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ORIGINAL ARTICLE

Clinical Features, Genetic Findings, and Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy: Data From a Brazilian Cohort

Natália, Quintella Sangiorgi Olivetti MD, PhD; Luciana Sacilotto, MD, PhD; Fanny Wulkan, PhD; Gabrielle, D'Arezzo Pessente BSc, MSc; Mariana, Lombardi Peres de Carvalho BSc, MSc; Danilo, Moleta MD; Denise, Tessariol Hachul MD, PhD; Pedro Veronese, MD, PhD; Carina Hardy, MD; Cristiano Pisani, MD, PhD; Tan Chen Wu, MD, PhD; Marcelo Luiz Campos Vieira, MD, PhD; Lucas Arraes de França, MD, PhD; Matheus de Souza Freitas, MD; Carlos Eduardo Rochitte, MD, PhD; Sávia Christina Bueno, MD, PhD; Vitor, Bastos Lovisi MD; José Eduardo Krieger, MD, PhD; Maurício Scanavacca, MD, PhD; Alexandre da Costa Pereira, MD, PhD; Francisco da Costa Darrieux, MD, PhD

BACKGROUND: Arrhythmogenic right ventricular cardiomyopathy (ARVC), a rare inherited disease, causes ventricular tachycardia, sudden cardiac death, and heart failure (HF). We investigated ARVC clinical features, genetic findings, natural history, and the occurrence of life-threatening arrhythmic events (LTAEs), HF death, or heart transplantation (HF-death/HTx) to identify risk factors.

METHODS: The clinical course of 111 consecutive patients with definite ARVC, predictors of LTAE, HF-death/HTx, and combined events were analyzed in the entire cohort and in a subgroup of 40 patients without sustained ventricular arrhythmia before diagnosis.

RESULTS: The 5-year cumulative probability of LTAE was 30% and HF-death/HTx was 10%. Predictors of HF-death/HTx were reduced right ventricle ejection fraction (HR: 0.93; *P*=0.010), HF symptoms (HR: 4.37; *P*=0.010), epsilon wave (HR: 4.99; *P*=0.015), and number of leads with low QRS voltage (HR: 1.28; *P*=0.001). Each additional lead with low QRS voltage increased the risk of HF-death/HTx by 28%. Predictors of LTAE were prior syncope (HR: 1.81; *P*=0.040), number of leads with T wave inversion (HR: 1.17; *P*=0.039), low QRS voltage (HR: 1.12; *P*=0.021), younger age (HR: 0.97; *P*=0.006), and prior ventricular arrhythmia/ventricular fibrillation (HR: 2.45; *P*=0.012). Each additional lead with low QRS voltage increased the risk of LTAE by 17%. In patients without ventricular arrhythmia before clinical diagnosis of ARVC, the number of leads with low QRS voltage (HR: 1.68; *P*=0.023) was independently associated with HF-death/HTx.

CONCLUSIONS: Our study demonstrated the characteristics of a specific cohort with a high prevalence of arrhythmic burden at presentation, male predominance, younger age and HF severe outcomes. Our main results suggest that the presence and extension of low QRS voltage can be a risk predictor for HF-death/HTx in ARVC patients, regardless of the arrhythmic risk. This study can contribute to the global ARVC risk stratification, adding new insights to the international current scientific knowledge.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key words: arrhythmogenic right ventricular cardiomyopathy ■ genetics ■ heart failure ■ heart transplantation ■ risk assessment ■ sudden cardiac death

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Correspondence to: Natália Quintella Sangiorgi Olivetti, MD, PhD, Arrhythmia Unit and Laboratory of Genetics and Molecular Cardiology (LGMC), Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 44 – 05403-090 São Paulo, Brazil, Email nataliaolivetti@gmail.com or Francisco da Costa Darrieux, MD, PhD, Arrhythmia Unit, Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 44 – 05403-090 São Paulo, Brazil, Email frdarrieux@gmail.com/francisco.darrieux@incor.usp.br

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WHAT IS KNOWN?

- Today, several risk predictors of arrhythmic risk were identified, which enabled risk stratification to prevent arrhythmic sudden death, but it still lacks understanding the progression to end-stage heart failure, heart failure death, or heart transplantation in arrhythmogenic right ventricular cardiomyopathy.

WHAT THE STUDY ADDS

- This is the first study of arrhythmogenic right ventricular cardiomyopathy risk stratification in South America to date.
- Low QRS voltage is a well-known marker of heart failure severity in most common causes of heart failure, although it was not explored as a candidate for risk prediction in patients with arrhythmogenic right ventricular cardiomyopathy until now.
- The study data suggested that low QRS voltage is associated with heart failure severity outcomes, regardless of the arrhythmic risk.

Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic right ventricular cardiomyopathy
HF	heart failure
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LTAE	life-threatening arrhythmic event
RV	right ventricle
RVEF	RV ejection fraction
TWI	T wave inversion
VA	ventricular arrhythmia
VT	ventricular tachycardia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease caused by a loss of function mutation in genes encoding for desmosomal complexes.[1] This leads to disruption of intercellular junctions, myocyte detachment and cardiomyocyte death.[2] Impairment of desmosomal assembly induces a gene transcriptional switch from myogenesis to adipogenesis and fibrogenesis,[2] causing progressive replacement of the myocardium by adipose and fibrous tissue. This ventricular scar is the arrhythmogenic substrate that predisposes to development of ventricular tachycardia (VT), sudden cardiac death (SCD), heart failure (HF), and heart transplant (HTx).[3] ARVC is one of the leading causes of arrhythmic cardiac arrest, especially at younger ages and athletes.[3] Although initially thought to affect only the right ventricle (RV), it is recognized that the left ventricle (LV) can also be involved, and in some cases, it may predominate.[4,5]

Pharmacological therapies and catheter ablation have not been proven effective in changing the natural course of the disease,[6] and an implantable cardioverter defibrillator (ICD) may be the only option to prevent SCD.[7] Patients who experienced cardiac arrest, sustained VT and reduced RV ejection fraction have a Class I indication for ICD.[6] Conversely, ICD placement for primary prevention is challenging.

Different cohorts pointed out several risk predictors.[5–10] The International Task Force Consensus Statement of Treatment of ARVC proposed an algorithm classifying risk as high, intermediate, or low.[6] Other guidelines consolidated the indications of ICD in high-risk groups.[11–15] A new predictor model (ARVC risk calculator) provides quantification of an individual patient's risk.[16]

There are several tools improving arrhythmic risk stratification to prevent SCD, but scarce information about predictors of progression to end-stage HF in ARVC[17] has been published. In a large registry of HF from different etiologies, low voltage on the ECG is one of the markers of the HF severity and is a risk factor for adverse outcomes.[18,19] To the best of our knowledge, low QRS voltage was not yet explored as a candidate for risk prediction in patients with ARVC.

Our aim was to describe the clinical features, genetic findings, natural history, the occurrence of life-threatening arrhythmic events (LTAE), HF death, or heart transplantation (HF-death/HTx), and identify risk factors associated with increased severity outcomes.

METHODS

The investigation conforms with the principles outlined in the *Declaration of Helsinki*. The study protocol was approved by our Institutional Review Board (# 4042.14.022), and written, informed consent was obtained from the patients. The authors declare that all supporting data are available within the article and its Supplemental Material.

Study Outcomes

The primary study outcome was death for end-stage heart failure or heart transplant (HF-death/Htx). Secondary outcome was LTAE, defined as a composite of the occurrence of sustained VT, aborted SCD, appropriate ICD therapies, arrhythmic syncope, and electrical storm. Combined events were defined as a composite end point of at least one of the following: LTAE, HF-death, and HTx events.

Risk Predictors

Potential risk predictors were prespecified based on clinical experience and current literature on risk stratification in ARVC, including the International Task Force Consensus Statement for Treatment of ARVC as well as the variables in ARVC risk calculator.[6,7,12,16] Variables of interest were considered: age of disease onset, gender, proband status, family history of SCD, heart failure symptoms, cardiac syncope, prior sustained VT/ventricular fibrillation, number of leads with T wave inversions

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(TWI), number of leads with low QRS voltage, the presence of epsilon wave; right and left ventricle ejection fraction. Each predictor variable was determined at the time of diagnosis, and always prior to occurrence of the outcome.

Data Collection

All patients underwent a complete review of the clinical history, including HF diagnosis and symptoms,[20] demographic data, laboratory tests, ECG, high resolution ECG, 24-hour Holter monitoring, imaging data from echocardiogram (ECHO), and cardiac magnetic resonance imaging (MRI). We manually measured the QRS voltage in all 12 leads of the ECG. Low QRS voltage was defined according to traditional ECG criteria, if QRS <0.5 mV in limb leads or QRS <1.0 mV in precordial leads.[21,22] The criterion was applicable in every limb and precordial lead, and we considered positive when at least 2 contiguous leads presented low QRS amplitude.

Genetic Analyses and Panel Design

Next-generation sequencing technology[23] was performed in a broad panel of 160 genes of cardiomyopathies. Gene panel included all the main genes associated with ARVC, according to the Clinical Genome Resource (Clingen) framework.[24] The variants classification was based on the American College of Medical Genetics (ACMG) guidelines.[25]

Statistical Analysis

Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, New York) and R version 4.0 (R Core Team, 2021). Phenotypic Characteristics of ARVC Patients at diagnosis were reported as mean±SD or median (IQ range) for continuous variables and frequencies with percentages for categorical variables. HF-death/HTx, LTAE, and combined events survival curves were estimated using Kaplan-Meier estimator and were compared with the log-rank test. The characteristics with $P<0.10$ in the univariable Cox proportional hazards regression analysis entered as candidate variables in a multivariable model. The final multivariable model was selected using a backward-elimination algorithm (retention threshold $P<0.05$). Individuals who did not experience any events during the follow-up time were censored at the time of the last visit or at a maximum follow-up period of 15 years. A $P<0.05$ was considered statistically significant.

RESULTS

Study Population

Overall, 111 patients met definite ARVC diagnostic criteria and were enrolled; the mean age at diagnosis was 36.3 years. Most patients were men (80/111; 72%) and probands (93/111; 83.8%). A total of 24.3% (27/111) probands had a family history of unexplained SCD before 35 years. One-third (37/111; 33.3%) had cardiac syncope before presentation; more than two-thirds of patients had palpitation (85/111; 76.6); more than half of patients had sustained VT at the time of diagnosis (63/111; 56.8%) and a minority had aborted SCD (8/111; 7.2%). HF symptoms were present in 18.9% (21/111) patients. Detailed information is provided in Table S1.

ECG Features

PR interval, QRS, and QT duration were within normal values. TWI in V1-V3 leads was present in 80.2% (89/111) patients, whereas in 16.2% (18/111) TWI extended to V6 lead. In inferior leads, TWI occurred in 49.5% (55/111) while in high lateral leads (I e aVL) in 10.8% (12/111). The mean number of leads with TWI was 6 (min 2 and max 12). Epsilon wave was detected in 36% (40/111) of patients (Figure S1). Low QRS voltage was observed in 33.3% (37/111); 29.7% (11/37) of them in >8 leads.

Genetic Findings

Next-generation sequencing was performed in 82/93 probands (88.2%). In 6 probands, the DNA was not collected due to logistic difficulties and the remaining 5 probands died before genetic testing was available. A pathogenic or likely pathogenic variant was found in 54% (44/82) probands. Variants of uncertain significance were found in 24.4% (20/82). The majority of pathogenic or likely pathogenic variants were in desmossomal genes. The predominant mutation was truncating type, occurring in 38/44 (86%) of pathogenic or likely pathogenic variants. The demographic, baseline characteristics and main genetic findings are summarized in Table 1. Detailed information of the variants in Tables S3 and S4.

Clinical Course and Natural History

The cumulative probability of combined event during lifetime was 40% in 5 years and 70% in 15 years. The cumulative probability of HF-death/HTx during lifetime was 10% in 5 years (95% CI, 20%–16%) and 40% in 13 years (95% CI, 18%–56%).

Overall, 16.2% (18/111) of patients presented the primary outcome (HF-death/HTx) after a mean 5.6 years of follow-up. Almost half of them (8/18; 44.4%) underwent HTx due to severe and refractory HF, with inotropes dependence. HF death was notified in 14 patients as follows: 10 deaths from end-stage HF, and 4 after acute complication of HTx.

The cumulative probability of LTAE was 30% in 5 years (95% CI, 20%–39%), and 50% in 13 years (95% CI, 47%–65%). LTAE occurred in 45% (50/111), distributed as sustained VT in 42% (47/111), ICD was placed in 64% (71/111), appropriate ICD therapies occurred in 25% (28/111), electrical storm in 7% (8/111), and 1 SCD. Comparison between groups with or without prior sustained ventricular arrhythmia (VA) showed an earlier and higher arrhythmic event during follow-up in the group with prior VA. (Figure 1)

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Table 1. Phenotypic and Genetic Characteristics of ARVC Patients at Diagnosis

	N: 111 (100%)
Demographics	
Age, y; mean±SD	36.3±14.7
Male n/N, %	80/111 (72)
Proband, %	93/111 (84)
Clinical manifestations at presentation n/N (%)	
Palpitations	85/111 (77)
Syncope	37/111 (33)
Heart failure symptoms, n/N (%)	21/111 (19)
Arrhythmias, n/N (%)	
Sustained atrial arrhythmias	36/111 (32)
Nonsustained VT	62/111 (56)
Sustained VT	63/111 (57)
Cardiac arrest/aborted sudden death	8/111 (7)
ECG repolarization positive criteria, n/N (%)	
TWI V1-V3	89/111 (80)
ECG depolarization positive criteria, n/N (%)	
Epsilon wave	40/111 (36)
Transthoracic echocardiogram	
FAC (%), mean	26 (8–50)
Strain FWLS	15.9 (8–20)
LVEF (%), IQR median (25th–75th)	62 (59–66)
Cardiac MRI	
Fibrofatty infiltration, n/N (%)	13/93 (14)
LGE in RV, LV or both, n/N (%)	43/93 (44)
RVEF (%), mean (min–max)	36 (10–63)
LVEF (%), mean (min–max)	57.9 (20–76)
Genetic features, n/N (%)	
Pathogenic/likely pathogenic	44/82 (53.7)
PKP2	30/44 (68.2)
DSC2	4/44 (9.1)
DSG2	4/44 (9.1)
DSP	5/44 (11.4)
TMEM 43	1/44 (2.3)

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DSC2, desmocollin 2; DSG2, desmoglein 2; DSP, desmoplakin; FAC, fractional area change; FWLS, free-wall longitudinal strain; HR, hazard ratio; LGE, late gadolinium-enhancement; LV, left ventricle; LVEF, left ventricle ejection fraction; MRI, magnetic resonance imaging; NSVT, nonsustained ventricular tachycardia; PKP2, plakophilin 2; RV, right ventricle; RVEF, right ventricle ejection fraction; TMEM43; transmembrane protein 43; TWI, T wave inversion; and VT, ventricular tachycardia.

Event Predictors in the Overall Cohort

Predictors of HF-death/HTx were reduced RV ejection fraction (RVEF; HR: 0.93; *P*=0.010), HF symptoms (HR: 4.37; *P*=0.010), epsilon wave (HR: 4.99; *P*=0.015) and number of leads with low QRS voltage (HR: 1.28; *P*=0.001), in the univariable analysis. The results of HR regarding the variable low QRS voltage were per lead. For each additional lead with low QRS voltage the risk of HF-death/HTx increased by 28%. Cox multivariable analysis showed a significant and independent increase in the risk of HF-death/HTx associated with the number of leads with low QRS voltage (HR: 1.49; *P*=0.0073; Table 2).

Predictors of LTAE were prior syncope (HR: 1.81; *P*=0.040), number of leads with TWI (HR: 1.17; *P*=0.039), number of leads with low QRS voltage (HR: 1.12; *P*=0.021), younger age (HR: 0.97; *P*=0.006) and prior VA/ventricular fibrillation (HR: 2.45; *P*=0.012) in the univariable analysis. The results of HR regarding the variables low QRS voltage and TWI were per lead. The multivariable analysis showed that younger age (HR: 0.97; *P*=0.024) and prior VA/ventricular fibrillation (HR: 4.37; *P*=0.017) were associated with LTAE (Table 3).

Event Predictors in Patients Without Prior VA

Predictors of HF-death/HTx were reduced right ventricular ejection fraction (HR: 0.93; *P*=0.056), HF symptoms (HR: 5.11; *P*=0.054), epsilon wave (HR: 11.70; *P*=0.028), and number of leads with low QRS voltage (HR: 1.68; *P*=0.023), in the univariable analysis. The multivariable analysis found a significant and independent increase in the risk of HF-death/HTx associated with the number of leads with low QRS voltage (HR: 1.68; *P*=0.023; Figure 2). Estimates from multivariable Cox regression models in 40 patients without VA before diagnosis of ARVC are in Table S2.

Degree of Extension of Leads With Low QRS Voltage

The absolute and relative frequencies of the combined event were evaluated according to the number of leads affected by the low QRS voltage. It was observed that all individuals with > 8 leads affected by low QRS voltage experienced a combined event.

These patients 11/111 (10%) with extensive low QRS voltage (>8 leads) presented with high events rate: 72.7% (8/11) of LTAE and 54.5% (6/11) of HF-death/HTx. The distribution of events was: 8 LTAE, 6 of them received appropriated ICD therapy, 2 of them were submitted to a HTx due to end-stage HF; both patients died of complications from HTx (massive bleeding and infection). One of them died due to decompensated HF. Three patients died from end-stage HF without prior VA. Two of these patients had compound heterozygous mutations in desmossomal genes (PKP2 and DSG2), one patient had a single pathogenic variant in PKP2, in one case, it was not found any variant related to ARVC, and 2 patients did not undergo genetic testing (Figure 3).

DISCUSSION

Main Findings in Our Cohort and Prior Studies

In this article, we described the clinical course of ARVC in our cohort, with a high rate of LTAE and HF-death/HTx.

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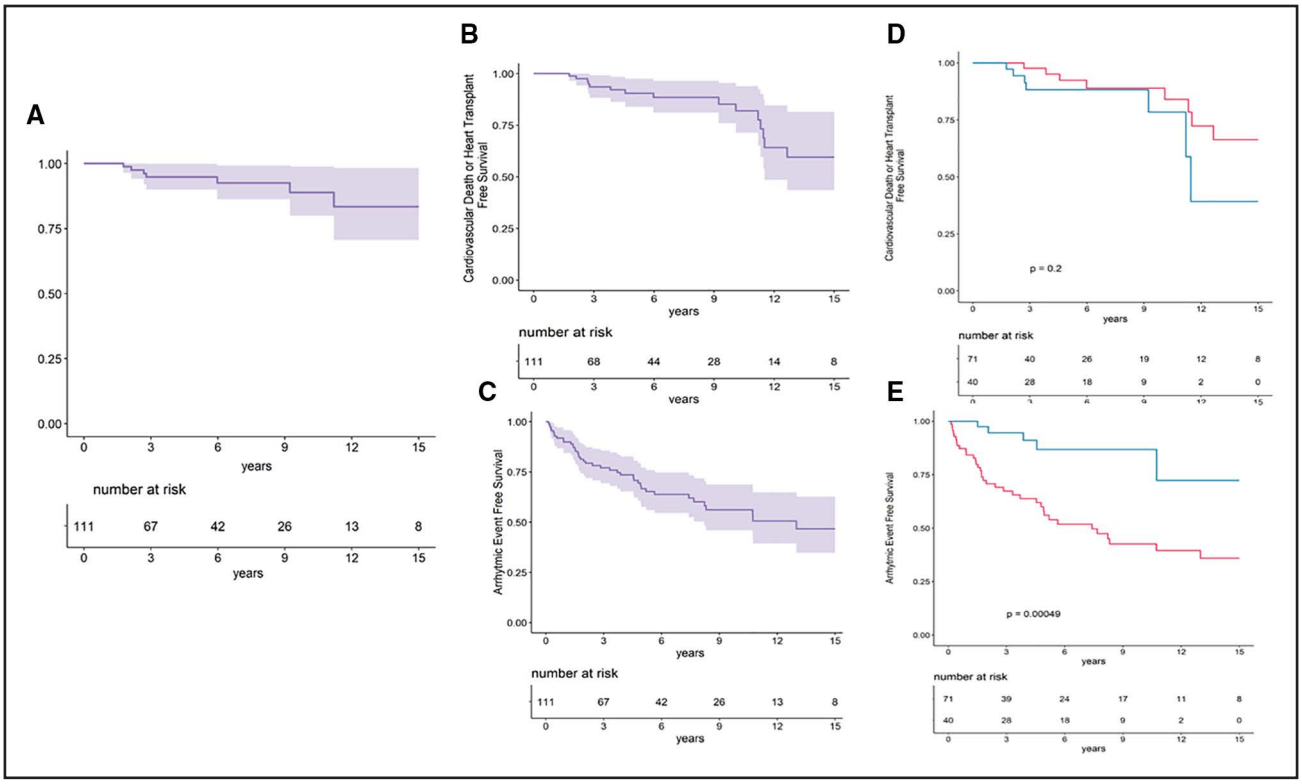

Figure 1. Survival free from combined events (life-threatening arrhythmic event [LTAE], HF death, or heart transplantation [HF-death/HTx]).

A, Survival-free from combined event for the entire cohort. **B**, Survival free from HF-death/HTx for the entire cohort. **C**, Survival-free from LTAE for the entire cohort. **D**, Comparison between groups (with or without prior ventricular arrhythmia [VA]) showed there was no difference on HF-death/HTx (*P*=0.2). **E**, Comparison between groups showed an earlier and higher arrhythmic risk during follow-up in the group with prior VA (*P*=0.00049). Red curve indicates patients with prior VA at diagnosis and blue curve indicates patients without prior VA at diagnosis.

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The mean age at first presentation in our cohort was 36 years. This is in accordance with the young age at first presentation, between 20 and 40 years, also observed in other cohorts.[7] The male predominance observed in our study is also common among other related cohorts.[7,8,16] In one of the largest cohort studies on ARVC, by Groeneweg et al,[8] a high rate of arrhythmias at clinical presentation was also remarkable. The prevalence of VA in the Groeneweg et al cohort was 50% and cardiac arrest in 11%, whereas in our cohort, VA occurred at presentation in 57% of patients and cardiac arrest in 7% of patients. Syncope was seen more often in our cohort (33%) than the 10% to 20% observed in other representative studies.[7,16] Our study provides additional information about HF symptoms, found in almost 20% of patients.

It is noteworthy that our patients had a more severe phenotype profile, and some questions need to be raised. One of the possible reasons could be the higher prevalence of probands (84%) in our cohort, since the "proband status" is often related to disease severity.[7,16] Our cohort found 54% of genetic diagnostic yield, quite similar to other main cohorts.[24] Of note, background data regarding gene variants in arrhythmogenic cardiomyopathies are largely derived from cohorts with western European ancestry.[12] We additionally observed a high prevalence of truncating variants (86%), however whether this could determine the phenotypic expression is a matter of debate that we could not demonstrate with our data.

The approach to ARVC risk stratification includes several risk markers to consider clinical, electrical, genetic and structural findings to a better perspective of disease severity.[5] The main ARVC risk markers are: younger age; male gender; proband status; previous history of sustained VA/ ventricular fibrillation; high burden premature ventricular contraction; NSVT; cardiac syncope; complex genotype, degree of exercise restriction; and several structural characteristics, as RVEF and LVEF, that translate severity of myocardial involvement.[11,12,14,16] One of the predictors of LTAE in our study was younger age, in accordance with other several prior studies.[7,9,16] In fact, patients younger than 20 years at first clinical presentation (from 13 to 19) were 16 patients overall. The majority of them (11/16; 69%) presented LTAE at follow-up, 3 died due to end-stage HF at young age (at 16 years, 21 years and 34 years), and 1 presented SCD after he refused ICD placement at 25 years old. A history of prior suspected arrhythmic syncope, a risk marker first identified by Marcus et al[26] and supported by other authors,[7,9,16,27] was also observed as a risk predictor in our study.

Table 2. Predictors of HF-Death/HTx in ARVC Cohort at Follow-Up

	Univariable model		Multivariable model	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	0.98 (0.95–1.02)	0.344		
Gender (male)	0.43 (0.15–1.26)	0.124		
RVEF, %	0.93 (0.88–0.98)	0.010		
LVEF, %	0.97 (0.94–1.00)	0.060		
Number of leads with low QRS voltage	1.28 (1.11–1.47)	0.001	1.49 (1.11–1.99)	0.0073
Heart failure symptoms	4.37 (1.43–13.37)	0.010		
Number of TWI leads	1.12 (0.89–1.40)	0.342		
Epsilon wave	4.99 (1.37–18.15)	0.015		
LGE RV or LV	2.36 (0.60–9.26)	0.219		
Prior VA/VF	1.38 (0.12–15.22)	0.794		
Genetic pathogenic variant	0.95 (0.13–6.86)	0.957		
Family SCD	0.98 (0.31–3.13)	0.969		
Prior syncope	1.05 (0.35–3.18)	0.930		
PVC> 1000/24 h	1.86 (0.54–6.41)	0.323		
NSVT	1.23 (0.41–3.69)	0.709		

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; HF, heart failure; LGE, late gadolinium-enhancement; LV, left ventricle; LVEF, left ventricle ejection fraction; NSVT, non sustained ventricular tachycardia; PVC, premature ventricular contraction; RV, right ventricle; RVEF, right ventricle ejection fraction; SCD, sudden cardiac death; TWI, T wave inversion; VA, ventricular arrhythmia; and VF, ventricular fibrillation.

The extent of ECG abnormalities reflects the degree of myocardial involvement. Orgeron et al. described that TWI in ≥3 precordial leads predicted appropriate ICD therapy.[9] Later, Cadrin-Tourigny et al[16] demonstrated that the more leads with TWI, the greater the risk, in line with the extent of TWI association to LTAE observed in our study. In our data, patients with prior sustained VA presented with earlier and higher arrhythmic event risk during follow-up. This data is in accordance with the concept that a history of VA can predict appropriate ICD therapy for any future VA, as demonstrated by other studies.[7,9,10,28] These data reinforce the concept that a history of any sustained VA should encourage ICD treatment consideration. Migliore et al[29] already demonstrated that the extent of

Table 3. Predictors of LTAE in ARVC Cohort at Follow-Up

	Univariable model		Multivariable model	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	0.97 (0.95–0.99)	0.006	0.97 (0.95–1.00)	0.024
Gender (male)	1.04 (0.54–2.00)	0.908		
Prior VA/VF	2.45 (1.22–4.93)	0.012	4.37 (1.30–14.70)	0.017
Genetic pathogenic variant	1.66 (0.89–3.12)	0.113		
RVEF, %	0.98 (0.96–1.01)	0.158		
LVEF, %	0.99 (0.97–1.01)	0.394		
Family SCD	1.07 (0.58–1.96)	0.832		
Prior syncope	1.81 (1.03–3.19)	0.040		
PVC> 1000/24 h	0.96 (0.53–1.75)	0.892		
NSVT	1.30 (0.72–2.36)	0.380		
Number of leads with low QRS voltage	1.12 (1.01–1.18)	0.021		
Heart failure symptoms	1.01 (0.51–2.00)	0.968		
Number of TWI leads	1.17 (1.01–1.35)	0.039		
Epsilon wave	1.36 (0.77–2.40)	0.287		
LGE RV or LV	1.45 (0.76–2.76)	0.259		
Proband	2.70 (0.84–8.73)	0.096		

LV indicates left ventricle; LVEF, left ventricle ejection fraction; NSVT, non sustained ventricular tachycardia; PVC, premature ventricular contraction; RV, right ventricle; RVEF, right ventricle ejection fraction; SCD, sudden cardiac death; TWI, T wave inversion; VA, ventricular arrhythmia; and VF, ventricular fibrillation.

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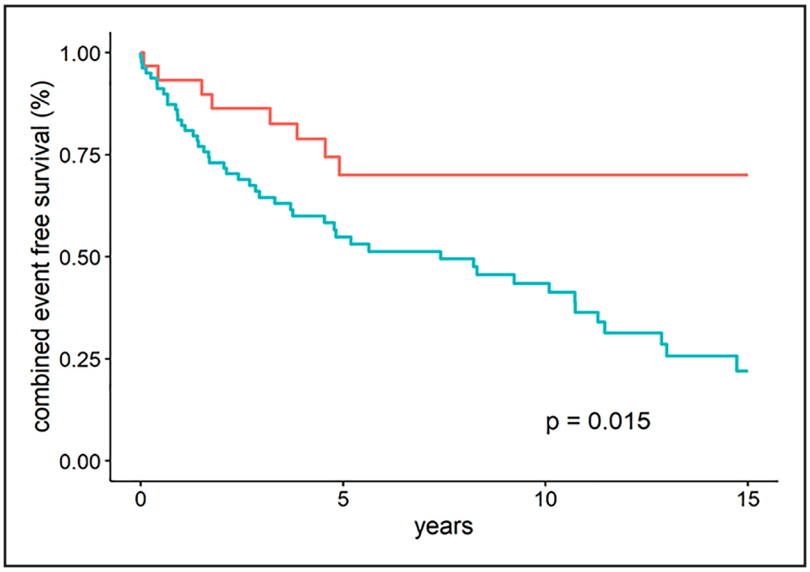

Figure 2. Low QRS voltage as predictor of HF death/heart transplantation (HF-death/HTx) in arrhythmogenic right ventricular cardiomyopathy.
Kaplan-Meier estimate of cumulative survival free from HF-death/HTx variated significantly by presence or absence of low QRS voltage, evaluated at presentation in 40 patients without life-threatening arrhythmic event at diagnosis. Red curve indicates patients without low QRS voltage, and blue curve indicates patients with low QRS voltage.

low-voltage areas in endocardial voltage mapping is an independent predictor of LTAE in ARVC. This finding is in accordance with our study data that the extent of leads with low-voltage QRS is associated with LTAE.

In this cohort, the predictors of HF-death/HTx were reduced RVEF, HF symptoms, epsilon wave, and number of leads with low QRS voltage. Our cohort data suggested that the presence of low QRS voltage can be an independent predictor of HF-death/HTx in ARVC, regardless of the arrhythmic risk. The low QRS voltage is described among the ECG characteristics of ARVC patients,[19,30,31] although it had not been described as a risk predictor of HF-death/HTx. Notably, the ARVC risk calculator, from the largest cohort of risk stratification in ARVC, did not include low QRS voltage as a candidate predictor between the variables studied.[16]

We first expected that LVEF would be a predictor to HF events. Our study was designed to include only ARVC patients with definitive diagnosis according to Task Force Criteria 2010, thus the majority of our cohort was composed of right ventricle predominant forms of arrhythmogenic cardiomyopathies. HF outcomes (HF death and HTx) were associated to RVEF and occurred independently of LVEF. This highlights the importance of decreased RVEF in this challenging disease and demonstrates that HF severe outcomes can occur due to RV dysfunction, even with preserved LVEF.

Late gadolinium-enhancement (LGE) may be difficult to appreciate in the RV due to its thin walls, and it leads to a large variation of interpretation between examiners. In this cohort, most patients have a right predominant ARVC and considering the limitations regarding the RV anatomy, this could explain why LGE did not have significant association to HFdeath/HTx. Also, when MRI is performed in an early stage of the disease, it might have a less expressive imaging feature that not necessary correlates with its future expression over time until HF onset. In addition, MRI acquisition and data were limited in patients with non-MRI-conditional ICD. In prior studies, it was not possible to demonstrate the correlation between RV LGE and ECG scar markers, such as low amplitude electrocardiograms, neither in invasive endocardial voltage mapping[32] nor in noninvasive electrophysiology mapping.[33] A prior study explored the relation of invasive electrophysiology mapping to RV LGE and found that 50% of electric scar substrates observed in the RV were not confirmed by LGE.[32]

Physiopathology and Mechanistic Rationale

The low QRS voltage occurs in several other cardiomyopathies and pericardial disease, for example, in myocarditis,[19,34] infiltrative cardiomyopathies,[35] amyloidosis,[36–38] phospholamban cardiomyopathy,[39] pericardial effusion,[40] hypothyroidism,[41] and cardiac metastases.[42] The Padua Criteria, a recent approach to arrhythmogenic left ventricle cardiomyopathy, include low QRS voltage in limb leads as an ECG minor criterion to diagnosis.[4]

There is an association between low QRS voltage, fibrofatty replacement,[13] and LV late gadolinium enhancement (LGE) identified by MRI,[19] especially in the LV.[43] The mechanism involved in the reduction of QRS voltages consists of the decrease of LV myocardial mass, reducing the electrical activity.[43] Myocardium scars are an arrhythmic substrate that predispose ARVC patients to VA and HF. The prognostic role of low QRS voltage extension in ARVC has already been suggested by Gallo et al. In a study on the long-term ECG features in ARVC, it was demonstrated that the low QRS voltage progresses over time.[44] In Chagas disease, a prevalent cardiomyopathy in South America, low QRS voltage has a 2.57-fold risk of death.[45] Therefore, the low QRS voltage is an ECG marker of fibrofatty infiltration or fibrosis and of a more severe clinical profile as well.

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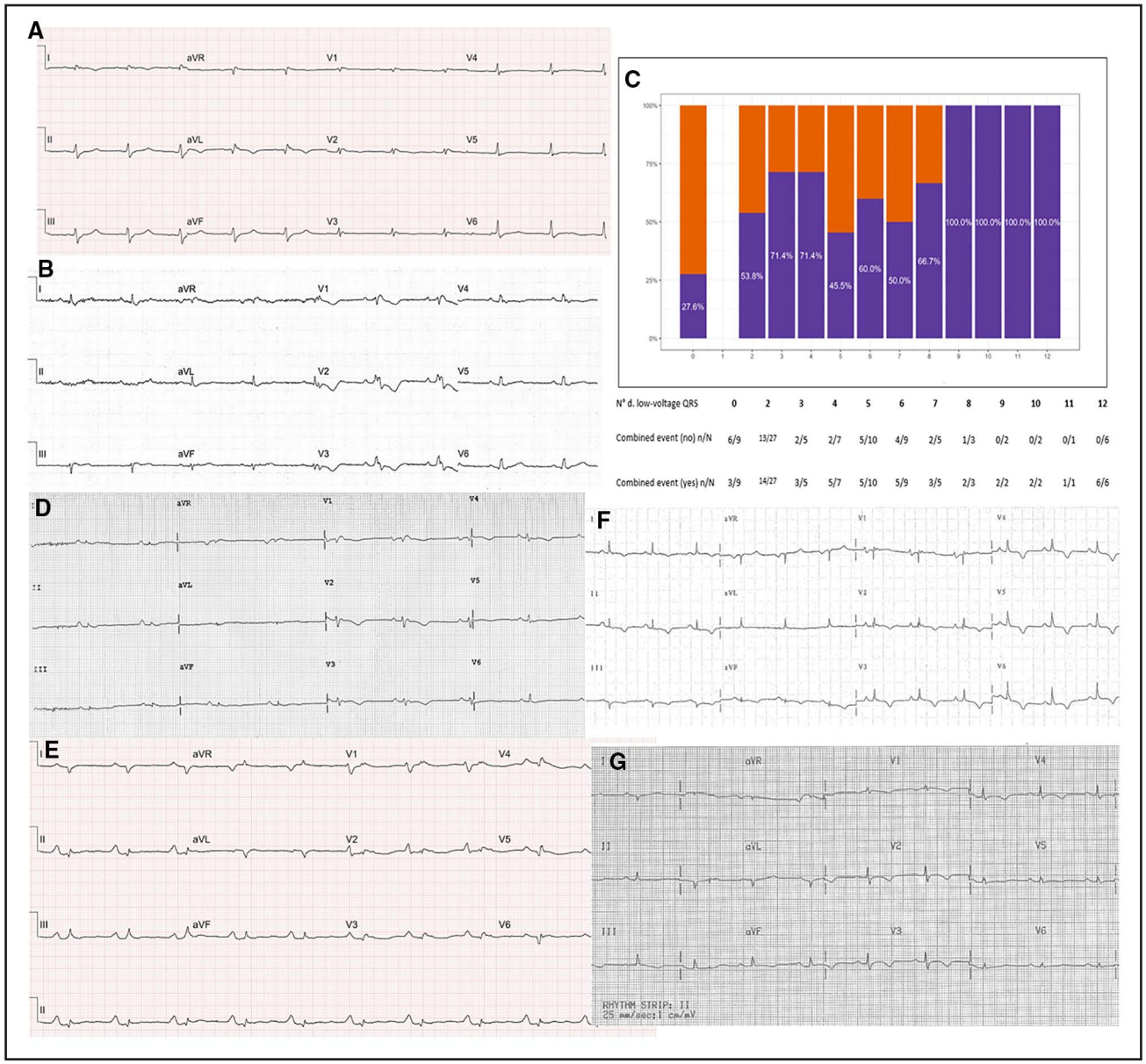

Figure 3. Electrocardiogram (ECG) examples of 2 patients with extensive low QRS voltage.
A, ECG of a 19-year-old female with a PKP2 NM_004572.4 c.2062T>C p.Ser688Pro likely pathogenic variant and a PKP2 NM_004572.4 c.1669A>G p.Asn557Asp VUS variant. **B**, ECG of a 33-year-old male with a DSG2 NM_001943.5 c.621_626del p.Tyr207Ter pathogenic variant and a DSG2 NM_001943.5 c.691-1G>A pathogenic variant. **C**, Absolute and relative frequencies of the combined event according to the number of leads affected by the low QRS voltage. **D**, ECG of a 27-year-old female that did not undergo genetic testing. **E**, ECG of a 16-year-old male, his genetic test did not find any variant related to the phenotype. **F**, ECG of a 36-year-old male, with a PKP2 NM_004572.4 c.1689-1G>C pathogenic variant (**G**) ECG of a 36-year-old male, he did not undergo the genetic testing. DSG2 indicates desmoglein 2; ECG, electrocardiogram; and PKP2, plakophilin 2.

Limitations

The study has some strengths and weaknesses. First, it was carried out in a tertiary referral center in cardiology. Most of the patients already had presented a sustained VA at the time of the diagnosis. So, a potential referral bias with overestimated severity cannot be precluded. We tried to adjust it by distinguishing patients in groups with and without VA, but this adjustment reduced the number of patients that were selected to the statistical analysis. Screening of relatives and diagnosing patients with less severe clinical manifestations could help to better balance the bias.

In Brazil, our public health care system has many operational difficulties and health inequities, especially regarding access to primary care and limited capacity of tertiary hospitals to absorb the demand. Sometimes patients experience challenging barriers to be referred from primary health care to a tertiary referral hospital. Complexity of ARVC diagnosis and a long way to the first evaluation by specialists are possible major contributors

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for system failure. As ARVC is a rare disease with challenging diagnosis, most general or family physicians are unaware about the disease severity and may underestimate their symptoms. Patients most often are referred to a first appointment with a cardiologist already in an advanced stage of the disease, what may contribute to a more severe phenotype at presentation in our cohort.

Our study did not demonstrate significant association between LTAE and some other known risk markers. These issues can be explained by the relatively small sample size, bias selection, relative differences in the study populations and genotype composition.

Conclusions

Our study demonstrated the characteristics of a specific cohort derived from a different ethnic population in South America, with a high prevalence of arrhythmic burden at presentation, male predominance, younger age, considerable genetic diagnostic yield and a high LTAE rate event. The main result from our cohort suggests that the presence and the extension of low QRS voltage can be an independent risk predictor associated to HF-death and HTx in ARVC patients, regardless of the arrhythmic risk. This finding need to be further validated in larger cohorts. This study can contribute to the global ARVC risk stratification, potentially adding new insights to the international current scientific knowledge.

ARTICLE INFORMATION

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Affiliations

Arrhythmia Unit (N.Q.S.O., L.S., G.D.P., D.T.H., P.V., C.H., C.P., T.C.W., S.C.B., V.B.L., M.S., F.d.C.D.). Laboratory of Genetics and Molecular Cardiology (LGMC) (N.Q.S.O., F.W., M.L.P.d.C., J.E.K., A.d.C.P.). Echocardiogram Imaging Unit (D.B.M., M.L.C.V.). Division of Cardiovascular Magnetic Ressonance Imaging, Instituto do Coração (InCor), Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil (M.d.S.F., C.E.R.). Echocardiogram Imaging Unit, Hospital Israelita Albert Einstein. São Paulo, Brazil (D.B.M., M.L.C.V., L.A.d.F.).

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Disclosures

None.

Supplemental Material

Supplemental Methods I–VII
Tables S1–S4
Figure S1
References[46,47]

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