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Long-term prognosis of out-of-hospital cardiac arrest due to idiopathic ventricular arrhythmias

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Abstract

Life-threatening ventricular arrhythmias (VA) may occur in patients with unknown cardiac disease. A sizable part of them remains labeled as idiopathic VA and limited data is available regarding their natural history. Our aim was to evaluate the long-term clinical outcomes of survivors of an idiopathic life-threatening VA. Patients who survived an idiopathic life-threatening VA referred to an ICD were included and followed for a median follow-up of 7 years. Clinical and device data were collected and a comparison between genders was made. A total of 29 patients, 41% female, mean age of 50 (19) years were studied; all were implanted with an ICD at index hospitalization. At follow-up, an etiological diagnosis was established in 38% of patients. Genetic testing improved the diagnosis and allowed the identification of a distinct clinical entity in 60% of patients (p=0.04, OR=7.0), especially in women. Regarding ICD data, 31% received appropriate therapies with a median time to the first appropriate shock of 39 months (IQR 12-46 months). Men had a significantly higher prevalence of appropriated shocks (50% *vs* 8%, p=0.04), with a similar time to the first arrhythmic event between genders. Two of the patients died, both from non-arrhythmic causes. Etiologic diagnosis and recurrence prediction in patients with idiopathic VA is challenging, even with long-term follow-up and sophisticated diagnostic evaluation. Genetic testing significantly improved the diagnostic yield, especially in women. Arrhythmia recurrence occurred in about one-third of patients and is significantly higher in men, underscoring the importance of ICD implantation.

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Introduction

Sudden cardiac death (SCD) represents a major public health problem, accounting for approximately 50% of all cardiovascular deaths. Noteworthy, a significant amount of them are the first manifestation of cardiac disease [1-3]. Ischemic heart disease remains the most common underlying substrate associated with SCD, although this incidence appears to be decreasing [4]. Despite uncommon events in the absence of structural heart disease, life-threatening ventricular arrhythmias (VA) may occur in patients without evidence of cardiac disease, a sizable part of them classified as idiopathic VA [2,5]. Combining clinical assessment with up-to-date diagnostic tools such as genetic testing (GT) can provide a specific diagnosis in 13% to 60% of younger SCD survivors 6. Still, a significant and heterogeneous group of patients remains labelled as Idiopathic VA and limited data is available regarding their natural history. In these patients, an ICD is strongly recommended if meaningful survival greater than 1 year is expected [2,5]. For patients with recurrent episodes of idiopathic VA triggered by short coupled ventricular premature beats with a consistent QRS morphology, ablation is useful and should be considered [2,7].

The aim of this study was to evaluate the long-term clinical and device outcomes of survivors of an aborted SCD due to idiopathic ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT).

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Materials and Methods

Study population

The present study included a sample of consecutive patients from January 2005 to April 2019 who survived a SCD caused by idiopathic VA (VF or pVT) referred to ICD implantation at Centro Hospitalar Universitário São João, a tertiary center in Porto, Portugal. Patients who did not implanted ICD were excluded. Clinical data, as well as the results of different ancillary tools (namely, blood test, electrocardiogram, echocardiogram, cardiac catheterization, etc.), were collected at presentation. Follow-up, including ICD data, were retrospectively collected and analyzed from physical and digital records, including data from other health institutions. Were considered as baseline ECG the first exam available in patient-record (usually at hospital or emergency department admission). Most ECGs in our institution were electronically recorded and all the exams were assessed and reviewed by cardiologists. All patients were followed in a specialized cardiac implantable electronic devices (CIED) consultation at least one day, one week and 3 months after implantation; after 3 months, most of the patients were followed each 6 months. Most of the CIED records were on paper and all data were reviewed by cardiologists. Idiopathic VA was considered when no evidence of underlying structural or electrical heart disease were found after a comprehensive evaluation during index hospitalization. The diagnostic process was undertaken by and at the discretion of the medical staff, but three investigators reviewed medical reports to ensure that appropriate diagnostic criteria were used. Before cases were labeled as idiopathic VA, all investigations performed or planned during the index hospitalization were considered.GT was not considered a baseline assessment since their results are only acknowledged several weeks later and do not alter the initial diagnosis and management; its impact on further redefining diagnosis during follow-up was explored. This study was approved by the Institutional Ethics Committee.

Statistical analysis

Data are presented as mean (SD) or median (IQR) for continuous variables and as percentages for categorical variables. One-sample Kolmogorov-Smirnov test was performed to evaluate normal distribution. Categorical variables were compared using Fisher's exact test; odds ratios (OR) are presented when considered relevant. Continuous parametric variables were compared using *t*-test and non-parametric variables using Mann-Whitney U test. Differences were considered statistically significant when p-value <0.05. Statistical analysis was performed in IBM SPSS Statistics version 25.

Table 1. Patients' characteristics.

N	29
Age	50 (19) years-old
Female	41%
Hypertension	38%
Diabetes	7%
Dyslipidemia	21%
Smoker or previous smoker	21%
Prior kidney disease	3%
Atrial fibrillation	14%

Results

A group of 29 survivors of aborted SCD due to VA were included and followed with a median follow-up of 7 years (5-12 years). Patient characteristics are summarized in Table 1. The mean age at index was 50 (19) year-old and 41% of the patients were female. Of all patients implanted with an ICD at the index hospitalization, most received a transvenous ICD device (71% a single chamber transvenous ICD, 25% a dual chamber transvenous ICD) and 1 patient received a subcutaneous ICD. Regarding index arrhythmic event, initial rhythm was VF in 76% and pVT in 24%. Cardiac arrest occurred during daily life activities in 15 patients (52%), after emotional stress in 4 (14%), during efforts, in rest and asleep in 2 patients each (7%); the SCD context was unknown in 4 patients (14%). Baseline ECG was normal in 74%; in the remaining, atrial fibrillation was the most frequent finding, 2 patients presented complete right bundle branch block (RBBB), 1 patient incomplete RBBB and 1 patient 1st degree Mobitz I atrioventricular block. To exclude possible VA causes, all patients were submitted to coronary angiography and echocardiogram; neither patient had coronary artery disease nor structural heart disease (all presented preserved biventricular systolic function with normal ventricular volumes). As adjunctive, 68% performed a cardiac magnetic resonance, 20% an electrophysiologic study, 12% a pharmacological provocative test with flecainide or ajmaline and 4% were submitted to endomyocardial biopsy. GT to inherited channelopathies or cardiomyopathies were performed as ancillary diagnostic test in 35% of the cases. During follow-up, an etiological diagnosis was established in 38% of patients (Figure 1): 3 events were attributed to coronary vasospasm, 3 to SC polymorphic VT, 2 presented long QT syndrome, 2 had Brugada syndrome and in 1 patient an Ankyrin-B Syndrome was identified. GT was performed in 10 patients and allowed identification of a causative mutation in 6; GT improved the diagnostic probability of a distinct clinical entity during follow-up [diagnosis achieved in 60% if GT performed *vs* 18% if not, p=0.04, OR=7.0 (95% CI 1.2-41.4); Figure 2]. Regarding ICD data, 31% received appropriate therapies during follow-up; the median time to first appropriate shock was 39 months (12-46) with an annual incidence rate of 4.5%. Unappropriated shocks occurred in 19%, 60% due to sinus tachycardia (3 patients with median age of 20 years) and 40% due to supraventricular tachy-

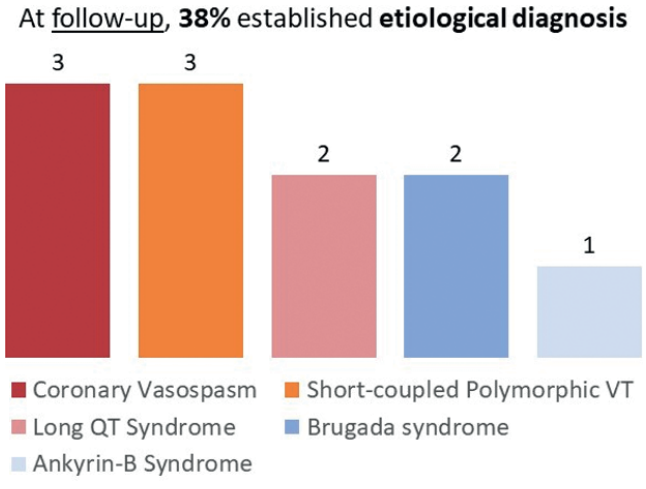

Figure 1. Definitive diagnosis established during follow-up of idiopathic VA patients.

cardia; ICD was programmed, with no unappropriated shocks recurrence. Two of the patients (7%) died, both from non-arrhythmic causes. Table 2 compares data between men and women. Concerning sex differences, there was no statistical difference in patient's age, follow-up time and time free from appropriate shocks. During follow-up, the etiological diagnosis was similarly achieved. Although performed at an identical rate, GT only significantly improved the diagnosis in women (diagnosis established in all women performing GT during follow-up, p=0.002; Figure 2). Men had significantly more appropriate shocks (50% *vs* 8%, p=0.04).

Discussion

Idiopathic VA remains nowadays a challenging entity and a considerable heterogeneity in initial diagnostic workup in survivors of unexplained SCD persists among different heart centers.

Our study included patients labelled as idiopathic VA and showed that a distinct clinical entity was identified in approximately one third of idiopathic VA cases after an extensive workup and long-term follow-up. Regarding GT, we demonstrated that a definitive diagnosis of SCD etiology was possible in 60% of patients performing GT (*vs* 18% of patients not submitted to that testing). A lower diagnostic ability was already reported in a real-world report by the Paris-SDEC registry, with a definitive diagnosis during follow-up obtained in only 6% [8]. This difference may be explained by a longer follow-up (7 *vs* 4 years) and a higher genetic screening (35% *vs* 18%) carried out in our study [8]. Indeed, other publications confirmed that addition GT to non-invasive assessment led to the diagnosis in 40% and 56% of unexplained aborted SCD [6,9]. Although current guidelines underline the importance of a comprehensive workup before labelling cases as idiopathic VA, no standardized testing set is recommended for such patients [2,5]. This led to underusing some key investigation tools, as observed in our paper and other reports [8,10], showing an exhaustive diagnostic assessment achieved in less than 20% of patients.

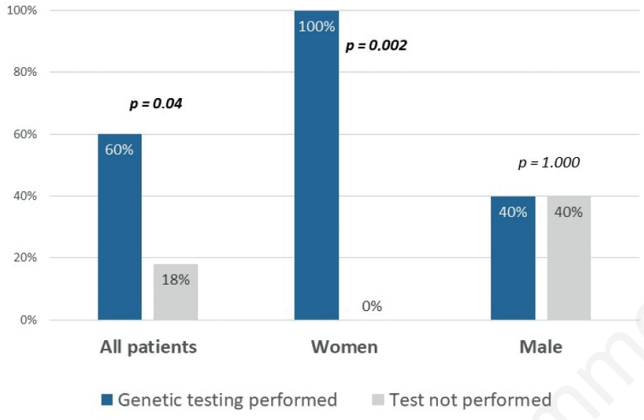

Figure 2. The etiological diagnosis during follow-up in patients performing or not performing genetic testing, in all patients, women or men. Fisher's exact test was used to analyze the difference between groups.

SC polymorphic VT or SC torsade de pointes is a polymorphic VT variant initiated by an extremely SC premature ventricular contraction (<300 ms) arising frequently from peripheral His-Purkinje system 2. Previously considered a rare variant of idiopathic VT, this variant was observed in up to 30% of idiopathic VF [10-12]. Our study emphasizes the hypothesis of this pathology as a major trigger in this group of patients since SC polymorphic VT was one of the most frequent diagnoses at follow-up (27% of cases).

Regarding patient's follow-up, one-third experienced arrhythmic recurrence after a median time of 39 months; these results are in accordance with previous data [5,8,13,14] and additionally underscore the importance of maintaining regular specialized clinical and device assessment.

Sex differences in cardiac arrhythmic diseases have been studied and described, with an essential role associated with sex hormone modulation and ion channel expression [15]. A recent report in idiopathic VF patients showed that Purkinje ectopy originates predominately from the right ventricle in men and predominantly from the left ventricle or from both ventricles in women [15,16]. In our cohort, GT proved to be more useful in women. Despite a similar time to the first appropriate shock in both genders, men had more appropriate shocks. The association of male sex and arrhythmic risk was already identified in other cardiac diseases, namely Brugada syndrome and ischemic heart disease [15,17].

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Table 2. Sex differences in baseline and follow-up data.

	Women	Men	p-value
N	12 (41%)	17 (59%)	
Age, years, mean (SD)	52 (17)	41 (19)	0.11
Follow-up time, years, median (IQR)	6 (3-11)	8 (5-12)	0.42
Time to first appropriated shock, months, median (IQR)	37 (37-37)	41 (10-46)	0.75
Normal ECG	6 (50%)	14 (82%)	0.37
ICD type			0.05
Single chamber transvenous	6 (50%)	14 (87%)	
Dual chamber transvenous	5 (42%)	2 (13%)	
Subcutaneous	1 (8%)	0%	
Etiological diagnosis during follow-up	4 (33%)	7 (41%)	0.72
Genetic testing	4 (33%)	6 (40%)	1.00
Etiological diagnosis in patients performing genetic testing	4 (100%)	2 (40%)	
Appropriated shocks	1 (8%)	7 (50%)	0.04
Unappropriated shocks	1 (8%)	4 (27%)	0.34

SD, standard deviation; IQR, interquartile range; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator.

Limitations

The present study was a single-center retrospective observational study, which was its major limitation. The small number of patients included in this paper recommends some caution in data generalization. Data should be validated and confirmed in future studies, especially prospective ones.

Conclusions

Our study, a real-life study with one of the longest follow-ups available to date, highlights the challenge of idiopathic VA diagnosis and arrhythmic recurrence prediction in idiopathic VA patients. Also, it reveals new data concerning sex differences in this population. Genetic testing significantly improved the diagnostic yield, especially in women, leading to a definitive diagnosis of a distinct clinical entity in more than half of patients. Recurrence of life-threatening arrhythmias occurred in about one third of patients and is significantly higher in men, underscoring both the dismal prognosis of SCD by idiopathic VA and the importance of ICD implantation.

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