# Idiopathic Ventricular Fibrillation survivor and family screening outcomes: A Multicenter Experience

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ABSTRACT

Background- Early repolarization (ER) has been linked to poorer outcomes in idiopathic ventricular fibrillation (IVF) with horizontal ST segments being suggestive malignant features. The role of family screening in IVF is not clear. Objectives- Reviewing predictors for poorer outcomes and evaluate the role of family screening in IVF. Method- Retrospective multicenter cohort study including all patients diagnosed with IVF. Data was collected on baseline characteristics, ECG findings and recurrence of ventricular arrhythmia (VA) during follow-up. ECG findings were reviewed in first-degree relatives that were screened. Results- A total of 66 patients were included with male predominance (42/66, 64%) and Caucasian ethnicity (47/66, 71%). Mean age at cardiac arrest was 38yrs ± 11. Thirty-one patients had ER (47%) predominantly with J point amplitude ≥2mm and horizontal ST segments (18/31, 58%). Recurrent VA was seen in 13 patients (20%). Horizontal ST segments were associated with increased rates of VA recurrence (OR of 11 95% CI 2.7-43.7:p=0.0007). ER was seen in 20% of the 72 first-degree relatives and was more common if the proband had persistent ER pattern (OR 10.7, 95% CI 2.2-51.5; p=0.003). Conclusion- VA recurrence was lower than previously reported. ER was common in this IVF cohort and horizontal ST segments were suggestive predictor for poorer outcomes. Persistent ER in proband was associated with ER in first-degree relatives. With better understanding of its predictive value and the relationship to IVF, this information could potentially be used to guide family screening & identify new mutations using family members with persistent ER.

## BACKGROUND

Idiopathic ventricular fibrillation (IVF) predominantly affects young and otherwise healthy individuals after extensive investigations have excluded the presence of structural heart disease or underlying inherited channelopathy (1). The pathophysiology of IVF is poorly understood and this limits our ability to both identify those patients at risk and counsel family members as to their future risk of events. Follow up data from IVF cohorts have reported significantly increased rates of recurrence of ventricular arrhythmias (VA) (12) and inappropriate shocks (13) in these patients. Mortality rates have also been shown to be approximately 3% over a five-year period (12).

Several studies have identified an increased prevalence of early repolarization (ER) in patients with IVF compared to matched cohorts (2) and this has also been associated with poorer outcomes (2, 3). There is marked controversy regarding the importance of ER in the general population (4). ER with a horizontal ST segment (5) and J point amplitude of ≥2mm is more commonly seen in those with cardiovascular death or IVF (2, 6-8).

In the CASPER Registry, ER was identified in 13/56 IVF cases (9). However, it has as of yet not been shown whether these ER features independently influence long-term outcomes in IVF. However, in a general population study of more than 20,000 patients with no evidence of heart disease, ER had no impact on cardiovascular mortality at ten years regardless of J-wave morphology (J-point elevation vs. slurred QRS) or ST-segment type (ascending vs. flat or descending) (10). This highlights the challenge in managing IVF survivors with ER and their relatives particularly with regard to identifying pathophysiological, phenotypic and genetic factors determining prognosis. There is no clear consensus on the role of family screening in IVF. A study including families of patients with sudden cardiac death (SCD) has shown an increased frequency of ER on the ECGs of the relatives compared to age/sex matched healthy controls (11). If this is true in an IVF cohort, it could justify family screening and targeted genetic studies to better understand etiology.

This study aimed to evaluate: (i) ECG patterns & results of family screening in a cohort of IVF patients and (ii) Outcomes in terms of recurrent VA and device complications, in order to better understand the optimal management of patients.

## METHOD

This was a retrospective observational cohort study across two large tertiary centres including all patients diagnosed with IVF. These patients were identified from pre-existing databases that had been established as part of their clinical management. The diagnosis of IVF was made once underlying structural heart disease or inherited channelopathies had been excluded through extensive investigations: ECGs, signal average ECGs (saECG), diagnostic coronary angiogram, transthoracic echocardiogram (TTEs), cardiac magnetic resonance imaging (cardiac MRI), sodium channel blocker provocation testing (with ajmaline or flecainide) and exercise testing or adrenaline challenge (14). Adrenaline challenge was performed if exercise testing was not feasible. All of these cases in the pre-existing databases were reviewed to ensure these patients had undergone all of the relevant investigations to ensure the diagnosis of IVF was correct. All of these patients underwent ICD implantation for secondary prevention.

### *Data collection*

Retrospective data was collected using paper/electronic health records. Data was collated on baseline characteristics including age at the time of arrest, sex and ethnicity. Activities prior to the cardiac arrest (CA) and cardiac symptoms such as chest pain, shortness of breath, palpitations, pre-syncope and/or syncope pre-existing to the CA was recorded. Any past medical or family history particularly of SCD was also recorded. Patient data was anonymised.

Serial ECGs including those before and 48hours after the CA and those performed as an outpatient during follow-up were all reviewed by an independent blinded process. All ECG findings were double checked by two individuals (SH and NS) to ensure agreement and when disagreement occurred a third person acted as the adjudicator. ER was defined as the presence of J point elevation after the

QRS that could be notched, slurred or both of ≥1mm in two continuous inferior and lateral leads on baseline ECGs. Presence of ER in other leads was also recorded. We also reviewed whether the ER pattern was intermittent or persistent. A persistent ER pattern was defined as the presence of the same ER pattern on all the ECGs that the patient had during follow up including those as a part of exercise testing and holter monitoring. The ST segments in all cases of ER were reviewed and defined as either horizontal/depressed or ascending. A horizontal ST segment was defined as <0.1mV elevation of the ST segment within 100ms as per the recent Consensus Report (15). An ascending ST segment was defined as >0.1mV within 100ms, after the J point. J point amplitude was also measured from the isoelectric point to the peak of the J point and expressed in millimeters. We also assessed all ECGs for the presence of low amplitude T waves. A low amplitude T wave defined as any T wave in lead I, II or V4-V6 that was either inverted, biphasic or had an amplitude that was both 0.1mm and 10% of the R wave amplitude in the same lead. Amplitudes of R and T waves were measured in leads II and V5 (16). Mean QTc intervals were manually measured using Bazett's formula.

All device interrogations were reviewed during the period of follow up. We recorded all episodes of ventricular tachycardia (VT) treated with anti-tachycardia pacing (ATP) and the number of appropriate shocks for either VT or VF. Recurrences of VA were defined as either VT or VF requiring ATP or ICD shock. We also recorded the number and the reason for inappropriate shocks in all patients. Data on lead failure and device infections were also collected.

*Family screening*

We identified all patients whose 1$^{st}$ degree relatives underwent screening. Eighty six percent of the probands were offered family screening of 1$^{st}$ degree relatives as part of their clinic management. We reviewed the investigation findings, any history of cardiac symptoms and their ECGs as per the previous method described. At least two ECGs were reviewed for each relative.

*Statistical analysis*

This was performed using SPSS (IBM SPSS Statistics, Version 20 IBM Corp, Armonk, NY, USA). Continuous variables as displayed as mean ± standard deviation (SD). Categorical variables are presented as number and percentage. Categorical variables were compared with the two-tailed Fisher's exact test. A student t-test was used to compare continuous variables and Mann Whitney U test was used to compare non-continuous variables. Odds ratio was calculated. P-value of <0.05 was seen as being significant.

## RESULTS

A total of 66 patients were diagnosed with IVF between 1986 and 2015 across two tertiary centres. All patients experienced the CA at a young age with a mean age of 38 years ± 11. No patients had pre-existing cardiac disease and 53 patients (80%) had no cardiac symptoms prior to the CA (Table 1). The cohort was predominantly male (M: F ratio of 1.8:1) with Caucasian ethnicity (47/66; 71.2%) being more common (Table 1). There was a history of SCD in a family member in two out of 66 patients (3%; Table 1).

### *ECG findings (Table 2 and figure 1)*

ER was present in 31 out of 66 patients (47.0%) and was more frequently seen in the inferolateral chest and limb leads (13/31; 41.9%). No patients had ER beyond the inferolateral leads. The ST segments were predominantly horizontal/depressed in the context of the ER rather than ascending (18 vs. 13). Sixteen out of the 31 patients (51.6%) had a persistent ER pattern on serial ECGs whilst the remaining had an intermittent pattern. J point amplitude was ≥2mm in 18 patients (58.1%). The two patients with a family history of SCD had persistent ER pattern on their ECG. ER with low amplitude T waves was present in four out of 31 patients with ER (12.9%).

### *Family screening*

Thirty-three patients underwent family screening with a total of 72 1$^{st}$ degree relatives being screened. Out of these 33 patients 18 had ER (55%). The mean age was 36 years ± 13 with a M:F ratio of 1:1. All relatives underwent ECGs, saECGs and TTEs (table 2). The screening did not reveal any

abnormalities in the relatives and only four had cardiac symptoms (5.6%) of which all were palpitations with no documented arrhythmias. ER was seen in 14 out of the 72 family members (19.4%). There was no documented ER unless present in the proband. ER in a relative was more common if the proband had a persistent ER pattern (OR 10.7, 95% CI 2.2-51.5; p=0.003). The ER pattern in the relatives was of the same pattern to that of the proband (figure 2). This was more common than in 1st degree relatives in a healthy control population (OR 2.0, 95% CI 1.04-4.0; p=0.038) (11).

*Outcome*

During a mean follow up 68 months ± 56, a total of 13 patients had a recurrence of VA (19.7%). Out of these, two had VT requiring ATP and 11 had ICD shocks either due to VT (n=3) or VF (n=8). There were a total of 24 shocks during follow-up. The mean time from the CA to recurrence of the VA was 31 months ±27. There were no deaths. Inappropriate shocks occurred in nine patients (13.6%) secondary to atrial arrhythmias with fast ventricular response (six atrial fibrillation and two atrial tachycardia) and in one patient due to noise on the right ventricular St Jude Riata lead. Seven patients experienced lead failure (10.6%) that required intervention. This involved the right ventricular lead in six patients and right atrial lead in one patient. There were no device infections.

*Relationship of ER Patterns to VA Recurrence*

There was a trend to a higher proportion of ER in patients having VA recurrence versus those without (table 2; p=0.12), OR of 3.17 (95 % CI 0.5 -6.2; p=0.08). However, the presence of ER with horizontal/depressed ST segments was significantly more common in the VA recurrence group (p=0.004; Table 2) with an OR of 11 (95% CI 2.7-43.7:p=0.0007). Out of those with recurrent VA and an ER pattern, all had a horizontal/depressed ST segment (figure 3). The Kaplan-Meier curves also demonstrate that those with ER with horizontal/depressed ST segments had lower rates of freedom from VA recurrence compared to those with no ER with horizontal/depressed ST segments (p=0.01, figure 4). J point amplitude was not different between those with and without VA and was not a predictor of outcome (OR 2.4, 95% CI 0.6-9.2; p=0.19). ER with low amplitude T waves was

associated with a trend towards an increase risk of VA recurrence (OR 4.6 95% CI 0.59-27; p=0.15) however there was no significant difference in the T/R ratio between these two groups (lead II p=0.30/V5 p=0.12).

## DISCUSSION

We have been able to demonstrate that rates of ER on ECGs in patients with IVF are substantially higher than the rates of 1-13% reported in the general population (8, 17). Furthermore, we have shown that ER with horizontal/depressed ST segments is associated with significantly increased risk of VA recurrence in IVF, which has not previously been demonstrated. Previous studies have not reported on ST segments when assessing the relationship between ER and outcomes. However, it has been shown that ER with horizontal/depressed ST segments is more common in an IVF cohort compared to age and sex matched controls (5). Contrary to the findings of *Roten L et al*, we did not demonstrate as high prevalence of low amplitude T waves in our cohort (13% vs. 29%) (15). However, the prevalence of low amplitude T waves is greater than what has been reported in a healthy population (15). Furthermore, ER and low amplitude T waves were shown to have a trend towards an increased risk of VA recurrence (OR 4.6 95% CI 0.59-27; p=0.15). These findings thereby suggest that low amplitude T wave together with horizontal ST segments are possible "malignant" forms of ER. This may thereby play a role in the risk stratification of patients with IVF.

Previous studies have reported high recurrence rates of VA events around 31% and mortality rates of 3.1% over a five-year period (12). The recurrence rate in our cohort was 19.7% during a similar follow up period, which is lower than that previously documented. We also had no deaths in our cohort. Furthermore, our rates of inappropriate shocks are also lower than that reported in the literature (13.6% vs. 44%) (13). These findings thereby suggest that these patients have better outcomes than previously thought. It may also reflect the more conservative ICD programming in our centres where of IVF patients' devices are programmed with a single VF zone of > 230/min.

Familial ER has been reported to have an autosomal dominant inheritance pattern with incomplete penetrance. Two independent population-based studies also have suggested some degree of inheritance of the ER patterns in the general population (18), but the familial inheritance of malignant ER patterns has not been clearly demonstrated. A candidate gene approach in IVF patients with ER has identified a mutation in KCNJ8, which encodes a pore-forming subunit of the ATP-sensitive potassium channel leading to shortening of action potential duration, but this has not been repeated in other studies of IVF with co-segregation (19, 20). Mutations in the L-type calcium channel genes, including CACNA1C, CACNB2B, and CACNA2D1 as well as loss-of-function mutations in SCN5A have also been associated with IVF with ER (21). However, clinical validation and co-segration data is lacking to confirm their pathophysiological significance. Given the high prevalence of ER in the general population, ER is likely to have polygenic basis that is also influenced by environmental, autonomic & non-genetic factors. Population based genome wide association studies have failed to identify genetic causes of ER when validation in separate cohorts is performed, indicating its polygenic aetiology and the fact that these cohorts are loosely characterised in terms of the patterns and distribution of ER (18). What is required is a detailed familial genotype-phenotype analysis of IVF families incorporating an analysis of ER patterns. Our previous work has shown an increased rate of ER in 1$^{st}$ degree relatives of SCD patients compared to age/sex/ethnicity matched healthy controls (11). In this study we have shown that ER was more common in 1$^{st}$ degree relatives of patients that had a persistent ER pattern on their ECG and when present it was of the same pattern as in the proband (OR 10.7, 95% CI 2.2-51.5; p=0.003). The lower rates of ER in families of patients with an intermittent ER pattern could be secondary to the families also demonstrating an intermittent pattern and thereby being missed during screening. However, all of the families screened had at least two ECGs during their screening process. Our findings thereby raise a possibility of familial inheritance of ER when this is persistent in nature. This is important as it will enable linkage analysis to be performed which is more likely to yield positive results as the phenotype is more distinct. With our findings it might be more appropriate to target those patients & families with a persistent ER pattern in future studies.

## CONCLUSION

In this cohort of IVF patients across two tertiary centres over an extensive follow up period we have been able to demonstrate lower rates of VA events and inappropriate shocks compared to the existing evidence. This highlights that the outcome in these patients is better than previously thought. Patients with ER and a horizontal/depressed ST segment had an increased risk of recurrence of VA indicative that this is more of a "malignant" form of ER. We also show a higher rate of ER in 1$^{st}$ degree relatives where the proband had persistent ER. With better understanding of its predictive value and the relationship to IVF, this information could be used to identify new mutations using trios of such family members with persistent ER.

## DISCLOSURES

None

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FIGURE LEGEND

*Figure 1*- Shows the number of patients with ER in the IVF cohort and the ST segment pattern, J point amplitude and low amplitude T waves in relation to the ER.

*Figure 2*- Shows the 12 leads ECGs of three probands (A, B and C) and their 1st degree relatives (a, c and d). A and a- ER in the inferolateral chest and limb leads with ascending ST segments and J point amplitude of 1mm. B and b- ER in the inferolateral chest and limb leads with ascending ST segments and J point amplitude of 1mm. C and c- ER in the inferolateral chest and limb leads with ascending ST segments and J point amplitude of 1mm.

*Figure 3*- The number of IVF patients with ER and no ER on 12 lead ECG that had VA during follow up and also the proportion of those with ER that had horizontal/depressed and ascending ST segments.

*Figure 4*- Kaplan-Meier Curves for VA recurrence in subjects with ER with horizontal/depressed ST segments compared to no ER with horizontal/depressed ST segments

| Baseline characteristics | All IVF patients n=66 | Patients with recurrent VA n=13 | Patients without recurrent VA n=53 | p-value |
|---|---|---|---|---|
| Male n (%) | 42 (64) | 6 (46) | 36 (68) | 0.14 |
| Mean Age at CA in Years ± SD | 38 ± 11 | 40 ± 10 | 38 ± 11 | 0.72 |
| **Ethnicity n (%)** | | | | |
| Caucasian | 47 (71) | 10 (77) | 37 (70) | 0.61 |
| South Asian | 9 (14) | 2 (15) | 7 (13) | 0.83 |
| Afro-Caribbean | 8 (12) | 1 (8) | 7 (13) | 0.30 |
| East Asian | 1 (2) | 0 | 1 (2) | 0.61 |
| South American | 1 (2) | 0 | 1 (2) | 0.61 |
| **Activity prior to CA n (%)** | | | | |
| Rest | 41 (62) | 5 (38) | 36 (68) | 0.02 |
| Sleep | 8 (12) | 3 (23) | 5 (9) | 0.19 |
| Walking | 11 (17) | 3 (23) | 8 (15) | 0.49 |
| Exercise | 6 (9) | 2 (15) | 4 (8) | 0.39 |
| **Cardiac symptoms pre-existing to the CA n (%)** | 13 (20) | 4 (31) | 9 (17) | 0.26 |
| Palpitations | 4 (31) | 2 (50) | 2 (22) | 0.12 |
| Palpitations + Syncope | 1 (8) | 1 (25) | 1 (11) | 0.27 |
| Palpitations + Syncope + Pre-syncope | 2 (15) | 0 | 1 (11) | 0.61 |
| Syncope | 3 (23) | 1 (25) | 2 (22) | 0.54 |
| Pre-syncope | 3 (23) | 0 | 3 (33) | 0.38 |
| **Family history of SCD n (%)** | 2 (3) | 1 (8) | 1 (2) | 0.27 |
| 1st degree relatives n | 2 | 1 | 1 | |

| | | | | |
|---|---|---|---|---|
| 2nd degree relatives | 2 | 0 | 2 | |
| Mean follow up months ± SD | 68 ± 55 | 74 ± 41 | 66 ± 59 | 0.63 |

*Table 1- Shows the baseline characteristics, symptoms and activity prior to cardiac arrest in the cohort as a whole and subcategories to those with and without VA recurrence*

*Table 2- Demonstrates the ECG findings and ER pattern in the IVF cohort*

¥ SCD- sudden cardiac death

| ECG findings | All IVF patients n=66 | Patients with recurrent VA n=13 | Patients without recurrent VA n=53 | p-value |
|---|---|---|---|---|
| **Mean QTc ± SD** | 400 ± 25 | 393 ± 27 | 402 ± 24 | 0.30 |
| **Early repolarisation n (%)** | 31 (47) | 9 (69) | 22 (42) | 0.12 |
| Inferolateral limb & chest leads | 13 (42) | 5 (38) | 8 (36) | 0.11 |
| Inferolateral chest leads | 2 (6) | 1 (8) | 1 (5) | 0.36 |
| Inferolateral limb leads | 5 (16) | 3 (23) | 3 (14) | 0.32 |
| Inferior leads | 6 (18) | 0 | 6 (27) | 0.14 |
| Lateral limb and chest leads | 3 (10) | 0 | 2 (9) | 1.00 |
| Lateral chest leads | 2 (6) | 0 | 2 (9) | 1.00 |
| Lateral limb leads | 0 | 0 | 0 | 1.00 |
| ST segment horizontal/depressed | 18 (58) | 9 (100) | 9 (41) | **0.004*** |
| J point amplitude ≥2mm | 18 (58) | 5 (38) | 13 (50) | 1.00 |
| Slurred J points | 9 (29) | 2 (22) | 7 (32) | 0.69 |
| Notched J points | 13 (42) | 3 (33) | 11 (50) | 0.45 |
| Both notched & slurred | 9 (29) | 4 (44) | 4 (18) | 0.18 |
| Low amplitude T wave | 4 (13) | 2 (22) | 2 (9) | 0.56 |
| Mean T wave amplitude in lead | | | | |
| II ±SD | 0.29 ± 0.26 | 0.36 ± 0.30 | 0.17 ± 0.11 | 0.07 |
| V5 ±SD | 0.31 ± 0.19 | 0.37 ± 0.17 | 0.20 ± 0.20 | 0.02 |
| T/R wave ratio in lead | | | | |
| II ±SD | 0.32 ± 0.24 | 0.36 ± 0.27 | 0.26 ± 0.17 | 0.30 |
| V5 ±SD | 0.24 ± 0.12 | 0.26 ± 0.13 | 0.19 ± 0.10 | 0.12 |

*Table 3- Shows the baseline characteristics, investigations performed in the 1st degree relatives during family screening and the ECG leads with ER pattern*

| | **1st degree relatives n=72** |
|---|---|
| Mean Age yrs ±SD | 36 ± 13 |
| Male n (%) | 36 (50) |
| 1st degree relatives screened | |
| Parents n (%) | 8 (11) |
| Siblings n (%) | 40 (56) |
| Children n (%) | 24 (33) |
| ECG n (%) | 72 (100) |
| saECG n (%) | 72 (100) |
| 24h tape n (%) | 55 (83) |
| TTE n (%) | 72 (100) |
| Exercise test n (%) | 32 (48) |
| Cardiac MRI n (%) | 5 (8) |
| Ajmaline or Flecainide challenge n (%) | 3 (5) |
| Adrenaline challenge n (%) | 1 (2) |
| ER n (%) | 14 (19) |
| Inferolateral limb and chest leads | 10 (71) |
| Inferior leads | 1 (2) |
| Lateral chest and limb leads | 3 (21) |
| ST segments horizontal | 7 (50) |
| ST segment ascending | 7 (50) |
| J point amplitude ≥ 2mm | 5 (36) |