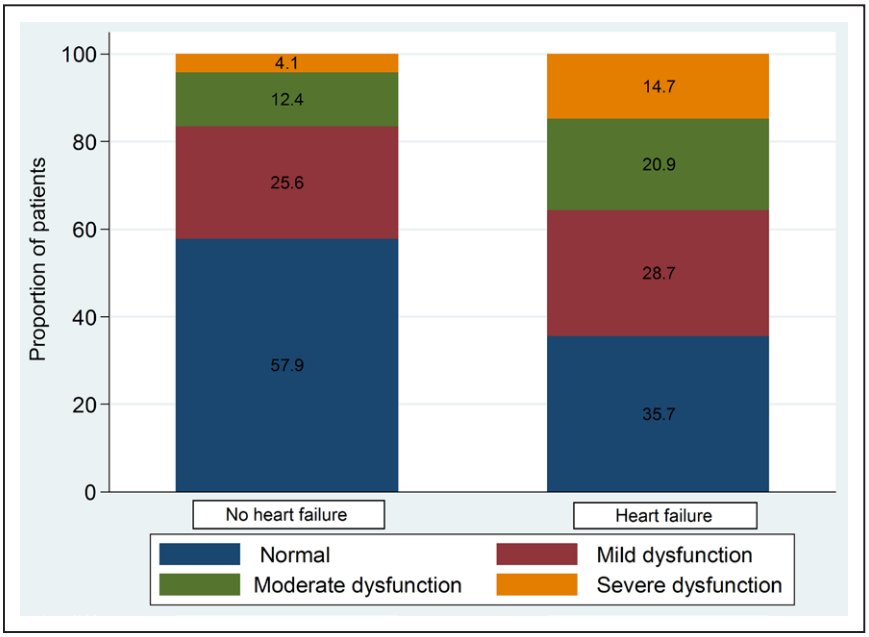

Figure 1. Degree of right ventricular dysfunction.
Proportion of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with varying degrees of right ventricular dysfunction on transthoracic echocardiogram categorized by whether or not they have heart failure.

Table 4. Predictors of Heart Failure in 289 Patients With ARVC/D on Univariate and Multivariable Logistic Regression Models

Clinical Variable	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female sex	1.49 (0.94–2.38)	0.089	2.20 (1.21–4.01)	0.010
Age at ARVC/D presentation	1.00 (0.98–1.02)	0.93	1.00 (0.97–1.01)	0.35
Pedigree (proband)	1.27 (0.75–2.15)	0.37	1.44 (0.72–2.88)	0.30
Presence of genetic mutation	1.00 (0.62–1.60)	0.99	1.01 (0.56–1.83)	0.97
Right ventricular dysfunction on echo				
Mild	1.82 (0.992–3.32)	0.053	1.71 (0.88–3.34)	0.12
Moderate	2.74 (1.32–5.70)	0.007	2.59 (1.13–5.92)	0.024
Severe	5.78 (2.02–16.57)	0.001	4.65 (1.36–15.9)	0.014
Stroke	5.45 (0.63–47.30)	0.12	5.02 (0.45–55.82)	0.19
Hypertension	2.73 (1.15–6.47)	0.022	7.43 (1.91–28.8)	0.004
Negative T wave in V_1 through V_4 in the presence of complete RBBB, minor criterion	2.87 (1.22–6.76)	0.016	1.91 (0.70–5.18)	0.207
Negative T wave in leads V_4 through V_6, minor criterion	9.95 (1.24–79.62)	0.030	9.87 (1.07–91.1)	0.043
Left ventricular ejection fraction	0.98 (0.95–1.00)	0.040	1.00 (0.97–1.04)	0.80

ARVC/D indicates arrhythmogenic right ventricular cardiomyopathy/dysplasia; CI, confidence interval; OR, odds ratio; and RBBB, right bundle branch block.

Because fatigue can be a symptom of arrhythmia or medication effect in ARVC/D, we conducted a subanalysis in which the 18 patients with fatigue as the only symptom/sign were reclassified as not having HF. The overall frequency of HF was then reduced to 43%. Those with HF were then more likely to have atrial fibrillation (23/124 versus 12/165; *P*=0.03), stroke (5/119 versus 1/163; *P*=0.039), chronic kidney disease (3/119 versus 0/163; *P*=0.042), and hypertension (17/120 versus 8/163; *P*=0.023), whereas history of VT storm became insignificant.

DISCUSSION

Ventricular arrhythmias are abundantly detected in patients with ARVC/D; however, HF is not as frequently reported in these patients. This observational study is the first to our knowledge to describe the prevalence, presentation, and predictors of HF in a large US ARVC/D cohort meeting the 2010 Revised Task Force Criteria. We found that HF is more prevalent in the ARVC/D patient population than has been described

Table 5. Clinical Events Based on the Presence or Absence of Heart Failure Signs/Symptoms in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Outcome, n (%)	Without HF n=147	With HF n=142	Total n=289	*P* Value
Arrhythmia				
Composite arrhythmic event	95 (65)	100 (70)	195 (67)	0.29
Age at composite arrhythmic event, mean±SD	36±14	35±13	36±14	0.74
Atrial fibrillation/flutter	12 (8)	24/138 (17)	36 (13)	0.024
ICD	124 (84)	123 (87)	247 (85)	0.59
ICD therapy	67/123 (54)	75/121 (62)	142/244 (58)	0.23
VT storm	21 (14)	36 (25)	57 (20)	0.034
VT ablation	51 (35)	62 (44)	113 (39)	0.12
Inducibility at EP study	81/110 (74)	86/108 (80)	167/218 (77)	0.27
Advanced therapy/mortality				
Transplant	1 (1)	15 (10.5)	16 (5.5)	<0.001
LVAD	0 (0)	1 (1)	1 (0.3)	0.53
Death	0 (0)	7 (5)	7 (2)	0.006

EP indicates electrophysiology; ICD, implantable cardiac defibrillator; LVAD, left ventricular assist device; and VT, ventricular tachycardia.

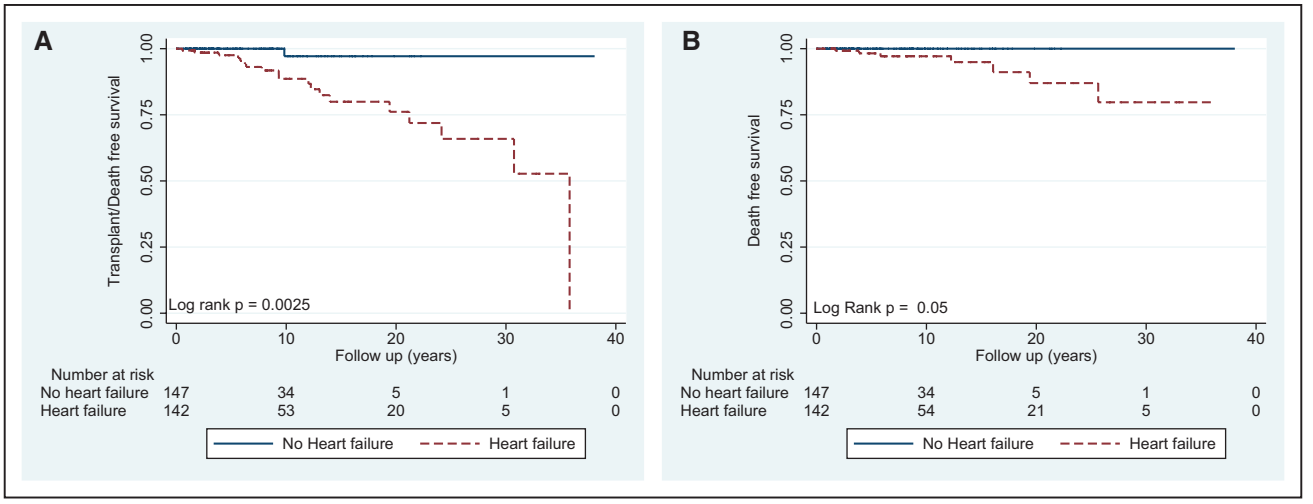

Figure 2. Kaplan–Meier event-free survival in arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with and without heart failure.
A, Event-free survival from combined outcome of heart transplant, ventricular assist device, or all-cause death. **B**, Event-free survival from all-cause death.

previously. Although only a smaller proportion had features associated with traditional HF such as volume overload and biventricular dysfunction, we found that ≈50% of patients with ARVC/D had HF signs or symptoms. There is a subgroup of patients who develop HF symptoms before their ARVC/D presentation, and these patients have a lower arrhythmic burden. Additionally, we found that ECG changes are associated with HF and LV involvement.

HF Presentation in ARVC/D

The frequency of HF symptoms in our study is substantially higher than previous reports. Protonotarios reported that in a cohort of 73 ARVC/D patients with desmosomal mutations only 2 patients had HF symptoms at presentation, and 12 developed HF at an age of 36±15 years, a lower frequency but similar age to our cohort.[10] A North American registry has also found prevalence of HF to be lower than we did, however, assessed only at the time of presentation: of 108 patients with newly diagnosed ARVC/D, 5 had New York Heart Association class II–IV right HF and only 2 patients had moderate LV dysfunction.[11] In contrast, we found that 31 of 289 patients had HF signs/symptoms before presentation for ARVC/D. The previously reported lower prevalence is likely in part because of previous work defining HF as evidence of volume overload and inclusion of at-risk family members (not only affected individuals).[8] Those factors considered, in our current study, we identified volume overload in 57 patients (20% of the entire cohort), which would suggest that the prevalence of HF has indeed increased over time and that the higher prevalence cannot solely be attributed to the HF definition used or population studied.

Although patients with HF had more significant findings of RV dysfunction on echocardiogram, they did not have more severe TFC grading of structural changes (ie, normal, minor, or major). Additionally, 22 patients in our cohort had HF signs or symptoms despite lacking ventricular dilatation or dysfunction on cardiac imaging. It is clear that echocardiographic assessment has limitation when it comes to assessing RV function, and even at rest, evaluation of RV hemodynamics may not be a comprehensive representation of RV function. These patients with dyspnea on exertion and seemingly normal appearing right ventricles may have a lack of RV functional reserve.[12,13] Additionally, structural progression does occur at a significant rate over time, but it seems to be a slow and variable process,[9] and thus may lag behind or lack correlation with symptom development.

Although a large proportion of our cohort had HF symptoms, a substantially smaller group had evidence of volume overload. The majority of patients with ARVC/D have right rather than LV failure, and physical examination findings can therefore differ. Those with right-sided symptoms may have elevated jugular venous pressure, ascites, hepatomegaly, or edema. The low numbers of patients with signs of HF may be because of the nuances of physical examination,[14] or a limited physical examination, with the majority of cardiac care focused on electrophysiological aspects of the disease, particularly ventricular arrhythmias that can be fatal in this population.

Clinical, Genetic, and Biological Predictors for HF

Despite its Mendelian autosomal dominant transmission, ARVC/D has been more commonly described in men than in women, with men having a more severe

disease form, including higher incidence of LV involvement.[15] Our study cohort was nearly equally male and female, and interestingly, women had a higher risk of having HF although sex differences were not seen based on the presence of LV involvement.

Certain genetic mutations have been shown to have more frequent LV involvement. For example, Fressart et al[16] demonstrated that of 5 desmosomal mutations, *DSG2*, was more likely to have a low LVEF (<45%; 6/12 patients; *P*=0.006). However, before their study, LV involvement was associated with *DSP* gene mutations.[17,18] In a study by Groeneweg et al,[19,20] we found that nondesmosomal phospholamban mutation carriers more often had LV involvement when compared with desmosomal mutation carriers. Patients with double mutations have also been shown to be more likely to have a lower LVEF than those with a single mutation (60% versus 19.3%; *P*=0.07). In our study, the likelihood of HF did not differ based on the presence or absence of a genetic mutation; however, all 8 patients with multiple mutations did have symptomatic HF and a *DSP* mutation was more predominant in patients with LV dysfunction.

Electrophysiological Findings

We found repolarization abnormalities, specifically lateral precordial T-wave inversions to be predictive of clinical HF, particularly of symptomatic LV HF. Previous studies have demonstrated that progressive ECG changes occur with disease progression, and patients with repolarization abnormalities have reduced time to major adverse cardiovascular events.[21,22] Our group has demonstrated previously that ECG changes can provide differential arrhythmic risk stratification.[23] However, based on our current findings, further study of how these changes relate to development of progressive HF is warranted.

We did not find major arrhythmic differences between those patients with and without clinical HF, even when taking LV dysfunction into consideration. These results may have been driven by a smaller sample size or because those without LV dysfunction still had significant RV structural disease, which is known to be associated with worse arrhythmic outcomes. With recognition and treatment of these fatal arrhythmias, the ARVC/D population is living longer, and therefore a shift in focus toward recognition and treatment of the chronic consequences of ARVC/D, primarily progressive HF, is warranted.

There is, however, a subgroup of patients who develop HF signs or symptoms before ARVC/D presentation. We found that these patients had less arrhythmic burden, were diagnosed at a later age, and met fewer TFC, and therefore may represent a milder arrhythmic ARVC/D phenotype. These differences may all actually reflect lack of prompt recognition of ARVC/D and emphasize that, in the right context, ARVC/D should be considered as a diagnosis in the setting of HF signs or symptoms.

Potential Clinical Implications

In our cohort, as expected, patients with HF were more likely than those without HF to be on diuretics and aldosterone antagonists. Although preload-reducing therapy with diuretics has recently been demonstrated to reduce progression to ARVC/D in a plakoglobin-deficient mouse model, clinically diuretic use is limited to symptomatic therapy of fluid overload because of side effects.[24] Based on low detection of volume overload in this study, likely because of less traditional manifestations, screening for subtle volume overload may be warranted. In our study, there were no differences in frequency of β-blocker or ACE-inhibitor use in HF versus non-HF patients. The use of β-blockers (particularly sotalol) in the ARVC/D population is influenced by their efficacy in protection from arrhythmia. The benefits of ACE-inhibitors and angiotensin receptor blockers are widely known, and use of these agents is guideline recommended in LV systolic dysfunction.[25] However because of the primarily RV involvement of ARVC/D, the benefits of ACE-inhibitors in this disease are less clear.

Patients with ARVC/D have also been reported to undergo orthotopic heart transplant for both ventricular arrhythmia and refractory HF. We have described previously in detail a cohort of 18 patients with ARVC/D undergoing heart transplant from our Registry.[26] Despite likely earlier development of subclinical HF symptoms, most of these patients have a prolonged course before transplant (17.6±13.3 years from ARVC/D diagnosis and 7.2±6.4 years from HF diagnosis), however, with a younger age at presentation. Patients with ARVC/D referred for transplantation additionally differ from the majority of patients undergoing heart transplantation as they are more likely to have function-limiting RV failure with or without volume overload or refractory ventricular arrhythmia rather than classic LV dysfunction. These processes make them poor LV assist device candidates, and therefore transplant may be the only advanced HF therapy option for this cohort. In fact, the ARVC/D patient population is not alone in its unique HF presentation. Several parallels may be drawn between the development and treatment of HF in ARVC/D and hypertrophic cardiomyopathy patients, for example. These are both groups who have benefited from life-saving ICD therapy but are now at risk of progressive advanced HF requiring heart transplantation, however without the classic ventricular geometry of the majority of patients with advanced HF.[27] Therefore, there is still much to be learned about these special HF populations.

Given the high ventricular arrhythmia burden in ARVC/D, this disease remains a primarily electrophysiologist-managed condition. With prevention of sudden death, however, these patients are living longer and are subsequently at risk of developing HF. We recom-

mend continued focus on prevention of arrhythmia with β-blockers, antiarrhythmics and ICDs, symptomatic treatment of HF with diuretics, and treatment of HF risk factors such as hypertension. In those patients with clear evidence of reduced LV function, use of ACE-inhibitor or angiotensin receptor blocker, plus potential aldosterone antagonists in those patients with New York Heart Association class II–IV symptoms, is appropriate. Patients with ARVC/D do run the risk of long-term progression to worsening HF and therefore there should be a low threshold to refer to a HF specialist for long-term management, including potential referral for heart transplantation.

Limitations

This analysis although unique has inherent limitations. It relies on registry data, retrospective chart review, and patient-reported symptoms, and thus recall bias, for HF adjudication. In addition, our definition of HF relies on literature primarily from LV systolic dysfunction as a specific HF definition in patients with ARVC/D has not been described previously. We elected to define HF as having at least 1 sign or symptom of HF in the setting of ARVC/D structural abnormalities. This differs from the Framingham criteria for HF; however, as we demonstrate, the expected classical major criteria from the Framingham criteria are often absent in this specific population.[28] If we instead required ≥2 signs or symptoms, the prevalence would decrease to 30%, still significantly higher than reported previously. Despite these limitations, this is the largest description of HF in an ARVC/D cohort.

CONCLUSIONS

Symptomatic HF is prevalent in patients with ARVC/D. Although overall there is a smaller subset of patients with evident volume overload and LV dysfunction requiring diuretic therapy, there is a larger portion of patients with HF symptoms that may go unrecognized. The findings of this study encourage ARVC/D patient providers to be vigilant about identifying HF signs and symptoms. This study also highlights the fact that further research is needed in regard to the best management of ARVC/D patients with HF because the majority have RV rather than LV dysfunction and this subset of patients has been less studied in large clinical HF trials.

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FOOTNOTES

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Circulation
Heart Failure

Heart Failure Is Common and Under-Recognized in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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SUPPLEMENTAL MATERIAL

Submission: Heart Failure is Common and Under-Recognized in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Included:
Supplemental Tables 1-4

Supplemental Table 1. Comparison of Arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with and without heart failure based on presence of left ventricular (LV) dysfunction.

	(-) Heart Failure n=147	(+) Heart failure (n=142)		Total (n=287)	p*
		LV dysfunction ABSENT (n=113)	LV dysfunction PRESENT (n=29)		
Male, n(%)	82(56)	48(42)	17(59)	147(51)	0.120
Proband, n(%)	105(71)	84(74)	24(83)	213(74)	0.343
Pathogenic mutation, n(%)	88(60)	70(62)	15(52)	173(60)	0.316
DSP mutation, n(%)		1/70(1.4)	3/15(20)		0.016
Age at ARVC/D presentation, mean±SD	33.5±14	33.9±13.7	32.8±16.3	33.6±14.1	0.721
Number of Task Force Criteria, mean±SD	6±1.6	5±1	7±1.5	6±1.6	0.561
ARVC/D PRESENTATION, n (%)					
Type of presentation					0.159
Sudden cardiac arrest	6(4)	3(3)	3(10)	12(4)	
Symptomatic	102(69)	90(80)	20(69)	212(73)	
Asymptomatic	39 (26)	20(18)	6(21)	65(22)	

Cardiac syncope	57(39)	39(34.5)	11(38)	107 (37)	0.126
COMORBIDITIES, n (%)					
Hypertension	8/145(6)	15/110(14)	4/28(14)	27/283(10)	0.929
Diabetes mellitus	3/145(2)	1/109(1)	1/28(4)	5/282 (2)	0.296
Dyslipidemia	21/145(14)	15/109(14)	6/28(21)	42/282(15)	0.315
Chronic kidney disease	0/145(0)	2/109(2)	1/28(4)	3/282(1)	0.575
Stroke	1/145(1)	3/109(3)	2/28(7)	6/282(2)	0.269
Coronary artery disease	4/145(3)	1/109(1)	2/28(7)	7/282(2)	0.045
MEDICATIONS, N (%)					
Loop diuretic	1/146(1)	12/113(11)	12/28(43)	24/141(17)	<0.001
Ace-inhibitor	36/146(25)	26/113(23)	17/28(61)	43/141(30)	<0.001
Angiotensin receptor blocker	5/146(3)	6(5)	3/28(11)	9/141(6)	0.295
Aldosterone antagonist	2/146(1)	7(6)	7/28(25)	14/141(10)	0.003
Beta-blocker	111/146(76)	91(81)	23/28(82)	114/141 (81)	0.846
Antiarrhythmic	50/146(34)	51/112(46)	15/28(54)	116/286(41)	0.446
ELECTROCARDIOGRAM FINDINGS, N (%)					
Negative T wave in leads V1-V3	116(79)	96(85)	16(55)	228(79)	0.001
Right bundle branch block with negative T in V1-V4	8(5)	14(12)	6(21)	28(10)	0.067

Negative T wave in leads V4-V6	1(1)	2(2)	7(24)	10(3)	<0.001
Number of precordial leads with T inversion	3.6±1.4	4.0±1.3	4.3±1.6	3.8±1.4	0.293
Epsilon wave in one of leads V1-V3	13(9)	13(12)	3(10)	29(10)	0.845
Prolonged TAD>55 msec in one of leads V1-V3	51(35)	37(33)	15(54)	103(36)	0.088
Holter ectopy, median (IQR)	1645(5175)	2561 (4817)	4501 (6560)	2489(5410)	0.339
ECHOCARDIOGRAM, mean±SD					
LV ejection fraction	56±9(n=133)	57±7(n=106)	38±16(n=29)	55±11(n=268)	<0.001
LV end diastolic dimension	4.8±0.6(n=117)	4.6±0.5(n=98)	5.5±1.1(n=24)	4.8±0.7(n=239)	<0.001

*p value comparing 113 patients without biventricular dysfunction to 29 patients with biventricular dysfunction

Supplemental Table 2. Clinical events based on presence of absence of left ventricular (LV) dysfunction in patients with Arrhythmogenic right ventricular cardiomyopathy/dysplasia and heart failure signs/symptoms.

Outcome, n (%)	LV dysfunction ABSENT (n=113)	LV dysfunction PRESENT (n=29)	Total n=142	P
ARRHYTHMIA				
Composite Arrhythmic Event	79(70)	21(72)	100(70)	0.134
Age at composite arrhythmic event, mean±SD	36±13	35±14	35±13	0.888
Atrial fibrillation/flutter	18/111 (16)	6/27 (22)	24/138(17)	0.46
ICD	96(85)	27(93)	123 (87)	0.250
ICD Therapy	60/94(64)	15/27(56)	75/121 (62)	0.435
VT storm	25/112 (22)	11(38)	36/141 (26)	0.086
VT Ablation	52(46)	10(34)	62 (52)	0.264
Inducibility at EP study	69/88(78)	17/20(85)	86/108 (80)	0.652
ADVANCED THERAPY/MORTALITY				
Transplant	8(7)	7(24)	15(11)	0.008
LVAD	0(0)	1(8)	1(1)	0.255
Death	3(3)	4(14)	7(5)	0.013

EP: electrophysiology; ICD: implantable cardiac defibrillator; LVAD: left ventricular assist device; VT: ventricular tachycardia

Supplemental Table 3. Predictors of left ventricular dysfunction among patients with heart failure on multivariate regression model.

Clinical variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Female gender	1.92 (0.84-4.39)	0.123	1.28 (0.45-3.57)	0.641
Pedigree (proband)	1.66 (0.58-4.74)	0.347	1.95 (0.50-7.69)	0.339
Presence of genetic mutation	0.66 (0.29-1.50)	0.318	0.55 (0.21-1.48)	0.238
Coronary artery disease	8.31 (0.73-95.16)	0.089	7.72 (0.56-106.1)	0.127
Negative T wave in leads V1-3, major criterion	1.01 (0.98-1.03)	0.016	0.51 (0.15—1.75)	0.284
Negative T wave in leads V4-6, minor criterion	18.5 (3.59-95.3)	<0.001	18.42(2.92-116.18)	0.002

Supplemental Table 4. Characteristics of 20 patients with Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) meeting combined endpoint of death or heart transplant.

Male, n(%)	15(75)
Age at ARVC/D presentation, mean±SD	30±13
Proband, n(%)	19(95)
Pathogenic mutation, any	8(40)
PKP2	5(25)
CH/HO/DG	3(15)
Number of Task Force Criteria, mean±SD	6.6±1.7
ARVC/D PRESENTATION, n (%)	
Sudden cardiac arrest	2(10)
Symptomatic	16(80)
Asymptomatic	2(10)
Cardiac syncope	11(55)
COMORBIDITIES, n (%)	
Hypertension	1(5)
Diabetes mellitus	1(5)
Dyslipidemia	3(15)
Chronic kidney disease	2(10)
Stroke	1(5)
Coronary artery disease	0(0)
MEDICATIONS, n (%)	
Loop diuretic	10(50)

Ace-inhibitor	8(40)
Angiotensin receptor blocker	2(10)
Aldosterone antagonist	4(20)
Beta-blocker	11(55)
Antiarrhythmic	13(65)
ELECTROCARDIOGRAM FINDINGS, N (%)	
Negative T wave in leads V1-3	15(75)
Right bundle branch block with negative T in V1-V4	6(30)
Negative T wave in leads V4-V6	2(10)
Number of precordial leads with T inversion, mean±SD	5±1
Epsilon wave in one of leads V1-V3	4(20)
Prolonged TAD>55 msec in one of leads V1-V3	12(60)
Holter ectopy, median (IQR)	6865±5915
STRUCTURAL ABNORMALITIES, n (%)	
Severe right ventricular dysfunction	9(45)
Severe right ventricular dilatation	12(60)
Left ventricular ejection fraction, mean±SD	43±20
Left ventricular end diastolic dimension, mean±SD	5.4±1.3
Task Force Criteria for Major RV Structural Abnormality	16(80)
ARRHYTHMIA	
Composite Arrhythmic Event	19(95)
Atrial fibrillation/flutter	7/18(39)
ICD	17(85)

ICD Therapy	17(85)
VT storm	12(60)
VT ablation	8(40)
SIGNS/SYMPTOMS, n(%)	
≥2 present	17(85)
≥3 present	10(50)
Volume overload present	11/19(58)

ICD: Implantable cardiac defibrillator; VT: ventricular tachycardia