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Idiopathic ventricular fibrillation – Long term prognosis in relation to clinical findings and ECG patterns in a Swedish cohort

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ABSTRACT

Background: Idiopathic ventricular fibrillation (IVF) is a rare cause of sudden cardiac arrest which may pose therapeutic and prognostic challenges. To date, the only effective treatment for survivors of cardiac arrest is the insertion of an implantable cardioverter-defibrillator (ICD). We sought to review the long-term outcome of a Swedish cohort with IVF.

Methods and results: Fifty patients with IVF diagnosis between 1988 and 2016 (mean age at index 34.3, 56% male), were followed for a median 13.8 years in this retrospective multicenter observational study. No cardiac mortality was reported. 32% ($n = 16$) of patients had recurrence of ventricular fibrillation or sustained ventricular tachycardia, requiring ICD therapy, at a median time of 1.9 years (range 0.1–20.3) from the index event. Annual incidence rate of ventricular tachyarrhythmia was 3.1%. Abnormal ECG at baseline did not predict appropriate ICD therapy ($p = 0.56$). During the follow-up period, 14% ($n = 7$) patients received a cardiac diagnosis. Follow-up genetic testing was low (26%), however did confirm pathogenic mutations in three cases.

Conclusion: Idiopathic VF is a rare diagnosis with a relatively good prognosis provided ICD therapy is initiated. Routine clinical follow-up is recommended due to potential late emerging cardiac pathology. ECG changes are common, but have no prognostic value in determining the risk of ventricular arrhythmias recurrence. Screening for genetic diseases has previously been low, and this calls for improvement, especially since cheaper and more comprehensive genetic panels are now readily available.

Background

Cardiovascular disease remains the leading cause of death in the developed nations [1]. In Europe, yearly >300,000 patients suffer from out-of-hospital sudden cardiac death (SCD) [2,3], primarily due to acute ventricular tachyarrhythmias triggered by coronary artery disease followed by valvular heart disease and cardiomyopathy [4,5]. In 75–80% of patients with out-of-hospital-cardiac-arrest (OHCA), the first recorded rhythm is ventricular fibrillation (VF) [6]. In patients below the age of 35, the cause may not be initially apparent, but is most often caused by inherited cardiac disorders, either structural heart disease or primary arrhythmia syndromes [4]. In the absence of structural heart disease, channelopathies, metabolic, toxic and respiratory causes i.e. unexplained sudden cardiac arrest, idiopathic ventricular fibrillation (IVF) is diagnosed [7]. Reportedly accounting for 6.8% of all patients who survive an out-of-hospital cardiac arrest, IVF is an entity which may pose therapeutic and prognostic challenges [5]. The clinical outcome remains uncertain as studies have reported ventricular arrhythmia recurrence rates of 11–45% [8]. Beta-blockers are empirically used but the only effective treatment of patients who have survived VF induced cardiac arrest is the insertion of an implantable cardioverter-defibrillator (ICD) [9–12]. Follow-up is essential as 7% to 35% of IVF cases may have a change in diagnosis during clinical re-evaluation, which could have implications for the treatment of these patients and screening of their first degree relatives [13,14].

The aim of this study was to review the long-term prognosis of a Swedish cohort of IVF survivors, equipped with an ICD, and examine to which proportion a definitive cause of the OHCA could be determined. Furthermore, the prevalence of specific ECG abnormalities and their association to recurrent arrhythmia events during the long-term follow-up was investigated.

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Methods

Study population

We conducted a retrospective multicentre study of survivors of cardiac arrest with IVF between 1988 and 2016 at three university hospitals in Sweden. Patients were identified from systematic review of medical records for patients with ICDs implanted for secondary prevention after survived IVF. Demographic information and clinical data were collected from electronic medical records. A proportion of patients received primary diagnosis at one hospital, but had follow-up at other sites, either due to registered home address or patient relocation. A letter was therefore sent to each patient for written consent to retrieve medical records. The cause of death and primary in-hospital diagnosis were obtained from the Swedish National Board of Health and Welfare cause of death register and inpatient register. Mortality data were available for events between 1990 and 2018 whereas for hospital admissions, data were available for the period between 1990 and 2017. The study was approved by the local ethics committee and complies with the Declaration of Helsinki.

Electrocardiography analysis

12 lead standard ECGs from before or during the index hospitalization and follow-up were obtained from electronic ECG databases and reviewed by two electrophysiologists independently of each other and blinded to clinical outcome. Any discrepancies were adjudicated for consensus. Pathological ER changes were identified as described by Macfarlane et al. [15] as end-QRS notch or slur ≥0.1 mV above baseline on the downslope of a prominent R-wave (J-point), in two or more contiguous inferior leads (II, III and aVF) and/or lateral leads (I, aVL, $V_{4\text{-}V6}$) and QRS duration <120 ms. Fragmentation of QRS was positive if the rSr' pattern was observed in V_1–V_2 and when QRS < 120 ms [16]. Ventricular depolarization abnormality in the right precordial leads (terminal activation delay or S-upstroke time), which may be the early ECG sign of arrhythmogenic right ventricular cardiomyopathy, was defined as the time from the S-wave nadir to the end of QRS complex in lead V_1 using the same cut-off of 55 ms as per Task Force 2010 diagnostic criteria for ARVC [17]. Any repolarisation and depolarisation changes were looked for and documented. See Fig. 1 for details.

Electrophysiology testing

Invasive electrophysiological testing protocol was performed according to local practice at respective sites, and included programmed stimulation from the right ventricular apex and base, with up to three progressively shortened extra stimuli until 200 ms.

Implantable cardioverter-defibrillator analysis

ICD data, either from manual interrogation or remotely (Merlin®, CareLink® or Latitude® remote monitoring) were obtained from electronic medical records. Information retrieved included date for appropriate and inappropriate antitachycardia pacing (ATP) and shock therapy respectively, type of ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation) and presence of electrical storm defined as 3 or more sustained episodes of ventricular arrhythmias or appropriate shocks from an ICD within 24 h.

Genetic testing

Initial genetic evaluation was carried out according to local practice and varied between centers. Follow-up genetic testing in autumn 2018 was performed by XON array (CytoScan XON, Applied Biosystems, Thermo Fisher) of a panel of 115 genes associated with channelopathies and cardiomyopathies (supplement table 1). For exome sequencing, libraries were constructed using the SureSelect XT HS Clinical Research Exome V2 (CREv2 kit, Agilent) and sequencing was performed with an Illumina NextSeq 500. Genome version GRCh37/hg19 was used as reference sequence. Genetic changes were classified as pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines [18].

Endpoint

The primary endpoint was defined as a combination of appropriate ICD therapy (ATP and/or shock) for ventricular tachyarrhythmias, and cardiovascular death.

Statistical analysis

Categorical data were expressed as frequencies and percentages. Continuous data were reported as mean ± standard deviation or as median (interquartile range [Q1-Q3]) as appropriate. Categorical variables were compared with the $\chi 2$ test. P value <0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics (v. 25, IBM Corporation, NY, USA).

Results

Baseline characteristics

Fifty patients were included in the study. Their baseline characteristics at the index event are presented in Table 1. Comprehensive investigations were performed per current practice at the respective hospitals.

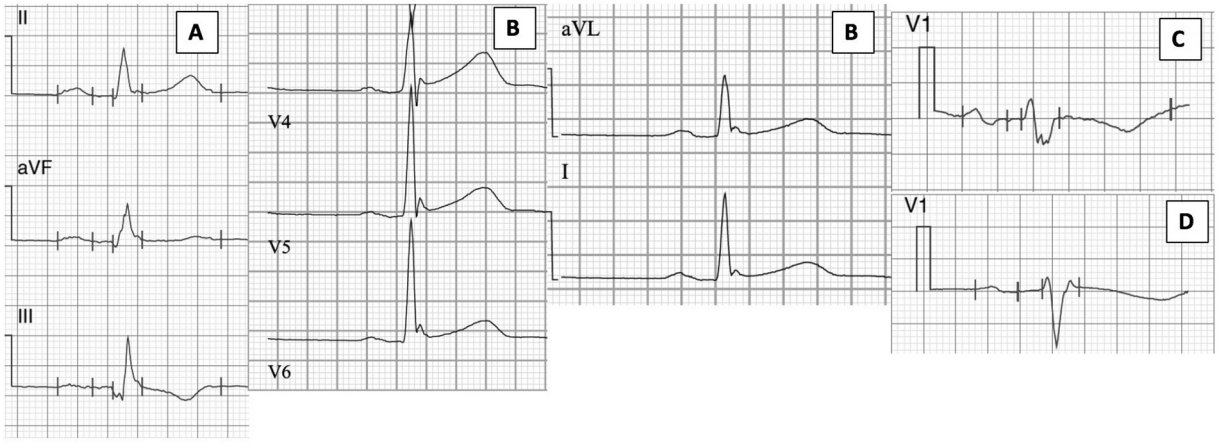

Fig. 1. Examples of ECG abnormalities. (A) Inferior early repolarization pattern. (B) Lateral early repolarization pattern. (C) Notched S in V1. (D) rSr' pattern.

Table 1
Baseline characteristics and results of investigations performed. Mean (SD) or *n* (%)is used.
Patients ($n = 50$).

	Mean (±SD) or *N* (%)	Normal finding *n* (%)	Abnormal finding - comment
Age (years)	34.3 ± 13.3		
Men	28 (56)		
Hypertension	4 (8)		
Diabetes mellitus	2 (4)		
Echocardiography	50 (100)	48 (96)	2 bicuspid aortic valves
Coronary angiogram	38 (76)	34 (68)	4 subtle nonobstructive atherosclerosis
Coronary computed tomography angiography	2 (4)	2 (100)	
Cardiovascular magnetic resonance imaging	27 (54)	27 (100)	
Ajmaline test	9 (18)	9 (100)	
Signal-averaged ECG	22 (44)	22 (100)	
Endomyocardial biopsy	3 (6)	3 (100)	
Exercise tolerance test	30 (60)	30 (100)[a]	
Holter monitoring	12 (24)	12 (100)[a]	Short PQ-interval, but not seen on 12 lead ECG.
Electrophysiology studies	17 (34)	13 (76.5)	4 sustained polymorph ventricular tachycardia or VF induced

[a] No Sustained ventricular arrhythmia.

Investigations performed are presented in Table 1. All patients had an echocardiogram done during the index admission. Initial presumed post-resuscitation changes of left ventricular dysfunction were observed, but in all cases subsequently normalized on either repeat echocardiogram or cardiovascular magnetic resonance (CMR) imaging during the same admission. Two patients had bicuspid aortic valve without valvular stenosis, which was not deemed to be related to their cardiac arrest. Initial ECGs from the index event were available for analysis in 47 subjects, and were done at a median of 2 days post VF; Table 2. The median QRS was 96 ms. The corrected QT interval according to Bazett's formula was median 424 ms, with a range 355 to 521 ms.

Diagnostic findings during follow-up

During the follow-up period, 14% ($n = 7$) patients received a cardiac diagnosis. One patient was diagnosed with hypertrophic cardiomyopathy after 7.2 years. One patient was admitted with heart failure after 5.4 years, however no echocardiographic data was available for adjudication. One patient progressed to severe left ventricular dysfunction with EF 25%, global hypokinesia, mildly concentric hypertrophy with preserved left ventricular size after 18.4 years. The latter had no reported admissions for heart failure, but 3 episodes with ventricular arrhythmia, the first one after 16.1 years. One patient was diagnosed with restrictive cardiomyopathy after 23.4 years. One patient was diagnosed with long QT syndrome type 2 after 6.9 years. One patient was diagnosed with ARVC after 6.5 years and lastly one was found to be Lamin AC gene (LMNA) positive after 3.3 years.

Forty-seven patients with follow-up ECGs (recorded >1 year after the index event) were available for review. One ECG was excluded for analysis as it showed ventricular paced rhythm. ECGs were done at a median 10.5 years after VF date (QR 6.5–18.2). Median QRS 96 ms. Mean (SD) QTc time according to Bazett's formula was 421 ms (± 28.3). At baseline, 34% ($n = 16$) of patients had normal ECG. Of these 75% ($n = 12$) developed abnormalities during follow-up. Sixty-six percent ($n = 31$) had abnormal ECG at baseline. Of these patients, 29% ($n = 9$) normalized their ECGs during follow-up, and 71% ($n = 22$) continued to show abnormalities.

Echocardiography was done during follow-up in 80% ($n = 40$) of patients, the latest examination was at a median time of 7.9 years from index date. In all cases but one, the ejection fraction was ≥50%.

Genetic testing

Genetic testing at baseline or in the immediate follow-up period was done in 18% ($n = 9$) of patients. One patient was diagnosed with long QT syndrome type 2 after a positive genetic yield (KCNH2 mutation) 6.9 years after index event, with baseline ECG revealing QTc 488 ms. Follow-up genetic testing with a broad panel for channelopathies and cardiomyopathies were done in 12 subjects (24%). Eight of them underwent first time genetic screening and four had had genetic testing at baseline, but for targeted genes. Two out of 12 patients (16.7%) had pathogenic mutations diagnostic for underlying cardiac pathology as probable cause of VF; ARVC with PKP2 gene positive and LMNA gene positive. Variants of uncertain significance in potential disease related genes were found in 8 cases (66.7%), but according to ACMG guidelines these were not considered pathogenic, but are reported in supplement table 2.

Cardiac arrhythmias and mortality

Patients were followed by device interrogations for arrhythmias for a median of 12.3 (QR 8.1–19.8) years. During this time 32% ($n = 16$) patients had recurrence of ventricular fibrillation or sustained ventricular tachycardia, requiring ICD therapy, at a median time of 1.9 years (range 0.1–20.3) from the index event. Annual incidence rate was 3.1%, see Table 3 for further details. Abnormal ECG at baseline did not

Table 2
ECG characteristics at baseline and follow-up in relation to subsequent adequate ICD therapy.

ECG characteristics at baseline	% of total cohort ($n = 47$)	No ICD therapy ($n = 33$)	With ICD therapy ($n = 15$)	ECG characteristics at follow-up, $n = 46$	% (n)	No ICD therapies, $n = 34$	ICD therapies, $n = 13$
Normal ECG	34% [16]	10	6		13 (28.3%)	7	6
ER inferior	6.4% [3]	3	0		7 (15.2%)	7	0
ER lateral	6.4% [3]	2	1		4 (8.7%)	3	1
Notched S upslope in V1	17% [8]	6	2		12 (26.1%)	10	2
Left or right axis deviation	13.7% [6]	4	2		4 (8.7%)	3	1
LBBB/RBBB	4.3% [2]	2	0		2 (4.3%)	2	0
T-negative in other than V1 or III	27.7% [13]	11	2		13 (28.3%)	8	5
RSR' pattern	8.5% [4]	3	1		8 (17.4%)	6	2

Table 3
ICD therapy.

	N (%)
First adequate ATP therapy, *n* (%)	5 (10)
ATP followed by immediate shock, *n* (%)	2 (4)
Direct adequate shock therapy, *n* (%)	10 (20)
> 1 episode of ventricular arrhythmia with shock therapy, *n* (%)	8 (16)
Ventricular storm, *n* (%)	2 (4)
Inappropriate shock therapy	4 (8)
Lost to follow-up[a]	4 (8)

[a] According to discharge registry, two of these patients were admitted with sustained ventricular arrhythmias during follow-up.

predict ECG-pathology at follow-up ($p = 0.98$), nor did it predict appropriate ICD therapy ($p = 0.56$), see Table 2 for details.

Four patients had their ICD explanted without re-implantation of a new system. Cause for explantation was patient preference as no arrhythmic events after index VF had occurred ($n = 2$), device endocarditis ($n = 1$) and device-related complications (n = 1, further details unavailable). During the follow-up period pre- and post ICD extraction, no syncopal or arrhythmic events reported requiring hospital admission (*see* Table 4).

Follow-up information regarding mortality was done through national registries after a median of 13.8 (QR 9.0–20.2) years. Two patients died (one from malignancy and one from acute kidney failure), but there was no cardiovascular mortality (Table 5).

Discussion

We present a Swedish cohort of patients who have survived a cardiac arrest due to presumed idiopathic VF. Total mortality over 14 years' follow-up was 4%, and no cardiac cause of death was reported. The risk of recurrent ventricular tachyarrhythmias in this group was 32% (3.1% per year). Visser et al. reported near similar results, 30% ventricular arrhythmia recurrence during a median 7.9 years of follow-up [14]. Furthermore in a meta-analysis by Ozaydin et al., a 31% recurrence rate of ventricular arrhythmia and a 3.1% mortality rate were reported during an average of 5 years follow-up [19]. Despite the rarity of the disease and variable follow-up period, there is a resultant favourable outcome [5,19].

Predictive value of ECG findings for arrhythmias during follow-up:

During the follow-up period, 14% of patients received a definitive cardiac diagnosis associated with known increased risk of ventricular arrhythmias. This finding confirms the importance of regular structured clinical re-evaluations, despite extensive investigations at baseline, since a diagnostic finding may have implications for treatment, and for screening of relatives. In patients with confirmed long QT syndrome, ARVC and LMNA, the initial VF event was most likely a manifestation of the subsequent underlying cardiac diagnosis. In ARVC patients, there is a phase of arrhythmia risk without manifest cardiac structural changes [17]. For the four patients who subsequently developed dilated or hypertrophic cardiomyopathy, cardiac arrest may have been the first manifestation of disease, but this will only be speculative since they had normal left ventricular ejection fraction and morphology at discharge after the index event.

Inferior and/or lateral early repolarization changes, described as a separate syndrome associated with risk of VF, has also been observed in the general population. Albeit higher prevalence in the former, the repolarization changes have no predictive value for recurrence of malignant arrhythmias [7,20,21]. Similarly a so called rSr' pattern in lead V1-V2 can be a benign phenomenon, but may also a sign of underlying cardiac pathology [16]. In our cohort, depolarization and repolarization changes were observed on the ECG, both at baseline and at follow-up, but had neither predictive value for future ventricular arrhythmic episodes nor for subsequent cardiac diagnosis. Early repolarization changes were seen in 12.8% of cases at baseline and in 23.9% at follow-up, but were not significantly associated with malignant arrhythmias or ICD therapy in our cohort. In epidemiological studies, ER prevalence has been 13.1%, i.e. to a similar extent as in our material [22].

Review of multiple ECGs in all patients confirmed that abnormal findings are dynamic, especially as pathological ECG findings subsequently normalized and vice versa. This highlights that ECG changes are variable, and subsequently the risk of suffering from malignant ventricular arrhythmias is dynamic, requiring both a trigger and a substrate.

Extensive cardiac investigations were performed at all three centres at baseline, a necessity to diagnose IVF [7,12]. However, the amount of investigations performed at baseline and during follow-up varied significantly. Considering that our population is relatively young (mean age 34), a hereditary cause for VF could be the primary diagnosis in a significant proportion of cases. In spite of this, in our cohort, a low proportion underwent genetic testing; 18% at baseline and 24% at follow-up despite the rapid developments in the area. There are presently more known disease-causing mutations and lower costs for genetic testing compared to when screening initially emerged. This has potential implications for the patient and their relatives as there is an uncertainty, a grey zone encompassing IVF diagnosis. Though a small proportion underwent genetic screening during follow-up, our results show a modest diagnostic yield for common known genetic variations for channelopathies and cardiomyopathies (23.1%) in keeping with a recent study by Broendberg et al. [4], where the diagnostic yield for disease causing mutation was 24% ($n = 19/80$). Variants of uncertain significance (class III) in arrhythmogenic disease associated genes, is a common finding, including in our cohort. Potentially they could be associated with diseases that may unmask an underlying cardiac disease causing cardiac arrest. This calls for continued liberal genetic screening in cardiac arrest survivors, in order to determine the future prospect of pathogenicity or not.

Limitations

Some patients were lost to follow-up, and even if data from the Swedish National Board of Health and Welfare hospital discharge registry were used for adjudication, ICD therapies could theoretically have been missed if the patient was not hospitalized and hence did not receive a diagnosis for the arrhythmia. Baseline ECGs were acquired early after the OHCA and therefore the impact of drugs and post-resuscitation therapy on abnormal ECGs changes are unknown. There is little data correlating the presence of a bicuspid aortic valve with

Table 4
ICD explantation.

	Age at index VF	Duration of ICD (years)	Cause for explantation	Age at explant	Duration follow-up after explantation (years)	Syncope or arrhythmic events after explantation	Cardiac diagnosis
Male 3	29	11.6	Patient preference	40	18.0	No	Restrictive cardio myopathy, 23.4 years after VF index event and 11.7 years after explantation
Male 4	18	5.7	Device complications	23	22.0	No	No
Male 5	22	20.1	Patient preference	42	0.42	No	No
Female 2	39	12.3	Device endocarditis	51	5.6	No	No

Table 5
Mortality and appropriate ICD therapy for VT/VF.

	Age at index VF	Cause of death	Time to death in years	Arrhythmic episodes	First therapy	Time to arrhythmia in years	Cardiac diagnosis	Age at death	Duration of ICD (years)	Genetic yield
Female 1	66	Acute kidney failure	18.5	Device deactivated	–	–	Heart failure	84	18.5	–
Male 1	45	Renal carcinoma with metastases	12.1	VT	ATP	4.7	–	57	12.1	–
Female 2	38	–	–	Ventricular storm	Shock	1.6	–	–	11.7	–
Male 2	34	–	–	Ventricular storm	Shock	0.8	–	–	6.8	–
Male 3	41	–	–	VT	Shock	16.1	–	–	19.5	–
Male 4	13	–	–	VT[a]	ATP	0.8	–	–	2.8	LMNA[b]
Female 3	33	–	–	VF/polymorph VT	Shock	0.2	–	–	12.5	–
Male 5	49	–	–	VF	Shock	13.0	–	–	21.0	–
Female 4	49	–	–	VT	ATP followed by shock	3.5	–	–	23.2	–
Female 5	25	–	–	VF	Shock	2.2	–	–	13.4	–
Male 6	37	–	–	Polymorph VT	Shock	0.6	–	–	3.8	–
Male 7	31	–	–	VT	Shock	0.1	–	–	16.6	–
Female 6	39		–	VF	Shock	3.3	–	–	7.9	–
Male 8	18	–	–	VT	ATP followed by shock	0.3	–	–	8.0	–
Female 7	13	–	–	Polymorph VT	Shock	1.4	–	–	8.4	–
Male 9	47	–	–	VT	ATP	13.1	–	–	13.8	–
Male 10	51	–	–	VT	ATP	20.3	–	–	27.5	–

[a] Positive phenotype. Low amplitude P-waves with biphasic morphology suggestive of intra-atrial block, predisposing the patient to atrial fibrillation which in this case triggered ventricular fibrillation due to rapid atrioventricular conduction.
[b] Screening of relatives was performed.

ventricular tachyarrhythmias and cardiac arrest, but we cannot completely rule out an association in the two patients with bicuspid aortic valve. The proportion of patients undergoing genetic testing was low, in part due to that clinical diagnostic follow-up was only done in 24% of patients. However, it should be noted that in the 1990s, routine genetic investigation was not initiated in this patient cohort. Not all patients were offered, or accepted invitation to, comprehensive clinical follow-up visits (apart from ICD interrogation follow-up, which was 100%). Non-participation in clinical follow-up may reflect that patients have accepted their IVF diagnosis and simply want to continue to live as normally as possibly without further reminders of their underlying cardiac disease.

Conclusion

Idiopathic VF is a rare diagnosis with a relatively good prognosis provided ICD therapy is initiated. The VF recurrence rate was 32% over median 12.3 years in our cohort. Routine clinical follow-up is recommended due to potential late emerging cardiac pathology. ECG changes are common, but have no prognostic value in determining the risk of ventricular arrhythmias recurrence. Screening for genetic diseases has previously been low, and this calls for improvement, especially since cheaper and more comprehensive genetic panels are now readily available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.06.016.

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