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Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: Genetic characteristics☆,☆☆,★

Annina S. Vischer [a,*], Silvia Castelletti [b], Petros Syrris [c], William J. McKenna [c], Antonios Pantazis [d]

[a] Medical Outpatient Department, University Hospital Basel, Basel, Switzerland
[b] Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmia of Genetic Origin, Milan, Italy
[c] Institute of Cardiovascular Science, University College of London, London, United Kingdom
[d] Cardiomyopathy Service, Royal Brompton Hospital, London, United Kingdom

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ABSTRACT

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder. The incidence of heart failure (HF) in ARVC has been reported at 5–13%. We aimed to define the genotype and disease progression of ARVC patients with HF.
Methods: Patients with a definite diagnosis of ARVC who underwent genetic testing were consecutively recruited. Detailed clinical data was collected at baseline and during follow up. Clinical endpoint was a composite of heart transplantation and death due to HF.
Results: 135 patients were included. 8 (5.9%) patients reached the endpoint. Patients reaching the endpoint were significantly more likely to carry a Plakophilin 2 mutation than patients without HF, and 50% had multiple variants, however only one patient had 2 pathogenic mutations.
Conclusions: HF is a rare but significant outcome of patients with a definite diagnosis of ARVC. Patients with HF predominantly carried Plakophilin 2 mutations and often had multiple variants. RV dysfunction appears to be a determinant of heart transplantation and death.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder characterised by disruption of the myocytic architecture resulting in electrical instability and increased risk for life-threatening ventricular arrhythmias in some patients [1–3]. Disease causing mutations have been reported in genes encoding for desmosomal and more rarely non-desmosomal proteins [4–13].

However, arrhythmias are only one possible outcome for patients with ARVC. Heart failure (HF) is a rare, but important outcome for patients with ARVC. In a large cohort of patients with definite ARVC, the incidence of HF was reported 13%, with 4% of patients proceeding to heart transplantation (HTx) [14]. Another study reported death due to chronic HF in 11% of patients, with the age at onset being significantly higher than in patients presenting with arrhythmia [15]. In a cohort of patients carrying an ARVC-associated gene mutation, the incidence of HF has been reported at 5% [16]. Patients with multiple mutations are thought to develop a more severe phenotype [16–18] and patients with a desmoplakin (DSP) mutation to more likely develop HF [16].

Aim of our study was to define the genotype and disease progression of patients with HTx or death due to HF with arrhythmogenic right ventricular cardiomyopathy.

2. Methods

Patients referred to the Inherited Cardiovascular Disease Unit at The Heart Hospital in London, and to St Georges Hospital, London (before 2003), with a suspicion for ARVC, or with a premature sudden cardiac death (SCD) and/or known ARVC in the family (with the initial family member not checked at our hospitals), and who had undergone genetic testing, were consecutively recruited. Only patients who fulfilled diagnostic criteria according to the 2010 task force criteria [1] at any time throughout the course of their disease were included. Family members were excluded in order to study those patients with the most complete phenotype [19]; therefore, all patients were unrelated.

Detailed clinical and genetic data was collected at baseline and during follow up.

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* Corresponding author at: Medical Outpatient Department, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland.
E-mail address: annina.vischer@usb.ch (A.S. Vischer).

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2.1. Clinical data

Clinical evaluation included personal and family history, 12 lead electrocardiogram (ECG), signal averaged ECG (SAECG) and 24 h-ECG, 2D-echocardiography, and cardiopulmonary exercise test (CPEX).

Follow up visits were performed as clinically necessary, usually every 6–12 months. Patients who had not been seen for at least 2 years were contacted by telephone in January 2015. Using a structured questionnaire, information about current medication, ICD implantation/discharges, hospitalisations, comorbidities and new cases of ARVC in the family was collected.

Paper prints of the ECGs were evaluated with regard to electrical axis, QRS duration in leads V1 and V6, duration of terminal activation measured from the nadir of the S wave to the end of the QRS in leads V1 and V2, presence of T wave inversions in all leads, presence of Q waves in all leads, presence of low voltage, presence of delayed R progression, presence of left or right bundle branch block, presence and configuration of ventricular ectopics.

Automated interpretation of SAECGs was analysed with regard to filtered QRS duration, duration of the terminal QRS, low-amplitude signal duration (LAS), root-mean-square voltage of the terminal 40 ms (RMS), the same parameters in only the Z axis, the number of beats analysed and the documented noise. SAECGs with a noise ≥0.5 μV and <300 beats were excluded.

Automated interpretation of 24 h-ECGs was utilized for the number of ventricular ectopics, couplets, triplets, tachycardias, and supraventricular ectopics and tachycardias and prevalence of atrial fibrillation, and full disclosure was available if needed.

CPEX was performed using a standard Bruce protocol. Maximal oxygen consumption (VO2max), its percentage of predicted, peak heart rate and its percentage of predicted, respiratory quotient, minutes of exercise (always rounded down to the next lower), achieved power in Watts, occurring arrhythmias and current medication were taken from the standardised reports.

All echocardiographic measurements were taken from the standardised reports. Information on decreased right ventricular function, dilatation and wall motion abnormalities were also taken from the written reports, unless there were conflicting reports, in which case three cardiologists with a special interest in cardiomyopathies reviewed the images independently (ASV, SC, AP).

In all above mentioned investigations the last available was used as the follow up examination.

Genotyping was performed using next generation sequencing as described previously for hypertrophic cardiomyopathy [20]. Sequence variants were classified according to the American College of Medical Genetics (ACMG) guidelines [21].

2.2. Endpoint

Clinical endpoint was a composite endpoint of HTx and death caused by HF. HF was defined as signs and symptoms of HF without documentation of arrhythmias. Patients were then divided into two groups, one consisting of those patients reaching the composite endpoint, the other of the remainder.

2.3. Statistical analysis

Continuous variables were compared between the groups with mean ± SD and categorical variables as number (percentages) of all cases using independent sample *t*-test and Fisher's exact test. Parameters were evaluated using Odds Ratios (OR) and their Area Under the Curve (AUC) to assess their accuracy to discriminate between patients with and without heart failure. All data were analysed with SPSS Version 22 for Mac. An alpha level of 0.05 and *p*-values of <0.05 were considered as statistically significant.

3. Results

ARVC diagnosis was definite in 135 patients. Of these, 8 patients (5.9%) reached the composite endpoint of death caused by HF or HTx during a mean follow-up of 83.6 ± 31.5 months. The patients not reaching the endpoint were followed for 112.5 ± 65.8 months. HTx was performed in 5 patients, one of which died due to a dilated cardiomyopathy developing in the transplanted heart. The remaining 3 died due to HF. Of the latter, two were considered for HTx at some point

Table 1
Patients with heart failure outcome.

No	Presentation	Age at first presentation	LV dys-function	RV dys-function	ICD	Endpoint	Variant	ARVD/C Genetic Variants Database classification and variant ID	ACMG classification	GenomAD MAF
1	Cardiac symptoms	16	+	+	+	HTx, † fatal stroke	DSG2 c.3G>C; p. Met1Ile	Pathogenic; 7537 [31]	VUS	Not reported
							DSG2 c.998T>C; p. Ile333Thr	VUS; 8230 [19]	VUS	Not reported
2	VT	6	-	+	-	Declined HTx, † HF	PKP2 c.2197_2202delinsG; p.His733AlafsX8	Pathogenic; 7495 [32]	Pathogenic	2.12E-05
							PKP2 c.1941T>G; p. Cys647Trp	-	VUS	2.12E-05
3	VT	50	+/-	-/+	+	Considered for HTx, then improved, † HF	No variants			
4	VT	55	-	+	+	† HF	PKP2 c.1613G>A; p. Trp538X	Pathogenic; 7468 [19]	Pathogenic	1.59E-05
							JUP c.1159-2A>T	-	Pathogenic	Not reported
5	Cardiac symptoms	16	-	+	+	HTx	PKP2 c.775G>T; p. Glu259X	Pathogenic; 8227 [19]	Pathogenic	Not reported
6	Cardiac symptoms	59	-	+	+	HTx	PKP2 c.2197_2202delinsG; p.His733AlafsX8del	Pathogenic; 7495 [32]	Pathogenic	2.12E-05
7	Cardiac symptoms	56	+	+	+	HTx, † HF (DCM in transplanted heart)	PKP2 c.419C>T; p. Ser140Phe	Pathogenic; 7446 [33]	Likely benign	2.29E-03
							LMNA c.725C>T; p. Ala242Val	-	Likely Pathogenic	7.954E-06
8	VT	49	+	+	+	HTx, early primary graft dysfunction	PKP2 c.184C>A; p. Gln62Lys	VUS; 7441 [34]	VUS	1.68E-04
							PKP2 c.1237C>T; p. Arg413X	Pathogenic; 7462 [32]	Pathogenic	1.42E-05

Sequence variants identified in ARVC cases were cross referenced to the updated version of the ARVD/C Genetic Variants Database (https://molgenis07.gcc.rug.nl/# - accessed on 15 October 2018) [35]. Classification of identified variants was according to the American College of Medical Genetics (ACMG) guidelines for the interpretation of sequence variants [21]. Missense variants were evaluated using the InterVar bioinformatics software tool (http://wintervar.wglab.org/) [36] and the pathogenicity of nonsense, frameshift and splice site variants was determined with the online Genetic Variant Interpretation Tool provided by the University of Maryland, School of Medicine at http://www.medschool.umaryland.edu/Genetic_Variant_Interpretation_Tool1.html/ [37].

LV: left ventricular, RV: right ventricular, VT: ventricular tachycardia, ICD: implantable cardioverter defibrillator, HTx heart transplantation, HF: heart failure, †: death, DSG: desmoglein, PKP2: Plakophilin 2, JUP: junctional Plakoglobin, LMNA: Lamin A/C, VUS: variant of unknown significance.

throughout the course of their disease. Of those two patients, one declined HTx, and the other improved initially, however later died due to HF. All patients with HF had RV dysfunction at some point throughout the course of their disease, but only 4 (50%) had LV dysfunction (Table 1).

3.1. Baseline

HF patients either presented because of cardiac symptoms (4 patients, 50%) or VT/VF (4 patients, 50%). No patients were referred due to family screening or incidental findings. Among the 8 patients with HF, 5 (62.5%) had a pathogenic desmosomal gene mutation in comparison to 57 patients (44.9%) without heart failure (p 0.469). Four HF-patients had a single desmosomal pathogenic mutation, 1 had 2 desmosomal mutations (Table 1). A pathogenic Plakophilin-2 mutation was identified in 5 HF-patients (62.5%), a significantly higher percentage of patients compared to 34 (26.8%) patients in the control group (p 0.045, OR 4.56, AUC 0.68) (Table 2, Appendix Tables A.1 and A.2, Fig. 1).

At presentation, 4 patients (50%) who developed HF, reported dyspnea (19 patients (15.8%) in the control group, p 0.034) (Table 3, Appendix Table A.3).

With regard to ECG, patients with heart failure showed more extensive T wave inversions in the precordial leads. They also had more inverted and flattened T waves in leads I and aVL. Also, they presented more often with a complete or incomplete RBBB (37.5% vs. 9.0%, p 0.041, OR 6.06) (Table 3, Appendix Table A.4).

As for SAECG, patients with a HF outcome presented with a trend towards a longer filtered QRS duration (140.8 ± 31.0 ms vs. 115.9 ± 21.1 ms, p 0.050), lower RMS of the last 40 ms (4.7 ± 1.1 μV vs. 24.5 ± 19.0 μV, p 0.076) and longer LAS duration (67.2 ± 25.2 ms vs. 41.9 ± 20.0 ms, p 0.036) (Table 3, Appendix Table A.5).

In their baseline echocardiograms, 7 patients (87.5%) presented with a reduced RV function and all of them had RV dilatation as reported by the echocardiographer. In accordance to this, they had a larger RVOT diameter. No patients with HF showed dyskinesia or bulging of the RV. The left ventricular posterior wall was thinner in patients with HF (Table 3, Appendix Table A.8).

There was only a very small number of 24 h-ECGs available in patients with HF (Appendix Table A.6).

3.2. Follow up

During follow-up 5 patients (62.5%, vs. 16 patients (18.0%), p 0.011) reported dyspnea. Among the 8 patients with HF, 4 patients (50%) underwent an electrophysiological study, 7 patients (87.5%) were implanted with an ICD (e-component Table 1, Appendix Table A.9).

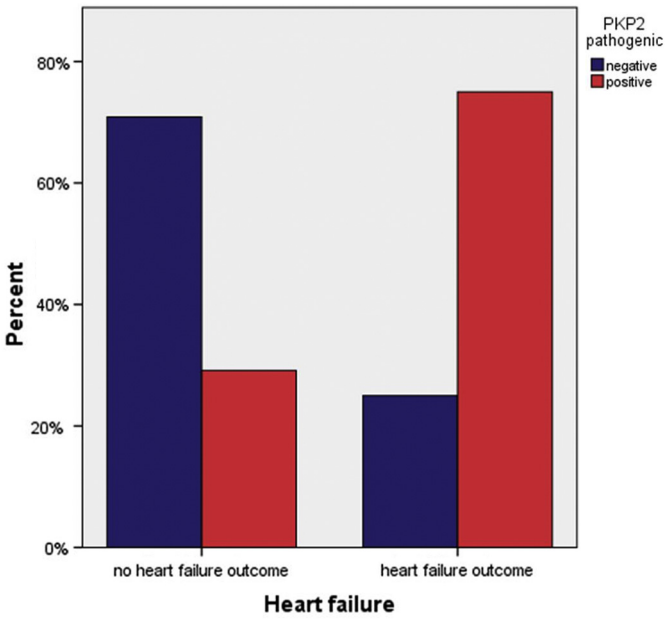

Fig. 1. Prevalence of Plakophilin 2 mutations.

All patients with HF were medically treated during follow-up (e-component Table 1, Appendix Table A.10).

On their follow-up ECGs, patients with HF showed more T wave flattening and more complete left bundle branch blocks (e-component Table 1, Appendix Table A.11).

There was only one follow up signal averaged ECG available of the patients with HF (e-component Table 1, Appendix Table A.12).

Only 2 CPEX investigations were available from patients with HF (e-component Table 1, Appendix Table A.14).

All patients with HF showed RV dysfunction, dilatation and regional wall motion abnormalities in their follow-up echocardiograms. Patients with HF had a lower LVEF at the time of follow up (e-component Table 1, Appendix Table A.15).

4. Discussion

HF is a rare outcome for patients with ARVC. The prevalence varies highly depending on the definition of HF in previous studies [15,16].

Table 2
Baseline characteristics.

		HF	No HF	p-value	Odds ratio (95% CI; p-value)	AUC (95% CI; p-value)
Baseline characteristics (n = 8/127)	Age at diagnosis	38.4 ± 21.7	41.1 ± 14.2	0.611	0.99 (0.94–1.04; 0.608)	0.52 (0.27–0.77; 0.868)
	Time of follow up (months) at THH	83.6 ± 31.5	112.5 ± 65.8	0.222	0.99 (0.98–1.01; 0.221)	0.63 (0.49–0.77; 0.228)
	Male sex	5 (62.5%)	77 (60.6%)	1.000	1.08 (0.25–4.73; 0.916)	0.51 (0.30–0.72; 0.929)
	Caucasians	8 (100%)	119 (95.2%)	1.000	108,603,347 (0.00-NA; 0.999)	0.52 (0.33–0.72; 0.820)
	Family history SCD	2 (25.0%)	56 (48.3%)	0.281	0.36 (0.07–1.84; 0.219)	0.62 (0.43–0.81; 0.272)
	Multiple family members with SCD	0 (0.0%)	12 (9.6%)	1.000	0.00 (0.00-NA; 0.999)	0.55 (0.36–0.74; 0.650)
Genetics (n = 8/127)	Desmosomal pathogenic gene mutation	7 (87.5%)	74 (58.3%)	0.144	5.01 (0.60–41.97; 0.137)	0.65 (0.48–0.82; 0.166)
	Plakophilin2 pathogenic mutation	5 (62.5%)	34 (26.8%)	**0.045**	**4.56 (1.03–20.12; 0.018)**	**0.68 (0.55–0.91; 0.030)**
	2 desmosomal mutations, same gene	3 (37.5%)	8 (6.3%)	**0.018**	**8.93 (1.80–44.22; 0.007)**	0.66 (0.43–0.88; 0.140)
	JUP pathogenic mutation	1 (12.5%)	1 (0.8%)	0.115	**18.00 (1.02–318.87; 0.049)**	0.56 (0.34–0.78; 0.579)
Diagn. criteria (n = 8/127)	Structural major criterion	8 (100%)	63 (50.0%)	**0.007**	205,139,656 (0.00-NA; 0.997)	**0.75 (0.63–0.87; 0.018)**
Reason for screening (n = 8/124)	Family history as reason for screening	0 (0.0%)	42 (33.1%)	0.057	0.00 (0.00-NA; 0.998)	0.67 (0.52–0.81; 0.117)
	VT/VF as reason for screening	4 (50.0%)	38 (29.9%)	0.255	2.34 (0.56–9.86; 0.246)	0.60 (0.39–0.81; 0.342)
	Cardiovascular symptoms as reason for screening	4 (50.0%)	40 (31.5%)	0.437	2.18 (0.52–9.14; 0.289)	0.59 (0.38–0.80; 0.381)
	Incidental findings as reason for screening	0 (0.0%)	4 (3.1%)	1.000	0.00 (0.00-NA; 0.999)	0.52 (0.31–0.72; 0.881)

HF: heart failure; CI: confidence interval; AUC: area under the curve; THH: The Heart Hospital.
Bold entries correspond with statistically significant values, i.e. alpha level is 0.05, p-values < 0.05, null hypothesis value is 1.

Table 3
Significant parameters at baseline.

	Baseline parameters	HF	No HF	*p*-value	Odds ratio (95% CI; *p*-value)	AUC (95% CI; *p*-value)
Symptoms at presentation ($n = 8/124$)	Dyspnea	4 (50.0%)	19 (15.8%)	**0.034**	**5.32 (1.22–23.12; 0.026)**	0.67 (0.46–0.89; 0.106)
ECG at baseline ($n = 8/122$)	Negative T wave V4	7 (87.5%)	46 (37.7%)	**0.008**	**11.57 (1.38–97.03; 0.024)**	**0.75 (0.60–0.90; 0.019)**
	Positive T wave I	2 (25.0%)	91 (74.6%)	**0.007**	**0.11 (0.02–0.59; 0.010)**	**0.75 (0.57–0.93; 0.019)**
	Positive T wave aVL	1 (12.5%)	72 (59.0%)	**0.021**	**0.10 (0.01–0.83; 0.033)**	**0.73 (0.58–0.89; 0.028)**
	RBBB (complete and incomplete)	3 (37.5%)	11 (9.0%)	**0.041**	**6.06 (1.27–28.80; 0.024)**	0.64 (0.42–0.87; 0.178)
SAECG at baseline ($n = 3/90$)	QRS duration	140.8 ± 31.0	115.9 ± 21.1	0.050	1.04 (1.00–1.09; 0.073)	0.76 (0.49–1.00; 0.123)
	QRS duration ≥140 ms	2 (66.7%)	10 (11.1%)	**0.043**	**16.00 (1.33–192.76; 0.029)**	0.78 (0.46–1.00; 0.103)
	RMS	4.7 ± 1.1	24.5 ± 19.0	0.076	0.60 (0.34–1.05; 0.072)	**0.95 (0.90–1.00; 0.009)**
	RMS ≤ 6 uV	3 (100%)	8 (8.9%)	**0.001**	605,803,060 (0.00-NA, 0.996)	0.96 (0.91–1.00; 0.007)
	LAS	67.2 ± 25.2	41.9 ± 20.0	**0.036**	1.04 (1.00–1.09; 0.057)	0.83 (0.65–1.000; 0.056)
CPEX at baseline ($n = 6/113$)	Arrhythmias at rest	6 (100.0%)	43 (38.4%)	**0.004**	225,415,093 (0.00-NA; 0.997)	**0.81 (0.70–0.91; 0.011)**
	NSVT during recovery	1 (16.7%)	1 (0.9%)	0.100	**22.2 (1.21–408.76; 0.037)**	0.58 (0.32–0.84; 0.516)
	%VO2max	51.0 ± 19.9	81.0 ± 23.9	**0.003**	**0.93 (0.89.0.98; 0.007)**	**0.84 (0.70–0.99; 0.005)**
	VO2 max (ml/min/1.73 m2)	14.3 ± 3.1	24.3 ± 7.4	**0.001**	**0.74 (0.59–0.93; 0.009)**	**0.88 (0.80–0.97; 0.002)**
	Min	6.2 ± 0.8	8.6 ± 2.4	**0.016**	**0.641 (0.44–0.94; 0.022)**	**0.84 (0.76–0.92; 0.005)**
	Watts	74.0 ± 21.3	152.8 ± 58.1	**0.003**	**0.97 (0.94–0.99; 0.010)**	**0.91 (0.83–0.99; 0.002)**
Echo at baseline ($n = 8/124$)	Reduced RV function (incl borderline)	7 (87.5%)	55 (44.4%)	**0.026**	**8.78 (1.05–73.53; 0.045)**	**0.72 (0.56–0.87; 0.041)**
	Reduced RV function (excl borderline)	7 (87.5%)	54 (43.5%)	**0.024**	**9.07 (1.08–75.99; 0.042)**	**0.72 (0.56–0.88; 0.038)**
	RV dilatation (excl upper normal)	8 (100%)	73 (58.9%)	**0.023**	177,038,337 (0.00-NA; 0.997)	0.71 (0.57–0.84; 0.052)
	RVOT PLAX (cm)	4.6 ± 1.1	3.6 ± 0.7	**0.000**	**4.53 (1.69–12.14; 0.003)**	**0.79 (0.60–0.99; 0.011)**
	RVOT PLAX ≥4.4 cm	4 (57.1%)	8 (9.1%)	**0.004**	**13.33 (2.53–70.41; 0.002)**	**0.74 (0.51–0.97; 0.035)**
	RVOT PLAX/BSA	2.6 ± 0.6	1.8 ± 0.3	**0.000**	10.03 (0.15–691.65; 0.286)	0.78 (0.46–1.00; 0.197)
	RVOT PLAX/BSA ≥ 2.0	4 (80.0%)	13 (19.1%)	**0.009**	**16.9 (1.74–164.32; 0.015)**	**0.80 (0.59–1.00; 0.024)**
	RVOT PSAX/BSA	2.2 ± 0.3	1.6 ± 0.3	**0.017**	15.18 (0.02–10,230.20; 0.413)	0.75 (0.20–1.00; 0.439)
	Posterior LV wall	0.7 ± 0.2	0.8 ± 0.2	**0.044**	0.00 (0.00–1.03; 0.051)	0.72 (0.52–0.93; 0.034)
	EF	48.8 ± 18.4	58.4 ± 11.6	**0.030**	**0.95 (0.90–1.00; 0.038)**	0.66 (0.46–0.85; 0.136)

HF: heart failure; CI: confidence interval; AUC: area under the curve; ECG: electrocardiogram; RBBB: right bundle branch block; SAECG: signal averaged ECG; RMS 40: root-mean-square of the last 40 ms; LAS: low amplitude signal duration; VPB: ventricular premature complexes; SVE: supraventricular ectopics; CPEX: cardiopulmonary exercise testVO2max: maximal oxygen uptake; %VO2max: VO2max, % of predicted; RV: right ventricle/ventricular; RVOT: right ventricular outflow tract; PLAX: parasternal long axis view; BSA: body surface area; PSAX: parasternal short axis view; RVIT: right ventricular inflow tract; LV: left ventricle/ventricular; LVEF: left ventricular ejection fraction.
Bold entries correspond with statistically significant values, i.e. alpha level is 0.05, p-values < 0.05, null hypothesis value is 1.

About 1% of patients undergoing heart transplantations have ARVC as their underlying disease [22]. In our cohort, 5.9% of patients with definite ARVC were either transplanted and/or died of HF. Pathogenic mutations in Plakophilin 2 were significantly more prevalent in patients reaching the HF endpoint. Half of the patients with HF had multiple gene mutations, however only one of them had multiple pathogenic mutations. Also, most of them presented with RV failure early on in the course of the disease and all of them signs of RV failure during their last follow-up examination.

To our knowledge, this is first complete analysis of genetic mutations in the era of next generation sequencing in patients with HF in the context of definite ARVC and specifically in recipients of heart transplantation for heart failure. One short report was published by Tedford et al., however the rate of patients genetically tested was not disclosed. In those patients who were genetically tested, PKP2 mutations were predominant, similarly to our study [23]. Similar results were reported by a recently published study on HTx in patients with ARVC, taken from a registry, [24]. However, genetic results were available in only about half of the patients undergoing HTx, but again PKP2 mutations were predominant [24]. There was no information on genetic results in the largest cohort of ARVC patients undergoing HTx reported to date [25].

Bhonsale et al. [16] reported that patients with Desmoplakin mutations had a four-fold increased incidence of LV dysfunction and heart failure in comparison to Plakophilin 2 carriers. However, LV dysfunction was defined as LVEF <55% and HF as "evidence of structural heart disease including RV abnormalities and symptoms directly attributed to heart failure" and therefore differ completely from our definition of a hard endpoint as HTx and death due to heart failure. In the tables in the named study, it appears that only patients with Plakophilin 2 mutations died or underwent heart transplantation. The percentage of patients dying or undergoing HTx out of all patients is smaller than ours, however in this study family members were included, which are generally thought to have a better prognosis. Loss of Plakophilin 2 in knockdown zebra fish has shown a loss of desmosomal proteins and hence cell adhesion, resulting in cardiac oedema and blood pooling, which can be interpreted as signs of HF [26].

RV dilatation and dysfunction are a component of the diagnostic criteria for ARVC [1]. Their occurrence has been reported to be a predictor of an adverse outcome [27,28]. The reason for the bad prognosis due to RV failure may lie in the difficulty of drug therapy. Medical treatment for RV failure is limited, with the usual therapeutic options used for LV failure remaining without success. So far the best data exists for phosphodiesterase type 5 inhibitors, but also this treatment is not fully developed [29]. Right ventricular assist devices and biventricular assist devices are generally only indicated in patients eligible for transplantation [30], however we are not aware of any reports in ARVC patients. As only half of the patients had LV dysfunction, but all of them had RV dysfunction, it appears that RV dysfunction is the major contributor to the development of heart failure leading to transplantation or death.

We were unable to demonstrate an age difference between patients with and without HF in contrast to was has been previously reported [15]. However, numbers of patients with HF were small in both studies, which can significantly influence this result.

4.1. Limitations

This is a retrospective study. The outcome of HF was very rare, therefore we were unable to find predictors by multivariable analysis.

5. Conclusion

Heart transplantation or death due to HF occurred in about 6% of patients with a definite diagnosis of ARVC. Most patients with HF in ARVC had a genetic mutation in Plakophilin 2. Half the patients have multiple mutations. RV dysfunction appears to be a marker of heart transplantation or death due to HF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.065.

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The authors declare that there is no conflict of interest.

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