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EDITORIAL COMMENT

Idiopathic Ventricular Fibrillation

Preventable Cause of Sudden Cardiac Death in Need of Global Collaboration*

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Idiopathic ventricular fibrillation (IVF) is defined as a resuscitated cardiac arrest victim with documented ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicological causes have been excluded through comprehensive clinical evaluation, and is estimated to account for 5% to 7% of all out-of-hospital cardiac arrests (OHCA).[1] With evidence mounting on the multitude of candidate genes underlying IVF in up to 27% cases, thanks to the advances in genetic testing and the greater availability of whole-exome and whole-genome sequencing, a protocol for thorough follow-up, reassessment of diagnosis, and reappraisal of management strategy of individuals diagnosed with IVF has recently been established.[2,3] Because the efficacy of antiarrhythmic drugs lacks clear evidence,[4] an implantable cardioverter-defibrillator is the prime therapeutic option for the secondary prevention of sudden cardiac death (SCD). The 2 main challenges we are currently facing is how best to identify the IVF patients with covert channelopathies, cardiomyopathies, or other diseases masquerading as normal cardiac phenotype and how best to prevent SCD in family members of IVF patients.

In this issue of *JACC: Clinical Electrophysiology*, Pannone et al[5] have shown that the diagnostic yield for (likely) pathogenic variants was 6.7% in a cohort of IVF probands undergoing genetic analysis with a broad gene panel, and that being a carrier of a (likely) pathogenic variant or variant of uncertain significance (VUS) was a predictor of poor prognosis. Forty-five patients (predominantly Caucasian) from 5 European centers with a diagnosis of IVF throughout the follow-up period (105 ± 77 months) since their OHCA were included in this retrospective analysis. Interestingly, 26 patients with an inherited cardiomyopathy or channelopathy diagnosed while on follow-up were excluded from the study, along with patients that did not undergo a genetic analysis (n = 92) or had incomplete baseline or follow-up data (n = 11). In other words, of 174 consecutive OHCA survivors with a diagnosis of IVF over a period of 26 years, 26 (15%) were diagnosed with inherited cardiomyopathy or channelopathy during follow-up. However, as this group was excluded from the study, we do not have any further information on this important subset of patients. It would have been worthwhile for the investigators to provide data on the proportion with and without a detectable cardiac phenotype among the total eligible patients as we can expect a 4-fold increase in genetic testing yield between the phenotype-negative and phenotype-positive groups.[6]

Given that 27% of the study subjects had prior syncope, with significantly more syncope among those with (likely) pathogenic variants, some insights into the potential triggers or associated factors for syncope and the inciting OHCA event, such as exercise, activity, rest or sleep, would have been helpful in drawing meaningful genotype-phenotype associations.[4,7] Due to lack of an in-depth family history or information pertaining to clinical/genetic screening of family members, except that 6 subjects had a family history of SCD, it is unclear whether 3-generational pedigree analyses and clinical screening of first-degree relatives with an

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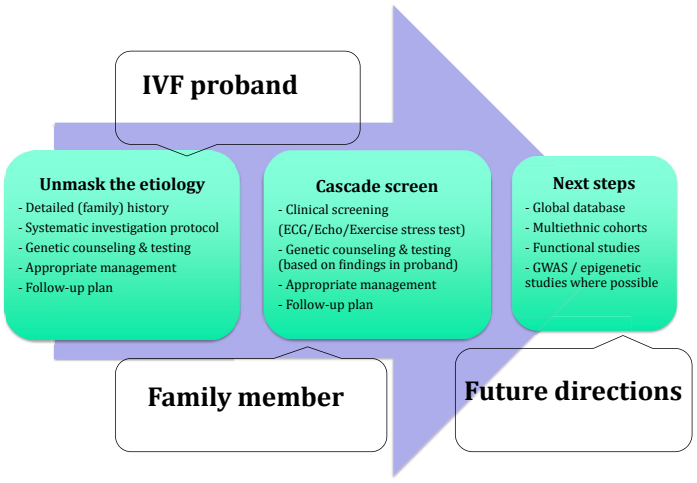
FIGURE 1 Steps in Unraveling the IVF Mystery



Graphical illustration outlining the steps in unmasking the underlying etiology in the proband with idiopathic ventricular fibrillation (IVF), screening the family members, and the future research directions. ECG = electrocardiogram; GWAS = genome-wide association study.

electrocardiogram, echocardiogram, and exercise stress test were performed. Also, the investigators have not shone light on whether any of the subjects had documented short-coupled ventricular premature beats during follow-up, as this is well known to elicit torsades de pointes or immediate ventricular fibrillation in a limited number of patients with the Dutch *DPP6* haplotype.[2]

As the study subjects were enrolled over a prolonged period from the year 1994, the investigators have applied the American College of Medical Genetics and Genomics reclassification criteria to all the reported genetic variants, after which (likely) pathogenic *RYR2* variants were identified in 2 patients and an *FKTN* variant in 1 patient; 9 patients were carriers of VUS; and 33 patients either had (likely) benign variants or no variants. Of note, an additional VUS was reported in 2 of the 3 patients with (likely) pathogenic variants, and 1 other patient had 2 VUS in candidate genes (*RYR2* and *FKTN*). The lack of sufficient research on this rare condition and the ensuing paucity in knowledge leaves us wondering whether the polygenic hypothesis and the second-hit hypothesis, whereby 2 or more gene mutations or the result of accumulated mutations, respectively, might have a role in etiopathogenesis of these IVF cases.[2]

All 4 mutated *RYR2* patients reported by the current study[5] had a negative exercise test and a ventricular arrhythmia recurrence during follow-up, in alignment with the recently described distinct inherited arrhythmia syndrome caused by loss-of-function variants in *RYR2* termed *calcium-release deficiency syndrome*. Patients with calcium-release deficiency syndrome are at risk for ventricular fibrillation but do not appear to have provocable ventricular tachyarrhythmias during exercise stress testing.[8] This contrasts with gain-of-function variants in *RyR2* that lead to spontaneous calcium ion release and catecholaminergic polymorphic ventricular tachycardia, typically diagnosed when bidirectional/polymorphic ventricular tachyarrhythmias are elicited on the exercise stress test. However, the lack of functional studies precludes a clear judgment on this aspect of the *RYR2* variants as well as other VUS reported in this study.

A recent genome-wide association study has identified 4 novel loci and 2 risk genes (*PKN2* and *CCR7*) for idiopathic ventricular tachyarrhythmias in the Chinese population.[9] The investigators postulate that there is a strong link between *CCR7* and *PKN2* and genes involved in inherited arrhythmias and ECG abnormalities, such as that noted in *RYR2* and *NOS1AP*, thereby providing a molecular mechanism by which overexpression of these genes can cause ventricular arrhythmias. Another recent publication has described the potential effects of epigenetics involving noncoding RNAs, DNA methylation, and other regulatory mechanisms, on the ventricular arrhythmia susceptibility genes.[10]

The steps that need to be followed to unmask the underlying etiology in IVF probands and identity the affected family members along with the focus areas of future research are shown in **Figure 1**. Putting things in perspective, because all the gene variants identified in the present study have already been implicated in channelopathies and cardiomyopathies, can we safely conclude that the subjects without any variants are the true IVF cases and that they have a significantly better arrhythmia-free survival than the subset with variants? Or is it wise to say that the inherent limitations of research pertaining to rare conditions, such as small cohorts, minimal multiethnic representation, and lack of functional studies, preclude us from drawing any meaningful conclusions, as yet? Although we have undoubtedly made commendable progress in our understanding of the underlying etiopathophysiology of IVF and have learnt to manage the condition better, it is also imminently clear that further global collaborative efforts are needed to help solve the

many mysteries still surrounding this medical enigma.

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