Published in final edited form as:

J Cardiovasc Electrophysiol. 2016 May ; 27(5): 555–562. doi:10.1111/jce.12947.

Clinical Presentation and Outcomes by Sex in Arrhythmogenic Right Ventricular Cardiomyopathy: Findings from the North American ARVC Registry

Naila Choudhary, M.D.^{*}, Christine Tompkins, M.D.[†], Bronislava Polonsky, M.S.[‡], Scott McNitt, M.S.[‡], Hugh Calkins, M.D.[§], N. A. Mark Estes III, M.D.[¶], Andrew D. Krahn, M.D.^{**}, Mark S. Link, M.D.[¶], Frank I. Marcus, M.D.[†], Jeffrey A. Towbin, M.D.[‡], and Wojciech Zareba, M.D., Ph.D.[‡]

^{*}Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA

[†]Division of Cardiology, University of Colorado School of Medicine, Aurora, Colorado, USA

[‡]Division of Cardiology, University of Rochester School of Medicine, Rochester, New York, USA

[§]Division of Cardiology, John Hopkins University School of Medicine, Baltimore, Maryland, USA

[¶]Division of Cardiology, Tufts University School of Medicine, Boston, Massachusetts, USA

^{**}Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada

[†]Division of Cardiology, University of Arizona College of Medicine, Tucson, Arizona, USA

[‡]Division of Pediatrics, University of Tennessee, Memphis, Tennessee, USA

Clinical Presentation and Outcomes

Background—Sex differences in clinical presentation and outcomes of hereditary arrhythmias are commonly reported. We aimed to compare clinical presentation and outcomes in men and women with arrhythmogenic right ventricular cardiomyopathy (ARVC) enrolled in the North American ARVC Registry.

Methods—A total of 125 ARVC probands (55 females, mean age 38 ± 12 ; 70 males, mean age 41 ± 15) diagnosed, as either “affected” or “borderline” were included. Baseline clinical characteristics and time-dependent outcomes including syncope, ventricular tachycardia (VT), fast VT (>240 bpm), ventricular fibrillation (VF), and death were compared between males and females.

Results—The percentage of ARVC subjects diagnosed as “affected” (84% vs. 89%; $P = 0.424$) or “borderline” (16% vs. 11%; $P = 0.424$) was similar between females and males. Among the baseline characteristics, inverted T-waves in V2 trended to be more common in women ($P = 0.09$),

Address for correspondence: Christine Tompkins, M.D., Division of Cardiology, University of Colorado School of Medicine, CO, USA. Fax: 303-734-2049; ; Email: Christine.tompkins@ucdenver.edu

Other authors: No disclosures.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix: Participating Centers.

whereas abnormal signal-averaged ECGs (SAECGs; $P < 0.001$) and inducible VT/VF ($P = 0.026$) were more frequent in men. During a mean follow-up of 37 ± 20 months, the probability of ICD-recorded VT/VF or death was not significantly different between men and women ($P = 0.456$). However, there was a trend toward lower risk of fast VT/VF or death in women compared to men (hazard ratio 0.41, 95% CI 0.151–1.113, $P = 0.066$). Abnormal SAECG and evidence of intramyocardial fat by cardiac MRI was associated with adverse outcomes in men ($P = 0.006$ and 0.02 respectively).

Conclusion—In the North American ARVC Registry, we found similar frequency of “affected” and “borderline” subjects between men and women. Sex-related differences were observed in baseline ECG, SAECG, Holter-recorded ventricular arrhythmias, and VT inducibility. Men showed a trend toward greater risk of fast VT than women.

Keywords

clinical outcomes; arrhythmogenic right ventricular cardiomyopathy; gender differences

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial disorder pathologically characterized by progressive replacement of cardiac ventricular myocytes with fibrofatty tissue.^{1–3} Mutations in genes encoding cardiac desmosomal proteins located in the intercalated disks are responsible for ARVC.⁴ Mutations in five genes (plakophilin-2 [PKP2], desmocollin-2, desmoglein-2, desmoplakin, and plakoglobin) account for the majority of index cases.⁵ These mutations result in electromechanical uncoupling of myocytes, triggering the histopathological changes in ARVC that create the substrate for ventricular dysfunction and ventricular arrhythmias that may lead to sudden death.^{1–3} The diagnosis of ARVC is based on international task force criteria that was originally published in 1994 and revised in 2010.²

Studies investigating sex-based differences in the incidence of ARVC are conflicting. European studies report that it is more common in males,^{6,7} whereas studies from the United States and the Dutch ARVC cohorts report similar incidence between males and females.^{8,9} Studies also suggest sex-based differences in clinical diagnostic features of ARVC, but no difference in the incidence of ventricular arrhythmias.^{6,7}

The specific aims of the present investigation were (1) to compare the baseline clinical characteristics in men and women enrolled in the North American ARVC registry, (2) to compare the incidence and risk of cardiac events (death and ventricular arrhythmias) in males and females with ARVC, and (3) to identify unique risk stratifiers associated with adverse cardiac events by sex in ARVC patients enrolled in the North American ARVC registry.

Methods

North American ARVC Registry

The study design and protocol of the North American ARVC registry has already been published.¹⁰ This multidisciplinary study was initiated in 2001 with participation from 18 enrolling centers within the United States and Canada, a clinical center at the University of Arizona (Tucson, AZ, USA), a data coordinating center at the University of Rochester (Rochester, NY, USA), a genetic center at Baylor College of Medicine (Houston, TX, USA), 6 core laboratories in the United States and Europe, and a National Institutes of Health (NIH)-appointed Data and Safety Monitoring Board (see the online Appendix).

After obtaining institutional review board approved informed consent, patients 12 years or older with clinically suspected ARVC were enrolled in the registry and underwent noninvasive and invasive testing at their enrolling centers. The selection of diagnostic tests was left to the discretion of the physician at the enrolling center. The noninvasive tests included chest radiography, 12-lead ECG, 24-hour Holter monitor, SAECHG, echocardiography, and cardiac magnetic resonance imaging (MRI). Invasive studies included cardiac catheterization with right ventricular angiography, electrophysiology (EP) testing, and endomyocardial biopsy. Standardized protocols for the performance of the diagnostic tests were developed and implemented at the enrolling centers. The electrophysiology study protocol was based on that used in the Multicenter Unsustained Tachycardia Trial (MUSTT).¹¹ Blood samples were obtained for analysis of known causative gene mutations. Mutational analysis was performed for desmosomal genes encoding desmocollin-2, desmoglein-2, desmoplakin, plakoglobin, and plakophilin-2. All studies (noninvasive and invasive testing) were blindly analyzed by core laboratories. The diagnostic test results were sent to the data coordination center and entered into a secure web-based data management system.

Initially, patients were excluded if they had an implantable cardioverter defibrillator (ICD) placement before enrollment. Because patients and their personal physicians often became aware of this registry after ICD implantation, the Data Safety Monitoring Board agreed to allow enrollment of patients whose ICDs were implanted within 6 months during the second year of registry enrollment. In the last 4 years of the study, patients were permitted to be enrolled if they had an ICD implanted for fewer than 2 years. Single or dual chamber ICD implantation and programming was left to the discretion of physicians at the enrolling centers. Stored electrograms were reviewed and interpreted by electrophysiologists at the ICD core lab after each device therapy and at the time of scheduled follow-up. Patients were contacted at least once yearly. A total of 137 probands (81 males, 56 females) were enrolled in the registry. For the purposes of the present study, 125 ARVC probands were included. The probands were classified according to the 2010 revised task force criteria as either “affected” by the presence of two major or one major and two minor criteria or four minor criteria, or “borderline” by the presence of one major and one minor or three minor criteria.²

The clinical endpoints used for this study were syncope, ventricular tachycardia (VT), fast VT (defined as VT rate > 240 bpm), ventricular fibrillation (VF), and death. Cardiac events,

defined as a composite of syncope, VT/VF and all-cause death, were compared between men and women.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation and compared using the non-parametric Wilcoxon test. A chi-square test or Fisher exact test was used for the comparison of categorical variables, which were expressed as proportions. Kaplan–Meier curves with statistical comparison by log-rank method were used to analyze time to each of the end-points. Multivariate Cox analysis was used to determine whether sex influenced the outcome. All P values were two-tailed and considered to be significant when <0.05 . All the analysis was performed using SAS 9.2 software (Cary, NC, USA).

Results

Baseline Characteristics

Among the 125 subjects, 55 (44%) were females and 70 (56%) were males. Using the 2010 revised task force criteria, 46 (84%) women and 62 (89%) men were diagnosed as affected ($P = 0.424$), while 9 (16%) women and 8 (11%) men were diagnosed as borderline ($P = 0.424$). The average number of diagnostic criteria points (two points for fulfilling a major criterion and one point for fulfilling a minor criterion) per person was not significantly different between men (5.6 ± 2.2) and women (5.6 ± 2.6), $P = 0.834$.

Baseline clinical characteristics of male and female ARVC probands (affected and borderline) are shown in Table 1. There was no difference in mean age at enrollment (38 ± 12 vs. 41 ± 15 years; $P = 0.12$), prior arrhythmic events (67% vs. 71%; $P = 0.616$), history of syncope (26% vs. 22%; $P = 0.607$), or family history of ARVC (23% vs. 18%; $P = 0.56$) between females and males. A total number of 59 (84%) men and 42 (76%) women had an ICD ($P = 0.360$).

Electrophysiological Characteristics

On the resting ECG, T-wave inversions in lead V2 tended to be observed more frequently in women (71% vs. 55%; $P = 0.095$). Abnormal SAECG findings (defined as ≥ 1 abnormal parameters according to the 2010 revised task force criteria²) were more commonly seen in men when compared to women (81% vs. 48%; $P < 0.001$) as shown in Table 2. The median number of ventricular premature beats (VPBs) over a 24-hour period was significantly higher in women than men (2200 vs. 1089; $P = 0.016$). During EP study, VT/VF was induced less frequently in women (40% vs. 60%; $P = 0.026$). The induced VT was more likely to originate from the right ventricular (RV) apex in both men and women (71% vs. 77%; $P = 0.510$). VT originating from the RVOT was more common in men than women (52% vs. 27%; $P = 0.008$).

Cardiac Imaging

The results of cardiac imaging including echocardiography and cardiac MRI are shown in Table 3. The mean left ventricle (LV) ejection fraction (EF) was slightly lower in men versus women ($59 \pm 8\%$ vs. $63 \pm 10\%$; $P = 0.020$) by echocardiography but not cardiac MRI.

Cardiac MRI revealed a trend toward reduced RVEF in males vs. females ($41 \pm 11.1\%$ vs. $46 \pm 11.5\%$; $P = 0.076$), but no sex-related differences in the presence of intramyocardial fat in the RV (61% vs. 51% ; $P = 0.305$) or LV (19% vs. 10% ; $P = 0.196$). The incidence of regional LV and RV wall motion abnormalities by cardiac MRI was not significantly different between men and women, except for RV mid-wall akinesis, which was more commonly observed in women (44% vs. 25% ; $P = 0.035$). There was no significant difference in LV or RV end-diastolic volumes (EDV) adjusted for body surface area (BSA) between men and women by cardiac MRI; however, LV systolic and diastolic diameters were smaller in men compared to women.

Genetic Testing and biopsy

Subjects who underwent genetic testing (men: $n = 61$, 87% ; women: $n = 48$, 87%) were screened for mutations affecting five genes: desmocollin, desmoglein, desmoplakin, plakoglobin, and plakophilin. Genotype testing positivity did not differ between women and men (46% vs. 31% ; $P = 0.116$). Mutations in plakophilin-2 were most frequently found in both men and women (27% vs. 17% ; $P = 0.181$) followed by plakoglobin in men (5%) and desmoplakin in women (9%), Table 4. A minority of patients had two or more known mutations for ARVD; women: $n = 4$ (7%); men: $n = 5$ (7%). More men underwent cardiac biopsy compared to women (61% vs. 44% ; $P = 0.048$); however, there was no sex-related difference in the frequency of positive biopsy results (81% vs. 80% ; $P = 1.00$).

Endpoint analysis

The mean duration of follow-up was similar between women and men (3 ± 1.7 years vs. 3.1 ± 1.8 years; $P = 0.565$). Analysis of ventricular arrhythmias (VT/VF) was restricted to those who received an ICD (59 men, 42 women). Men tended to experience more appropriate and inappropriate therapies when compared to women, but this was not significant (Table 5). There was no difference in mean VT cycle length (women: 284 ± 56 milliseconds vs. men: 278 ± 42 milliseconds; $P =$ non-significant) or the frequency of VT/VF episodes (Fig. 1). The cumulative probability of VT, VF, and death did not differ between men and women ($P = 0.456$); however, women tended to have a lower risk for developing fast VT (defined as rate > 240 bpm), VF or death when compared to men (hazard ratio 0.41 , 95% confidence interval 0.151 – 1.113 , $P = 0.066$); Figure 2A,B. There was no significant difference between men and women in the frequency of cardiac transplantation (3% vs. 2% ; $P = 1.00$) and death (3% vs. 0% ; $P = 0.50$). Cardiac events (defined as a composite of syncope, VT/VF, and all-cause death) were more common in women between ages of 31 – 40 years as compared to men of the same age group; however, there were no sex differences in cardiac events in other age groups (Fig. 3).

Factors Associated with Adverse Cardiac Events (Syncope, VT, VF or Death)

Sub-group analysis was performed on ARVC subjects who experienced adverse cardiac events (i.e., syncope, VT, VF, or death) to identify any unique high-risk characteristics by sex (Table 6). The percentage of subjects with cardiac events was similar between females and males (42% vs. 53% ; $P = 0.10$). However, cardiac events were more commonly observed in “affected” vs. “borderline” subjects, irrespective of sex. Within the “affected” cohort, cardiac events were principally driven by VT/VF or death in men (81%) and VT/VF

in women (71%). Although the mean age at enrollment did not differ between men and women in the study cohort, cardiac events were more common in women between the ages of 31–40 years compared to men at the same age ($P = 0.027$). Cardiac events were also more commonly observed in men with negative T-waves in the inferior leads, but not women (73% vs. 57%; $P = 0.217$). The SAECG was abnormal in 83% of men compared to 44% women with adverse cardiac events ($P = 0.006$). Conversely, women with adverse outcomes more frequently had normal SAECGs ($P = 0.006$). The median number of VPBs did not differ in men and women with or without cardiac events (data not shown). By cardiac MRI, the presence of intramyocardial fat was observed more frequently in men than women with cardiac events (81% vs. 50%; $P = 0.02$). However, intramyocardial fat involving the RV outflow tract (RVOT) correlated with adverse cardiac events in women but not men with ARVC ($P = 0.07$). Finally, although women with cardiac events were more likely to have positive genetic testing when compared to men (50% vs. 26%; $P = 0.08$); women with cardiac events were equally likely to have negative genetic testing (50% vs. 50%).

Discussion

Our study provides comprehensive information regarding sex-related differences in clinical characteristics and outcomes in a large multicenter prospective clinical trial of patients with ARVC. We had similar proportions of male and female subjects with ARVC, which provides a unique opportunity to analyze clinical characteristics and outcomes by sex. Unlike other hereditary disorders like Brugada syndrome or long-QT syndrome, we found no correlation between age, sex, and the timing of cardiac events (syncope, ventricular arrhythmias, or death). We observed no differences in clinical characteristics (i.e., number of major or minor criteria), disease severity (i.e., number affected, prior arrhythmic events), or clinical outcomes in men vs. women with ARVC. This suggests that sex has little effect on outcomes when ARVC disease severity is similar between men and women.

However, we did observe significant sex-based differences in the phenotypic presentation (EP characteristics and cardiac substrate by imaging) of ARVC. Precordial T-wave inversions tended to be more common in women; women had more frequent VPBs on Holter monitoring and larger left ventricular dimensions than men. Men more commonly presented with abnormal SAECGs, positive cardiac biopsies, and more frequently inducible VT/VF during EP testing. SAECG and cardiac MRI poorly discriminated between women with and without cardiac events. Instead, age 31–40 years and evidence of fibrofatty infiltration in RVOT were the only clinical markers that correlated with adverse cardiac events in women. Abnormal SAECG and evidence of fibrofatty infiltration regardless of ventricular location correlated with adverse outcomes in men.

Several prior ARVC studies have reported a higher prevalence of this disorder in males. In the report of 24 cases by Marcus *et al.*, the male to female ratio was 2.7:1.¹ Corrado *et al.* analyzed 42 subjects in their multicenter study, of which 27 were men and 17 were women.⁶ Baucé *et al.* included 171 patients with ARVC in their study, and reported 71% men and 29% women in their study population ($P = 0.02$).⁷ Furthermore, in a series of 149 index patients with and without mutations, Cox *et al.* found male predominance in both groups (71% and 80%).⁵ Our study challenges these findings, demonstrating similar numbers of

“affected” and “borderline” male and female (56% vs. 44%) ARVC subjects, suggesting that referral bias may be contributing to discrepancies in disease prevalence.

Prior reports have provided conflicting results regarding differences in diagnosing ARVC in males versus females. Earlier reports of four families carrying desmoplakin mutation suggested that prevalence of ARVC was higher in men based on diagnostic criteria.¹² Similarly, in a report of nine families carrying plakophilin-2 mutation, more men were noted to be affected than women.¹³ More recent studies, however, found no sex difference in major and minor criteria.⁷ There was no significant difference in our cohort regarding age at presentation and overall clinical presentation measured by number of major and minor criteria present. However, there were some sex-related differences in baseline characteristics.

It is known that starting at puberty, sex-related differences become apparent on the surface ECG. Indeed, both the amplitude and duration of the QRS complex are greater in men versus women without structural heart disease.^{14,15} Sex based differences in SAECG have also been reported.¹⁶ Yakubo *et al.* reported SAECGs in 482 (278 women and 204 men) normal healthy Japanese individuals and reported filtered QRS duration to be significantly longer in men ($P < 0.0001$). The root mean square amplitude of the terminal 40 milliseconds of the QRS (RMS 40) was also larger in men, but there was no significant sex-related differences in low-amplitude signal duration below 40 μ V (LAS 40).¹⁷ Despite these baseline differences, the current Task Force criteria do not take gender into consideration and instead use the same cutoff values to differentiate normal from abnormal SAECG in both men and women. Our observation that cardiac events were equally likely to occur in women with normal versus abnormal SAECGs raises concern that current diagnostic criteria may inadequately identify women at risk for cardiac events.

Conversely, there was a strong correlation between abnormal SAECG and subsequent cardiac events in males. Kamath *et al.* suggested that abnormal SAECG is strongly associated with larger RV volumes and reduced RVEF by cardiac MRI. However, abnormal SAECGs were not associated with spontaneous or inducible VT.¹⁸ A recent study by Santangeli *et al.* reported a significant association between abnormal SAECGs and cardiomyopathic involvement of the RVOT in patients with ARVC and those with myocarditis.¹⁹

In our study, sex differences in LVEF, RVEDV, LVEDV, and RV systolic and diastolic diameters indexed to body surface area did not reach statistical significance. Using non-indexed values, other authors have reported that men had larger RVEDV^{7,20} and LVEDV⁷ when compared to women. Sen-Chowdhry *et al.* also reported that men had lower RVEF ($P = < 0.0001$) and lower LVEF ($P = 0.0249$)²⁰ compared to women. A unique finding in our study is that the presence of intramyocardial fat by cardiac MRI was associated with cardiac events in men, but not women. The reason for this discrepancy is unknown. It is worth noting that women with cardiac events were equally likely to have no evidence of intramyocardial fat by cardiac MRI. This finding raises concern that these imaging modalities may not be as helpful at identifying women at risk for cardiac events as they appear to be in men.

The genotype–phenotype correlation in ARVC has been well studied, though remains complicated. In a recent report by Bhonsale *et al.*, the authors reported that specific genetic mutations impacted both the phenotypic expression of ARVC and clinical outcomes.⁸ Subjects with desmoplakin gene mutations, carriers with greater than one gene mutation, and male mutation carriers had worse clinical outcomes in their study. In a large cohort of 1,001 index ARVC patients and family members, Groeneweg *et al.* reported that the disease course and clinical outcomes did not differ between index patients with or without known genetic mutations. However, long-term outcomes in family members were negatively influenced by the presence of mutation. Mutations in plakophilin-2 were predominant in both index patients as well as family members.⁹ Similarly, in our study, mutations in plakophilin were the most common finding in both sexes. We did not find any significant difference in genotype positivity between men and women. Although more women with cardiac events tested positive for ARVC gene mutations as compared to men, an interesting finding in our study was that women with cardiac events were equally likely to test negative for genetic mutations. Thus, the role of genetic testing to guide risk stratification for patients with ARVC remains unclear, as this had no influence on clinical outcomes in our study.

Our findings are consistent with prior reports suggesting that among all patients with ARVC, the incidence of ventricular arrhythmia does not differ by sex.⁷ However, we observed a trend toward increased incidence of fast VT/VF/death in men. Whether this is a marker of greater disease severity is unknown. Importantly, we found that cardiac events (i.e., VT/VF) are common in “affected” ARVC patients (defined according to the 2010 revised task force criteria²) irrespective of sex. Thus, ICD implantation should strongly be considered in ARVC patients meeting “affected” diagnostic criteria. Corrado *et al.* reported that 24% of ARVC patients without prior history of sustained VT or VF had appropriate ICD interventions and 16% had shocks for life threatening VF or ventricular flutter. They reported syncope to be an important predictor of life-saving ICD therapies.²¹ Extensive RV dysfunction has also been identified as an independent predictor of ICD therapy in ARVC.²²

Conclusion

In the North American ARVC Registry, we found no differences in the clinical expression of ARVC based on major and minor diagnostic criteria. We did not find any significant difference in the probability of VT/VF/death between men and women. We identified age group 31–40 years and presence of intramyocardial fat in RVOT to be associated with adverse cardiac events in women. In men, we found that abnormal SAECG and presence of intramyocardial fat by cardiac MRI tend to correlate with adverse events. Findings from our study continue to highlight the challenges associated with identifying men and women with ARVC who are at greatest risk for adverse cardiac events based on current clinical presentation criteria. Importantly, while it is tempting to use noninvasive and invasive techniques (i.e., SAECG, cardiac MRI, inducibility of VT/VF at EP study) to identify patients with ARVC at greatest risk of sudden cardiac death, our study suggests that these diagnostic tests lack correlation with cardiac events in women. Our limited ability to identify women at greatest risk for cardiac events warrants further investigation.

Limitations

The main limitation of this study is selection bias. At enrollment, men and women exhibited similar phenotypic expression of ARVC based on current task force criteria. Thus, it is not entirely surprising that clinical outcomes were similar between men and women. Findings reported in our study are from the North American registry, which limits our ability to extrapolate these results to other nationalities or ethnicities. We also lack information regarding therapies provided to patients, which may influence time-dependent clinical events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Estes has served as a consultant to Boston Scientific, Medtronic, and St. Jude Medical. Dr. Krahn has served as a consultant to Medtronic.

References

1. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgeat Y. Right ventricular dysplasia: A report of 24 adult cases. *Circulation*. 1982; 65:384–398. [PubMed: 7053899]
2. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the task force criteria. *Circulation*. 2010; 121:1533–1541. [PubMed: 20172911]
3. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet*. 2009; 373:1289–1300. [PubMed: 19362677]
4. Noorman M, van der Heyden MA, van Veen TA, Cox MG, Hauer RN, de Bakker JM, van Rijen HV. Cardiac cell-cell junctions in health and disease: Electrical versus mechanical coupling. *J Mol Cell Cardiol*. 2009; 47:23–31. [PubMed: 19344726]
5. Cox MG, van der Zwaag PA, van der Werf C, van der Smagt JJ, Noorman M, Bhuiyan ZA, Wiesfeld AC, Volders PG, van Langen IM, Atsma DE, Dooijes D, van den Wijngaard A, Houweling AC, Jongbloed JD, Jordaens L, Cramer MJ, Doevendans PA, de Bakker JM, Wilde AA, van Tintelen JP, Hauer RN. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: Pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study. *Circulation*. 2011; 123:2690–2700. [PubMed: 21606396]
6. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom-Lundqvist C, Wlodarska EK, Fontaine G, Camerini F. Spectrum of clinicopathological manifestations of arrhythmogenic right ventricular cardiomyopathy/ dysplasia: A multicenter study. *J Am Coll Cardiol*. 1997; 30:1512–1520. [PubMed: 9362410]
7. Bauce B, Frigo G, Marcus FI, Basso C, Rampazzo A, Maddalena F, Corrado D, Winnicki M, Daliento L, Rigato I, Steriotis A, Mazzotti E, Thiene G, Nava A. Comparison of clinical features of arrhythmogenic right ventricular cardiomyopathy in men versus women. *Am J Cardiol*. 2008; 102:1252–1257. [PubMed: 18940302]
8. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD, Murray B, te Riele AS, van den Berg MP, Bikker H, Atsma DE, de Groot NM, Houweling AC, van der Heijden JF, Russell SD, Doevendans PA, van Veen TA, Tandri H, Wilde AA, Judge DP, van Tintelen JP, Calkins

- H, Hauer RN. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J*. 2015; 36:847–855. [PubMed: 25616645]
9. Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, Murray B, Wiesfeld AC, Sawant AC, Kassamali B, Atsma DE, Volders PG, de Groot NM, de Boer K, Zimmerman SL, Kamel IR, van der Heijden JF, Russell SD, Jan Cramer M, Tedford RJ, Doevendans PA, van Veen TA, Tandri H, Wilde AA, Judge DP, van Tintelen JP, Hauer RN, Calkins H. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet*. 2015; 8:437–446. [PubMed: 25820315]
 10. Marcus F, Towbin JA, Zareba W, Moss A, Calkins H, Brown M, Gear K. ARVD/C Investigators: Arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C): A multidisciplinary study: Design and protocol. *Circulation*. 2003; 107:2975–2978. [PubMed: 12814984]
 11. Buxton AE, Fisher JD, Josephson ME, Lee KL, Pryor DB, Prystowsky EN, Simson MB, DiCarlo L, Echt DS, Packer D, Greer GS, Talajic M. the MUSTT Investigators. Prevention of sudden death in patients with coronary artery disease: The Multicenter Unsustained Tachycardia Trial (MUSTT). *Prog Cardiovasc Dis*. 1993; 36:215–226. [PubMed: 8234775]
 12. Bauce B, Basso C, Rampazzo A, Beffagna G, Daliento L, Frigo G, Malacrida S, Settimo L, Danieli G, Thiene G, Nava A. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. *Eur Heart J*. 2005; 26:1666–1675. [PubMed: 15941723]
 13. Syrris P, Ward D, Asimaki A, Sen-Chowdhry S, Ebrahim HY, Evans A, Hitomi N, Norman M, Pantazis A, Shaw AL, Elliott PM, McKenna WJ. Clinical expression of plakophilin-2 mutations in familial arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2006; 113:356–364. [PubMed: 16415378]
 14. Simonson E, Blackburn H, Puchner TC, Eisenberg P, Ribeiro F, Meja M. Sex differences in the electrocardiogram. *Circulation*. 1960; 22:598–601.
 15. Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, Davignon A. Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol*. 1992; 8:690–695. [PubMed: 1422988]
 16. Marcus FI, Zareba W, Sherrill D. Evaluation of the normal values for signal averaged electrocardiogram. *J Cardiovasc Electrophysiol*. 2007; 18:231–233. [PubMed: 17338774]
 17. Yakubo S, Ozawa Y, Saito S, Kasamaki Y, Komaki K, Hanakawa K, Sasaki Y, Aruga M, Miyazawa I, Kanda T, Sekiguchi K, Shimabukuro H, Nakamura T, Okumura N. Normal limits of high-resolution signal-averaged ECG parameters of Japanese adult men and women. *J Electrocardiol*. 2000; 33:225–231. [PubMed: 10954375]
 18. Kamath GS, Zareba W, Delaney J, Koneru JN, McKenna W, Gear K, Polonsky S, Sherrill D, Bluemke D, Marcus F, Steinberg JS. Value of the signal-averaged electrocardiogram in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm*. 2011; 8:256–262. [PubMed: 20933608]
 19. Santangeli P, Pieroni M, Dello Russo A, Casella M, Pelargonio G, Di Biase L, Macchione A, Burkhardt JD, Bellocci F, Santarelli P, Tondo C, Natale A. Correlation between signal-averaged ECG and the histologic evaluation of the myocardial substrate in right ventricular outflow tract arrhythmias. *Circ Arrhythm Electrophysiol*. 2012; 5:475–483. [PubMed: 22423142]
 20. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insight into patterns of disease expression. *Circulation*. 2007; 115:1710–1720. [PubMed: 17372169]
 21. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, Basso C, Ward D, Boriani G, Ricci R, Piccini JP, Dalal D, Santini M, Buja G, Iliceto S, Estes NA 3rd, Wichter T, McKenna WJ, Thiene G, Marcus FI. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation*. 2010; 122:1144–1152. [PubMed: 20823389]
 22. Wichter T, Paul M, Wollmann C, Acil T, Gerdes P, Ashraf O, Tjan TD, Soeparwata R, Block M, Borggrefe M, Scheld HH, Breithardt G, Böcker D. Implantable cardioverter/defibrillator therapy in

arrhythmogenic right ventricular cardiomyopathy: Single-center experience of long-term follow-up and complications in 60 patients. *Circulation*. 2004; 109:1503–1508. [PubMed: 15007002]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

VT/VF episodes in men and women ARVC patients with ICD. P-value = 0.321 for all VT/VF episodes; males vs. females. VF = ventricular fibrillation; VT = ventricular tachycardia. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce

Figure 2.

A: Cumulative probability of VT/VF or death by sex. B: Cumulative probability of fast VT/VF or death by sex. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce

Figure 3.

Age of first cardiac event (syncope, VT/VF, or death) by sex For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce

TABLE 1**Patient Clinical Characteristics by Sex**

Clinical Characteristics	Females (n = 55)	Males (n = 70)	P-Value
Age at enrollment (years)	38 ± 12	41 ± 15	0.120
White race	46 (84%)	58 (83%)	0.908
BMI (kg/m ²)	25 ± 5	26 ± 5	0.040
No. of major criteria* (Mean ± SD)	2.6 ± 1.5	2.6 ± 1.4	0.945
No. of minor criteria* (Mean ± SD)	0.4 ± 0.9	0.5 ± 1.0	0.629
Affected	46 (84%)	62 (89%)	0.424
Borderline	9 (16%)	8 (11%)	0.424
Family history of ARVC	11 (23%)	12 (18%)	0.561
Prior arrhythmic events	37 (67%)	50 (71%)	0.616
History of syncope	13 (26%)	14 (22%)	0.607
Antiarrhythmic drugs	25 (56%)	34 (55%)	0.941
Beta-blockers	41 (91%)	47 (76%)	0.041
Implantable cardioverter defibrillator	42 (76%)	59 (84%)	0.360

* Using the 2010 revised international task force criteria.²

ARVC = arrhythmogenic right ventricular cardiomyopathy; BMI = body mass index; No. = number; SD = standard deviation.

TABLE 2

Electrophysiologic Characteristics Findings by Sex

	Females (n = 55)	Males (n = 70)	P-Value
ECG findings			
RBBB	6 (12%)	8 (12 %)	0.960
QRS duration in V2	0.101 ± 0.017	0.108 ± 0.022	0.097
Negative T-wave in V2	34 (71%)	36 (55%)	0.095
Negative T-wave in V3	27 (56%)	32 (49%)	0.460
Negative T-wave in inferior leads (II, III, aVF)	24 (44%)	39 (56%)	0.180
SAECG findings	22 (48%)	44 (81%)	<0.001
Filtered QRS, milliseconds	114 ± 25	127 ± 21	<0.001
Filtered QRS, 40 Hz > 120 milliseconds	12 (27%)	32 (58%)	0.002
Holter monitoring			
Average heart rate on Holter (bpm)	73 ± 12	65 ± 10	0.003
VPBs > 1,000/24 hours	33 (69%)	24 (51%)	0.079
Total number of VPBs (median)	2200	1089	0.016
EP study			
Any induced VT or VF	22 (40%)	42 (60%)	0.026
VT induced RV Apex	17 (52%)	30 (59%)	0.510
VT induced at RV RVOT	6 (25%)	22 (59%)	0.008

TABLE 3**Cardiac Imaging Findings by Sex**

Cardiac Imaging Findings	Females (n = 55)	Males (n = 70)	P-Value
Echocardiogram			
LVEF (%)	63 ± 10	59 ± 8	0.020
Cardiac MRI			
MRI LVEF (%)	59.3 ± 4.3	57.0 ± 6.5	0.135
MRI RVEF (%)	46 ± 11.5	41 ± 11.1	0.076
RVEDV (mL/m ²) index	97.5 ± 36.6	106.2 ± 39.8	0.489
RV diastolic diameter (mm/ m ²) index	25.6 ± 6.0	23.9 ± 5.1	0.316
RV systolic diameter (mm/ m ²) index	20.9 ± 6.8	20.0 ± 5.4	0.855
LVEDV (mL/ m ²) index	78.7 ± 18.3	80.4 ± 17.0	0.711
LV diastolic diameter (mm/ m ²) index	28.0 ± 4.5	25.0 ± 4.2	0.007
LV systolic diameter (mm/ m ²) index	18.4 ± 3.8	16.7 ± 3.9	0.074
RV presence of Intramyocardial fat	25 (51%)	40 (61%)	0.305
LV presence of Intramyocardial fat	5 (10%)	12 (19%)	0.196

ECG = electrocardiogram; Echo = echocardiogram; EP = electrophysiology; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MRI= magnetic resonance imaging; RBBB = right bundle branch block; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVOT=right ventricular outflow tract; SAEKG=signal-averaged ECG; VPBs = ventricular premature beats; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 4

Genetic Testing Findings by Sex

Genetic Testing	Females (n = 48)	Males (n = 61)	P-Value
Positive	22 (46%)	19 (31%)	0.116
> 1 Gene mutation	4 (8%)	5 (8%)	1.00
Desmocollin	1 (2%)	3 (5%)	0.629
Desmoglein	2 (4%)	3 (4%)	1.00
Desmoplakin	5 (9%)	3 (4%)	0.271
Plakoglobin	4 (7%)	4 (5%)	0.716
Plakophilin	15 (27%)	14 (17%)	0.181

TABLE 5**Endpoints Analysis in ARVC Patients Who Received ICD**

End-Points	Females (n = 42)	Males (n = 59)	P-Value
No. of ARVC affected patients	36 (86%)	51 (86%)	0.917
No. of ARVC borderline patients	6 (14%)	8 (14%)	0.917
Mean follow-up (months)	36 ± 20	37 ± 22	0.565
VT/VF requiring ICD therapy	16 (38%)	29 (49%)	0.270
VT/VF requiring ICD shocks	15 (27%)	29 (41%)	0.100
Fast VT/VF requiring ICD therapy	5 (9%)	14 (20%)	0.092
No. of appropriate therapies	4 ± 9	5 ± 9	0.321
Inappropriate therapy	4 (10%)	11 (19%)	0.204
Inappropriate shocks	4 (7%)	11 (16%)	0.149
No. of inappropriate therapies	0 ± 1	1 ± 2	0.197

ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter-defibrillator; No. = number; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 6

Frequency of Cardiac Events (i.e., Syncope, VT/VF, or Death) by Sex and Diagnostic Findings

Characteristics	Cardiac Events		P-Value
	Females (n = 21)	Males (n = 37)	
Affected *	19 (90%)	35 (95%)	0.615
Negative T-wave in II, III, aVF	12 (57%)	27 (73%)	0.217
Abnormal SAECG	8 (44%)	24 (83%)	0.006
RV/LV intramyocardial fat (by cardiac MRI)	9 (50%)	29 (81%)	0.020
Location of RV intramyocardial fat			
1. Apex	1 (6%)	6 (17%)	0.404
2. RVOT	6 (35%)	4 (11%)	0.062
3. Free wall	2 (12%)	3 (9%)	1
Genotype Positive	9 (50%)	9 (26%)	0.077
Positive biopsy	4 (80%)	13 (81%)	1.000

* Definition based on the 2010 revised international task force criteria.²

LV = left ventricle; RV = right ventricle; RVOT = right ventricular outflow tract; SAECG = signal-averaged ECG.