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**CLINICAL RESEARCH**
*Sudden death and ICDs*

# Out-of-hospital cardiac arrest due to idiopathic ventricular fibrillation in patients with normal electrocardiograms: results from a multicentre long-term registry

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**Aims** To define the clinical characteristics and long-term clinical outcomes of a large cohort of patients with idiopathic ventricular fibrillation (IVF) and normal 12-lead electrocardiograms (ECGs).

**Methods and results** Patients with ventricular fibrillation as the presenting rhythm, normal baseline, and follow-up ECGs with no signs of cardiac channelopathy including early repolarization or atrioventricular conduction abnormalities, and without structural heart disease were included in a registry. A total of 245 patients (median age: 38 years; males 59%) were recruited from 25 centres. An implantable cardioverter-defibrillator (ICD) was implanted in 226 patients (92%), while 18 patients (8%) were treated with drug therapy only. Over a median follow-up of 63 months (interquartile range: 25–110 months), 12 patients died (5%); in four of them (1.6%) the lethal event was of cardiac origin. Patients treated with antiarrhythmic drugs only had a higher rate of cardiovascular death compared to patients who received an ICD (16% vs. 0.4%, $P = 0.001$). Fifty-two patients (21%) experienced an arrhythmic recurrence. Age ≤16 years at the time of the first ventricular arrhythmia was the only predictor of arrhythmic recurrence on multivariable analysis [hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.18–0.92; $P = 0.03$].

**Conclusion** Patients with IVF and persistently normal ECGs frequently have arrhythmic recurrences, but a good prognosis when treated with an ICD. Children are a category of IVF patients at higher risk of arrhythmic recurrences.

**Keywords** Idiopathic ventricular fibrillation • Out-of-hospital cardiac arrest • Sudden cardiac death • Implantable cardioverter-defibrillator • Quinidine • Electrocardiography



### What's new?

- The prognosis of survivors of out-of-hospital cardiac arrest presenting with idiopathic ventricular fibrillation (IVF) and otherwise normal electrocardiograms (ECGs) is good.
- The rate of arrhythmic recurrences in patients with IVF and normal ECGs is considerable. Therefore, implantation of implantable cardioverter-defibrillator is warranted in all cases.
- Age ≤16 years at the time of the first ventricular arrhythmia is the only predictor of arrhythmic recurrence on multivariable analysis.

## Introduction

Sudden cardiac arrest is a major public health problem, with the leading cause being ventricular fibrillation (VF) in the context of coronary heart disease.[1] Out-of-hospital cardiac arrest (OHCA) due to VF in the absence of overt structural or electrical cardiac abnormalities is rare, occurring in 1.2% of all OHCAs presenting with a shockable rhythm.[2] Aetiology is identifiable in up to 90% of OHCA survivors when a complete diagnostic work-up including electrocardiogram (ECG), cardiac imaging (echocardiography and/or cardiac magnetic resonance), coronary angiography, and pharmacological challenges are undertaken.[3,4] The remaining cases are labelled as idiopathic ventricular fibrillation (IVF). In these patients, repeated ECG assessment during follow-up can lead to change in the initial diagnosis of IVF in up to 30% of cases.[2,5]

Very few OHCA survivors have no evidence of structural and electrical heart disease at the time of initial evaluation, and an ECG remaining normal during follow-up evaluations, without atrioventricular (AV) conduction disturbances (i.e. compete left bundle branch block or trifascicular block) or short-coupled premature ventricular complexes (PVCs). These patients are regarded as having had a truly IVF, a clinical entity whose long-term outcome is largely unknown.[2,6,7] The clinical, diagnostic, and genetic features of this category of IVF patients are ill-defined.

The purpose of this study was to investigate the clinical features, identify prognostic predictors, and assess the clinical course and outcome of OHCA survivors with IVF and otherwise normal ECGs.

## Methods

### Study population

An international web-based registry was established at Fondazione Cardiocentro Ticino (FCCT) in Lugano (Switzerland) on November 2015 in collaboration with 25 centres across 11 countries (Belgium, France, Germany, Greece, Israel, Italy, Mexico, Norway, Spain, Switzerland, and the UK). Centres were requested to retrieve all consecutive cases of OHCA survivors presenting with IVF up to December 2016. Data were collected retrospectively in accordance with regulations set by the local Institutional Ethics Committees and/or Institutional Review Board.

Patients presenting with OHCA due to IVF, completely normal ECGs at baseline and during follow-up, were considered eligible. Idiopathic VF was considered as idiopathic if a cardiac, respiratory, metabolic, and toxicological aetiology was excluded, and the patient maintained a normal 12-lead ECG and two-dimensional echocardiography (2D-TTE) throughout the entire follow-up.

Information on medical history, physical examination, baseline 12-lead ECG, 2D-TTE, 24-h Holter monitoring, exercise stress test, and coronary angiogram was obtained in all cases. Moreover, results of cardiovascular magnetic resonance (CMR) imaging, pharmacological challenges (flecainide, ajmaline, adrenaline, and ergonovine test), genetic testing, myocardial biopsy, and electrophysiological study (EPS) were collected. The diagnostic work-up of IVF was considered complete if coronary angiogram or computed tomography (CT) scan, CMR, and a sodium-channel blocker challenge were performed in addition to baseline ECG, 2D-TTE, and exercise stress test. Drug therapies, as well as type of implantable cardioverter-defibrillators (ICDs), were recorded.

A core team of investigators at FCCT blindly reviewed all medical records and ECGs of OHCA survivors entered in the database who received a diagnosis of IVF between 1977 and 2017 at each participating centre.

### Twelve-lead electrocardiogram analysis

All baseline and follow-up ECGs were independently reviewed by two experienced electrophysiologists (G.C. and T.O.); in case of disagreement, the ECG was reviewed by a third electrophysiologist (A.A.) and adjudication was done by consensus.

Patients presenting with signs of early repolarization, Brugada Type 1 or 2 ECG, prolonged corrected QT interval (QTc >480 ms), short-QT interval (QTc <320 ms), Wolff–Parkinson–White syndrome, complete left bundle branch block or trifascicular block, and short-coupled PVCs at the hospital admission or during the follow-up evaluations were excluded.

An early repolarization (ER) pattern was defined as QRS slurring (a smooth transition from the QRS segment to the ST segment) or notching (a positive J deflection of at least 1 mm inscribed on the S wave) in the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4–V6), or both.[8] An ECG was considered diagnostic of Brugada syndrome (BrS) if a coved type ST elevation ≥2 mm was documented in ≥1 lead from V1–V3 positioned in the 4th, 3rd, or 2nd intercostal space in the presence or absence of a sodium-channel blocker agent (Type 1).[8] Electrocardiograms with multiple PVCs with a short coupling interval (<260 ms) were identified and excluded. Atrioventricular and intraventricular conduction abnormalities were considered as bundle branch block of any type or first-degree AV block.

### Follow-up and classification of mode of death

Follow-up evaluation was based on clinical visits, usually, including physical examination, ECG and 2D-TTE performed at least every 12 months. Death from any cause and arrhythmic recurrences were assessed. Arrhythmic recurrence was defined as occurrence of sudden cardiac death (SCD; within 1 h of the onset of symptoms), sustained ventricular arrhythmias or appropriate ICD interventions. Appropriate interventions were defined as therapies delivered for ventricular tachycardia (VT) or VF; inappropriate interventions were defined as therapies delivered for causes other than VT/VF. All stored ICD electrograms were independently reviewed and classified by two investigators (G.C. and T.O.). An electrical storm was considered when three or more sustained episodes of VT, VF, or ICD appropriate shocks occurred within 24 h.

### Statistical analysis

All data were analysed using Stata 15.1 (StataCorp, College Station, TX, USA). Continuous data are presented as median and 25th–75th percentiles. Categorical data are presented as counts and percentages. Median follow-up and 25th–75th percentiles are computed with the inverse Kaplan–Meier method. The cumulative incidence of arrhythmic event (appropriate shock or sustained arrhythmia), of cardiac and non-cardiac death is, derived in the framework of competing risks. Kaplan–Meier curves are plotted for the composite endpoint of cardiac death and arrhythmic event. Cox models are fitted to assess the risk associated with a series of potential risk factors. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) are computed. A multivariable Cox model was then fitted on the following a priori identified potential predictors: age, gender, ICD, and complete diagnostic work-up. The Harrell's c statistic and bootstrapped 95% CI are reported for model discrimination. A two-sided *P*-value <0.05 was considered statistically significant.

## Results

A total of 278 patients were submitted in the registry. Of these, 33 patients were excluded from the final analysis because of incomplete baseline or follow-up data ($n = 17$), suspicion of inherited cardiomyopathy or channelopathy ($n = 7$), evidence of short-coupled PVCs ($n = 2$), and AV conduction disturbances (five patients with complete left bundle branch block and two with trifascicular disease). Idiopathic VF occurred in 245 patients treated in 25 centres over the last 41 years. Among them, 14 patients (5.7%) experienced an IVF between 1977 and 1992.

### Clinical features of patients with idiopathic ventricular fibrillation and normal electrocardiograms

Baseline characteristics are shown in *Table 1*. The median age of patients at the time of IVF was 38 years and no male predominance was observed. There were 14 patients (5.7%) younger than 16 years. A family history of SCD was present in 26 patients (11%). Fifty patients (20%) experienced a previous episode of syncope and 37 (15%) had a previously documented episode of atrial fibrillation (AF). No patient had sinus node dysfunction. The majority of OHCA occurred at rest and no episode of VF was related to a febrile status.

### Diagnostic work-up and therapeutic management

As shown in *Table 1*, a complete diagnostic work-up including coronary angiogram or CT scan, CMR, and sodium-channel blocker challenge was conducted in 113 patients (46%). Exercise stress test and EPS was performed in 195 (80%) and 144 (59%) patients, respectively. Programmed ventricular stimulation-induced sustained ventricular arrhythmias in 50 patients (35%). Ventricular fibrillation, polymorphic VT, and monomorphic VT were induced in 82%, 14%, and 4% of these patients, respectively. A genetic test was performed in 44 patients (18%) and no mutations considered pathogenic for BrS, long-QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), or arrhytmogenic right ventricular cardiomyopathy were detected. Intravenous adenosine and ergonovine test, and myocardial biopsy were performed in a small proportion of patients (3.7%, 3.2%, and 1.6%, respectively).

An ICD was implanted in 226 patients (92%), while 18 patients (8%) were treated with quinidine (sulfate or hydrochloride) or disopyramide and one patient refused both device and drug therapy.

Two-hundred and twelve patients (94%) received a transvenous device, while 14 (6%) underwent implantation of a subcutaneous ICD.

### Long-term follow-up

During a median follow-up of 63 months [interquartile range (IQR): 25–110], death occurred in 12 patients (4.9%), corresponding to an annual incidence of 0.74% (95% CI 0.4–1.3). Death due to cardiovascular causes occurred in four patients (1.7%), corresponding to an annual incidence of 0.24% (95% CI 0.09–0.65).

Among 19 patients who did not undergo ICD implantation, there were nine deaths (47%). Two patients treated empirically with antiarrhythmic drugs (AADs) died suddenly, one patient died because of

**Table 1 Characteristics of the study population**

| | Study population ($n = 245$) |
|---|---|
| Clinical features | |
| Male sex, *n* (%) | 145 (59) |
| Age, median (25th–75th) | 38 (29–49) |
| Children (<16 years), *n* (%) | 14 (5.7) |
| Family history of SCD, *n* (%) | 26 (11) |
| Previous AF, *n* (%) | 37 (15) |
| Hypertension, *n* (%) | 50 (20) |
| Current smokers, *n* (%) | 42 (17) |
| Dyslipidaemia, *n* (%) | 19 (8) |
| Diabetes, *n* (%) | 6 (2.5) |
| EF (%), median (25th–75th) | 60 (55–65) |
| Previous syncope, *n* (%) | 50 (20) |
| ECG features at hospital admission, median (25th–75th) | |
| HR (b.p.m.) | 73 (65–85) |
| PR (ms) | 170 (150–184) |
| QRS (ms) | 91 (85–100) |
| QTc (ms) | 412 (400–439) |
| VF circumstances, *n* (%) | |
| At rest | 161 (66) |
| During effort | 60 (24) |
| During sleep | 24 (10) |
| Diagnostic work-up, *n* (%) | |
| Complete work-up | 113 (46) |
| Coronary angiogram | 220 (90) |
| Cardiac CT scan | 25 (10) |
| CMR | 160 (65) |
| Sodium-channel blocker test | 156 (64) |
| Exercise stress test | 195 (80) |
| EPS | 144 (59) |
| VA inducibility | 50 (35) |
| Type of induced arrhythmias, *n* (%) | |
| Monomorphic VT | 2 (4) |
| Polymorphic VT | 7 (14) |
| VF | 41 (82) |
| Genetic test | 44 (18) |
| Myocardial biopsy | 4 (1.6) |
| Therapeutic management, *n* (%) | |
| ICD implantation | 226 (92) |
| Dual-chamber ICD | 66 (29) |
| Single-chamber ICD | 146 (65) |
| Subcutaneous ICD | 14 (6) |
| Drug therapy only | 18 (8) |

AF, atrial fibrillation; CMR, cardiac magnetic resonance; CT, computed tomography; EF, ejection fraction; EPS, electrophysiologic study; HR, heart rate; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

endocarditis, whereas in four patients the event was not related to cardiovascular causes (two infections and two cancers). The cause of death in the remaining two patients could not be determined. In contrast, only three patients in the ICD group died (1.3%). Cause of death was not of cardiac origin in two of them.

**Table 2 Clinical features of IVF patients with arrhythmic recurrences during the follow-up**

| | Study population ($n = 52$) |
|---|---|
| Clinical features | |
| Male sex, *n* (%) | 29 (56) |
| Age, median (25th–75th) | 39 (30–49) |
| Children (<16 yrs), *n* (%) | 7 (13) |
| Family history of SCD, *n* (%) | 7 (13) |
| Previous AF, *n* (%) | 6 (11.5) |
| Hypertension, *n* (%) | 9 (17) |
| Current smokers, *n* (%) | 8 (15) |
| Dyslipidaemia, *n* (%) | 2 (3.8) |
| Diabetes, *n* (%) | 0 |
| Previous syncope, *n* (%) | 14 (27) |
| EPS | 31 (59) |
| VT/VF inducibility, *n* (%) | 13 (25) |
| Complete work-up, *n* (%) | 19 (36) |
| ICD implantation, *n* (%) | 49 (94) |

AF, atrial fibrillation; EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; IVF, idiopathic ventricular fibrillation; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

A total of 52 patients (21%) experienced an arrhythmic recurrence, corresponding to an annual rate of 3.6% (95% CI 2.8–4.7) (*Table 2*). Median time to first arrhythmic recurrence was 29 months (25th–75th 12–70). Three patients had an arrhythmic death, and 49 patients had an appropriate ICD intervention (42 received an ICD shock and seven were successfully treated with anti-tachycardia pacing). Eleven patients (4.5%) experienced inappropriate shocks. Of these, nine patients had a single-chamber ICD, two a dual-chamber ICD, and one a subcutaneous system.

The cumulative incidences of cardiac death, non-cardiac death, and non-fatal arrhythmic events are shown in *Figure 1*: the incidence of non-fatal events was highest in the first 5 years after the index IVF, while both cardiac and non-cardiac mortality tended to occur later. At the end of follow-up, these were 5.5% (95% CI 1.1–15.6), 35.8% (10.7–62.3), and 39.5% (28.7–50.1), respectively.

## Correlates of arrhythmic events

The cumulative arrhythmic event-free survival was 94% (95% CI 0.90–0.96) at 1 year, 88% (95% CI 82–91) at 2 years, 78% (95% CI 71–84) at 5 years, and 67% (95% CI 57–74) at 10 years (*Figure 2*). In patients younger than 16 years the cumulative probability of arrhythmic recurrences was significantly higher compared with older patients (*Figure 3*).

In univariable analysis (*Table 3*), patients with ICD had a four-fold significantly higher risk of arrhythmic recurrences, while patients with complete work-up and patients below 16 years were two times more likely to have arrhythmic recurrences, though statistical significance was not reached. None of the other candidate predictors, such as sex, family history of sudden death, previous syncope, or cardiovascular risk factors, were associated with arrhythmic recurrences.

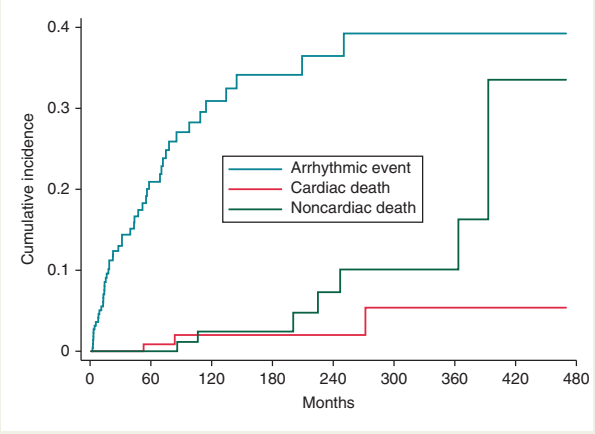


**Figure 1** Cumulative incidence (competing events).

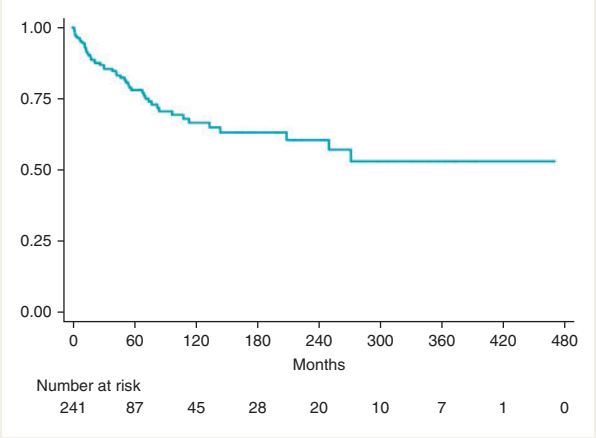


**Figure 2** Kaplan–Meier arrhythmic event-free survival estimate.

Moreover, inducibility of ventricular arrhythmias during EPS was not significantly associated with further arrhythmic events.

In multivariable analysis, including candidate predictors identified *a priori* by consensus (*Table 3*), only age was independently associated with the rate of arrhythmic events, with patients younger than 16 years showing a two-fold increase in the risk of arrhythmic recurrence. Of note, patients with ICD had three-fold increase in risk of arrhythmic recurrence, though not reaching statistical significance ($P = 0.054$). However, overall the model was not optimal in discriminating the risk of recurrence (Harrell'c = 0.63).

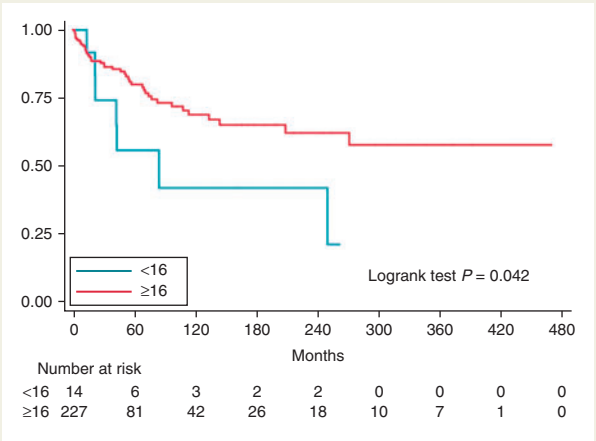


**Figure 3** Kaplan–Meier arrhythmic event-free survival estimate by age.

# Discussion

To the best of our knowledge, this is the first study systematically assessing the clinical features and prognosis of the largest series of IVF patients with persistently normal ECGs. Moreover, this is the longest follow-up ever reported for this category of patients. The minimal and maximal duration of follow-up was 0.5 and 35 years, respectively. There were 20 patients who were followed for a period longer than 20 years.

## Clinical and diagnostic features of patients with idiopathic ventricular fibrillation and normal electrocardiograms

Idiopathic VF is a rare condition, in which the diagnosis is established by exclusion of underlying diseases. Recently, Conte *et al.* reported a diagnosis of IVF in 1.2% of OHCA survivors, whereas Waldmann *et al.*[2,3] reported a diagnosis of IVF in 6.8% of survivors from OHCA of cardiac origin. However, the large difference might be explained by the lack of repeated diagnostic investigations during follow-up in the latter study.

In contrast to previously published data, no male predominance was observed in our study. This observation might be explained by a higher proportion of patients who received a complete diagnostic work-up, which may have led to exclusion of patients with underlying ischaemic heart disease or genetic disorders. Sekiguchi *et al.*[7] have previously reported male predominance in patients with IVF and ER and almost identical sex distribution in the absence of ER. Similarly, Waldmann *et al.*[3] reported male predominance (70%), but a comprehensive diagnostic work-up, consisting of baseline ECG, echocardiography, and coronary angiogram or coronary CT scan was performed in only 20% of these patients. In the present study, complete work-up, including CMR, pharmacological provocative tests, and genetic assessment was considerably higher, accounting for 46% of cases.

Furthermore, in contrast to the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS) study, showing a late occurrence of first ventricular arrhythmia in females affected by BrS, in our IVF patients there was no age difference at the time of VF between males and females.[9]

The importance of the re-evaluation of the diagnosis in IVF patients has already been reported and may have significant consequences for the assessment of a patient's prognosis, family screening, and possibly family counselling. In this respect, Matassini *et al.*[5] have reported a change in the initial diagnosis in up to 20% of patients presenting with unexplained cardiac arrest. The Cardiac Arrest Survivors With

**Table 3 Univariable and multivariable Cox models for arrhythmic events (sustained ventricular arrhythmia, appropriate shock or cardiac death)**

| Candidate predictor | Rate per 100 person year (95% CI) | Univariable model HR (95% CI) | *P*-value | Multivariable model[a] HR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| Age (years) | | | 0.072 | | 0.032 |
| <16 | 7.8 (3.7–16.3) | 1 | | 1 | |
| ≥16 | 3.3 (2.5–4.5) | 0.45 (0.20–0.99) | | 0.41 (0.18–0.92) | |
| Sex | | | 0.952 | | 0.861 |
| Female | 3.6 (2.4–5.4) | 1 | | 1 | |
| Male | 3.6 (2.5–5.2) | 0.98 (0.57–1.70) | | 1.06 (0.57–1.95) | |
| Work-up | | | 0.053 | | 0.173 |
| Incomplete | 2.3 (1.5–3.4) | 1 | | 1 | |
| Complete | 6.4 (4.1–10.1) | 1.92 (0.99–3.70) | | 1.58 (0.82–3.08) | |
| ICD | | | 0.005 | | 0.054 |
| No | 0.8 (0.2–2.3) | 1 | | 1 | |
| Yes | 4.7 (95.6–6.3) | 4.19 (1.26–13.00) | | 3.42 (0.98–11.94) | |
| Family history of SD | | | 0.855 | – | – |
| No | 5.3 (3.8–7.3) | 1 | | | |
| Yes | 4.9 (2.4–10.4) | 0.93 (0.41–2.09) | | | |
| Previous syncope | | | 0.780 | – | – |
| No | 3.6 (2.6–4.9) | 1 | | | |
| Yes | 3.8 (2.2–6.4) | 1.09 (0.59–2.01) | | | |
| Diabetes | | | 0.162[b] | – | – |
| No | 3.8 (2.9–5.0) | 1 | | | |
| Yes | 0 | NA | | | |
| Hypertension | | | 0.258 | – | – |
| No | 4.0 (3.0–5.4) | 1 | | | |
| Yes | 2.5 (1.3–4.7) | 0.67 (0.33–1.38) | | | |
| Dyslipidaemia | | | 0.196 | – | – |
| No | 3.8 (2.9–5.0) | 1 | | | |
| Yes | 1.7 [0.89 (0.42–1.89) 0.4–6.8] | 0.46 (0.11–1.81) | | | |
| Smoking | | | 0.755 | – | – |
| No | 3.4 (2.8–5.1) | 1 | | | |
| Yes | 2.9 (1.4–5.8) | 0.89 (0.42–1.89) | | | |

CI, confidence interval; ICD, implantable cardioverter-defibrillator; NA, not applicable; SD, standard deviation.
[a]Multivariable model $P = 0.013$, Harrell's c = 0.63 (95% CI 0.54–0.72).
[b]Log-rank test.

Preserved Ejection Fraction Registry (CASPER) showed that use of systematic non-invasive and invasive testing, including drug provocation, and the use of advanced cardiac imaging, led to a precise diagnosis in 56% of unexplained cardiac arrest due to VT/VF in patients with preserved left ventricular ejection fraction and normal coronary arteries.[4] Of these, 75% of patients were diagnosed with a primary electrical disease and the remaining 25% had underlying structural heart disease. Although the baseline 12-lead ECG is useful in identifying channelopathies, drug challenge should be considered. This latter point is not sufficiently emphasized in the most recent EHRA/HRS/APHRS expert consensus statement on ventricular arrhythmias and shall be reconsidered in future documents.[1] The value of CMR has been already reported for detection of the morphological substrate and/or underlying cardiac condition in patients with VT/VF without previously known heart disease.[10] All patients presenting with IVF should, therefore, undergo CMR prior to ICD implantation to exclude subtle structural abnormalities, even if 2D-TTE is completely normal.

Idiopathic VF has been frequently associated with a malignant pattern of ER in inferior and/or lateral leads of standard 12-lead ECG, or PVCs triggering the arrhythmic event.[6,11] Haïssaguerre *et al.*[12] recently reported abnormal electrograms in the epicardium in a significant proportion of patients with IVF. In the remaining patients without a myocardial abnormality, a high incidence of Purkinje triggers were observed. Due to the inability of current imaging techniques to identify subtle structural alterations, cardiac mapping may be useful in the characterization of patients with IVF. However, in contrast to previous studies reporting categories of IVF patients with abnormal ECGs or with VF triggers, we included exclusively those rare patients with IVF in whom the 12-lead ECG continued to be normal

over a long-term follow-up, without evidence of potential VF triggers. This category of patients may represent a completely different clinical entity for whom the trigger of the initial arrhythmic event remains elusive.

## Genotyping patients with idiopathic ventricular fibrillation and normal electrocardiograms

A genetic origin of IVF has been hypothesized.[13] However, for the majority of IVF patients, pathogenic mutations cannot be identified.[13] In line with these findings, no specific pathogenic mutations were identified in our patients. The genetic background of IVF is likely heterogeneous and could also be of non-monogenic origin. Moreover, a subset of patients originally diagnosed with IVF may carry clinically relevant genetic variants associated with inherited arrhythmogenic diseases.

Recently, Leinonen *et al.*[13] reported that using whole-exome sequencing and next-generation sequencing pathogenic or likely pathogenic variants residing in RYR2, CACNA1C, and DSP genes were found in 9% of IVF patients. Most of them were found in the RYR2 gene, associated with CPVT. In the present study, a large proportion of patients underwent exercise stress test but no polymorphic ventricular arrhythmias were observed. Furthermore, patients with suspected genetically related forms of cardiomyopathies or channelopathies were excluded from our study. Although genetic testing in IVF seems to be valuable, its diagnostic yield and prognostic significance in the setting of patients with completely normal ECGs need to be determined. Notably, the use of large gene panels in IVF does not increase the yield of positive results compared to targeted sequencing.[14]

Future guidelines should promote a standardized and systematic approach for patients with IVF and address indications of each available diagnostic test from non-invasive examinations and cardiac imaging to more advanced investigations including ergonovine challenge, genetic testing, and cardiac mapping procedures. Furthermore, whole-genome sequencing for non-coding variants in ion channel and cardiomyopathy genes may shed light on other aetiologies as knowledge grows in combination with exome analyses.

## Long-term follow-up of idiopathic ventricular fibrillation and normal electrocardiograms

The present study significantly expands current knowledge about the prognosis of patients with IVF and otherwise normal ECGs. Previous studies have reported recurrence of VF after 3 years from cardiac arrest in 30% of patients with IVF.[15] Idiopathic VF patients with ER or other ECG abnormalities have a worse outcome compared with patients with no ER.[2,6,7,16] In this regard, Haïssaguerre *et al.*[6] described a higher incidence of ER pattern in OHCA survivors and worse outcomes of OHCA survivors with such abnormalities. In our study, a relatively high rate of arrhythmic recurrences was observed. These data have important implications with regard to potential ICD removal at the time of replacement in patients with IVF and no arrhythmic recurrences during the follow-up. No predictors of further ventricular arrhythmias, other than age below 16 years, could be identified, though the prognostic role of ICD was only marginally non-significant. Children indeed represent a population of patients at high arrhythmic risk and should be carefully evaluated during the diagnostic work-up and therapeutic management. Indeed, it has been shown that recurrent VF is common in those paediatric patients with IVF developing a definite clinical phenotype during long-term follow-up.[17] Longer follow-up studies might help to establish the lifetime risk of arrhythmias in these patients.

Belhassen *et al.*[18] reported the feasibility of an antiarrhythmic treatment with Class IA agents using an electrophysiologically guided approach as an alternative to ICD therapy in selected cases of patients with IVF. In our study, patients without ICD and treated with AADs had a significantly lower rate of arrhythmic recurrences. This observation might be partially explained by the effectiveness of AAD therapy in IVF but also by the ICD programming with short detection time at the time of ICD interventions which may have led to higher rate of therapies for presumably non-sustained episodes of ventricular arrhythmias. However, two patients treated empirically with AAD therapy died suddenly. Therefore, as recommended by current guidelines, implantation of an ICD is still warranted in all patients with IVF, particularly when an EPS is not performed to test AAD therapy efficacy. Since the risk of device-related complications over the long-term period is not negligible, some patients may refuse ICD therapy. In these selected cases, electrophysiologic-guided antiarrhythmic therapy might be considered an alternative to ICD implantation.[19,20] Prospective randomized studies are needed to confirm the efficacy of this approach in a wider population of patients.

## Limitations

Our study has a certain number of limitations. Due to the rarity of the condition, it is a retrospective multicentre study conducted in a population with heterogeneous clinical characteristics. Given the retrospective nature of case selection, case consecutiveness cannot be ascertained. Furthermore, a median follow-up of 5.3 years may be considered short and unrepresentative of the lifelong risk of arrhythmias. The diagnostic approach to OHCA patients in our study was heterogeneous and variable throughout centres. The fact that CMR, ajmaline challenge and ergonovine test were not systematically performed in all patients, could have led to an increased number of cases considered as idiopathic. Moreover, EPS with programmed ventricular stimulation, genetic testing, and myocardial biopsy were performed in a limited number of cases. Although pharmacological challenges to unmask concealed channelopathies was performed in only 60% of patients, ECGs remained unchanged during a median follow-up of more than 5 years, reducing the likelihood of a missed diagnosis of channelopathy.

# Conclusions

Survivors of OHCA due to IVF with persistently normal baseline and follow-up ECGs have a high recurrence rate of arrhythmic events, but a good overall survival when treated with an ICD. Children are a category of IVF patients at higher risk of arrhythmic recurrences. The trigger of the initial clinical presentation, the truly underlying aetiology, and outcomes beyond 10 years remain unknown.

# Supplementary material

Supplementary material is available at *Europace* online.

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