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Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years†

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Aims Idiopathic ventricular fibrillation (iVF) accounts for up to 14% of VF incidence. Data regarding long-term outcome and clinical risk markers of arrhythmia recurrence are scarce. The objective of our study was to describe a long-term follow-up (FU) of a cohort of iVF survivors in our centre during the past 20 years, and to investigate the influence of clinical parameters, e.g. presence of an early repolarization pattern (ERP), on recurrence rate of arrhythmias.

Methods and results Thirty-five iVF survivors were identified and retrospectively analysed regarding recurrent implantable cardioverter-defibrillator (ICD) interventions and covariates potentially influencing arrhythmia recurrence. Appropriate ICD interventions occurred in 15 patients (43%) after a median of 6.6 years during a median FU period of 8.8 years. Two patients (13%) received the first appropriate therapy after an assumed average ICD battery longevity of 7 years, while in all other patients, the first therapy occurred within the first ICD period. Appropriate interventions were observed more often and earlier in patients with ERP (HR 3.9; 1.4–11.0; $P = 0.01$), whereas all other covariates failed to predict subsequent events. A high incidence of inappropriate ICD therapies (67 interventions in 14 patients) could be attributed to the occurrence of atrial fibrillation (66% of all inappropriate therapies).

Conclusion The recurrence rate of ventricular arrhythmias in iVF survivors is high and recurrence might occur delayed (>7 years after the initial event). ERP seems to be highly predictive with respect to early arrhythmia recurrence. Our results highlight that better pathophysiologic understanding of ERP might facilitate a better risk stratification before and an optimal treatment after an iVF event. The high rate of AF and ERP in iVF survivors might indicate an underlying heart disease or myocardial electrical disorder not apparent at the index event.

Keywords Idiopathic ventricular fibrillation • Sudden cardiac death • Early repolarization syndrome • Early repolarization pattern

Introduction

Ventricular fibrillation (VF) is the most common arrhythmia leading to sudden cardiac death (SCD) and predominantly occurs in patients with structural heart disease.[1] In addition, genetic alterations in ion channel proteins and their regulatory subunits can create an arrhythmogenic milieu predisposing to an increased risk for VF.[2] However, in 5–14% of cases of VF, no apparent underlying cause

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What's new?

- Our long-term follow-up analysis of a cohort of idiopathic ventricular fibrillation (iVF) survivors revealed
- that iVF patients still bear a relevant risk of arrhythmia recurrence, even after an event-free period of an average ICD longevity of 7 years after the index event.
- a high prevalence/incidence of atrial fibrillation as a causative factor for inappropriate ICD therapies in iVF survivors
- Confirmation that an early repolarization pattern (ERP) in the surface ECG seems to be the only predictive variable assessing the risk of ventricular arrhythmia recurrence in iVF survivors to date.

can be identified.[3] The phenomenon of such idiopathic VF (iVF) was first described more than 80 years ago.[4] Over the past decades, several factors were investigated as possible risk factors for the occurrence of iVF. Paul *et al.* suggested a role of the adrenergic system by showing abnormal ^{123}I-MIBG uptake in the inferior left ventricular wall of patients with iVF.[5] Others reported iVF as originating from the His-Purkinje system.[6] Yet, a conclusive mechanism for all iVF events remains to be elucidated.

However, with lacking a specific causative treatment implantable cardioverter-defibrillators (ICDs) have emerged as the primary treatment option for the prevention of SCD in patients who have survived iVF.[7] Information on long-term follow-up (FU) in such patients is very limited, as is the information on stratifying risk factors.[8,9] Here, we aimed to describe the FU of all consecutive SCD survivors due to iVF in our centre. We analysed their clinical and electrocardiographic characteristics, focusing on repolarization abnormalities including the ERP possibly related to a potential pathogenesis of iVF.

Methods

Patient selection

Patients were recruited from the Department of Medicine I at the Ludwig Maximilians University of Munich. All patients provided informed consent to participate in the study. The study was in accordance with all principles outlined in the declaration of Helsinki. Patients had to fulfil the following criteria to qualify for enrolment: (i) survived SCD with cardiopulmonary resuscitation due to iVF; (ii) subsequent treatment with an ICD for secondary prevention of SCD; (iii) documentation of primary iVF without preceding monomorphic ventricular tachycardia (VT) or asystole. Patients were excluded from the analysis for the following reasons: (i) abnormal cardiac physical examination; (ii) pathologic laboratory tests suggestive of acute myocardial infarction or metabolic causes for SCD; (iii) resting electrocardiogram (ECG) and exercise stress tests indicative of Brugada syndrome, catecholaminergic polymorphic VT, or long QT syndrome; (iv) ajmaline or flecainide testing demasking a type I Brugada electrocardiogram; (v) pathologic cardiac MRI; (vi) pathologic cardiac catheterization; (vii) pathologic EPS regarding severe abnormal parameters of sinus and atrioventricular nodal function; or (viii) administration of AAD prior to the index event. Follow-up was performed by routine investigations in our ICD outpatient clinic.

Between 1989 and 2012, we identified 44 patients who were referred to our hospital for resuscitated ventricular arrhythmia, in whom after exclusion of structural heart disease the diagnosis of iVF was established. Based on a detailed screening of the index ECGs from the medical records, we excluded six patients who presented with idiopathic VT instead of iVF. Three additional patients showed abnormal transthoracic echocardiographic examination results during FU indicating the delayed development of structural heart disease (1x arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), 1x hypertrophic, 1x dilated cardiomyopathy) and were hence excluded from the analysis. Our final cohort consisted of 35 patients with an established diagnosis of iVF.

Definition of early repolarization pattern

As previously described, ERP was defined as an elevated J-point $\geq$0.1 mV in $\geq$2 leads from the same regional territory of the 12-lead electrocardiogram.[10,11] The J-point transition had to occur as a slurring or notching at the terminal end of the QRS complex. Regional territories were defined by inferior leads (II, III, aVF), anterolateral leads (I, aVL, V4–V6), or both. Patients with ERP in right pre-cordial leads V1–V3 were excluded to avoid similarities with electrocardiographic signs of ARVC/D or the Brugada syndrome.[12] We categorized the ST segment morphology as ascending, horizontal, or descending according to the definition by Tikkanen *et al.*[13]

Non-invasive diagnostics

All enrolled patients received a detailed investigation of the medical history and physical examination, laboratory tests, including serum potassium and cardiac troponin levels, a 12-lead resting ECG, and an exercise stress test after the index event. Based on clinical judgement, additional evaluation was performed. A subgroup of patients (n = 12, 34%) received an intravenous sodium channel blocker stress test (Flecainide up to 2 mg/kg; ajmaline up to 0.7 mg/kg) to unmask a type I Brugada ECG. In another subset of patients (n = 13, 37%), MRI was performed to exclude structural abnormalities such as discrete right ventricular dilation or left ventricular late gadolinium enhancement indicating ARVC/D or myocarditis or subclinical signs of heart failure.

Invasive diagnostics

Electrophysiologic study

In patients in whom an EPS was performed (n = 27, 77%), the examination consisted of four basic drive cycle lengths (600, 500, 400, 330 ms) and up to three premature extra stimuli coupled at minimally 180 ms. Stimuli were applied in the right ventricular apex and the right ventricular outflow tract. The endpoint was the induction of sustained VT or VF.

Cardiac catheterization

In patients undergoing left cardiac catheterization (n = 35, 100%), the catheter was introduced under fluoroscopic guidance through the femoral artery to the heart. A significant coronary artery disease (CAD) was defined as stenosis $\geq$50% in one or more coronary vessels.

Adjudication of arrhythmia recurrence

To assess ventricular arrhythmia recurrence, we scrutinized all available medical records and the ICD database of our hospital. Wherever available, electrogram records of ICD therapies were used to adjudicate appropriate or inappropriate interventions. Due to the retrospective nature of our analysis, ICDs of various developmental stages were included. First-generation ICDs were not capable of antitachycardic pacing (ATP) with shock delivery as the only therapeutic option, thus preventing homogenous zone programming. For consistent study

results, we therefore considered appropriate shocks or ATPs as arrhythmia recurrence.

Statistical analysis

We present continuous variables as mean ± standard deviation or median (25th; 75th percentile; range) where appropriate, and discrete data as frequencies and percentage. We fitted Cox proportional hazards models for time-to-therapy analyses, and adjusted for sex and age at the time of the VF event. We plotted survival curves using Kaplan–Meier estimation, and compared differences by log-rank tests. The following variables were analysed regarding their influence on arrhythmia recurrence: age, sex, AF, inducibility on EPS, and significant ERP. For multiple events analyses, we used the Andersen–Gill model. A two-sided *P*-value of 0.05 was considered significant. Analyses were performed using SPSS (version 20.0; SPSS Institute, Chicago, IL, USA).

Results

Baseline characteristics

Clinical baseline characteristics of the study cohort are presented in *Table 1*. The final patient cohort consisted of 35 patients (66% men) with survived SCD due to iVF who were provided with an ICD implantation for secondary prevention. Three patients died after a median of 11 months (range 1–104 months) from non-cardiac causes (1x suicide, 1x sepsis, 1x cancer). The mean age at time of resuscitation was 47 ± 17 years. At the time of iVF, only two patients (6%) were younger than 20 years. Eleven patients (31%) were 20–45 years old, 15 (43%) were 45–65 years old, and 7 (20%) were older than 65 years. The median FU was 8.8 years (25th; 75th percentile 1.8; 15 years, range 0.01–23.5 years). The ECGs of all patients were normal with respect to configuration except for four patients, two with a left bundle branch block, and two patients with right bundle branch block pattern at time of the index event. ERP was positive in 13 patients (37%). Details concerning ERP characteristics are shown in *Table 2*. AF was diagnosed in 17% of patients (6/35; 83% paroxysmal and 17% persistent/permanent). The diagnosis of AF had already been apparent in three (9%) of patients before or within the index event diagnostic work up, while in another three (9%) patients AF occurred or was diagnosed during FU after the index event. Thereby, AF was not associated with the presence of ERP (ERP positive: 0% AF (0/6); ERP negative: 45% AF (13/29); $P = 0.06$).

All but seven patients (28/35, 80%) were on chronic betablocker therapy after resuscitation, 2/35 patients (6%) were discharged on amiodarone, and 2/35 (6%) on sotalol, respectively.

All patients had preserved left ventricular ejection fraction (LV EF) at time of ICD implantation (mean LV EF: 66 ± 8%) without evidence of regional wall motion abnormalities. A positive family history of SCD was documented in three (9%) patients.

All available non-invasive and invasive diagnostics, which were performed are presented in *Table 3*. MRI was performed in 13 patients (37%) without any evidence of structural abnormalities. No patient had significant CAD. Histologic assessment of right ventricular biopsies in 12 patients (34%) showed no signs of structural myocardial abnormalities. EPS was performed in 27 patients (77%) prior to ICD implantation. VF was inducible in 5/27 patients (19%) and VT in 3/27 patients (11%).

Table 1 Baseline clinical characteristics

Patients	*n* = 35
Age at ICD implantation, years	48 ± 17
Male sex, *n* (%)	23 (66%)
Baseline ECG	
Complete LBBB, *n* (%)	2 (6%)
Complete RBBB, *n* (%)	2 (6%)
Atrial fibrillation, *n* (%)	3 (9%)
Left ventricular ejection fraction, (%)	66.5 ± 7.8%
Positive family history of SCD	3 (9%)

LBBB, left bundle branch block; RBBB, right bundle branch block; SCD, sudden cardiac death.

Table 2 Analysis of ER phenomenon showing the distinct characteristics of ER pattern in the final patient cohort

Patients	*n* = 35
Presence of significant ERP	13 (37%)
Localization of ERP	
Inferior	2 (15%)
Lateral	5 (38%)
Both	6 (46%)
Max. amplitude	
≥0.1 mV	7 (54%)
>0.2 mV	6 (46%)
ST segment analysis	
Horizontal/descending ST segment	11 (85%)
Ascending ST segment	2 (15%)

ERP, early repolarization pattern.

Table 3 Performed invasive and non-invasive diagnostics to confirm idiopathic character of VF before ICD implantation

Patients	*n* = 35
Echocardiography, *n* (%)	35 (100%)
Invasive exclusion of CAD, *n* (%)	35 (100%)
Electrophysiologic testing, *n* (%)	27 (77%)
Ajmaline/Flecainide testing, *n* (%)	12 (34%)
Magnetic resonance imaging, *n* (%)	13 (37%)
Ventricular biopsy, *n* (%)	12 (34%)
RV angiography, *n* (%)	12 (34%)

RV, right ventricular.

Arrhythmia recurrence—appropriate ICD therapies

During FU, 15 of 35 patients (43%) received appropriate ICD therapies (shock and/or ATP) for ventricular tachyarrhythmias (*Figure 1*). The median time to the first appropriate therapy was 6.6 years [range 0.01–16.3 years]. Within the FU period, a total of 174 appropriate therapies were delivered. The majority of patients (10/15, 67%) with therapies received >1 appropriate therapies. We noted electrical storms with ≥3 consecutive ICD therapies for tachyarrhythmia episodes in five patients (14%).

Early repolarization

We found a significant association of more appropriate therapies in patients with ERP (HR 3.9; 95% confidence interval [CI] 1.4–11.0; $P = 0.01$; *Figure 2*). This difference remained significant after adjustment for age at date of index event and sex (HR 4.3; 95% CI 1.5–15.1; $P < 0.01$). The mean time to the first appropriate therapy was 4.1 ± 1.2 years in those with positive ERP and 11.3 ± 1.6 years in those without. Other than ERP, we did not identify additional independent predictors of arrhythmia recurrence (*Table 4*). Furthermore, an analysis with respect to subtypes of ERP, including inferior vs. anterolateral, localization, and ERP in combination with a horizontal/descending ST-segment showed no significant associations with arrhythmia recurrence.

In perspective of an average battery longevity of ~7 years in current-generation ICDs,[14] we found that 87% (13/15) of patients suffered arrhythmia recurrence within this period. However, two patients (13%) received their first appropriate ICD therapy later than the assumed ICD longevity (*Figure 3A*).

In secondary analyses of multiple per patient ICD therapies limited by statistical power, we confirmed a trend indicating a predictive role of ERP positive vs. ERP negative ECGs, even after adjustment for age and sex. An individual patient-specific timeline of events during FU is illustrated in *Figure 3B*.

Inappropriate ICD therapies

Besides appropriate therapies, we also observed a high number of inappropriate ICD interventions. In 14 patients (40%) who received inappropriate ICD interventions, we counted a total of 67 interventions, of which 62 (93%) were shocks. We found that in this context the occurrence of AF was significantly associated with the delivery of inappropriate ICD therapies (HR 5.2; 95% CI 1.5–17.8; $P < 0.01$, *Figure 4*). This difference remained statistically significant after adjustment for age at date of iVF and sex (HR 11.3; 95% CI 2.4–53.2; $P < 0.01$). Overall, inappropriate interventions were adjudicated to be triggered by AF in 44 episodes (66%), sinus tachycardia in 5 episodes (7%), lead fracture in 4 episodes (6%), and T-wave/noise oversensing in 14 episodes (21%).

Discussion

In our study, we describe a long-term FU of 35 patients with the diagnosis of iVF. A notable fraction of 15 patients (43%) suffered ventricular tachyarrhythmia recurrence with a high total number of 174 appropriate therapies during a median FU duration of close to 9 years. Significant ERP was the only variable, which was positively associated with arrhythmia recurrence. Furthermore, our analysis revealed that the occurrence of AF was the strongest predictor of inappropriate ICD interventions. However, once being treated with an ICD, the overall survival in this population is high.

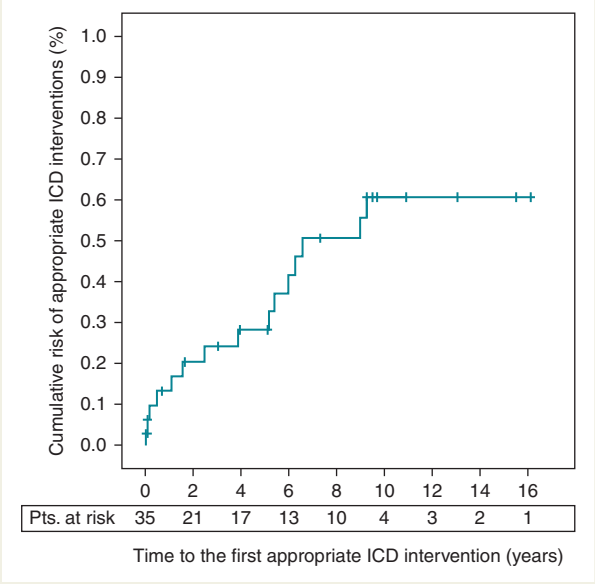

Figure 1 Time to the first appropriate ICD intervention (shock and/or ATP) in the overall patient cohort. Fifteen out of 35 patients (43%) had received at least one appropriate ICD intervention for ventricular tachyarrhythmia recurrence.

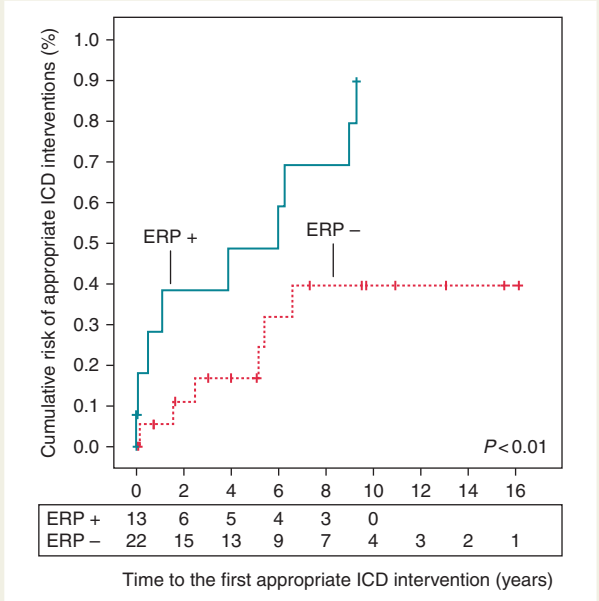

Figure 2 Representative figure. Time to the first appropriate ICD intervention according to the presence or absence of ERP; case subjects with a repolarization abnormality were at increased risk for recurrent VT/VF, when compared with those without such a phenomenon (HR 3.9, 95% CI; 1.4 to 11.0).

Table 4 Univariate and multivariate analyses of risk factors for arrhythmia recurrence

	HR unadjusted	*P*-value	HR adjusted	*P*-value
Male sex	0.8 (0.3–2.2)	0.59	0.6 (0.2–2.0)	0.40
Age at resuscitation	1.0 (1.0–1.0)	0.93	1.0 (1.0–1.0)	0.50
Significant ER pattern	3.9 (1.4–11.0)	0.01	4.3 (1.5–15.1)	<0.01
Atrial fibrillation	1.2 (0.3–4.3)	0.76	1.3 (0.3–5.1)	0.73
Inducibility on EPS	1.6 (0.5–4.9)	0.42	2.0 (0.6–6.5)	0.26

Positive ERP is associated with higher risk for ventricular tachyarrhythmia recurrence.

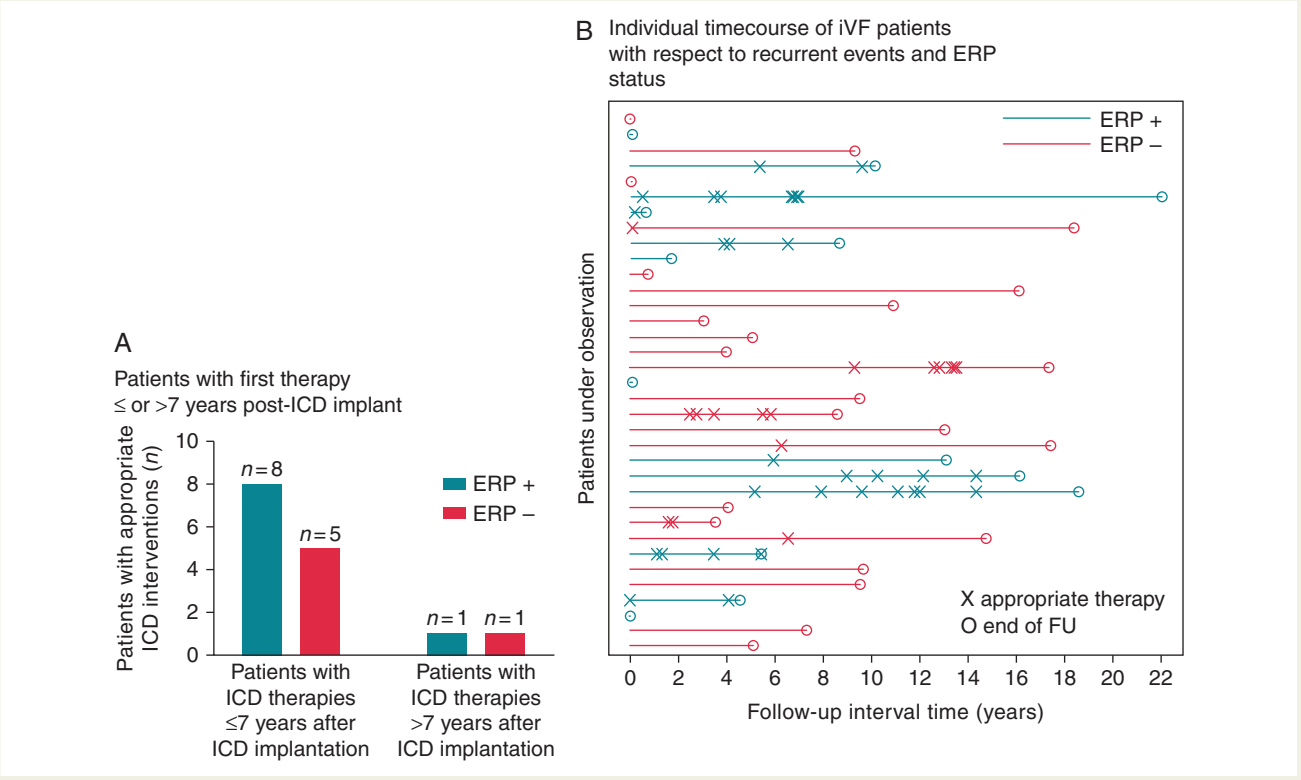

Figure 3 (*A*) Number of patients with appropriate ICD interventions within and after the first seven years after ICD implantation. Subgroups illustrated by turquoise and red bars represent patients with and without ERP, respectively. 13/15 patients (37%) received their first therapy within and 2/15 patients (14%) after the average device longevity of a current generation ICD. (*B*) Illustration of the patient-specific timeline of appropriate ICD interventions in iVF survivors with and without significant ERP.

Results of previous studies

The first description of iVF dates back to 1929 when Dock *et al.* reported a case of apparent iVF without any obvious underlying heart disease.[4] Based on the definition of the Joint Steering Committees of the *Unexplained Cardiac Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States*, iVF is a diagnosis of exclusion. Therefore, it refers to our current inability to identify a potential underlying cause for the life-threatening arrhythmia episode by invasive and non-invasive testing following the resuscitation event.[3] Yet, iVF might be the first manifestation of subclinical, hence undetected, structural or electrical heart disease, as already demonstrated for early stages of ARVC/D.[3] Of note, iVF does not imply complete absence of common abnormal findings like first degree atrioventricular block or AF.[3] In our pre-exclusion cohort, three patients initially considered to suffer from iVF, were subsequently diagnosed with structural heart disease during FU. Data from Derval. *et al.* support this hypothesis showing that extensive diagnostic evaluation including targeted genetic testing could establish a cause explaining iVF in more than 20% of individuals with apparently normal hearts.[15] As a consequence, iVF survivors should undergo regular, at least annual cardiologic examinations to rule out a delayed onset of heart disease, which could imply additional treatment.

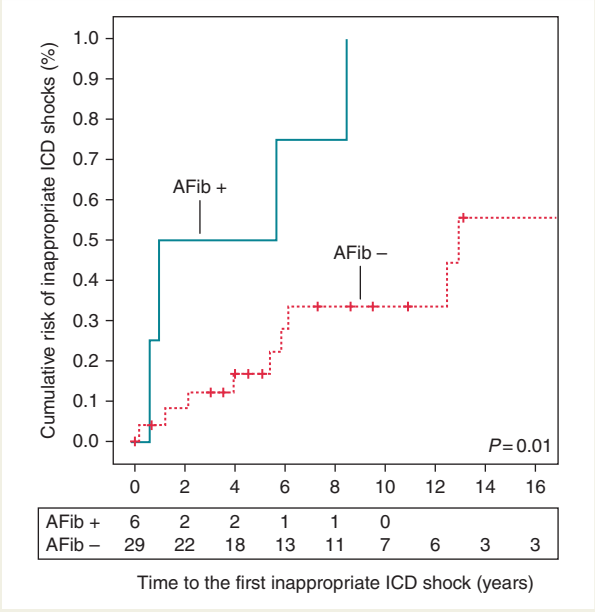

Figure 4 Time to the first inappropriate ICD intervention, according to the presence or absence of AF; case subjects with AF were at increased risk for inappropriate therapy delivery, when compared with those without AF.

Natural history of disease

As iVF often affects younger individuals, long-term FU is required to understand the natural course of the disease. Only few and sometimes conflicting factors are known or suspected to influence the arrhythmia recurrence rate. Young age, regional wall motion abnormalities, the failure to suppress frequent ventricular ectopy by use of AAD, a history of syncope, and a family history of SCD were considered as potentially influencing factors of arrhythmia recurrence.[8,16,17] Yet, a different source failed to show an influence of age, sex, ejection fraction, and arrhythmia inducibility in EPS on the rate of VT/VF recurrence.[18]

In our long-term observation of this iVF cohort, we observed two major findings with potential implications:

(i) Our study revealed a high number of appropriate ICD therapies ($n = 174$) in 43% of our patients. This is in line with prior studies reporting frequencies ranging from 37 to 39%.[9,19] As implantation of ICDs for secondary prevention is the current therapy of choice, the time-course of arrhythmia recurrence is of major importance. Particularly, iVF survivors with long event-free periods tend to challenge the appropriateness of ICD re-implantation after battery depletion of the initial device. Our study revealed arrhythmia recurrence in 13% of patients after the assumed average battery longevity of an ICD. We thus strongly emphasize the importance of re-implanting iVF survivors at risk for life-threatening arrhythmias, even after long event-free periods.

(ii) Despite observing many events in the long FU period, our analysis was not able to identify other clinical variables (age, sex or inducibility on EPS) associated with arrhythmia recurrence besides the presence of ERP, which was significantly associated with an early recurrence of arrhythmic events.

The role of early repolarization pattern on arrhythmia recurrence and vulnerable substrate

Early repolarization pattern is a common electrocardiographic finding that affects 3.3–13.1% of the European and US general population. Yet, it has been reported in up to 36% in a specific cohort of young athletes.[10,11,20,21] In 2008, Haissaguerre *et al.* suggested a relation between ERP and SCD, a fact in conflict with its thus far suggested benign nature.[22]

Yet, the pathophysiology of the phenomenon remains incompletely understood. In our present analysis of a well-characterized cohort with an established diagnosis of iVF, we demonstrated a significant association of ERP with appropriate ICD therapies during long-term FU, where ERP conferred an almost four-fold increased risk. We thereby confirm data by Haissaguerre *et al.*[22] who demonstrated a two-fold increased risk of arrhythmia recurrence in ERP positive individuals that had suffered an iVF episode. In addition, Aizawa *et al.*[23] showed an association between the presence of ERP and the onset of VF storms.

Based on our data and the results of previous studies, there is cumulating evidence for a potential causative association between ERP and the incidence of iVF.[22,24] The phenomenon of more and earlier arrhythmia recurrence in our ERP positive patients cautiously supports the hypothesis that ERP might represent a 'real' vulnerable arrhythmogenic ventricular substrate. In contrast to the results of ERP in iVF patients, there are also data on the benign nature of ERP in the general population without affecting the individuals' prognosis.[24]

Interestingly, there are data on other causative factors underlying the substrate for iVF. Some studies could show that iVF triggers originate from the His/Purkinje system.[6] Additional studies have been performed on mutations predisposing to iVF and found alterations in selective ion channel function of the purkinje system, which might also cause ERP-like ECG alterations.[25] Especially, the His-purkinje system seems to have a crucial impact on ventricular arrhythmogenesis, but cannot sufficiently be screened by surface ECGs due to the limited cumulative voltage change of the relatively low number of specific cells.[6] These data highlight the need for continued research on ER to ultimately provide a better understanding of the iVF pathophysiology.

Notably, specific subtypes of ERP have been previously described on a population level and in a cohort of patients with iVF. Such subtypes appear to carry an increased risk for developing arrhythmias, including an inferior localization, a higher amplitude, and ERP in combination with a horizontal or descending ST segment.[10,11,13,26] In this study, we were not able to show a modifying effect of these factors on the association between ERP and arrhythmia recurrence. However, we have to acknowledge that we might have been limited by our cohort size.

Inappropriate ICD therapies and onset of AF

Inappropriate ICD therapies are a major concern, as they both affect the patient's quality of life and increase morbidity and mortality.[27]

Such inappropriate ICD discharges in iVF patients are not rare, but remain incompletely understood. In this study, we found that up to 40% of our patients suffered inappropriate ICD shocks, mainly due to rapidly conducted AF that occurred in 17% of our cohort. Also in the wider spectrum of ICD patients, AF prevalence of up to 27% is a recognized issue.[28] Additionally, the question arises whether the occurrence of AF may indicate the presence of unidentified underlying heart disease also affecting the atria. Interestingly, the presence of ERP was not associated with the onset or diagnosis of AF in this cohort. Consistent with our findings, previous population-based analyses also have not shown an association between ERP and AF.[29] This is in contrast to other repolarization disorders such as the Brugada syndrome, which has been shown to be associated with a relatively high prevalence of AF.[30]

Potential clinical implications

IVF survivors, once being provided with an ICD, show excellent survival rates.[18] Despite ICD implantation being the primary therapeutic concept,[7] some studies demonstrated promising alternative treatment options including class I and III antiarrhythmic drugs,[9] or radiofrequency ablation of arrhythmogenic triggers originating from the His/Purkinje system or the moderator band.[6] It remains to be shown, if such supportive therapeutic options will be successful specifically in ERP positive patients at a more pronounced risk for arrhythmia recurrence. In this context, Haissaguerre *et al.* reported that iVF patients with ERP particularly seem to benefit from an antiarrhythmic treatment with quinidine rather than other class I or III AADs.[31] If so, such options could not only enhance the quality of life in these patients,[32] but also reduce morbidity and mortality due to reduction of both appropriate and inappropriate ICD shocks.[27] With regard to inappropriate therapies, we hypothesize that iVF patients might benefit from intensified screening and consequent therapy of incident AF or regular ICD telemonitoring interrogations. Such intensified treatment options could include early AAD therapy or first-line AF ablation strategies. Yet, prospective and controlled investigations are required to answer these questions.

Furthermore, the long-term goal of risk stratification for primary prevention in individuals with ERP has to be addressed. Based on our and prior work, at present, there are no consistent findings on other risk factors besides ERP. This further highlights the need for controlled prospective studies to identify additional risk factors. Such studies will need to include the analysis of new variables like Holter ECG recordings with quantification and characterization of PVCs, which have been implied to play an important role in iVF in the past.[6]

In addition, the role of the autonomic nervous system with respect to arrhythmogenesis in iVF is completely unclear. Non-invasive ECG parameters assessing autonomic tone have been shown to be significant predictors of prognosis in post-myocardial infarction patients.[33] Furthermore, there is evidence by nuclear imaging studies showing impaired sympathetic innervation in iVF survivors.[5] The potential value of such parameters in iVF patients has to be addressed in future studies.

Limitations

Our results benefit from a careful patient characterization and a relatively long FU. Yet, a number of limitations need to be acknowledged. Given the retrospective, observational nature of our cohort, some possibly important diagnostic tests have not been evaluated systematically at the index event. Such incomplete information particularly pertains to data on late enhancement on MRI potentially indicating structural abnormalities. In addition, patients did not undergo systematic genetic screening for inherited electrical or structural disorders, which may account for more than 20% of iVF patients.[15] Furthermore, the overall number of patients is small, and our study is lacking a representative control group. We excluded patients with asystole as the initial rhythm documented at the time of resuscitation, possibly underestimating patients with actual iVF whose rhythm deteriorated to asystole by the time medical first responders where present.

Finally, the inconsistent ICD tachycardia programming may have led to appropriate ICD therapies for non-sustained ventricular arrhythmias which otherwise might have terminated spontaneously.

Conclusions

In conclusion, we report the long-term FU of a well-characterized cohort of patients with an established diagnosis of iVF. First, we confirm that following ICD implantation, iVF patients suffer from recurrent arrhythmic events probably due to an underlying vulnerable substrate. Second, in a relevant fraction of iVF patients, the first arrhythmia recurrence occurs after the average battery life of current ICDs, supporting re-implantation even after several years of event-free periods. Third, ERP appears, as described before, to be a strong and consistent risk factor for arrhythmia recurrence in this patient population, which suggests that its pathophysiologic role should be further elucidated in detail in the future. Last, AF appears to be a major contributor to inappropriate ICD shocks in iVF patients, supporting intensified efforts for early diagnosis and treatment of this arrhythmia.

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