Clinical characteristics and follow-up of pediatric-onset arrhythmogenic right ventricular cardiomyopathy

Short title: Pediatric-onset arrhythmogenic right ventricular cardiomyopathy

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Structured Abstract

Objectives: To describe characteristics, cascade screening results, and predictors of adverse outcome in pediatric-onset arrhythmogenic right ventricular cardiomyopathy (ARVC).

Background: While ARVC is increasingly recognized in children, pediatric ARVC cohorts remain underrepresented in the literature.

Methods: We included 12 probands with pediatric-onset ARVC (<18 years at diagnosis) and 68 pediatric relatives (<18 years at first evaluation) referred for cascade screening. ARVC diagnosis was based on 2010 Task Force Criteria (TFC). Clinical presentation, diagnostic testing, and outcomes (sustained ventricular tachycardia [VT]; heart failure) were ascertained. Predictors of adverse outcome were determined by univariable logistic regression.

Results: Pediatric-onset ARVC was diagnosed in 12 probands and 12 (18%) relatives at age 16.6 (interquartile range 13.8-17.4) years, while 12 (18%) relatives reached ARVC diagnosis as adults (age 22.0 [interquartile range 20.0-26.7] years). Sudden cardiac death/arrest was the first disease manifestation in 3 (25%) probands and 3 (4%) relatives. In patients without ARVC diagnosis at presentation (n=61), ECG and Holter monitoring abnormalities occurred prior to development of imaging TFC (7.3±5.0 vs. 8.4±5.0 years). Clinical course was characterized by sustained VT (91%) and heart failure (36%) in probands, which were rare in relatives (2% and 0%, respectively). Male sex ($p<0.01$), T-wave inversion V1-3 ($p<0.01$), premature ventricular complexes/runs ($p\leq0.01$) and decrease of biventricular ejection fraction ($p\leq0.01$) were associated with VT occurrence.

Conclusions: Pediatric ARVC carries high arrhythmic risk, particularly in probands. Disease progression is particularly observed on ECG or Holter monitoring. Arrhythmic events are

associated with male sex, T-wave inversions, premature ventricular complexes/runs and reduced biventricular ejection fraction.

Keywords:

Arrhythmogenic right ventricular cardiomyopathy, cascade screening, genetics, heart failure, pediatric-onset, sudden cardiac death, ventricular tachycardia.

Condensed Abstract

While ARVC is recognized in young subjects, pediatric ARVC remains underrepresented in the literature. In this multicenter study of 80 (12 probands, 68 relatives) pediatric ARVC patients, disease penetrance peaked during late adolescence (median age at diagnosis 16.6[range 9-17] years). Notably, sudden cardiac death/arrest was the presenting symptom in both probands (n=3/12; 25%) and relatives (n=3/68; 4%), while clinical course after diagnosis was more benign in relatives compared to probands (2% vs. 91% ventricular tachycardia during follow-up). Arrhythmic events associated with male sex ($p<0.01$) ECG ($p<0.01$), Holter monitoring abnormalities ($p=0.01$) and reduced biventricular ejection fraction ($p\leq0.01$). These data may inform decision making in ARVC families.

Abbreviations list:

ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia; PVC = premature ventricular complex; RVEF = right ventricular ejection fraction; TFC = task force criteria; VT = ventricular tachycardia.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty replacement of predominantly the right ventricular myocardium, which may result in potentially lethal ventricular arrhythmias and progressive ventricular dysfunction (1). Definite ARVC diagnosis requires an extensive diagnostic work-up as described in the so-called "Task Force" Criteria (TFC), which were based on an adult population (1-3). Furthermore, penetrance of ARVC is highly variable and age-dependent (4). Although disease penetrance peaks during young adulthood, rare but severe cases of pediatric-onset ARVC have been described (5,6). As such, a diagnosis of pediatric-onset ARVC has important implications, because these individuals are exposed to radical lifestyle modifications at young age, frequent cardiovascular re-evaluations to monitor disease progression, and decisions on implantable cardioverter defibrillator (ICD) implantation (7).

Pediatric-onset ARVC has increasingly been recognized during the past decade, and cascade screening guidelines now recommend to start screening at the age of 10 years (7-10). Nonetheless, pediatric ARVC patients are still underrepresented in the literature, and diagnostic as well as management recommendations are based on the adult disease phenotype (3). Likewise, the yield of cascade screening and predictors of adverse outcome in pediatric subjects remain unknown.

To address these shortcomings, we aim to describe the clinical presentation, phenotypic characteristics, and outcomes of patients diagnosed with pediatric-onset ARVC. As a secondary objective, we sought to determine predictors of disease expression and adverse outcome among pediatric relatives referred for cascade screening.

Methods

Study Population

The patient population was drawn from the Netherlands Arrhythmogenic Cardiomyopathy Registry (www.acmregistry.nl) (11). This registry is a national, multicenter observational cohort that prospectively enrolls patients with ARVC and their relatives who are referred for ARVC cascade screening. For the purpose of this study, we included subjects who consented to our registry in the University Medical Center Utrecht, Amsterdam University Medical Center, or University Medical Center Groningen, and were evaluated for ARVC prior to the age of 18 years. The study was exempt from the Medical Research Involving Human Subjects Act as per judgement of the Medical Ethics Committee (18-126/C, Utrecht, the Netherlands).

Clinical evaluation

Patients were evaluated according the registry protocol (11). Detailed clinical information regarding demographics, presentation, and symptom onset was obtained for every participant using medical record review. Phenotypic characterization was performed upon discretion of the treating physician, and included 12-lead electrocardiograms (ECG), signal averaged electrocardiograms, exercise testing, Holter monitoring recordings, echocardiography, cardiovascular magnetic resonance (CMR), electrophysiological study and/or endomyocardial biopsy.

Genetic evaluation

Probands were defined as the first affected patient in a family in whom definite ARVC diagnosis was confirmed. Relatives were defined as family members of a proband with definite ARVC, as done previously (see **Supplementary Table 1** (5,6,11)). All probands underwent genetic testing

for the ARVC-associated genes, while relatives were only tested for the variant identified in their proband. Pathogenicity of variants was evaluated based on the guidelines developed by the American College of Medical Genetics and Genomics (12,13). Subjects with an autopsy diagnosis of ARVC who either did not undergo genetic screening or were obligate carrier were considered to carry the same variant as identified in their first-degree relatives.

Arrhythmogenic right ventricular cardiomyopathy diagnosis

Diagnosis of ARVC was based on the revised 2010 TFC (3). Definite ARVC was defined as either ≥2 major, 1 major and ≥2 minor or ≥4 minor TFC. Pediatric-onset ARVC was defined as a definite ARVC diagnosis prior to the age of 18 years. Precordial T-wave inversions were excluded from the TFC for patients prior to the age of 14 years (3,14,15). Age-appropriate criteria were used to assess late potentials on signal averaged electrocardiogram recordings, as published previously (16).

Follow-up and outcome definitions

Clinical management was performed upon discretion of the treating (pediatric) cardiologist. Follow-up was determined from the date of first evaluation until the most recent clinical evaluation. In case of cardiac transplantation or death, the dates at which these occurred were considered to be the dates of last follow-up.

For cascade screening analyses, we evaluated the presence or absence of disease progression, which was defined as the development of a new diagnostic 2010 TFC and/or progression from a minor to a major criterion at last follow-up, that was absent at first presentation.

Our primary outcome was the occurrence of potentially life-threatening arrhythmic events, which was defined as a composite of sustained ventricular tachycardia (VT), ventricular fibrillation, resuscitated sudden cardiac arrest, sudden cardiac death, or appropriate ICD intervention, as done previously (17). Secondary outcomes included symptomatic heart failure, cardiac transplantation, and death. Definitions are provided in **Supplementary Table 1**.

Statistical Analysis

All continuous data were presented as mean ± standard deviation or median (interquartile range), while categorical variables were presented as numbers (percentages). Continuous variables were compared using the independent Student *t*-test or Mann Whitney *U* test, and categorical data using Chi-square or Fisher's exact tests, as appropriate. By definition, serial cascade screening constitutes observed time, which was visually evaluated by Kaplan Meier curves to determine differences in survival free from disease progression. However, due to heterogeneity in the performed diagnostic modalities and/or baseline evaluation, comparison using log-rank tests was considered inappropriate. Data were therefore presented as incidence rates with 95% confidence intervals. Predictors of ventricular arrhythmias were determined by univariable logistic regression, which was chosen over Cox regression since many subjects presented with an event (i.e. the absence of observed time until the arrhythmic outcome limited our ability to perform survival analysis). A p-value of <0.05 was considered statistically significant. Data was analyzed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, USA) and GraphPad Prism version 8.3 (La Jolla, California, USA).

Results

Study Population

Figure 1 shows a flowchart of our study population. As of July 1st, 2020 the Netherlands arrhythmogenic cardiomyopathy registry includes a total of 1109 patients, of whom 80 (7%) patients were referred for genetic and clinical evaluation prior to the age of 18 years in the predefined enrolling centers (11). Their clinical characteristics at first presentation are presented in **Table 1.**

Characteristics of Probands

A total of 12 pediatric probands (67% male, 16.8 [13.7-17.1] years old at first evaluation) were identified (**Figure 1 and Table 1**). One (8%) proband (a 13-year old female) presented with sudden cardiac death and died upon presentation (**Supplementary Table 2**). Since no clinical evaluation was available prior to presentation, she was excluded from further analyses. The remaining pediatric probands most commonly presented with sustained VT (n=7, 58%), followed by recurrent syncope (n=2, 17%) and resuscitated sudden cardiac arrest (n=2, 17%). Among 11 pediatric probands who underwent genetic testing, 9/11 (82%) carried a pathogenic/likely pathogenic genetic variant. Variants in *PKP2* (n=5, 42%) were most prevalent, followed by digenic variants in *PKP2* and *DSG2* (n=2, 17%) and compound heterozygosity (n=2, 17%) (**Figure 2** and **Supplementary Table 3**).

Clinical evaluation was available in 11 probands who presented alive. An abnormal ECG (n=10, 91%) was the most frequently observed abnormality, with T-wave inversion in V1-3 among those >14 years of age as most common finding (n=9, 82%). Almost half (n=5, 46%) of probands had abnormal cardiac imaging, with a median right ventricular ejection fraction (RVEF) and left

ventricular ejection fraction (LVEF) of 33% [25-45%] and 49% [39-56%], respectively. A definite diagnosis of ARVC was made at presentation in 10/11 (91%) pediatric probands. Detailed information regarding evaluation and management of probands is described on a case-by-case basis in **Supplementary Table 4**.

Characteristics of Relatives

Overall, 68 pediatric relatives (44% male, 13.2 [10.1-15.3] years old at first evaluation) were identified (**Figure 1 and Table 1**). Two (3%) relatives (a 17-year old male and a 9-year old female) presented with sudden cardiac death and died upon presentation prior to cascade screening (see **Supplementary Table 2**). Both cases were asymptomatic prior to their death and were not recognized as possible ARVC cases during autopsy. Since no clinical evaluation was available prior to presentation, these subjects were excluded from further analyses. The remaining relatives were most commonly referred for clinical evaluation because of cascade screening (n=61, 90%), followed by (near)-syncope (n=2, 3%), palpitations (n=1, 2%), sustained VT (n=1, 2%), and resuscitated sudden cardiac arrest (n=1, 2%). A total of 19 (29%) relatives did not (yet) participate in genetic evaluation. Among 47 pediatric relatives who underwent genetic evaluation, 44 (94%) carried a pathogenic/likely pathogenic genetic variant. Variants in *PKP2* (n=34, 72%) and *PLN* (n=8, 17%) were most prevalent (see **Figure 2 and Supplementary Table 3**). Differences between the identified genetic variants of probands and relatives occurred because we included all subjects who were evaluated prior to the age of 18 years. This included relatives whose respective proband presented at adult age, and whose proband was excluded for this study.

Clinical evaluation was available in 66 relatives who presented alive (**Table 1**). An abnormal ECG was observed at first evaluation in 8 (12%) relatives. Abnormal imaging was

observed in 3 (5%) relatives, with a median RVEF and LVEF of 53% [46-57%] and 60% (57-64%), respectively. A definite diagnosis of ARVC was made at presentation in 6 (9%) living relatives. There was no difference in age (p=0.11) and sex (p=0.90) among relatives with and without a definite ARVC diagnosis at presentation. Detailed information regarding evaluation and management of relatives is described on a case-by-case basis in **Supplementary Table 5**.

Yield of Serial Evaluation in Subjects without Diagnosis at Presentation

Overall, one proband (male, 17 years old, who presented with palpitations) and 60 relatives (46% male, 12.6 [9.8–15.3] years old) did not fulfill ARVC diagnosis at time of first evaluation. Phenotypic development during follow-up in these individuals is shown in **Table 2** and **Figure 3**.

During 8.5 [5.2–12.4] years of follow-up, disease progression (defined as the presence of an abnormal TFC at last follow-up, which was absent at enrollment) was observed in 30/61 (49%) subjects (43% males, median age at first evaluation 13.8 [11.4–16.1] years old). Progression was most frequently observed on ECG (n=14/56, 25%), followed by CMR (n=12/59, 20%), and Holter monitoring (n=11/56, 20%). **Figure 4** shows progression on ECG, Holter monitoring and imaging during follow-up. Time to progression was 7.3±5.0 years for ECG/Holter monitoring abnormalities and 8.4±5.0 years for imaging changes (CMR and/or echocardiography). This corresponded to a 1-year incidence rate of 0.054 (95% confidence interval 0.035-0.081) for ECG/Holter monitoring, which was almost double the 1-year incidence rate for newly abnormal imaging (incidence rate 0.029, 95% confidence interval 0.017–0.048). Among ECG and Holter monitoring criteria, a newly prolonged terminal activation duration (n=10/56, 18%), premature ventricular complex (PVC) count >500/24hrs (n=8/56, 14%) and non-sustained ventricular tachycardia (NSVT, n=7/56, 13%) were the most prevalent findings. Regarding imaging criteria,

new CMR abnormalities (n=12/59, 20%) were more prevalent than new echocardiography criteria (n=6/59, 10%). None of the tests that were abnormal at presentation reverted to normal during follow-up.

Nineteen (1 proband and 18 relatives) subjects were diagnosed with ARVC during follow-up (31% of those without diagnosis at presentation). This specific proband was referred for evaluation of recurrent syncope and palpitations. While he did not meet the 2010 diagnostic TFC at first evaluation, he experienced disease progression and a definite ARVC diagnosis was made before 18 years of age. This made him eligible for inclusion as a pediatric proband in this study. The majority of these individuals were females (n=11, 58%) who reached diagnosis in young adulthood (median age at diagnosis 19.9 [16.2–22.6] years). There was no significant difference in duration of follow-up between those with and without definite ARVC diagnosis (median 8.6 [7.6–13.5] years vs. 8.1 [4.6–11.4] years, respectively, p=0.14).

Clinical Characteristics associated with Arrhythmic Events

The remaining analyses were performed among all 77 patients who presented alive. Overall, 12 (16%) subjects (10 probands and 2 relatives) experienced ventricular arrhythmias after median 1.8 [0.3 – 1.6] years of follow-up, which included 10 probands who had a first event at presentation but experienced a second event during follow-up (**Figure 3**). Heart failure developed in four (36%) probands after median 17.7 [6.0 – 24.1] years of follow-up, of whom one underwent cardiac transplantation (at age 47 years) and two died (at age 21 and 37 years) due to therapy-resistant congestive heart failure (**Figure 3)**. None of the relatives experienced heart failure or death. As shown in **Figure 3**, first sustained VTs typically occurred during late adolescence (median age 17.9 [17.2–18.8] years), whereas heart failure was only observed during adulthood (median age

35.6 [23.1–38.2] years). Overall, 20 (11 probands and 9 relatives) subjects had transvenous ICDs implanted, all of whom had a definite diagnosis at time of ICD implantation. ICD follow-up was complicated by lead revision in two patients, which included lead dysfunction in one patient and upgrade to a two-chamber system because of pacemaker syndrome in the other patient. Furthermore, one patient had two episodes of inappropriate shocks due to atrial tachycardia and atrial fibrillation. In addition, 20 patients (11 probands and 9 relatives) received antiarrhythmic medication: sotalol (n=12), betablockers (n=7) or flecainide (n=1). A total of five probands underwent VT ablation for recurrent sustained VT.

Table 3 shows the association of clinical characteristics with arrhythmic outcome in pediatric-onset ARVC. As expected, probands were more likely to experience ventricular arrhythmia compared to relatives ($p<0.01$). In addition, males had significantly increased risk of events compared to females ($p<0.01$), while the identification of a pathogenic/likely pathogenic genetic variant associated with arrhythmic occurrence with borderline significance ($p=0.06$). With regards to clinical evaluation, T-wave inversions in V1-3 ($p<0.01$), documentation of NSVT ($p<0.01$) and a higher PVC count on Holter monitoring ($p=0.01$) were associated with ventricular arrhythmias. In addition, both LVEF ($p=0.01$) and RVEF ($p<0.01$) were lower in subjects with arrhythmic events.

Discussion

This study reports the clinical characteristics of subjects with pediatric-onset ARVC, describes testing results during serial evaluation, and determines predictors of adverse clinical outcome. The main findings of the study are: 1) sudden cardiac death may be the first manifestation of ARVC in both pediatric probands and relatives; 2) definite ARVC diagnosis before adolescence is rare but should not be overlooked, as potentially lethal complications may occur; 3) ECG, Holter monitoring and CMR most frequently identify disease progression during follow-up; 4) T-wave inversions, frequent PVCs including NSVT, and reduced biventricular ejection fraction are associated with arrhythmic events.

Pediatric-onset ARVC in the literature

Studies evaluating pediatric-onset ARVC are hampered by small sample sizes (**Table 4**). Regardless, the available data suggests that the majority of pediatric-onset ARVC cases present during puberty and adolescence, which was also observed in our cohort. Most prior studies focused on diagnostic evaluation of pediatric ARVC cases, specifically investigating the diagnostic tests and criteria of the TFC (18-21). We now extend prior findings in one of the largest cohorts of pediatric-onset ARVC subjects, by evaluating the performance of diagnostic testing during cascade screening of relatives and focusing on pediatric-specific markers of arrhythmic risk.

Sudden cardiac death as mode of presentation in pediatric-onset ARVC

In our study, sudden cardiac death (n=3) or sudden cardiac arrest (n=3) was the mode of presentation in 6/80 (8%) of pediatric cases. While this percentage is much higher than in adult patients with ARVC (22) and in children with dilated cardiomyopathy (23), it is similar to high-risk pediatric hypertrophic cardiomyopathy cohorts (24). Of note, none of the subjects experiencing sudden cardiac death or sudden cardiac arrest were medically evaluated before their event, which suggests the absence of symptoms and/or short interval between symptom onset and arrhythmic events in these children (**Supplementary Table 2**) (25). While these events will therefore be difficult to prevent in probands, vigilance in relatives should be high. Indeed, we observed one relative with sudden cardiac arrest without prior participation in cascade screening. Importantly, none of the subjects experienced sudden cardiac death during follow-up after medical evaluation. This suggest that proper management by monitoring of disease progression, restriction of participation in sports, and ICD implantation may indeed prevent potentially lethal complications.

Penetrance of disease before and during adolescence

The majority of definite ARVC diagnoses occurred during adolescence or young adulthood, while the youngest proband with definite ARVC diagnosis was 9 years old. This age distribution is similar to observations in prior studies (**Table 4**) (8,10,18,19). In this context, it is important to note that the diagnostic TFC for ARVC were derived from a predominantly adult population and lack both sensitive and specific criteria for pediatric-onset of disease (3). For example, the cutoffs used for RV dilatation and dysfunction are likely to overdiagnose disease in pediatric patients (26). Development of pediatric-specific criteria may enhance the diagnostic performance of the TFC in

general and of specific modalities in particular, which however likely requires a large dataset derived from multiple longitudinal ARVC cohorts (17,19-22). Furthermore, future studies may elucidate the relation between environmental factors such as exercise and (epi)-genetic modifiers associated with early disease manifestation of ARVC (10,27).

Diagnostic testing during cascade screening

Our study showed that approximately one in three pediatric relatives develop definite ARVC during follow-up. It is important to note that the presence of multiple pathogenic variants plays a pivotal role in the early expression of an ARVC phenotype among pediatric probands and relatives, as has been suggested previously (10). This is also in line with our findings, which underline the role of multiple genetic variants influencing early expression of disease in very young ARVC patients. Of note, our study supports the current recommendation to start cascade screening at the age of 10 years old, since the youngest relative fulfilling ARVC diagnosis in our study was 11 years old. Furthermore, our findings confirm the suggested approach to perform periodic screening with ECG, Holter recording, exercise testing and cardiac imaging (7). However, the guidelines do not frame recommendations on the optimal screening interval and best combination of tests during cascade screening.

Our study suggests that ARVC is a slowly progressive disease, and that ECG criteria, a higher PVC count during Holter recording, and CMR imaging criteria are associated with disease progression during follow-up. This may aid the development of follow-up recommendations in this overwhelmingly young population. Although ECG parameters were important for diagnosis, only one case of epsilon waves was confirmed in this cohort. This may be explained by both 1) variability in the identification of epsilon waves in general; and 2) the rather significant amount of

activation delay which should be present for an epsilon wave to appear on the ECG, which is likely to be absent in our young pediatric population (28). In addition to the parameters tested in this study, newer techniques can aid early disease detection. One of those is echocardiographic deformation imaging, which was shown to have diagnostic and prognostic potential during cascade screening of adult patients. Future studies should evaluate the role of echocardiographic deformation imaging during cascade screening of pediatric patients, define criteria to aid ARVC diagnosis in children, and define pediatric-specific criteria for disease progression (29-31).

Predictors of ventricular arrhythmia

It has been suggested that arrhythmogenicity in ARVC depends on several coexisting mechanisms: triggered activity related to sympathetic activity, reentrant mechanisms due to myocardial fibrosis, myocardial inflammation and/or ion channel dysfunction (32,33). These factors may explain the observation of both fast, unstable rhythms such as polymorphic VT or ventricular fibrillation, and hemodynamically stable monomorphic VT in ARVC patients. In our cohort, T-wave inversion in the right precordial leads, NSVT, higher PVC count and reduced biventricular ejection fraction were associated with ventricular arrhythmias, similar to risk factors recently described in a risk prediction model for adult ARVC patients (www.arvcrisk.com) (17,22). Based on our results, risk stratification of pediatric patients evaluated for ARVC should be based on a minimal clinical evaluation including an ECG, Holter monitoring, exercise testing and imaging with either echocardiography and/or CMR. Future studies with a larger sample size should validate this risk prediction model in pediatric subjects before widespread use can be advocated in these young patients.

Limitations

The retrospective nature of this study and the small sample size may compromise generalizability of our results. Ascertainment bias may have occurred due to referral to our tertiary cardiogenetic clinics. The age cutoff of <18 years to define pediatric-onset of disease may be considered arbitrary. Although this age cutoff is frequently used in (Dutch) clinical practice to distinguish pediatric from adult cases, disease progression and severity should be assessed on a continuum. Participation in endurance exercise has long been suggested as risk factor for early ARVC occurrence; however, reliable exercise data was lacking in this cohort. Furthermore, based on the best available evidence, the 2010 TFC were used to define ARVC diagnosis. However, these criteria have not been validated in pediatric subjects. Since family history and genetic screening results play an important role in the 2010 TFC for relatives, a less severe phenotype may be observed in relatives who fulfill diagnostic TFC.

Conclusion

To the best of our knowledge, this is the largest study describing the clinical characteristics and outcomes of pediatric ARVC cases. Pediatric-onset ARVC is particularly recognized during adolescence, and is characterized by frequent ventricular arrhythmias in probands. However, definite ARVC diagnosis before adolescence should not be overlooked, because sudden cardiac death may be the first manifestation of disease in both probands and relatives. Disease progression during cascade screening is most frequently identified by ECG, Holter monitoring and CMR. Arrhythmic events are associated with male sex, the number of T-wave inversions in the precordial leads, ventricular ectopy on Holter monitoring, and reduced biventricular ejection fraction on cardiac imaging.

Clinical competencies

ARVC can also be a disease of adolescents, and is characterized by frequent ventricular arrhythmias particularly in probands. Disease in relatives is most commonly identified by cascade screening and has a more benign clinical course. Cascade screening and arrhythmic risk prediction should focus on ECG, Holter monitoring and CMR imaging.

Translational outlook

Future studies should establish pediatric-specific diagnostic criteria for ARVC, validate the performance of a prognostic risk prediction model (arvcrisk.com) in pediatric subjects, and address which (epi)genetic and environmental modifiers influence early disease manifestation in ARVC.

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Figure legends

Central Illustration. Cascade Screening and Follow-up in Pediatric-onset ARVC

The results of follow-up in probands and cascade screening in at-risk relatives are shown in the upper panel. Factors associated with sustained VT and disease progression during follow-up are shown in the lower panels. Abbreviations as in manuscript.

Figure 1. Flowchart of the Study Population

Flowchart of the included cohort from our ARVC registry, the selection of pediatric population, and clinical course of patients included in the study. Symptomatic was defined as (near)-syncope or palpitations. * = population stratified to enrolled centers as described in Methods: University Medical Center Utrecht, Amsterdam University Medical Center, or University Medical Center Groningen. ** = Cause of death was therapy-resistant congestive heart failure after a long history of VTs and heart failure. Abbreviations: Dx= definite ARVC diagnosis; HF= congestive heart failure; other abbreviations as in manuscript.

Figure 2. Molecular Genetic Analysis in the Study Population

Pathogenic variants identified during molecular genetic testing, stratified by probands and relatives and presented as percentages of tested individuals. Abbreviations: *PKP2*= Plakophilin-2; *DSG2*= Desmoglein-2; *PLN*= Phospholamban; *TTN*= Titin; Mult. PV.= multiple pathogenic variants. See **Supplementary Table 3** for a detailed summary of the identified variants.

Figure 3. Clinical Course and Follow-up among Patients Presenting Alive

552 Clinical course and follow up stratified by probands, relatives with definite ARVC diagnosis and
553 relatives without definite ARVC diagnosis. Abbreviations: HF = congestive heart failure; other
554 abbreviations as in manuscript.
555
556 **Figure 4. Serial Evaluation of Patients without Definite Diagnosis at Presentation.**
557 Panels A-C show Kaplan Meier curves per diagnostic modality depicting survival free from a new
558 diagnostic criterion during follow-up, which was absent at presentation. Per diagnostic test, only
559 patients with a normal evaluation of that specific modality at presentation were included in the
560 analysis. A 1-year incidence rate with 95% confidence interval was presented per diagnostic
561 modality. (A) New "electrical" (ECG, Holter monitoring) criteria versus new "imaging" (CMR
562 and echocardiogram) criteria. (B) "Electrical" criteria: new ECG versus new Holter monitoring
563 criteria. The difference between the number of included ECG and Holter monitoring cases is
564 explained by including only cases with normal evaluation of that specific test at baseline. (C)
565 "Imaging" criteria: new CMR versus new echocardiographic criteria. Abbreviations: CI =
566 confidence interval; IR = incidence rate.
567

Figures

Central Illustration

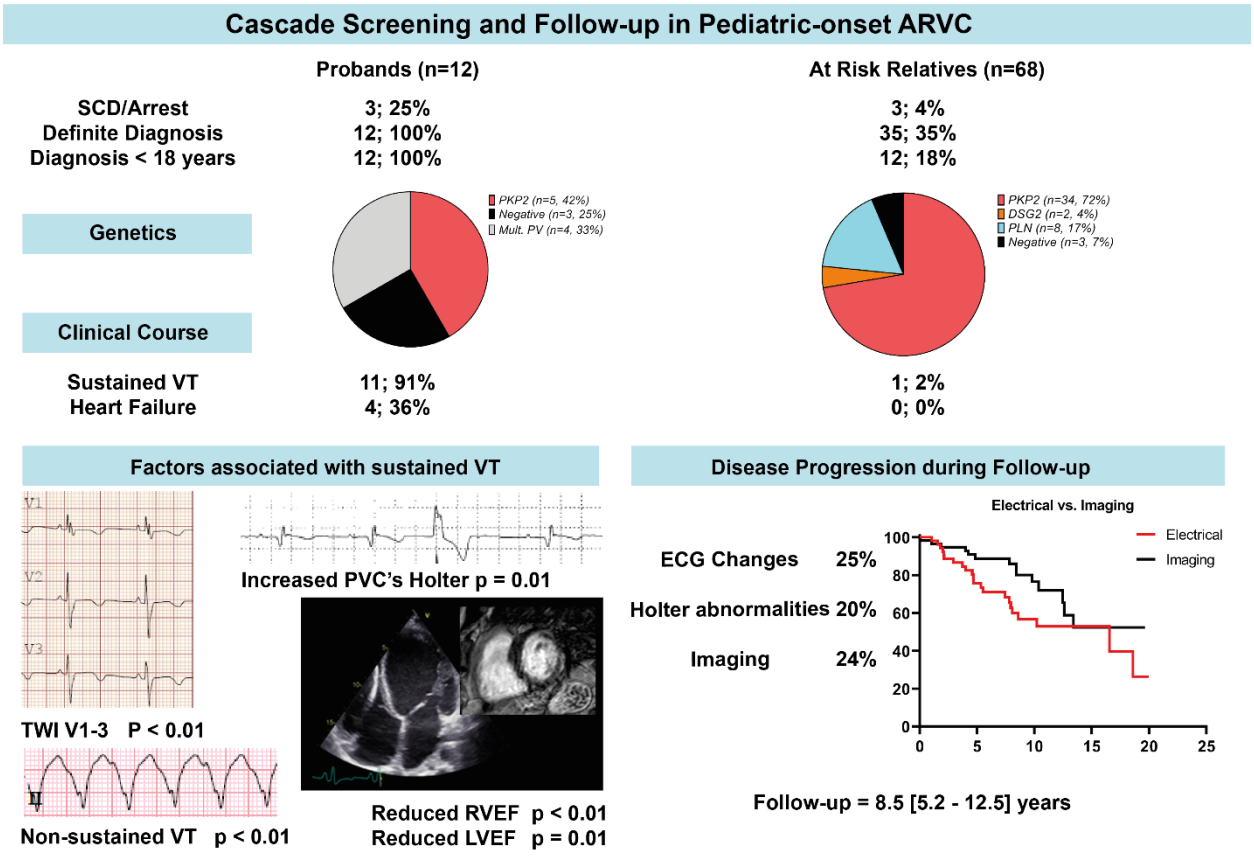
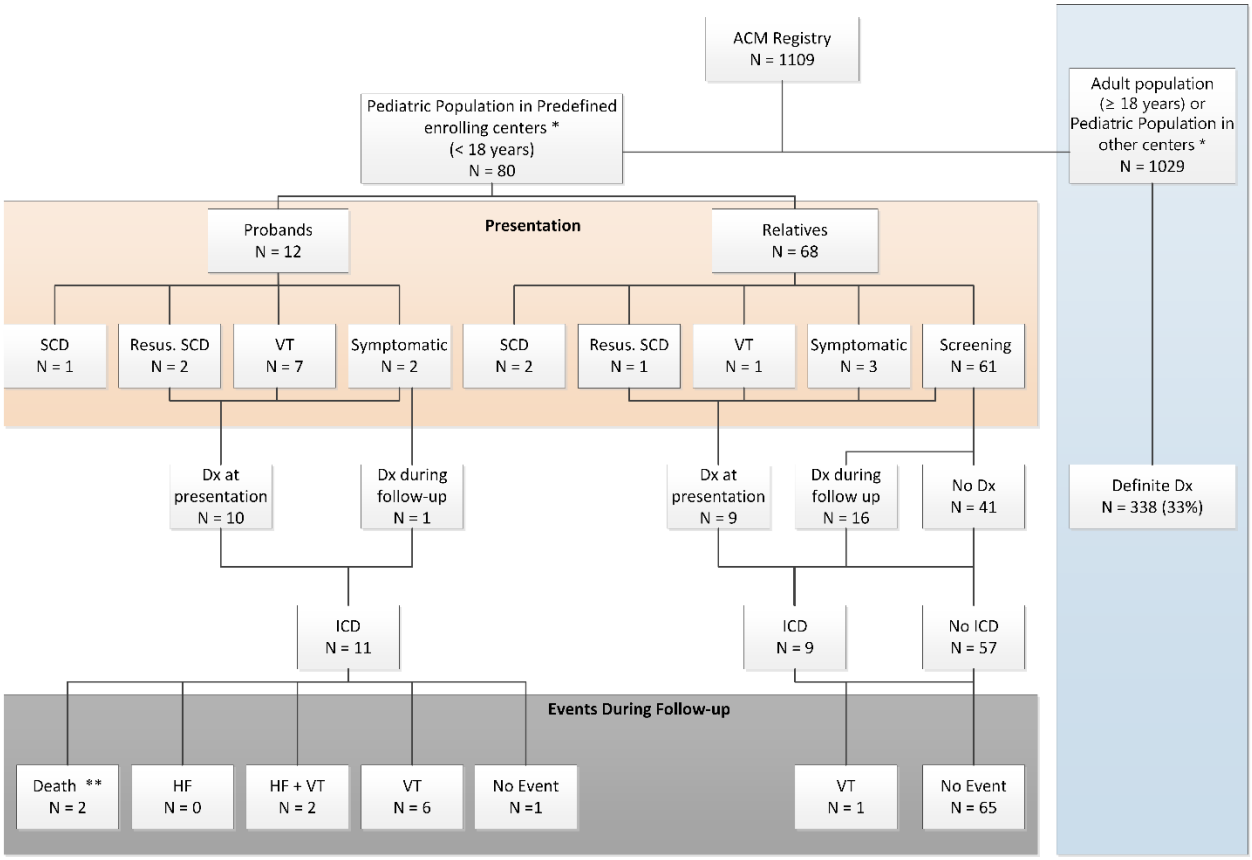
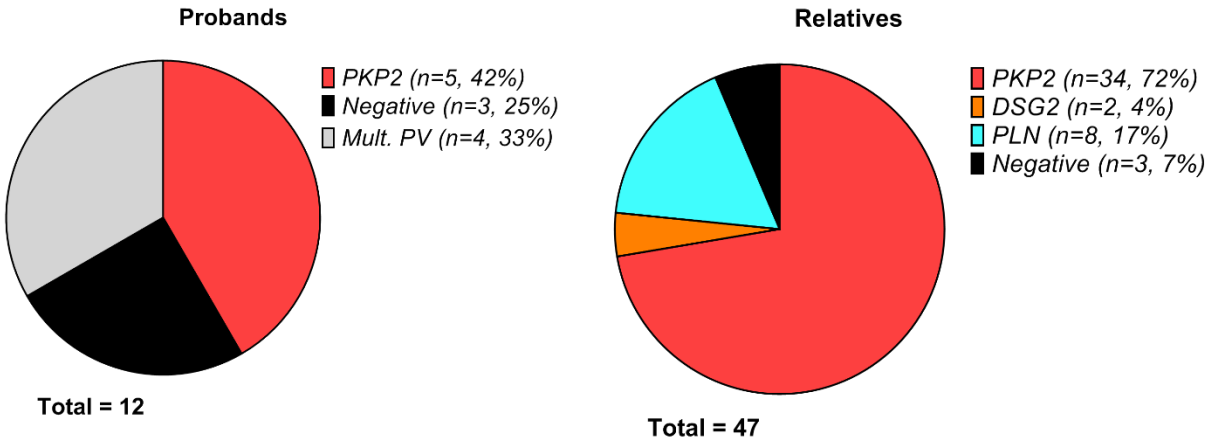


Figure 1.


ACM Registry
N = 1109
Pediatric Population in Predefined enrolling centers *
(< 18 years)
N = 80
Adult population
(≥ 18 years) or
Pediatric Population in other centers *
N = 1029
Presentation
Probands
N = 12
Relatives
N = 68
SCD
N = 1
Resus. SCD
N = 2
VT
N = 7
Symptomatic
N = 2
SCD
N = 2
Resus. SCD
N = 1
VT
N = 1
Symptomatic
N = 3
Screening
N = 61
Dx at presentation
N = 10
Dx during follow-up
N = 1
Dx at presentation
N = 9
Dx during follow up
N = 16
No Dx
N = 41
Definite Dx
N = 338 (33%)
ICD
N = 11
ICD
N = 9
No ICD
N = 57
Events During Follow-up
Death **
N = 2
HF
N = 0
HF + VT
N = 2
VT
N = 6
No Event
N =1
VT
N = 1
No Event
N = 65

574 **Figure 2.**

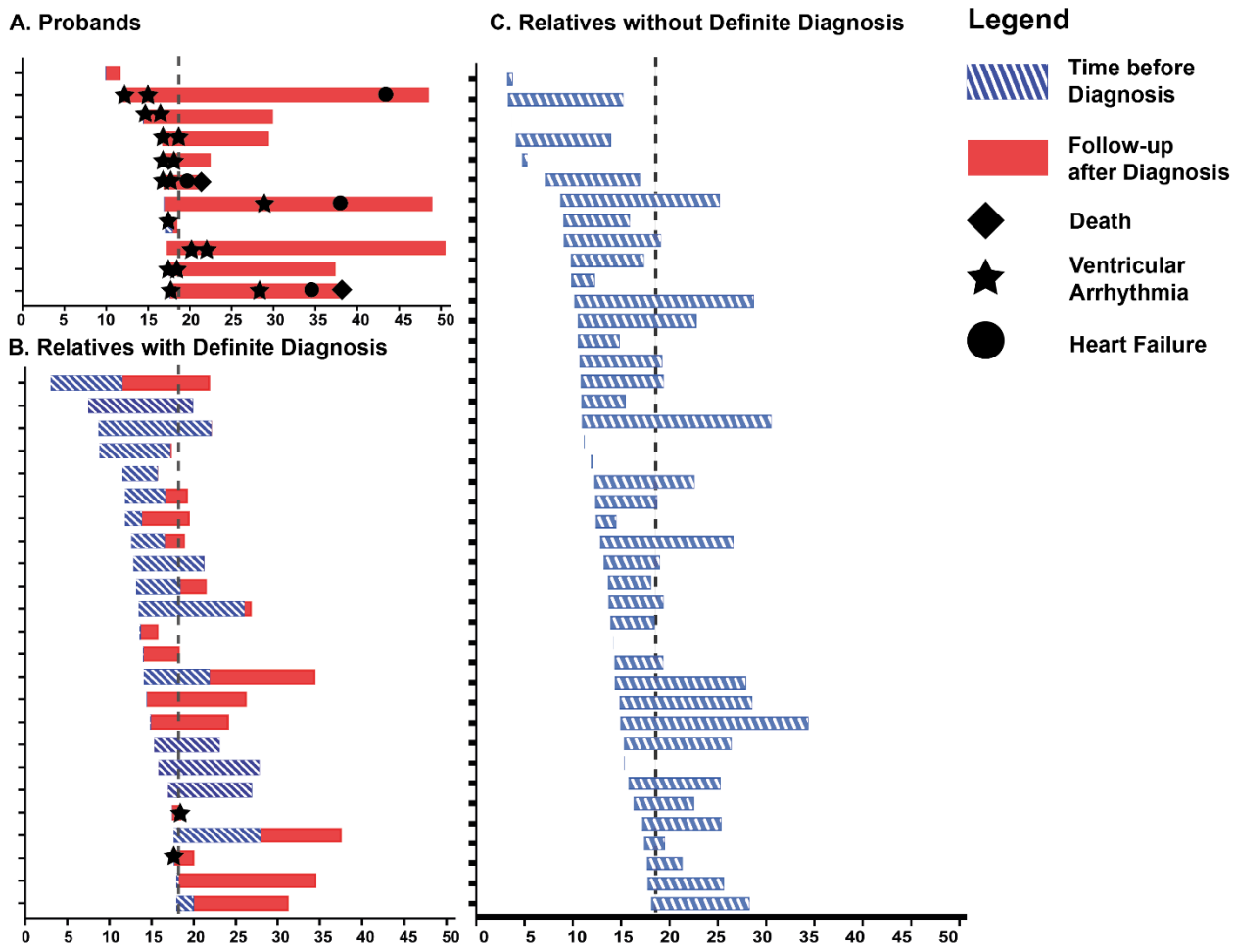


575

576

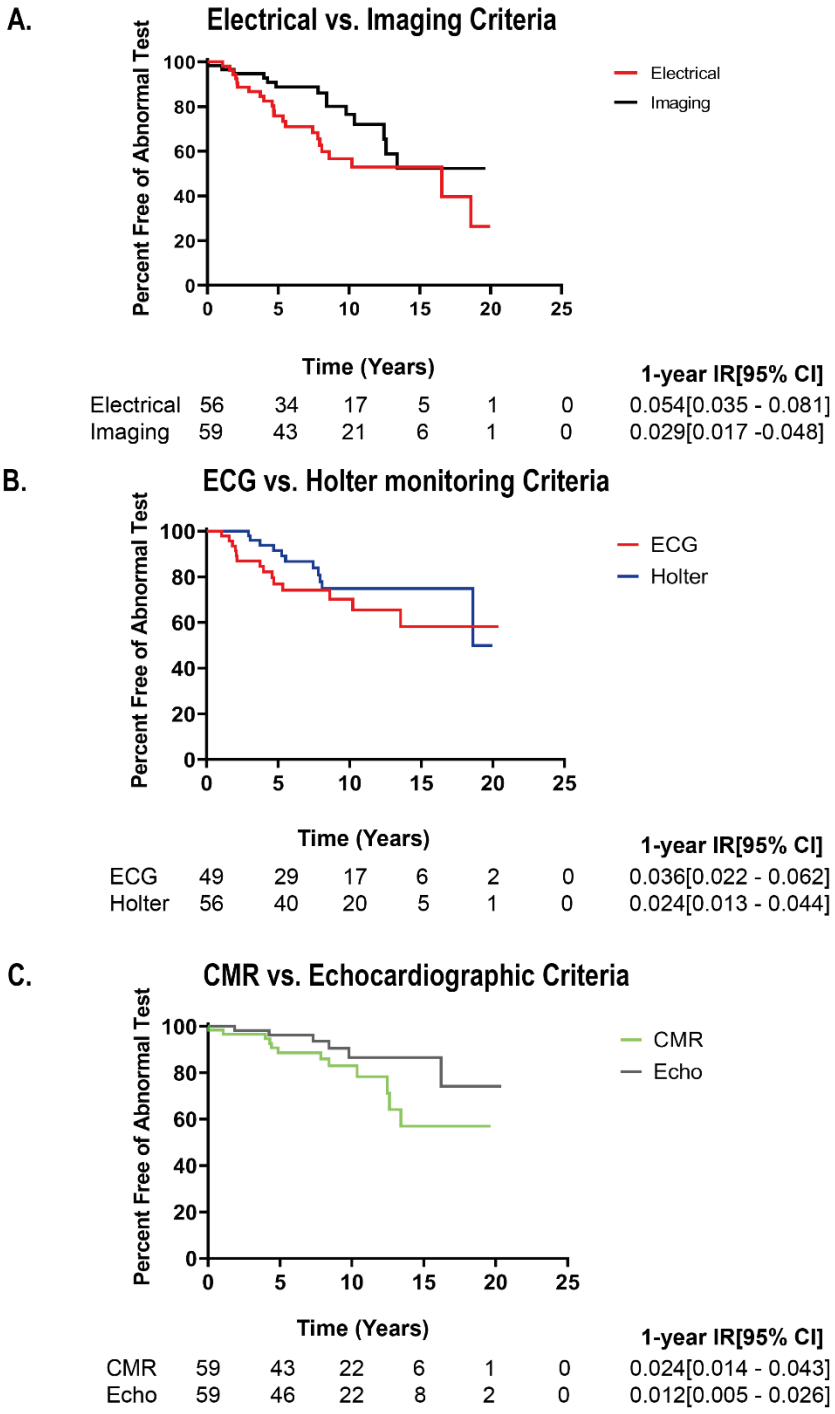
577 **Figure 3.**

578



579

Figure 4.


A.
Electrical vs. Imaging Criteria
Percent Free of Abnormal Test
100
80
60
40
20
0
0
5
10
15
20
25
Time (Years)
Electrical
Imaging
1-year IR[95% CI]
Electrical 56 34 17 5 1 0 0.054[0.035 - 0.081]
Imaging 59 43 21 6 1 0 0.029[0.017 -0.048]
B.
ECG vs. Holter monitoring Criteria
Percent Free of Abnormal Test
100
80
60
40
20
0
0
5
10
15
20
25
Time (Years)
ECG
Holter
1-year IR[95% CI]
ECG 49 29 17 6 2 0 0.036[0.022 - 0.062]
Holter 56 40 20 5 1 0 0.024[0.013 - 0.044]
C.
CMR vs. Echocardiographic Criteria
Percent Free of Abnormal Test
100
80
60
40
20
0
0
5
10
15
20
25
Time (Years)
CMR
Echo
1-year IR[95% CI]
CMR 59 43 22 6 1 0 0.024[0.014 - 0.043]
Echo 59 46 22 8 2 0 0.012[0.005 - 0.026]

583 **Tables**

584 **Table 1. Clinical characteristics at presentation stratified by probands and relatives.**

	Overall	Probands	Relatives
Demographics of all patients	**n=80**	**n=12**	**n=68**
Male	38 (48)	8 (67)	30 (44)
Age at presentation	13.5[10.5 - 16.7]	16.8[13.7 - 17.1]	13.2[10.1 - 15.3]
Type of presentation			
Ventricular tachycardia	8 (10)	7 (58)	1 (2)
Resuscitated sudden cardiac arrest	3 (4)	2 (17)	1 (2)
Sudden cardiac death	3 (4)	1 (8)	2 (3)
Symptomatic	5 (6)	2 (17)	3 (4)
Cascade screening	61 (76)	0	61 (90)
Molecular Genetic Analysis			
(Likely)Pathogenic variant *	53/58 (91)	9/11 (82)	44/47 (94)
Clinical evaluation in alive patients	**n=77**	**n=11**	**n=66**
Electrocardiogram			
T-wave inversion V1-V3	11 (14)	9 (82)	2 (3)
T-wave inversion V1-V2	5 (7)	1 (8)	4 (6)
T-wave inversion V4-V6	1 (1)	0	1 (2)
Epsilon wave	1 (1)	0	1 (2)
Prolonged terminal activation duration	10 (13)	2 (18)	8 (12)
Any 12-lead ECG abnormality	18 (23)	10 (91)	8 (12)
Electrophysiology			
Late potentials on signal averaged electrocardiogram	2/6 (33)	0	2/6 (33)
>500 PVCs/24h	7/48 (15)	2/4 (50)	5/44 (11)
Number of PVCs/24h	0 [0 - 58]	890 [23 - 11933]	0 [0 - 34]
NSVT	10/74 (14)	6/10 (60)	4/64 (6)
LBBB VT superior axis	3 (4)	2 (18)	1 (2)
LBBB VT other axis	7 (9)	6 (55)	1 (2)
Imaging			
RVEF (%)	52 [44 - 55]	33 [25 - 45]	53 [46 - 57]
LVEF (%)	59 [56 - 64]	49 [39 - 56]	60 [57 - 64]
Late gadolinium enhancement on CMR †	7/22 (32)	3/4 (75)	4/18 (22)
Any imaging test fulfilling TFC	8 (10)	5 (46)	3 (5)

Diagnosis			
Definite diagnosis at presentation	16/67 (24)	10/11 (91)	6/66 (9)
Median TFC score at presentation	2 [2 - 3]	6 [5 – 7]	2 [2 - 2]

Values are n (%), mean ± SD or median [interquartile range], as appropriate. Abbreviations as in manuscript. * class 4 or 5 likely pathogenic and pathogenic variants (12), see **Figure 2** and **Supplementary Table 3** for a detailed description. † all right ventricular associated late gadolinium enhancement in probands, one case of left ventricular associated and three cases of right ventricular associated late gadolinium enhancement in relatives. Abbreviations: LBBB = left bundle branch block, rest as in manuscript.

Table 2. Serial Evaluation among Subjects without Definite Diagnosis at Presentation.

	Overall (n=61)
Clinical evaluation during follow-up	
ECG progression*	**14/56 (25)**
T-Wave Inversion V1-3	5 (9)
T-Wave Inversion V1-2	4 (7)
T-Wave Inversion V4-6	1 (2)
Prolonged terminal activation duration	10 (18)
Holter monitoring progression*	**11/56 (20)**
>500PVC/24h	8 (14)
Number of PVC/24h	2 [0-191]
NSVT	7 (13)
Echocardiography progression*	**6/59 (10)**
Major echocardiographic criterion	4 (7)
Minor echocardiographic criterion	2 (3)
CMR progression*	**12/59 (20)**
Major CMR criterion	11 (19)
Minor CMR criterion	1 (2)
Disease progression on any test*	**30/61 (49)**
Events during follow-up	
Ventricular tachycardia	1 (2)
Heart Failure	0 (0)
Death	0 (0)
Cardiac transplantation	0 (0)

Values are n (%), mean ± SD or median [interquartile range]. * = Progression is defined as the occurrence of a new diagnostic TFC criterion during follow-up which was absent at first presentation. Abbreviations as in manuscript.

Table 3. Characteristics of patients presenting alive, stratified by any VT event

	VT (n=12)	No VT (n=65)	p-value
Demographics			
Proband status	10 (83)	1 (2)	<0.01
Male sex	10 (83)	27 (42)	<0.01
Pathogenic genetic variant	9/12 (75)	42/44 (96)	0.06
ECG and Holter monitoring			
T-wave inversion in V1-3	9 (75)	2 (3)	<0.01
Number of PVC/24h	3241 [413 – 6892]	3 [1 – 285]	0.01
NSVT	5/11 (46)	5/63 (8)	<0.01
Imaging			
LVEF	54 [49 – 59]	60 [57 – 64]	0.01
RVEF	32 [24 – 33]	53 [47 – 57]	<0.01
Late gadolinium enhancement on CMR	3/4 (75)	4/18 (22)	0.09

Values are n (%), mean ± SD or median [interquartile range]. Abbreviations as in manuscript.

603 **Table 4. Literature review of pediatric-onset ARVC**

First Author	Year	Definite ARVC cases	Mean age (yrs)	Sex (% males)	Evaluation	Findings	Ref.
Daliento	1995	17	14.9	59	Natural history	Based on 1994 TFC. High incidence sudden cardiac death.	(34)
Bauce	2011	14	15.0	79	Genotype-phenotype correlation	2010 TFC were superior over 1994 diagnostic criteria. High proportion of pediatric pathogenic variant carriers reached ARVC diagnosis.	(19)
Te Riele	2015	75	15.3	55	Natural history	Similar course of disease between adult- and pediatric-onset ARVC.	(8)
Etoom	2015	23	11.8	74	Diagnostic evaluation of CMR	Poor agreement between CMR and echocardiography 2010 TFC criteria.	(20)
Despande	2016	16	12.6	63	Histopathology-phenotype correlation	Only half of ARVC patients met histopathology TFC criterion.	(35)
Chungsomprasong	2017	24	15.2	56	Diagnostic evaluation of CMR	Association between right ventricular remodelling and left ventricular involvement.	(21)
Steinmetz	2018	12	14.0	66	Diagnostic evaluation of 2010 TFC	Genetic testing, CMR and ECG contributed to pediatric-onset ARVC diagnosis.	(18)
Sreetharan	2018	26	12.6	63	Histopathology-phenotype correlation	Poor agreement between phenotype and endomyocardial biopsy criteria.	(36)
Martins	2018	6	9.2	83	Diagnostic evaluation of CMR	Suggesting a role of myocarditis in pediatric-onset disease.	(37)
DeWitt	2019	32	15	56	Genotype-phenotype correlation	Association between specific pathogenic variants and right-dominant, left-dominant or biventricular disease.	(10)
Slesnink	2019	3	12	100	Histopathology-phenotype correlation	Correlation between biventricular fibrofatty replacement and CMR findings.	(38)
Pieles	2019	38	15	76	Diagnostic evaluation of echocardiography	Echocardiographic criteria, indexed to body surface area, did not differentiate between ARVC and controls. Reduced RV strain was associated with ARVC diagnosis.	(39)

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