UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO EM MEDICINA DO DESPORTO

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IDIOPATHIC VENTRICULAR FIBRILLATION IN THE YOUNG DOES IT REALLY EXIST?

ÁREA CIENTÍFICA DE MEDICINA DO DESPORTO

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NOVEMBRO/2020

FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

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ABSTRACT

Sudden cardiac death (SCD) usually affects patients under 40 years of age, with most of its victims displaying a cardiac abnormality, either previously known or even unrecognized. However, in up to 5–10% of cases, the underlying cardiac arrest takes the form of ventricular fibrillation and the context of no obvious cardiac pathology, in what researchers now agreed upon to correspond to idiopathic ventricular fibrillation (IVF). As expected, these patients represent a highly heterogeneous group, in whom both diagnosis and management are challenging.

Nowadays, it remains unclear if this condition really exhibits no cardiac abnormalities or if our exams are to blame as not being powerful enough to detect them. In fact, the goal of this review is to provide a broad insight into IVF potential underlying etiopathologies, even asking whether it represents a real individual clinical entity. In order to accomplish so, an extensive literature review, focused on the key aspects surrounding the concept of IVF, namely its definition, diagnosis, etiology, pathophysiology and follow-up, was performed.

IVF incidence seems to be decreasing in the last few decades, which can be, at last, partially attributed to the stipulation of new well-defined primary arrhythmia syndromes, the improvement in high-resolution imaging modalities and the further implementation of genetic testing. On the other hand, a majority of unexplained SCAs remain insufficiently investigated, thus resulting in the diagnosis of IVF to be still probably overused. Therefore, a constant diagnosis re-evaluation during a long-term follow-up seems of utmost importance in virtually all cases.

As such, there is a desperate need for international medical societies to frame management guidelines, so that standardized and systematic approaches could be implemented, in order to improve the proportion of definitive diagnosis in otherwise apparently unexplained SCAs and to ensure that opportunities for specific therapies and preventive strategies, including among family members, are not missed. After all, the rate of potentially lethal arrhythmic recurrences in IVF patients is not neglectable.

BACKGROUND

Sudden cardiac death (SCD) is defined as a sudden natural unexpected death from a cardiac cause occurring within 1h of onset of symptoms in patients without prior conditions that would appear fatal.[1,2] Most victims (>90%) happen to have a cardiac abnormality, either previously known or unrecognized,[3,4] namely of ischemic, electrical, infectious or structural nature.[5] In fact, data on SCD survivors show that only 5–10% of cases occur in the absence of any apparent underlying heart disease (so called idiopathic).[3,6-13] In 80%, SCD is because of ventricular fibrillation (VF) or rapid ventricular tachycardia (VT)[2]. The prevalence of IVF in survivors of SCD with otherwise normal electrocardiogram (ECG) who received an implantable cardioverter defibrillator (ICD) ranges between 8.4% and 10.8%.[9,14] Obviously, prevalence of IVF could be difficult to be established, as patient's phenotype might change during the follow-up.[14] In addition, its incidence will probably decline with advancements in diagnostic testing and the discovery of new primary arrhythmia syndromes.[15-17]

About IVF, two different consensus statements have been published, proposing two different definitions. The first is from the 1997 Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and the United States, which describes IVF as the terminology that best acknowledges the timely inability to identify a causal relationship between the clinical circumstance and the arrhythmia.[3] The second and more recent definition is from the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society Consensus Statement of Inherited Primary Arrhythmia Syndromes, and defines IVF as a resuscitated cardiac arrest, preferably with documentation of VF, in which known cardiac, respiratory, metabolic and toxicological causes have been excluded through clinical evaluation.[18] In other words, IVF diagnosis depends on the absence of a substrate for VF and exclusion of specific diseases, including structural cardiac disease (ie, myocarditis, cardiac sarcoidosis, arrhythmogenic, hypertrophic and dilated cardiomyopathy) and primary arrhythmia syndromes (ie, Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQTS), short QT syndrome (SQTS) and early repolarization syndrome (ERS).[16] In fact, the discovery of channelopathies has largely contributed to a decline in IVF incidence, since most of them were regarded as IVF before they were discovered. However, although the exact definition of IVF has changed during the years and although new diagnostic tools are available, no specific guidelines have been developed for the definition and diagnosis of IVF, as well as a protocol for exclusion of specific cardiac diseases that cause SCD.[16] On the other hand, despite major improvements in the diagnosis of these electrical syndromes, concealed forms of these known genetic disorders may still explain a proportion of IVF or SCD incidents.[16,19] For example, CPVT, typically caused by mutations in the ryanodine receptor gene (RYR2), may still get

misclassified as IVF.[20] Moreover, mutations in other arrhythmia-associated genes, such as SCN5A and KCNH2, may initially manifest as VF, even though in most cases an underlying electrical disease is later identified.[21,22] This situation illustrates that IVF is an appropriate "initial" or "working" diagnosis, because it reflects our current inability to establish a link between a life-threatening arrhythmic event and clinical information obtained by detailed invasive and noninvasive examinations.[3] In fact, recent studies have shown that in >50% of apparently unexplained sudden cardiac arrest (SCA), a specific etiology can be unmasked through a complete systematic medical assessment.[19,23,24] In their study, Conte G et al.[14] also reported that an initial diagnosis of IVF changed over the time in 27% of patients. This is crucial from several perspectives including prognostication, implementation of specific therapy when possible, appropriate lifestyle counselling, and also optimization of screening and prevention among relatives.[25-30] The characteristics and the extent to which such cases undergo a systematic thorough investigation in real-life practice are unknown.[15] In parallel, in up to 20% of IVF cases, a family history of SCD or IVF is present, suggesting that at least a subset of IVF is also hereditary.[12,15,31-35] In these cases, a primary electrical disease might be present in up to 93% of situations.[3,4] Because no cardiac abnormalities are observed, family members that may be at risk may not be identified.

Most patients with IVF share several characteristics: (1) the majority are men,[36,37] with male sex proportion ranging from 56% to 86%;[14,38-41] (2) the first arrhythmic event occurs during young adulthood,[15,42,43] namely being these patients usually <40 years of age.[2,37] Specifically, mean age ranges from 28 to 40.4 years, [5,36,39-41] whereas median age is reported to lie between 43 and 45 years, significantly lower than that of patients presenting with VF because of specific etiologies;[14,44](3) the primary arrhythmia - when documented - is polymorphic VT or VF triggered by a short-coupled premature ventricular complex (PVC),[7,33] presenting as syncope or cardiac arrest;[43] (4) the tendency – when compared to other causes of SCA – of not displaying specific cardiac symptoms during the weeks prior to the event (64%), with resultant less pre-SCA emergency medical service call and, thus, longer collapse-to-basic life support duration.[44] These findings fit particularly with a primary electrical cardiac disorder, giving hope that a specific syndrome may be defined, and emphasize the challenge represented by the prediction of such cases, where SCA may be the inaugural event,[33,45-47] Other less standardized particular features include higher left ventricle ejection fraction (LVEF)[14] and lower cardiovascular risk factor burden,[15] when compared to more common SCA etiologies. There also seems to be an at rest index cardiac arrest occurrence predominance (67% of events).[44]

The implantation of an ICD is currently advocated as first-line therapy for patients with IVF, even though, due to its relative rarity, most studies investigating patient outcomes are

small.[39] As for prognosis, it is perceived as being satisfactory, particularly when ICD therapy is provided.[40] In relative terms, it is generally better than other primary electrical disorders.[48]

IVF presents a unique challenge, as it represents a severe life-threatening condition notoriously difficult to predict and further characterize in a standardized fashion. Nowadays, it is not possible to identify a potential underlying cause for the life-threatening arrhythmia episode, both by invasive and non-invasive testing, following the resuscitation event.[3] However, extensive diagnostic evaluation, including targeted genetic testing, could establish a specific etiology for SCA in more than 20% of patients otherwise assumed to be IVF presenters.[6] On the other hand, the extent to which a so-called comprehensive cardiac assessment is carried out in the real-life setting has not been fully investigated. Moreover, IVF might be the first manifestation of subclinical, hence undetected, structural or electrical heart disease, as already showed for early stages of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).[3] In fact, IVF does not imply complete absence of common abnormal findings, like first degree atrioventricular (AV) block or atrial fibrillation (AF).[3] As a result, IVF survivors should undergo regular – at least annual – cardiologic examinations, to rule out a delayed onset of heart disease, which could imply additional treatment.[49]

The goal of this review is to provide a broad insight into IVF potential underlying etiopathologies, even asking ourselves whether it represents a real clinical entity in itself. In fact, given the successive emergence of different nosological conditions from what was otherwise regarded as idiopathic SCA, one might wonder if its definition is intrinsically a consequence of medical research underachievement.

METHODS

Relevant studies related to IVF, published from inception until May 31, 2020, were searched and identified in MEDLINE (through PubMed), Cochrane Controlled Register of Trials (CENTRAL), ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and EMBASE electronic databases. In addition, hand search of article references was also performed. The research was limited by language (english, spanish and portuguese) and type of subjects (humans and animal models) and focused on the main aspects surrounding the concept of IVF, namely its definition, diagnosis, etiology, pathophysiology and follow-up. Explicitly, the search equation, taken in its most complete form, was: “ventricular fibrillation” [title/abstract] [MeSH] AND “idiopathic”. Two reviewers independently searched the literature and extracted pertinent publications. Different articles arising from the same database were reduced to the last and most up-to-date one. Only full articles were eligible for inclusion, and no further study design restrictions were considered. This review prosecution followed the “Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA)” guideline, whenever possible. Moreover, this article was registered in “PROSPERO - International Prospective Register of Systematic Reviews”, with the number CRD42020198719. No funding was provided.

Taking resources from all the different databases and the hand search in aggregation, 1108 articles were first identified. Then, after remotion of duplicate elements and article screening through title and abstract, only 289 papers remained. Of these, 181 full texts were regarded as relevant, with 154 being included in this review, as showed in figure 1.

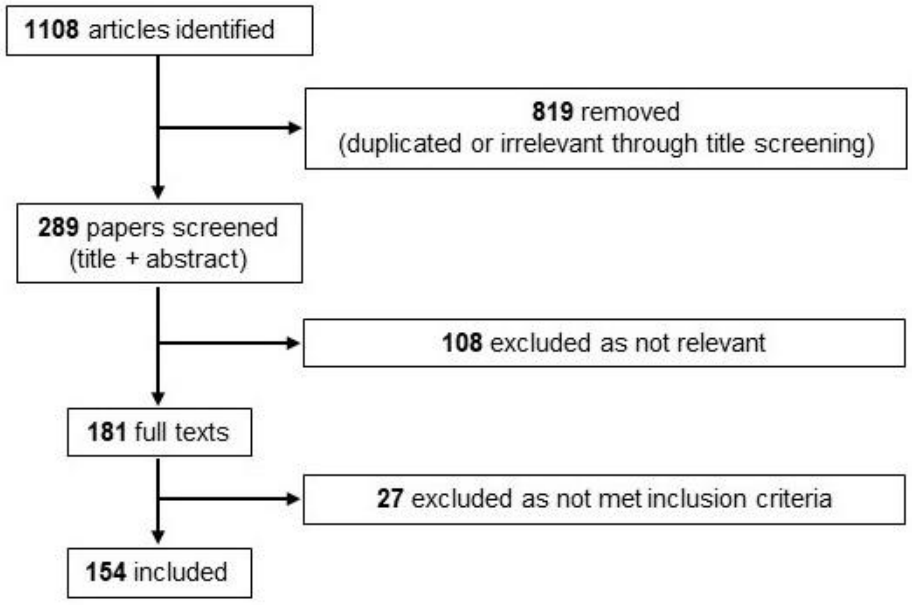

Figure 1 - Summary of evidence search and selection.

RESULTS

1- Differential Diagnosis of Patients With VF

VF has an extensive differential diagnosis consisting of many cardiac and noncardiac causes. As noncardiac causes of VF are usually easily detected by laboratory and toxicological assessment, we exclusively discuss the potential cardiac causes of VF. We reproduce a table by Visser M. et al,[16] pointing out, if known, an overview of the incidence and prevalence of the cardiac diseases to be considered in the differential diagnosis of VF, the percentage of patients presenting with (aborted) SCD as the condition's first manifestation, and the event rates of recurrences of VT/VF for each specific disease.

Disease	Incidence/Prevalence	SCD as First Manifestation of Disease	Event Rate
CAD/MI	Incidence MI: 785 000/y in the US; Prevalence CAD: 17.6 million in the US;	20%	Death rate CAD: 287–390/100 000/y for males and 201–277/100 000/y for females
Coronary artery spasm	Incidence: unknown Prevalence: unknown	2.4%	14% of patients with a secondary prophylactic ICD received appropriate ICD therapy (FU 3.2 y)
DCM	Incidence: 3.6–7.9/100 000 personyears Prevalence: 1/2700	Rarely	Unknown
HCM	Incidence: 1.4–3.6/100 000 personyears Prevalence: 1/500	Unknown Annual death rate SCD 0.7% 35% of all HCM-related deaths are sudden and unexpected	5%/y ICD discharge rate (skewed toward a more severe phenotype)
ARVD/C	Incidence: unknown Prevalence: 1/5000	13%	19% of primary prophylactic ICD patients showed recurrence of VF (FU 4.7 y)
BrS	Incidence: unknown Prevalence: 50–100/100 0005	Unknown	Event rate per year per group of presentation: Cardiac arrest: 7.5% Syncope: 1.8% Asymptomatic, spontaneous type 1 BrS ECG: 0.8% Total (all patients with BrS): 1.9%
LQTS	Incidence: unknown Prevalence: 50/100 000	Unknown 2% of young athletes with	13% (87/647) of genotyped patients with LQTS 1, 2, or 3 experienced cardiac arrest before the age of 40 years and

		SCD in postmortem studies	before initiation of treatment (FU 6.2 y)
CPVT	Incidence: unknown Prevalence: 10/100 000	Unknown	Arrhythmic event rate Probands: 21.7 per 1000 person-years Relatives with RyR2 mutation: 4.4 per 1000 person-years
SQTS	Incidence: unknown Prevalence: unknown	40%	16% of patients experienced VF (FU 60 mo)
ERS	Incidence ERS: unknown Prevalence ER: in normal population: 1% to 5% in patients with IVF: 7% to 31%	100% (presentation with VF or SCD is part of the definition of ERS)	Unknown
Myocarditis	Incidence: unknown Prevalence: unknown	16%	Unknown
Cardiac Sarcoidosis	Incidence: unknown Prevalence: 20–30/100 000 for pulmonary sarcoidosis, of which 5% has cardiac involvement	41% of patients with myocardial sarcoidosis confirmed on autopsy presented with SCD	Unknown
IVF	Incidence: Estimated 4900–47 000 patients/y in the US Prevalence: unknown	100%	Appropriate ICD therapy in 11% to 43%

Table 1 – Differential diagnosis of VF, proposed by Visser M. et al[16]
ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; BrS, Brugada syndrome; CAD, coronary artery disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; ER, early repolarization; ERS, early repolarization syndrome; FU, follow-up; HCM, hypertrophic cardiomyopathy; ICD, implantable cardiac defibrillator; IVF, idiopathic ventricular fibrillation; LQTS, long-QT syndrome; MI, myocardial infarction; SQTS, short-QT syndrome; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia; US – United States.

2- Diagnosis of IVF

Waldmann V. et al[15] reported that, among survivors of out of hospital SCA, 12.3% remained unexplained after ECG, echocardiography and coronary angiography. Cardiac magnetic resonance imaging (MRI) yielded the diagnosis in 3.5%, while other investigations accounted for 2.4% additional diagnoses. That way, 6.8% patients were assumed to have suffered from IVF. Among these, only 16.3% cases benefited from a complete workup (including pharmacological testing). Younger patients and those admitted to university centers were found to have been more thoroughly investigated. On the other hand, the CASPER registry[19] 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 (UCA) due to VT/VF in patients with preserved left ventricular ejection fraction and normal coronary arteries. Of these, 75% of patients were diagnosed with a primary electrical disease and the remaining 25% had underlying structural heart disease.

Literally, the diagnosis of IVF is made by excluding other potential causes of VF, what requires extensive diagnostic testing.[39] Based on published guidelines,[3,16,19,50] these patients must have: no clinical evidence of drug intoxication or electrolyte abnormality at the time of initial presentation; no identifiable structural heart disease, including valvular heart disease, myocarditis and other cardiomyopathies, demonstrated by normal echocardiographic and delayed gadolinium-enhanced cardiac MRI; no detectable coronary artery disease on coronary angiography, with or without ventriculography; no significant alterations on exercise testing (including QTc posture test); and no known electrophysiological disorders, namely long or SQTS, BrS, CPVT, ventricular pre-excitation syndrome or ERS, shown in ECG, Holter or telemetry monitoring. It should be noted, however, that in patients <45 years with a low risk for coronary artery disease, coronary computed tomography (CT) or MR angiography is a valid alternative for coronary angiography, because the sensitivity, specificity, and especially the negative predictive value are all high.[51,52] In fact, if coronary CT or MR are normal, coronary angiography is deemed not necessary.[16] Of course, routine testing should also comprise blood chemistry, with cardiac enzymes and thyroid function, and chest radiograph.[3,16,19,50] These screening exams are able to exclude the most common causes of VF. If no diagnosis is achieved, the mandatory additional diagnostic tests are: pharmacologic testing with infusion of a sodium-channel blocker (ajmaline, flecainide, procainamide or pilsicainide) to exclude BrS; catecholamine infusion (isoprenaline and adrenaline) to exclude CPVT, ARVC/D and LQTS; and ergonovine or acetylcholine provocation to exclude coronary artery spasm.[16,53] Optional additional diagnostic tests are endomyocardial biopsy and electrophysiological testing. In daily practice, the option of additional testing often provokes discussion, because the diagnostic value of some additional tests is debatable.[16] Recent data show, however, that the use of high-density electrophysiologic mapping may ultimately offer subclinical diagnoses of cardiac disease in about 90% of individuals with IVF.[49,53] Electrocardiographic imaging (ECGI) is an emerging high-resolution non-invasive imaging modality for mapping the electrical activity in the heart.[54,55] In healthy individuals, ECGI demonstrated that dispersion is small, namely for repolarization[56] However, ECGI did show increased dispersion in several arrhythmogenic diseases. ECGI can, therefore, play a pivotal role in characterizing arrhythmia mechanisms in patients with IVF, leading to diagnosis and treatment improvement. In addition, it seems to have the potential to detect arrhythmogenic substrate in individuals before their first event, offering the possibility of diagnosing and treating patients before SCA occurs. This is especially relevant in family members of victims of SCD who might have a predisposition for IVF.[56]

The yield of genetic testing in IVF is interesting, and it has definitely contributed immensely to the detection of primary arrhythmia syndromes. However, even with next generation sequencing, which screens large gene panels at once, its performance remains suboptimal and variants of uncertain significance (VUS) are often detected.[44] Therefore, a clinical suspicion, based on phenotype, should guide genetic testing.[16,19,56,57] Although targeted genetic testing has been reported to find causative mutations in up to almost 50% of cases of apparently unexplained SCA,[28] genetic screening for a large panel of genes in IVF patients is not currently recommended.[18,57] Yet, other authors[16] recommend genetic screening in otherwise assumed IVF patients with a basic panel of *SCN5A* and the most common LQTS genes (*KCNQ1* and *KCNH2*), as 50% of patients with BrS who present with SCA have a concealed phenotype, and ≈25% of genotype-positive LQTS patients have a normal QT-interval.[16,58,59] If a patient presents with exercise- or emotion-induced VF, the same authors recommend additional screening of RyR2 and *CALM1*. As conceivable, the yield of genetic testing seems to be higher if a family history of SCD at a young age is present.[50,57]

Screening of first-degree relatives of an unexplained SCA is essential and recommended, and several studies have shown its clinical relevance. Steinberg et al[27] reported cardiac abnormalities in 17–30% of a large population of 398 first-degree family members of unexplained SCA. In addition to enabling early, specific management in case of identification of a clear phenotype in relatives, family screening also has the potential to improve rates of etiological diagnosis among index cases.[23,27] These screening tests should include resting ECG, exercise testing and echocardiography. In selected cases, Holter, signal-averaged ECGs, MRI and pharmacologic testing may be performed.[53]

3 - Possible etiopathogenic conditions

3.1- Mitral valve prolapse

Another entity subliminally related to VTs and SCD is mitral valve prolapse (MVP). In general, MVP has a low prevalence in the pathology series of SCD.[60] The estimated occurrence of SCD in patients with MVP is as low as 0.2% to 0.4% per year.[61] It has also recently been showed that only a small proportion of competitive athletes with MVP develop adverse cardiovascular events (0.5% per year).[62] The worst prognosis is reported in those who have both regurgitation, with volume overload of the left ventricle (LV), and VTs, demanding a cautious restriction of competitive sports.[63-66] Noteworthy, SCD in MVP patients usually occurs while at rest or during sleep.[67] However, an association between even hemodynamically uncomplicated MVP and arrhythmic SCD was reported. In 1980, Lichstein[68] found that the most common site of origin of ventricular ectopy was the posterobasal portion of the LV. In 2013, in a study including survivors of OHCA with bileaflet MVP, Sriram et al[69] noted a

premature ventricular beat (PVB) configuration of outflow tract origin, mainly from the LV, alternating with papillary muscle (PM) or fascicular origin. The so-called “arrhythmic MVP” syndrome is, electrocardiographly, characterized by complex PVBs arising from one or both PMs, fascicular tissue, mitral annulus and LV outflow tract, as well as by T-wave inversion in the inferolateral leads.[67,69] Among the MVP-unrelated factors, ventricular repolarization abnormalities and a prolonged QT interval (ranging from 9% to 26%) have also been suggested in arrhythmic MVP patients.[61] Basso C. et al[67,70,71] first provided convincing evidence of a structural myocardial substrate of electrical instability, under the form of fibrosis in the LV myocardium closely linked to the mitral valve. It is unlikely that arrhythmic MVP patients with LV myocardial fibrosis have a coincident, unrelated IVF with Purkinje triggers amenable to ablation.[72] The consistent localization of PVB foci and abnormal tissue with slow conduction to the vicinity of the subvalvular mitral apparatus indeed suggests a structural association. Presumably, the heterogeneity of the tissue on these regions and its unique electrophysiologic properties are a primary abnormality, and the excessive motion and stretch with consequent scarring represent the secondary anomaly.[73] The genesis of malignant arrhythmias in MVP probably recognizes the combination of the substrate (regional myocardial hypertrophy and fibrosis and their relation with Purkinje fibers) and the trigger (mechanical stretch) because of primary morphofunctional abnormalities of the mitral annulus.[67,74,75]

3.2- Genetics

Genetic testing allows identification of a likely causative mutation in up to 32% of unexplained sudden deaths in children and young adults.[76-79] A genetic origin of IVF has also been hypothesized,[5] as several familial cases of IVF have been reported, suggesting that a subset of IVF is hereditary. However, the genetic background of IVF is likely heterogeneous and of polygenic nature.[5,16,80] Besides, its manifestation might be multifactorial, requiring discrete subclinical abnormalities, for example mild electrolyte disturbances, namely hypokalemia, or small areas of fibrotic myocardial tissue, which are currently undetectable with the available diagnostic modalities.[16] Moreover, a subset of patients originally diagnosed with IVF may carry clinically relevant genetic variants associated with inherited arrhythmogenic diseases.[5,80]

Compared to other arrhythmogenic diseases, there have been relatively few studies focusing on the genetic landscape of IVF,[16] not only because of the complexity and cost of the techniques but also because it is not routinely recommended in the 2013 European Heart Rhythm Society Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society expert consensus statement.[18] Previous studies have shown that the yield of genetic testing, particularly under the form of the so-called molecular autopsy, in IVF, although highly variable, is about 9%.[24,81] However, most of these studies have screened small gene panels, of a

maximum of 10 genes. Extensive genetic screening with whole exome or genome sequencing has identified several monogenic causes of IVF.[12,82,83] These include the well-established Dutch founder haplotype in the DPP6 gene[12] and SEMA3A,[84] identified in a Dutch family and in a Japanese cohort, respectively, as well as the newly-identified CALM1.[85] Other genes have been linked to IVF, including a loss of function variant in RYR2,[82,86] which causes VF at rest,[82] and IRX3,[83] which is associated with short-coupled *torsades des pointes*.[12,82,83,85]

Recently, Leinonen et al[5] provided the first evidence of a clearly quantifiable contribution by identifiable genetic cardiac disorders to the occurrence of IVF. Using whole-exome sequencing and next-generation sequencing approaches, pathogenic or likely pathogenic variants residing in RYR2, CACNA1C, and DSP genes were found in 9% of IVF patients. Most of them (71%) were found in the RYR2 gene, associated with CPVT. These genetic findings prompted a renewed clinical assessment of patients, causing disease reclassification. Additionally, in 9 patients (11.8%), 10 novel or extremely rare variants that were classified as of unknown significance were detected. Patients carrying pathogenic and likely pathogenic variants were generally younger at the time of the VF incident in comparison to the remaining patients (19.9±19.5 SD vs 32.4 ± 12.7 SD years, P=0.01).

In another report,[40] genetic testing screening at baseline or during follow-up period was done in 26% of patients diagnosed with IVF. One was diagnosed with LQTS type 2 after a positive genetic yield (KCNH2 mutation). A broad panel for channelopathies and cardiomyopathies were done in 12 subjects (24%); 2 out of 12 patients (16.7%) had ARVC/D with PKP2 gene positive and LMNA gene positive. VUS in potential disease-related genes were found in 8 cases (66.7%) although, according to American College of Medical Genetics and Genomics guidelines, these were not considered pathogenic. Though a small proportion underwent genetic screening, it did confirm pathogenic mutations in three cases, which shows a modest diagnostic yield for commonly known genetic variations for channelopathies and cardiomyopathies (23.1%), in keeping with a recent study by Broendberg et al,[87] in which the diagnostic yield for disease causing mutation was 24% (n=19/80).

In a long-term outcome of a pediatric cohort with an initial diagnosis of IVF,[34] 45 patients (83%) underwent genetic testing. A potential pathogenic mutation for inherited arrhythmia syndromes was identified in a third of the patients, namely RYR2 [n=7], TRDN [n=2], CALM1 [n=1], CASQ2 [n=1], SCN5A [n=1], KCNH2 [n=1], MYH7 [n=1] and SLC22A5 [n=1]. Variants in RYR2 were identified in close to half of the genotype-positive patients. Repeat genetic sequencing with an extended genetic panel was performed in 54% of the population at the discretion of the treating physician. One patient (2%) developed phenotypic evidence of hypertrophic cardiomyopathy (HCM) during follow-up. Of note, that patient had previously been identified as a MYH7 variant carrier. Consistent with these finding, Lahrouchi et al[88] reported that, in patients with sudden arrhythmic death syndrome, RYR2 variants were the most

commonly identified pathogenic/likely pathogenic variants following postmortem genetic testing (43% of genotype-positive cases). On the other hand, in a study by Visser and colleagues,[41] in which a large panel of 33 genes associated with SCD was screened in 79 patients, the overall yield for genetic testing was lower, at 15%, with only a quarter of genotype-positive patients harboring CPVT gene variants. Of note, patients included in Frontera's study,[34] as in that of Lahrouchi et al,[88] were significantly younger than the patients included by Visser et al.[41] It is important to acknowledge, however, that a significant proportion of apparently pathogenic RYR2 variants may not be disease causing.[34] About Visser and colleagues' study,[41] of the 12 detected pathogenic mutations, 4 were diagnostic, as the mutation revealed a specific diagnosis (CVPT in 3 patients and LQTS type 1 in 1 patient), 4 mutations were detected in arrhythmogenic cardiomyopathy patients, 3 patients carried the Dutch DPP6 haplotype and 1 patient revealed a MYL2 mutation, with a corresponding HCM phenotype. Variants of uncertain clinical significance were detected in 13 IVF patients. Genetic family screening was performed in 33 family members of the 12 patients with a pathogenic mutation and identified 12 mutation carriers. As a result, the yield of family screening was 36%, enabling prophylactic treatment in 58% of mutation carriers. However, only 4 diagnostic mutations were detected, and next-generation sequencing concurrently disclosed 13 variants of uncertain clinical significance.

In another study, Visser et. al.[44] described the findings of the extended next generation sequencing panel of 179 genes in 33 IVF survivors and report a yield of only one pathogenic or likely pathogenic variant: a truncating variant in the titin (TTN) gene, seen in a single patient. Whilst, at first glance, their findings portray a negative message regarding the utility of genetic testing in IVF, it must be noted that these 33 patients were a sub-selection of a larger cohort of apparent IVF survivors in whom previous genetic testing had already proven negative. Besides, of the 179 genes included in second-line testing, only a small number have been reliably associated with either IVF or with established phenotypes that carry a risk of VF; variants in sarcomeric genes MYBPC3, MYH7, TNNI3 and TNNT2 are recognized causes of HCM, while truncating variants in TTN are seen in cases of dilated cardiomyopathy (DCM) and peri-partum cardiomyopathy. One or more VUS was identified in 24% of patients with the initial 33-gene panel, which increased to 34% overall with the extended panel.

Alders et al.[12] performed a genome-wide haplotype sharing analysis to identify the responsible gene for IVF in 3 distantly related families from the Netherlands. The authors identified a mutation located on the chromosome 7q36 harboring a part of the dipeptidyl peptidase-like protein-6 (DPP6) gene, which encodes for a component of the transient outward potassium current (Ito). The correlation between the DPP6 mutation and IVF was confirmed in a larger population of 26 families, including 601 members, from the Netherlands. The mutation increased levels of the DPP6 mRNA 20-fold compared to controls. Penetrance of IVF was

high: 50% of risk-haplotype carriers experienced (aborted) SCD before 58 years of age. Posteriorly, Xiao et al.[89] demonstrated that DPP6 overexpression selectively increases the Ito current in the Purkinje fibers, leading to abnormal depolarization and early repolarization (ER), which may explain at least part of the pathogenesis of VF in this particular subgroup of patients. These results provide a potential rationale for the efficacy of quinidine, an Ito blocker, in IVF patients. In 2015, Sturm et al[90] identified the first missense mutation (p.H332R) of DPP6 in a proband with recurrent IVF. Yet, this variant was also rather frequently (0.5%) occurring in a control population without that specific phenotype, resulting in a challenging identification of supposedly pathogenic variants.[91] Ding et al[92] employed whole-exome sequencing in combination with arrhythmia-related gene-filtering to explore the possible causative gene for a chinese family with SCD, syncope and suspicious IVF. A second missense mutation (c.1578G>C/p.Q526H) of DPP6 was identified and co-segregated with affected patients in this family. This novel mutation (c.1578G>C/p.Q526H) is located in the cysteine-rich domain, which is responsible for ER-to-Membrane transport. This study is consistent with Sturm et al[90] research, confirming that both mutations may lead to gain of function of Kv4.3 and result in IVF due to a disturbance of the efflux of potassium ion. At present, ten DPP6 mutations have been identified in patients with different disease phenotypes.[44]

Among genes coding ion channels and their modulatory proteins, KCNE5 (KCNE1L) is located in the X chromosome and encodes an auxiliary β-subunit for K channels. KCNE5 has also been shown to modify the Ito. In 205 Japanese patients[93] with BrS or IVF who tested negative for SCN5A mutation, 2 novel KCNE5 variants were identified from 4 unrelated families: the variant p.Y81H was a single-nucleotide alternation (c.241T>C), resulting in an aminoacid substitution from a tyrosine at residue 81 with a histidine (p.Y81H). The second variant had 2 nucleotide changes (c.[276C>A and 277G>T]), causing an aminoacid substitution from an aspartate at residue 92 to a glutamate and from a glutamate at residue 93 to a stop codon (p.[D92E;E93X]). Functional consequences of the KCNE5 variants were determined through biophysical assay using cotransfection with KCND3 or KCNQ1. In the experiments with KCND3, which encodes Kv4.3, Ito was significantly increased for both KCNE5 variants, compared with wild-type, thus documenting increased VF risk. In contrast, there was no significant change in current properties with KCNQ1 cotransfection for neither wild-type KCNE5 nor the 2 variants. With a simulation model, both variants demonstrated notch-and-dome or loss-of-dome patterns. Given that KCNE5 is located in the X chromosome, the upregulation of Ito currents may occur preferentially in male and so male sex would be anticipated to have more lethal phenotypes than the female sex.

Paech et al[37] identified 2 novel, functional heterozygous mutations - c.6224T>C (p.Ile2075Thr, Exon 41) and c.13781A>G (p.Lys4594Arg, Exon 94) - on the RyR2 gene, in a family with at least 10 members who died or were resuscitated due to VF, with the most

probable diagnosis being IVF. No clinically affected patient was without mutation. In principle, RyR2 gene mutations cause enhanced sensitivity of the sarcoplasmatic calcium channel to either luminal or cytosolic calcium levels, which occur, for example, at higher heart rates during exercise. This leads to calcium overload and establishes the basis for store overload-induced calcium release, with consequent delayed after-depolarizations and the potential for ventricular arrhythmias. A publication of Priori and Chen[94] reported RyR2 mutations in patients with IVF. Interestingly, in 2002, this working group classified all patients with RyR2 mutations as CPVT patients. Yet, by 2011, this classification was superannuated. The differentiation between CPVT and IVF remains a difficult issue, mainly based on clinical characteristics and gross genetic classification. In this case, the family history, exercise testing, and epinephrine stress testing do not suggest an association between arrhythmia and adrenergic triggers, which makes CPVT unlikely. It currently seems more reasonable to classify patients with different RyR2 mutations according to the functional effects of the mutation,[95] meaning that patients with RyR2 mutations but lacking induction of ventricular arrhythmias during exercise stress testing are rather classified as IVF, assuming a different arrhythmogenic mechanism. The authors couldn't conclude whether the reported mutations cause a new entity of IVF or whether these patients experience a variant of CPVT with an atypical clinical course.

Nakano and colleagues from 13 centers in Japan studied two populations with UCA and documented VF.[84] Guided by their previous results in mice studies,[96] they focused on SEMA3A as a candidate gene. This gene is vital for normal neuronal pattern development and has been implicated in various disease conditions. Interestingly, murine cardiac-specific SEMA3A under-expression results in sinus bradycardia, while SEMA3A over-expression in a susceptibility to VT and SCD, putatively due to differences in the pattern of cardiac innervation.[96] In their study,[84] through resequencing and single nucleotide polymorphism genotyping of SEMA3A, it was found that a non-synonymous polymorphism (I334V, rs138694505A.G) in exon 10 of the SEMA3A gene was associated with UCA, with an odds ratio of 3.1 (95%CI 1.7–5.7). UCA patients with SEMA3AI334V also displayed slightly different autonomic nervous system control, apparently as a result of a higher incidence of sinus bradycardia. In fact, subsequent *in vivo* studies using cardiac biopsies revealed that UCA patients with SEMA3AI334V display aberrant sympathetic nerve fiber growth. Furthermore, *in vitro* studies using transfected HEK293T cells revealed that the I334V aminoacid replacement in SEMA3A indeed disrupts the normal function of the protein in neural growth inhibition and control of cardiac innervation.[84]

Calmodulin (CALM) association with the cardiac muscle RyR2 regulates excitation–contraction coupling.[97] Defective CALM–RyR2 interaction is associated with heart failure.[97] In addition, recent genetic studies have identified 5 missense CALM mutations associated with severe ventricular arrhythmia and SCD susceptibility.[98,99] 2 CALM mutations were associated

with stress-induced polymorphic VT reminiscent of CPVT (CPVT-CALM),[98] whereas the other 3 mutations led to recurrent cardiac arrest in infancy associated with severe QT prolongation reminiscent of a LQTS. Another recent study[85] has reported a novel CALM mutation (Phe90Leu;CaMF90L) as the causative missense genetic defect in a family with IVF and early onset SCD (childhood and adolescence). The mutation was present in 2 family members who displayed a marginally prolonged QT-interval during exercise. It is suggested that this mutation fallouts in altered Ca2+ binding, which leads to reduced ability to interact with the RyR2, thus producing dysregulated Ca2+ release.[85,97] This is compatible with [3H]ryanodine binding studies, which suggest that CALMF90L loses its ability to inhibit the RyR2 channel at a specific range of Ca2+ concentrations. These observations imply that CALMF90L may cause IVF due to a defective interaction with RyR2, leading to dysregulated SR Ca2+ release.[85,97]

ANK2 mutations have been reported[100] as the cause of various inherited primary arrhythmia syndromes, including LQTS type 4, SQTS, BrS, CPVT and IVF. ANK2 encodes ankyrin-B, which is a form of a membrane protein complex with some ion transporters in cardiomyocytes. So, the authors[101] state that ankyrin-B syndrome should also be considered as a differential diagnosis of IVF, as their investigation indicates that ANK2 mutations may play a role as an “accessory mutation”, as well as a causative mutation.

An Australian family with marked cardiac phenotype heterogeneity among 4 individuals was studied:[102] While some were asymptomatic, other presentations included left ventricular non-compaction, resuscitated cardiac arrest due to IVF, DCM and sudden unexplained death. In the absence of a unified clinical diagnosis, whole-exome sequencing was performed, identifying an Ala119Thr mutation in the alpha-actinin-2 (ACTN2) gene that segregated with disease. The variant affects an aminoacid in the highly conserved actin-binding CH1 domain. The diverse clinical phenotypes seen in this family, including IVF, suggest that mutations in the ACTN2 gene likely perturb a number of different mechanical and arrhythmogenic substrates. Haplotype analysis showed that this mutation segregated with the same unique haplotype in a second family also with clinically diverse cardiac disease, being likely inherited from a common ancestor. The spectrum of clinical presentations and outcomes is remarkably similar in both families. Indeed, there have been two SCDs in young people (aged under 35 years), one where HCM was identified and one in which no cause was detected at post-mortem. While phenotypic heterogeneity and incomplete penetrance are common features of inherited cardiac diseases, it is unclear how divergent cardiac phenotypes emerge from the same mutation. This paradigm is, indeed, exemplified by the structural and arrhythmogenic pathologies potentially caused by the Ala119Thr mutation in ACTN2.

Genetic screenings of Japanese IVF patients were performed and found a novel SCN5A missense mutation (S1710L) in one symptomatic IVF patient that did not exhibit the typical Brugada ECG.[103] Heterologously expressed S1710L channels showed marked

acceleration in the current decay, together with a large hyperpolarizing shift of steady-state inactivation and depolarizing shift of activation. However, enhanced inactivation due to accelerated current decay is not a unique feature specifically observed for S1710L. Similar channel property was observed in BrS mutation T1620M, although only at higher temperature, and was regarded as one of the relevant mechanisms for ST elevation. It has been a matter of controversy whether this IVF subgroup is a phenotypic variation of the BrS or a distinct disease, because ECGs of BrS patients are profoundly affected by an autonomic nervous system tone and exhibit time-dependent changes with occasional normalization. This finding has genetic relevance, indicating that BrS and this IVF subgroup are, at least, genetically overlapped, such as with other allelic disorders of the SCN5A gene, like LQT3 and hereditary AV block.

Loss-of-function mutations in the SCN5A-encoded sodium channel SCN5A or Nav1.5 have been identified in IVF, in the absence of BrS phenotype.[104] Nav1.5 is regulated by 4 sodium channel auxiliary b subunits. A novel missense mutation, Navb3-V54G, caused loss of the Navb3 function and a reduction in INa, possibly by interfering with the chaperone and cell membrane localization functions of the Navb3 subunit. This mutation was identified in a 20-year-old male diagnosed with IVF, whose ECG exhibited epsilon waves, despite presenting a structurally normal heart. The mutated residue was highly conserved across species, localized to the Navb3 extracellular domain, and absent in 800 reference alleles. It was found that HEK-293 cells had endogenous Navb3, but COS cells did not. Co-expression of Nav1.5 with Navb3-V54G (with or without co-expression of the Navb1 subunit) in both HEK-293 cells and COS cells revealed a significant decrease in peak sodium current and a positive shift of inactivation compared with WT. Co-immunoprecipitation experiments showed association of Navb3 with Nav1.5 and immunocytochemistry demonstrated a dramatic decrease in trafficking to the plasma membrane when co-expressed with mutant Navb3-V54G. Interestingly, the boy's mother was an asymptomatic gene-mutation carrier and exhibited J-point elevation (JPE) in her ECG. These findings support that the SCN3B-encoded Navb3 subunit interacts with SCN5A subunits, creating a loss-of-function phenotype, and that SCN3B may be a novel IVF-susceptibility gene. A possible overlap of BrS and IVF, previously reported,[92] and even an association with ER may, therefore, extend to the molecular level.

Familial ER has also been reported and, apparently, it displays an autosomal dominant inheritance pattern with incomplete penetrance.[42] Two independent population-based studies have suggested some degree of inheritance of the ERPs in the general population,[105] but the familial inheritance of malignant ERPs has not been clearly demonstrated. A candidate gene approach in IVF patients with ER has identified several possibilities. Gain-of-function mutations in *KCNJ8*, which encodes a pore-forming subunit of the ATP-sensitive potassium channel, leading to shortening of action potential duration (APD), has been identified in IVF with

ER.[104,106] Decreased calcium currents also have been proposed as a mechanism for IVF associated with ER; Particularly, mutations in L-type calcium channel genes, including *CACNA1C*, *CACNB2B*, and *CACNA2D1,* have recently been identified.[107] However, functional studies are not yet available.[107] Moreover, other 3 missense mutations of *SCN5A* (A226D, R367H, and L846R) were identified in 3 out of 26 IVF patients.[108] These variants affect highly conserved residues, and all of the mutant SCN5A channels failed to generate any currents when expressed in heterologous expression systems. R367H and L846R are thought to be located in the pore region, and were not found in the genomes of 200 healthy control individuals. Immunostaining revealed that cells expressing A226D channels showed cytoplasmic fluorescence, while cells expressing wild-type channels showed marked peripheral fluorescence, suggesting that the mutation results in trafficking defect. On the other hand, cells expressing R367H channels and those expressing L846R channels showed a similar fluorescence pattern to wild-type channels, suggesting that these mutations do not affect trafficking. The 3 unrelated probands shared similar clinical phenotypes: multiple episodes of syncope; prolongation of the PR interval; sodium channel blocker administration not inducing a type I Brugada ECG pattern; ERP mainly located in inferior leads; prolonged His-ventricular interval (55ms, 65ms, 68ms). Facing this evidence, the authors concluded that loss of sodium channel function plays a role in IVF associated with ER, and that *SCN5A* is a causative gene of this particular entity.

All supra-mentioned pathogenic or likely pathogenic genes are summarized in table 2.

Gene	Protein	Genetic Incident	Comments
ACTN2	Alpha-actinin-2	Ala119Thr	Identified in an Australian IVF-family with marked cardiac phenotype heterogeneity [102]
ANK2	Ankyrin-B	NM_020977.3	Associated with various inherited primary arrhythmia syndromes, including LQTS type 4, SQTS, BrS, CPVT and IVF[100,101]
CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C	F30:p.Gly402Ser	Related with LQTS and IVF with ER;[5,107]
CACNB2B	Beta subunit of voltage-dependent calcium channels	-	Related with LQTS and IVF with ER;[5,107]
CACNA2D1	Alpha-2/delta subunit of voltage-dependent calcium channels	-	Related with LQTS and IVF with ER;[5,107]
CALM1	Calmodulin 1	CALMF90L	Frequently associated with CPVT and LQTS;[85] Screening recommended in exercise- or emotion-induced VF. [34,85,97,98,99]
CASQ2	Calsequestrin 2	Deletion of exon 1	SCD during sleep. [34]
DPP6	Dipeptidyl Peptidase Like 6	At present, ten DPP6 mutations have been identified.[44] p.H332R[90] c.1578G>C/p.Q526H[92]	Overexpression selectively increases the Ito current in the Purkinje fibers, leading to abnormal depolarization and ER;[89] Well-established haplotype for IVF; [12,41,44,89,90,91,92] with a 50% penetrance;[12] In the central part of the Netherlands and in families originating from the Gouda region, screening is recommended, as the DPP6 haplotype accounts for over 25% of IVF cases in this area;[91] Also associated with scTdP in Dutch Patients.[91]
DSP	Desmoplakin	I12:p.Gln620	May cause several cardiomyopathies and keratodermas, including skin fragility-woolly hair syndrome.[5] One Italian patient from Leinonen cohort[5] carried a pathogenic nonsense mutation, resulting in clear changes in cardiac electrophysiology, but without definite clinical manifestations typical for DSP-associated cardiomyopathies. This Italian cohort contained 3 other carriers of rare variants in DSP, classified as VUS.
IRX3	Iroquois-class homeodomain protein	1262G>C (R421P) 1453C>A (P485T)	Associated with scTdP and physical activity; Functional perturbation in the His-Purkinje system.[83]
KCNE5	Potassium voltage-gated channel subfamily E regulatory beta subunit 5	p.Y81H c.241T>C c.276C>A 277G>T	Gain-of-function effects on Ito [93]
KCNH2	Potassium Voltage-Gated Channel Subfamily H Member 2	-	May initially manifest as VF, even though in most cases an underlying electrical disease is later identified, namely LQTS2. [19,22,34,40]
KCNJ8	Potassium Inwardly Rectifying Channel Subfamily J Member 8	-	Gain-of-function mutation associated with ER[104,106]
LMNA	Lamin A/C	-	Associated with ARVC/D and DCM[40]
MYH7	β-myosin heavy chain	-	Associated with HCM[34]

PKP2	Plakophilin 2	-	Associated with ARVC/D[40]
RYR2	Ryanodine receptor 2	c.6224T>C[10] c.13781A>G[10]	Often identified in genotype-positive patients; [34,37,82,86,88,94,95] Frequently associated with CVPT;[5,20,34] A significant proportion of variants may not be disease causing;[34] If IVF exercise- or emotion-induced, screening is recommended.[16]
SCN3B	Sodium Voltage-Gated Channel Beta Subunit 3	-	May be a novel IVF-susceptibility gene[104]
SCN5A	Sodium voltage-gated channel alpha subunit 5	A226D[108] R367H,[108] L846R,[108] S1710L[103] Navb3-V54G[104] 5432-5433insGAGT, identified in IVF-CRBBB.[142]	Frequently associated with BrS; Loss-of-function mutations have been identified in IVF, with or without ER [34,103,104,108,142]
SEMA3A	Semaphorin-3A	I334V, rs138694505A.G	Non-synonymous polymorphism identified in a Japanese cohort; Over-expression may be associated with IVF[84]
SLC22A5	Solute Carrier Family 22 Member 5	-	Identified in a pediatric cohort [34]
TRDN	Triadin	-	Identified in a pediatric cohort [34]
TTN	Titin	c.52198G>T p.E17400	Truncating variant; Associated with DCM and peripartum cardiomyopathy[44]

Table 2 – Pathogenic or likely pathogenic genes reported in IVF or presumable IVF patients.
ARVC/D - arrhythmogenic right ventricular cardiomyopathy/dysplasia; BrS-Brugada syndrome; CPVT- catecholaminergic polymorphic ventricular tachycardia; DCM-dilated cardiomyopathy; ER-early repolarization; HCM-hypertrophic cardiomyopathy; Ito- transient outward potassium current; IVF-idiopathic ventricular fibrillation; LQTS-long QT syndrome; scTdP-short-coupled *torsades des pointes;* SQTS-short-QT syndrome; SCD-sudden cardiac death; VUS-variants of uncertain significance; VF-ventricular fibrillation;

3.3 - Microstructural myocardial substrate

In high-resolution experimental setups, typical VF requires a continuous reentry for its maintenance, of which a critical determinant is the presence of normal (fiber arrangement) vs. abnormal (fibrosis) structural heterogeneities.[53] Because patients with IVF are deemed to be free of structural heart disease, one might have expected that VF reentries would be distributed homogeneously across both ventricles. However, a clustering of reentries was observed, and mapping of these regions in sinus rhythm revealed, in some of them, abnormal electrogram characteristics, indicating the presence of a “microstructural” cardiomyopathic alteration. In a study[53] involving electrophysiological analysis, myocardial areas manifesting low-amplitude and prolonged fractionated signals were found in 67% of patients. The abnormal tissue was found to be clustered in 1 or 2 areas, whereas 4 patients had scattered abnormal areas. In a previous study, the abnormal surface area covered a mean of 13±5cm^2, ranging from 6 to 22cm^2, representing 3.9±1.7% of the total ventricular surface. This finding is in keeping with prior experimental studies, which showed that even small ventricular lesions in the range of 4 cm^2 are sufficient to promote VF. The right ventricle was the structure preferentially harboring the abnormal area, whereas the LV or the septum were less frequently affected. The comparison of endocardial and epicardial recordings at the same location showed that these abnormal signals were recorded in only one side, mostly epicardial, indicating that the pathology involved a part of the ventricular wall rather than being transmural, which may explain why these abnormalities tend to be unperceived by MRI. Among all abnormal areas, 86% colocalized within or at the border of a main driver region, what indicates that the mechanism of VF is, indeed, linked to microstructural alterations acting as a substrate maintaining reentry, in the same way as overt pathological heterogeneities maintain VF in structural heart diseases. A phenotypic screening performed in 48 consecutive patients referred for IVF unveiled that: 23% presented a Purkinje abnormality without a microstructural myocardial abnormality; 67% showed microstructural myocardial abnormalities, with 10.4% also displaying Purkinje triggers; 5 patients had neither apparent Purkinje nor microstructural abnormalities. Therefore, only 10% of IVF remained completely unexplained after comprehensive investigations. In these cases, unexplained SCD may result from an external ephemeris factor (as fever, vagal burst, hypokalemia, etc), considered necessary to reach a critical arrhythmogenic threshold, or concealed causes, such as LQTS, which may become detectable during follow-up or by genetic testing. It is likely that both common and distinct nosological processes are involved in these different substrates and that a spectrum of different diseases, such as genetic, inflammatory, or acquired cardiomyopathies, can affect them.

3.4 - Early repolarization and J Wave

The detection of a J-wave has been considered an innocuous finding and even a normal variant.[36,49,104] Epidemiologic studies have detected this variant in 1–24% of the general population.[7,49,109,110] However, the introduction of a new clinical entity, ERS, and the subsequent demonstration of the importance of the J wave in survivors of SCD, being present in 23 to 60% in IVF cases worldwide,[6,7,111,112] have generated renewed interest in the ECG J waves. ERS is one of the so-called J wave syndromes, together with BrS and with other particular situations, namely hypothermia, acute myocardial ischemia, silent coronary artery disease, inflammatory diseases, such as pericarditis, electrolyte or metabolite disorders, such as hypercalcemia, and drug intoxications, such as with cocaine or with antidepressants.[113] J-wave syndromes are defined as a distinct electrocardiographic phenotype (slurring/notch) affecting the junction between the QRS complex and the ST segment. Recent data provide evidence for heterogeneous substrates, related to either delayed depolarization due to microstructural alterations or real ER abnormalities.[53] Nonetheless, all this highlights the possibility that J waves may be more important than previously recognized and may serve as a common mechanism of VF in various clinical settings.[9]

J waves are commonly observed in healthy individuals, predominantly in young males,[114,115] mimicking BrS epidemiology, and especially among athletes (in up to 36%),[109-111] and particularly in those involved in competitive sports and in young black subjects.[111] As for athletes, Cappato et al.[116] reviewed the ECG of 21 athletes with cardiac arrest or sudden death obtained before or immediately after the event and found a J wave and/or QRS slurring in any lead in 28.6% of cases and in 7.6% of control athletes (p=0.006). However, arrhythmia recurrence did not differ in the group with cardiac arrest between those with and those without the ECG pattern. ERP was present in 10 of 21 competitive athletes who suffered a cardiac arrest (47%) as compared with 108 of 365 control healthy athletes (29,6%). ERP was also found in 25 of 54 (46%) professional soccer players who had a significantly lower heart rate and higher left atrial filling pressure.[117] The ERP was located in the precordial leads only in 18 athletes (33%), whereas in 7 athletes (13%) the ERP was also present in the inferior leads. On the other hand, J wave prevalence was also demonstrated to be race-dependent, being more common in black patients.[114] In addition, heritability of ER has been shown in a population-based study,[105] and, as in other arrhythmia syndromes, such as LQTS and BrS syndrome, ion channel genes are responsible for IVF associated with ER.[104,106-108] On the one hand, a family history of SCD is reported in 18% of ER patients.[118] On the other hand, an increased rate of ER in first-degree relatives of SCD patients compared with matched healthy controls has been demonstrated.[111] In that particular study,[111] 33 patients and 72 first-degree relatives were screened. Out of these 33 patients, 55% had ER, and ER was seen in 19.4% out of the 72 family members. ER in a relative was more common if the proband had a

persistent ERP (OR 10.7, 95% CI 2.2–51.5; P = 0.003). The ERP in the relatives was of the same pattern to that of the proband. It was also more common than that in first-degree relatives in a healthy control population (OR 2.0, 95% CI 1.04–4.0; P = 0.038). These findings thereby raise a possibility of familial inheritance of ER when this is persistent in nature, what is important as it will enable linkage analysis to be performed. This information could potentially be used to guide family screening and identify new mutations using family members with persistent ER.

The association between J waves and IVF was first described by Haïssaguerre et al.,[7] who showed that they were more frequently recognized in patients with IVF than in matched healthy control subjects (as many as 1 out of 3 IVF patients demonstrated J waves and ST-segment elevation) and that there was a higher (two-fold) incidence of recurrent VF and even electrical storm in case subjects with ER than in those without. Indeed, patients with "IVF and ER" seemed to have a worse (rather than a different) form of IVF.[115] Their findings were confirmed by numerous authors, namely Nam et al.[119] and Rosso et al.,[111] as well as, later on, Aizawa et al.[38,120] Moreover, Siebermair et al.[49] demonstrated a significant association of ERP with appropriate ICD therapies during long-term follow-up, where ERP conferred an almost four-fold increased risk. These observations were, finally, re-enforced by reports underlining that the ERP may be associated with an increased mortality risk even in the general population.[109,110] As it seems, the Haissaguerre et al. study[7] triggered a "fear of J waves."

ERP should be differentiated from ERS, which is diagnosed in patients with unexplained VF or polymorphic VT and documented ER, or in SCD victims with a negative autopsy and a previous ECG demonstrating ER.[18] Until recently, ERS was regarded as a subentity of IVF. However, ERS has a distinctive phenotype and has shown to have a separate genetic substrate, as several candidate genes for a familial inheritance of a malign ERP have been identified.[107,121] Therefore, ERS is considered a separate disease entity, being distinct from IVF. This concept more famously came to light with the release of the 2013 consensus statement on the primary arrhythmia syndromes.[18] If a patient shows ER that does not fulfill diagnostic criteria, then these abnormalities are not explanatory and the diagnosis IVF remains.[16]

J waves may exhibit dynamic changes, occurring in IVF and being closely related to VF occurrence.[7,38,111,119] In fact, augmentation of the J-wave amplitude is common before VF occurrence. This finding is similar to prominent right precordial ST elevation just before VF episodes that occurs in patients with BrS.[112,122,123] In addition to this augmentation before VF occurrence, J waves may show transient nature.[38,40] Actually, in 5 of 40 patients with aborted SCD, J waves disappeared spontaneously within weeks.[38,120] This dynamicity of J waves has also been studied experimentally and may even reach a beat-to-beat variation standard.[122]

J waves were well reproduced in animal studies, and Ito expressed predominantly in the epicardial myocardium were shown to be their cellular and ionic basis, as well as the mechanism backing arrhythmogenic potential.[122] When Ito was inhibited by 4AP or quinidine, the phase 1 notch of the action potential decreased, with the concomitant diminution of J waves. On the other hand, an augmentation of Ito is observed at slower rates and is considered to be the underlying mechanism of a pause-dependent augmentation of J waves.[124,122] Diverse antiarrhythmic drug therapy has been shown to impact this mechanism.[38,122,125] However, to date, no drug challenge test has proven utility to improve diagnosis or stratify the risk of arrhythmic events, as has been demonstrated in other primary electrical diseases (BrS and LQTS).[126] Likewise, factors for the genesis and dynamicity of J waves are still not fully understood. Besides, J waves may be observed in association with myocardial ischemia and J waves may appear preceding vasospasm and/or development of VF.[14,124] In a study,[127] among the 67 patients with proven coronary spasm, 20.9% revealed J waves in the baseline ECGs, and J waves were augmented (>0.1 mV) in 50% of patients during intracoronary acetylcholine administration. Furthermore, 4 of the 7 patients with J-wave augmentation developed VF. Among the remaining 53 patients without J waves at the baseline, J waves were newly induced by intracoronary acetylcholine in 5 patients (9.4%), but VF developed in none of 53 patients. On the other hand, hypothermia is known to result in ECG changes similar to ERP. In a retrospective cohort study,[128] therapeutic cooling significantly increased the prevalence and mean amplitude of ER in the overall VF cohort.

Risk seems to vary markedly with the degree of ER, quantified as the magnitude of JPE. Thus, patients with a JPE magnitude >0.2 mV are at about twice the risk of cardiac arrhythmic death as compared with those with JPE defined using a more conventional cut-off of ≥0.1 mV.1 Furthermore, patients with ER who have experienced an episode of IVF have a mean JPE magnitude of around twice that seen in those without arrhythmia.[7,36,111,128] In a study,[123] the J–RR slope (mm/s) was greater in patients with IVF than in controls (3.5±0.7 vs 2.4±0.8; $P<0.01$), just as was J-wave amplitude (mm), at an RR interval of 1.2 seconds (2.8±0.9 vs 2.0±0.6; $P<0.05$). In another study,[112] the J wave amplitude was significantly higher ($P<0.0001$), more significantly influenced by the autonomic tone and more closely associated with heart rate and with high frequency components (vagal activity index) on frequency-domain heart rate variability analysis in subjects with than without IVF. Inferolateral J wave elevation, present in between 1 and 9% of healthy adults,[123] as opposed to precordial J wave elevation, has since been identified in several studies as also a marker of arrhythmic risk in the general population as well as in those with cardiovascular disease.[7,53,109,111,112,118,119,122,126] Moreover, ER in the right precordial leads has also been associated with IVF.[108] Similarly, a more extensive J wave lead distribution seems to confer worse prognosis.[36,61] Besides, the combination of ER with a horizontal/descending ST segment was, likewise, strongly associated

with an increased risk of arrhythmic death.[42,129,130] Rosso et al.[130] reported that 68.4% of the 19 IVF patients with ER had horizontal/descending ST segments, which was also almost equal to Sekiguchi et al.[131] results (75%). Significant fluctuations of the J-wave over time, such as those recorded by Holter monitoring or triggered by abrupt RR changes, also seem to be associated with a higher risk of arrhythmic events.[126]

Patients with IVF and J waves also display other specific electrocardiographic findings: they tend to have QTc intervals in the lower normal range,[132,108,120] which fail to prolong adequately during heart rate slowing,[115] and, likewise, lower slopes of QT-RR and QaT-RR regression lines and impaired prolongation of QT and QaT at longer RR intervals;[133] a minority displays AV conduction disturbances;[14] most have a slower heart rate and longer PR intervals and QRS durations;[108,118,120] a minority presents initial QRS abnormalities resembling the classic delta-wave of Wolff–Parkinson–White (WPW) pattern, a so-called "pseudo" delta-wave.[134] In addition, the high rate of AF and ERP found by Siebermair et al. in IVF survivors might indicate an underlying heart disease or myocardial electrical disorder not apparent at the index event.[49]

As pointed out by Wellens cited in Lévy S. et al,[113] the combination of ERP with IVF is, even so, quite rare, whereas the ERP is common in the young healthy population. In asymptomatic subjects with the ERP but without familial history of sudden death, the prognostic significance of the ECG anomaly is still unclear. Thus, it is believed that, in a patient with this asymptomatic "isolated" ERP, caution should be observed not to generate unnecessary anxiety in informing the patient of the possible relation of the ECG pattern with SCD as the odds are extremely low. The risk of developing IVF in this situation has been calculated, by Rosso et al,[111] to be 1/10,000. We should, therefore, avoid the "fear of the J waves", as rightly pointed out by Viskin[115] and try to develop (preferably non-invasive) tools that might be helpful for risk stratification of subjects with asymptomatic "isolated" ERP. In that regard, and although desirable, a prospective multicentre study to determine the prognostic significance of the asymptomatic "isolated" ERP is difficult to perform because, as shown by Tikkanen et al.,[109] the survival curves in subjects with versus without the ERP start to diverge only after a 15-year follow-up. In addition, as the population becomes older, other causes may be responsible for total mortality and IVF becomes rare in the older age group. However, electrophysiologists may still be consulted about the arrhythmic-death risk after an incidental discovery of J waves. Unfortunately, they do not know yet how to distinguish "arrhythmogenic" from "normal" J waves, resulting in poor prediction of recurrence of malignant arrhythmias.[18,40] Since IVF is a rare disease, and there are no tests for confirming or excluding it in the asymptomatic patient, asymptomatic patients with J waves may not benefit from further testing.

3.5 - Sympathetic innervation

Cardiac innervation has been considered a predisposing arrhythmogenic factor.[135] Indeed, various authors have examined the role of cardiac innervation as a possible contributor to IVF, with a putative role of the sympathetic system as a trigger of VTs being suggested in different clinical settings, namely LQTS.[1,10,33,135]

In 1999, Schäfers et al.[136] first described presynaptic sympathetic innervation defects in 25 patients with IVF. In particular, the group reported significantly reduced segmental Iodine123-metaiodobenzylguanidine (123I-MIBG) uptake in IVF patients, and available evidence at that time suggested that lack of 123I-MIBG uptake in the inferior wall of the LV might represent a risk factor for VF recurrence. However, this was not found to be a consistent finding. When employing the same methodology in a small group of 8 Italian IVF patients, Biffi M. et al.[135] reported an increased uptake of 123I-MIBG in the anterolateral wall of the LV. Therefore, these authors postulated that anatomic site and the extent of increased sympathetic activity might be important markers of enhanced vulnerability to VF, especially in the absence of structural abnormalities. In fact, cardiac sympathetic innervation is highly heterogeneous, even though predominant in anterolateral segments in normal subjects. Patients with IVF may exhibit the same distribution, despite demonstrating a significantly greater density of sympathetic terminals in the anterolateral segments, which may promote VTs.[135]

Mechanistically, the finding of a reduced tracer activity in the inferior wall could result from either a reduced re-uptake of MIBG/catecholamines, an increased release of MIBG/catecholamines into the synaptic cleft or a combination of the two. All mechanisms would lead to an enhanced catecholamine concentration in the synaptic cleft, with subsequent downregulation of postsynaptic β-adrenoceptor density. This was, in fact, previously demonstrated by quantitative PET studies in patients with idiopathic right ventricular outflow-tract tachycardia or arrhythmogenic right ventricular cardiomyopathy. Moreover, as in patients with BrS, the initial arrhythmic event of the IVF population with reduced 123I-MIBG uptake in the inferior leads, 75% occurred at rest. This clinical observation, in combination with the described MIBG findings, is, indeed, suggestive of an autonomic unbalance, under the form of a mismatch between enhanced parasympathetic activity and reduced sympathetic activity, in IVF patients. This pathophysiological condition predisposes to abnormal conduction and dispersion of refractoriness, which may trigger and maintain VTs. This autonomic mismatch is aggravated at times of physiological downregulation of adrenergic activity and may partly explain the propensity for VTs and SCDs to occur at rest or during sleep, in these patients. However, the definite mechanism linking 123I-MIBG SPECT results with VF/VT recurrences remains to be elucidated, as no proof of a causal relationship can be provided from this study.

3.6 Specific lone triggers

Emotional stress is well established as a trigger of SCD in the context of CAD and Takotsubo cardiomyopathy, but its role in patients experiencing cardiac arrest with apparently normal hearts is unknown. In a study,[137] it was shown that, for the 6 months before the IVF event, 20 patients out of 25 displayed moderate-to-severe stress while only 5 exhibited low stress. Moreover, during the preceding 24 hours, 9 patients with IVF showed moderate-to-severe stress, with all the remaining presenting low stress. Given that the prevalence of stress in patients with IVF actually exceeded that of patients with CAD, the authors concluded that psychosocial stress may as well be a precipitating factor of IVF. The mechanisms underlying this association between psychological stress and cardiac arrest in IVF are likely to involve autonomic and neurohumoral stimulation of VTs.[137,138] In fact, acute stress is associated with high levels of circulating catecholamines. Conversely, chronic stress may be associated with a decrease in vagal tone, which is, in itself, an established risk factor for cardiac mortality.[123,138] However, other authors[31,115] reported no epidemiologic link between spontaneous arrhythmias and psychological stress.

As for stress, overwork has also been studied as a precipitant factor of IVF. Interestingly, in Japan, the term “karoshi” was invented to describe unexplained sudden death associated with overwork.[48] A case of a 43-year-old man with IVF following a period of overwork and sleep deprivation was also described by Wong et al.[48] Retrospectively, he reported working on two jobs, and only slept for estimated 4 hours a day in the preceding 2 months. His ECG on admission revealed a wide complex tachycardia, of uncertain type, but with a patent Osborn wave, even though no definite features of ER were found. As previously anticipated, case–control studies have found an association between prolonged working time and acute myocardial infarction, with an up to two-fold higher risk being reported. However, it is often difficult to prove a causative relation between overwork and SCD, due to potential recall and confounder biases, given that, for instance, working extra hours, sedentarism, unhealthy diet and sleep deprivation often go hand in hand. Commonly, the proarrhythmic mechanism is attributed to the catecholamine release.

Unreliable cases or case series also reported high fever as a rare potential trigger of IVF.[123,139] Indeed, a mechanistic approach for this event has already been established: high temperature might affect sodium channel function, particularly if encoded by a variant form of SCN5A.[140] Pasquié et al.,[139] for instance, reported 3 patients, in whom Brugada or LQTS were excluded, who developed VF attacks in the context of fever. Omori K. et al.[140] also reported a rare case of recurrent IVF induced by high fever. In turn, Amin et al. and Lim et al., cited by Omori et al.,[140] reported that a fever-induced prolonged QT interval also resulted in VF attacks. It has been unclear, however, why the reported patients did not suffer from cardiac arrest

events when they exhibited high fever during childhood, for instance in the context of infectious diseases.[140]

In turn, Aizawa et al.[141] showed that complete right bundle branch block (RBBB) is more prevalent in patients with IVF than in control subjects. Of note, this ECG morphology might mask the characteristic features of BrS, itself a major cause of VF with no structural heart disease. However, a case report[142] managed to related IVF with RBBB (IVF-RBBB), rather than with BrS. In this case, a novel SCN5A mutation, 5432-5433insGAGT, was identified, illustrating a potential genetic background for IVF-RBBB.[142]

4 - Pathophysiological Mechanism of IVF

The pathophysiology of IVF can be grossly subdivided into 3 electrophysiological phases: trigger sources, initiation and maintenance/perpetuation, which are further described below.[17]

4.1 – Trigger sources

SCD is thought to result from an interaction between a substrate and a trigger, as might be exemplified by LQTS.[137] Substantial evidence suggests that, as the severity of the substrate increases, the intensity of the trigger required to induce an event decreases.[137]

In the majority of cases, VF is triggered by PVCs or by the transition from a VT.[41,45,76] These PVCs may result from abnormal automaticity, triggered activity or, more rarely, reentry, either of phase 2 or reentry using the Purkinje system.[76] In a multicenter study of patients with IVF, PVCs triggering VF arose from the right Purkinje system in 45.7% of patients, followed by the left Purkinje system in 40% and the right ventricle outflow tract (RVOT) in 11.4%.[31]

a) IVF arising from generic PVCs

A review of IVF patients' records showed that the number of PVCs in 24h exceeded 1000 in 8 of 52 subjects studied by 24-hour Holter ECG and that LPs were present in 21.4% of cases. In addition, in 4 cases, ventricular stimulation induced sustained polymorphic VT, which later degenerated into VF.[5]

The pathogenesis of short-coupled PVCs is largely unknown, although a genetic origin might be detected in a limited number of patients with short-coupled *torsades des pointes* (scTdP)/VF, including the Dutch *DPP6*-haplotype, *RyR* mutation that causes scTdP at rest and *IRX3* mutation.[12,82,83] However, the main cellular mechanism of short-coupled PVCs and scTdP seems dependent on the Ito of the His and Purkinje fibers. An increase in Ito causes a deeper phase 1 of the cardiac action potential. Because Ito tends to increases only in Purkinje fibers, a strong local repolarization gradient is created with the adjacent ventricular myocardium,

which may result in local ectopy and short-coupled PVCs. PVCs with a short-coupled interval (ie, “R-on-T” phenomenon) can cause phase 2 reentry and, hereby, elicit VF.[89]

The origin of ectopic triggers can be demonstrated by mapping the earliest origin or by pace mapping if ectopies are rare. The RVOT, and, less frequently, the LVOT, with their usual monomorphic PVCs, are the reported locations in 15% of cases.[53] On the other hand, in cases where runs of polymorphic PVCs have been reported, not only the initial one but also subsequent beats can be associated with Purkinje activity, suggesting repetitive reentry or triggered activity.[53]

b) IVF arising from RVOT, papillary muscles and moderator band PVCs

PVCs originating from the RV, namely in the region of the RVOT, papillary muscles and the moderator band (MB), may occasionally trigger VF.[17,31,32,53,76,101,143-147] In particular, several investigators[17,31,32,146] have already reported RVOT PVCs-triggered IVF. In most patients, PVCs arose from the septal area of the RVOT[17,31,32] Of note, one study[146] described that malignant PVCs, inducing polymorphic VTs and/or VF, had shorter coupling intervals when compared with benign PVCs of the same morphology. However, this finding was not consistent with a study by Noda et al.,[32] which compared IVF-associated PVCs with benign RVOT PVCs and noted no significant difference regarding the number of isolated PVCs per day, their coupling interval (always > 320ms) and even their QRS duration. In addition, in the originating area of the PVCs, no fragmentation, double or delayed potentials were found. However, after PVC ablation, the elimination of one focus was followed by the onset of a new PVC morphology only in IVF patients. As for PVCs originating from the MB, previous studies[147,148] showed that those were found to be responsible for VTs, and, likewise, that catheter ablation of those foci might be effective in preventing SCA and ICD shocks. The main characteristics of these PVCs were a narrow duration, an LBBB pattern with precordial transition later than V4, intrinsicoid deflection in the precordial leads of < 10 ms, and a left superior axis.[101,147] Of note, it was considered that the site of the PVC origin may be deeper down the endocardial surface. The long-term prognosis of patients with PVCs originating from the MB is not obvious, as cases with PVCs causing VTs are relatively few. In addition, the mechanism of the arrhythmogenicity behind the MB is also not clear, although it seems likely that Purkinje cells might affect VT occurrence.[101] An intriguing hypothesis, which can possibly relate arrhythmia originating from the MB to bradycardia, is mechanical stretch. Mechanical stimulation of ventricular myocytes seems to directly result in membrane depolarization, action potential prolongation and triggered activity-induced PVCs and VT.[148] Stretch-activated receptors, including gadolinium receptors, result in the activation of multiple current components of sodium, calcium and potassium, with a net positive current leading to membrane depolarization and afterdepolarizations. Interestingly, the MB appears particularly prone to mechanical stretch

during bradycardia, due to increased ventricular filling. On the other hand, an interesting case of left ventricular fascicular VT involving the MB was reported. In this case, however, the VT mechanism was considered to be reentry.[148]

c) IVF arising from Purkinje system-related arrhythmias

The Purkinje system may generate or even maintain arrhythmias by automaticity, triggered activity or, more rarely, reentry, during multiple conditions, such as electrolyte imbalance, catecholaminergic stimulation, drug exposure and myocardial ischemia. In fact, in these circumstances, Purkinje fibers may survive within the necrotic muscle, therefore providing the arrhythmogenic substrate.[31,53,148-150] However, the His-Purkinje system cannot be sufficiently screened by the surface ECG, due to the limited cumulative voltage change of the relatively low number of its specific cells,[151] thus presenting an obstacle to its consideration as a potential key underlying substrate source.

In patients with IVF, arrhythmia-triggering PVCs – identifiable via a characteristic early sharp pre-PVC potential – may originate from the Purkinje system, namely from its distal portion, in up to 93% of the cases.[31,53,148,150,151] In a multicenter experience,[31] PVCs arising from the Purkinje system of the LV were characterized by a relatively short QRS duration (115±11ms) and a wider area of origin, as compared to RVOT PVCs. Indeed, PVCs with right ventricular origin mostly arise from the anterior wall and display a significantly longer QRS duration (143±10ms; $p<0.01$). In Purkinje-related ectopies, a shorter PVC coupling interval and a higher prevalence of spontaneous polymorphic PVCs were also noted. Furthermore, in the Purkinje system IVF group, a family history of SCD and arrhythmic storms were more common. Likewise, these ectopies commonly have short-coupling R-on-T intervals. Importantly, radiofrequency ablation of these beats resulted in suppression of recurrent VF episodes. On the other hand, long conduction times, fragmented Purkinje activity and dissociated activity between contiguous bipoles are also suggestive of alterations in the Purkinje system or its myocardial connections. These alterations may be of structural or electrical nature (e.g. defective gate function) and likely result in heterogeneity of refractoriness, leading to nonuniform conduction across the Purkinje system.

As previously described, the electropathologic mechanism of IVF may correspond to macro-reentry within the His-Purkinje network, being often triggered by closely coupled PVCs. On the other hand, abnormal automaticity in the Purkinje fibers likely results from a deficient calcium regulation by the sarcoplasmic reticulum.[76] Likewise, triggered activities themselves, such as early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs), are commonly recorded in the Purkinje cells and can result from Ca^{2+} overload.[76,149] Particularly, EADs occur more readily in the Purkinje system than other regions. The ionic mechanism of EADs in Purkinje cells is attributed to ICa and the reactivation of INAL2.[160] It seems even likely

that triggered activity acts both as the trigger as well as the mechanism for perpetuation in the presence of single PVC induction of VF in an otherwise normal heart. In addition, an SCN5A-related channelopathy has recently been described with families affected by multifocal ectopic Purkinje-related PVCs, associated with SCD.[152]

Purkinje triggers are, however, often transient, being present only during short arrhythmic periods. Therefore, challenging the Purkinje conduction may reveal itself a valid approach for these patients. It can be performed retrogradely, by pacing close to the Purkinje network, which is a simple technique, or anterogradely, by His-bundle or fascicular pacing. Its goal would be to reveal functional abnormalities in the conduction system, which can, in turn, underlie an arrhythmogenic substrate, thus offering a method for detecting a subclinical "Purkinjopathy" in patients who are at risk for VTs and SCD.[150] In a study[53], the authors have observed 5 patients, survivors of IVF, who had neither short-coupling Purkinje ectopy nor microstructural myocardial alteration. A distinct electrophysiologic response was, however, observed during programmed stimulation at the distal left fascicular system. Specifically, no VF or repetitive activity was induced by stimulation from the RV, while pacing from the left posterior fascicle could consistently induce repetitive polymorphic VT within the distal Purkinje system. The polymorphic QRS complexes were associated with distal Purkinje potentials on a beat-to-beat basis, whereas the proximal Purkinje fascicle and bundle branch potentials were slower or absent (excluding a bundle branch reentry). The variations in ventricular cycles were preceded by a similar change in Purkinje cycles and arrhythmia termination was preceded by the disappearance of Purkinje activity. Although triggered activity cannot be ruled out, the repetitive responses are likely reentries induced in peripheral Purkinje system, with a gradual shift in trajectory and ventricular exit, as demonstrated by computer modeling studies.

Recent data focus on PVCs arising from both the RVOT or the Purkinje system.[17,31,32,151] For instance, Kleissner M. et al.[153] reported that in one IVF patient the trigger site was both in the Purkinje network and in the myocardium of the RVOT.

4.2 – Initiation and maintenance/perpetuation of VF

Evidence on IVF initiation and maintenance was, again, summarized in a review by Tilz et al.,[17] and their findings are next described. VF ensues when an electrical wave break induces reentry and triggers a cascade of new wave breaks. The theory of ongoing wave break postulates that this wave break, which continues as long as VF persists, initially involves the reentry mother circuit, which, in turn, disappears at the moment of VF initiation. An opposing theory asserts that the mother wave survives as long as VF is sustained and that the multiple wave breaks occur as an epiphenomenon, given a fibrillatory conduction block in outlying regions, unable to conduct 1:1. Another theory postulates that there is no reentry mother circuit but a central firing focus. This focus underlies a fibrillating activity with the same

epiphenomenon of various wave breaks in outlying regions unable to conduct 1:1. It appears that factors regulating cell membrane properties, affecting APD, cell excitability, and conducting velocity throughout tissue are critical for wave stability. Accumulating evidence suggests that electrical properties of the cell membrane predisposing tissue to VF could be directly determined by abnormal calcium release from the sarcoplasmic reticulum.

The observations of successful outcome after ablation despite the persistence of isolated short-coupled Purkinje-associated ectopy suggests that there is a potential to sustain activity within the Purkinje network.[53] On the other hand, some authors hypothesize that, in RVOT PVCs-associated IVF, the rapid firing of a local focus could be responsible for both the initiation and the perpetuation of the arrhythmia. Indeed, it has been shown that rapid pacing from that area gave rise to a polymorphic morphological change in the QRS configuration in 2 out of 7 patients. The polymorphic change of QRS complexes following rapid pacing from the point of ablation was observed also in a single case report of RVOT PVCs-associated IVF. This hypothesis is supported by the observation that VF can occur following very fast pacing or a spontaneous high ventricular rate. This is, for example, observed clinically, if AF or atrial flutter is rapidly conducted to the ventricles over an accessory pathway.

Another theory is that IVF depends on rapid firing of multiple foci.[32]

5 - Necessity of Follow-Up and Reassessment of Diagnosis

The importance of re-evaluation of the diagnosis in IVF patients has already been reported and may have significant consequences for both the assessment of a patient's prognosis and family screening and counselling.[80] Since the underlying disease substrate is often unknown, routine clinical follow-up is recommended, due to potential late emerging of cardiac pathology, as 7% to 50% of patients initially diagnosed with IVF will later reveal a specific disease.[14,24,40,41,80] In fact, while repeated ECG assessment alone during follow-up may lead to a change in the initial diagnosis of IVF in up to 30% of cases,[14,80] a global work-up strategy, using a systematic algorithm including pharmacological, exercise and genetic testing, may allow the identification of cardiac abnormalities in more than 50% of apparently IVF sufferers.[19,23,24] Waldmann V. et al.,[15] to the best of our knowledge the first study evaluating the completeness of medical assessment among survivors of unexplained SCA in the community, reported that less than 20% of the patients diagnosed with IVF received a comprehensive investigation. In particular, while cardiac MRI was performed in the majority of cases (80%), coronary vasospasm provocative testing and ajmaline tests were clearly underused. Also, the very low utilization of exercise testing and Holter-ECG recordings could have led to missed opportunities to diagnose CPVT or LQTS.[5] These striking findings illustrate that: 1) very few investigations are performed during follow-up subsequent to the initial

evaluation during index hospitalization; 2) the gap between results reported by highly specialized electrophysiology teams working in tertiary centers and the real-world approach involving numerous unselected hospitals is huge, underlining the importance of referring these patients to expert centers.[15]

In the light of the above, we propose a systematic algorithm for IVF diagnosis in suspicious patients:

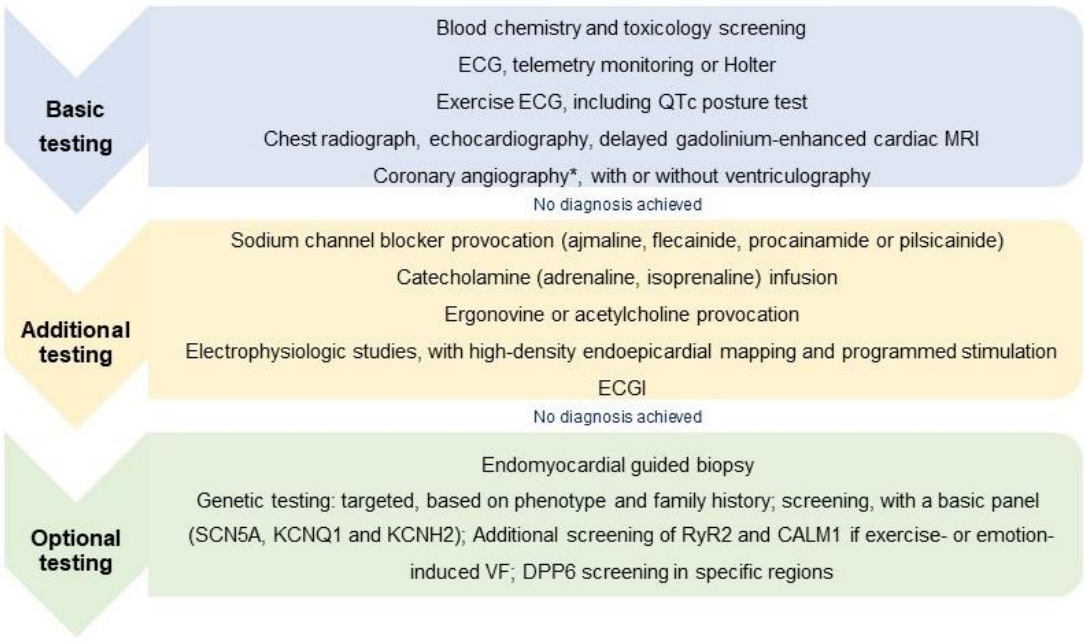

Figure 2 – Proposed IVF diagnosis algorithm.
* In patients <45 years with a low risk for coronary artery disease, coronary-CT or MR angiography is a valid alternative;
CT- computed tomography; ECG- electrocardiogram; ECGI- electrocardiographic imaging; MRI- magnetic resonance imaging.

Only few and sometimes conflicting factors are known or suspected to influence arrhythmia recurrence rate and, ultimately, vital prognosis.[49] Young age, regional wall motion abnormalities, electrical storm occurrence, failure to suppress frequent ventricular ectopy by use of antiarrhythmic drugs, personal history of syncope and aborted SCD and family history of SCD are generally considered potentially influencing factors of arrhythmia recurrence.[34,49,80,118] Yet, different sources failed to show an influence of age and ejection fraction, as well as of sex and arrhythmia inducibility in electrophysiologic study, on the rate of VT/VF recurrence.[11,49] On the other hand, Conte et al.[80] reported that age ≤16 years at the time of the first VT was the only predictor of arrhythmia recurrence on multivariable analysis, disclosing a two-fold increase in its risk, whereas none of the other candidate predictors, such as previous syncope, family history of SCD and presence of cardiovascular risk factors, were associated with arrhythmic recurrences. In yet another study, this time by Siebermair J. et al.,[49] which unveiled results from a single center long-term follow-up investigation of over 20 years,

ERP was found to be the only predictor of arrhythmia recurrence in IVF survivors, being even significantly associated with an early recurrence of arrhythmic events. Furthermore, this analysis revealed that the occurrence of AF was the strongest predictor of inappropriate ICD interventions. This high rate of AF in these IVF survivors might indicate an underlying heart disease or a myocardial electrical disorder not apparent at the index event, which, once again, shows that follow-up of these patients is particularly important. In addition, ECG features themselves, such as Tpeak-Tend >100ms with U waves and right bundle branch block, were associated with more arrhythmia recurrences in a pediatric cohort,[34] in line with results from similar research directed towards the adult population.[88] These ECG markers could potentially modulate arrhythmic risk stratification but, based on the limited size of cohorts, these results should be interpreted with caution.[34] Furthermore, in a study by Chaudhry et al.,[40] at baseline, 34% of patients had a normal ECG. Of these, 75% developed abnormalities during follow-up. Conversely, of patients with an abnormal ECG at baseline, 29% normalized their ECGs during follow-up. However, abnormal ECG at baseline did not predict ECG pathology at follow-up, nor did it predict appropriate ICD therapy, ending up having no prognostic value in determining the risk of ventricular arrhythmia recurrence.

The rate of arrhythmic recurrences in adult patients with IVF and normal ECGs is considerable. In the aforementioned Conte et al. study[80], the authors reported that 21% of 245 IVF patients with normal ECG experienced an arrhythmic recurrence, corresponding to an annual rate of 3.6%, with a median time to first arrhythmic recurrence of 29 months. In a supra-mentioned smaller cohort,[40] 32% of IVF patients, both with normal and abnormal ECGs, experienced recurrence of VF or sustained VT at a median time of 1.9 years (range 0.1–20.3) from the index event, resulting in an event rate of about 3.1% per year, over a median 12.3 years. Other studies have reported adult ventricular arrhythmia recurrence rates of between 11 and 45%,[3,16,17,39,41,49] with about 30% as the most frequently reported proportion. However, and as a consequence of what was described above, the highest frequency of repeated arrhythmic events seems to be observed in pediatric IVF cohorts,[34] with 57% of cases experiencing recurrences, namely under the form of VF. Despite an overall higher arrhythmic burden, these recurrent arrhythmic events in children occurred at a later stage, as compared with those reported in the adult population. These findings suggest that, in pediatric IVF patients, the disease process is associated with a more malignant course, with ongoing arrhythmic risk extending over a more prolonged period of time.[34] In a long-term follow-up study of an IVF cohort,[49] a high number of appropriate ICD therapies (n = 174, in 43% of patients) was recorded, what is in line with a prior study, reporting frequencies ranging from 37 to 39%.[2] As for event timing, in the abovesaid Conte et al. study[80], it is reported that the incidence of non-fatal events was highest in the first 5 years after the index IVF, whereas both cardiac and non-cardiac mortality tended to occur later. Furthermore, as many as 95,5% of

patients experienced an appropriate ICD intervention.

In the aforementioned study by Conte el al.,[80] death occurred in 4.9% of IVF patients, corresponding to an annual incidence of 0.74%, during a median follow-up of 63 months. Among 19 patients who did not undergo ICD implantation, there were 9 deaths (47%). In contrast, only 3 patients in the ICD group died (1.3%), and the cause of death was deemed not to be of cardiac origin in 2 of them. Ozaydin et al.[39] reported data in line with this outcome, over a median follow-up of about 5 years, whereas Visser[41] cited a mortality rate of as high as 9%, over a median follow-up of 10.2 years. In the same Ozaydin et al.[39] meta-analysis, which aggregated 23 studies (encompassing a total of 639 patients), SCD was responsible for 80% of the total mortality rate. However, another study accounted that, in a cohort of 40 patients followed through national registries for a median 13.8 years, no cardiac mortality event was reported.[40]

Even though being generally considered a high-risk subgroup, there is relative paucity of data on the natural history and long-term outcome of patients of pediatric age who present with IVF. Of course, that stems primarily from the fact that the majority of arrhythmic SCDs in young patients are attributable to structural cardiac diseases or primary arrhythmic syndromes.[57] However, in the above-mentioned first study[34] that systematically explored long-term outcomes in a pediatric population with an initial diagnosis of IVF, among 54 patients (with a median age of 12.7±3.7 years at the time of index VF episode, and with a median of 109±12 months of follow-up), the majority (67%) of SCD events occurred in the context of high adrenergic tone. Moreover, in 39% of patients, recurrences of ventricular arrhythmia also occurred in the context of high adrenergic tone, being it exercise or intense stress/emotion. Similarly, close to 20% of patients were revealed to possess variant alterations in genes implicated in CPVT, even though only a small minority (3.7%) of patients would develop evidence of an underlying cardiac phenotype during long-term follow-up. Moreover, concretely, the cardiac disease would be either HCM or LQTS, with none of patients actually displaying an undisputed evolution to a CPVT diagnosis. These findings suggest that both the clinical course and the underlying arrhythmogenic substrate in pediatric patients with IVF are distinct from those previously reported for adult IVF cohorts, thus potentially contributing to an even lower etiologic and diagnostic yield of testing in this particular patient population.

6 - Future Perspectives

Future guidelines should promote a standardized and systematic approach for patients with IVF. In particular, they should begin by addressing the specific indications of more readily available non-invasive diagnostic tests, namely cardiac imaging examinations. Then, they

should move to further standardize more advanced investigations, including ergonovine challenging, cardiac mapping procedures and genetic testing.

In the case of imaging, in the future, quantitative measurements of the presynaptic noradrenaline recycling and postsynaptic β-adrenergic receptor density using PET may render insights into the pathophysiology and risk assessment of IVF.[154] Likewise, studies in larger cohorts are required to validate the significance of 123I-MIBG SPECT as a new imaging-based risk assessment tool in IVF patients.[17] The increased sympathetic innervation of the left anterolateral wall may also be used as a diagnostic marker of this poorly understood disorder.[135]

As for genetic testing, whole-genome sequencing for non-coding variants in ion channel and cardiomyopathy genes may shed light on confounding etiologies, as knowledge grows in combination with exome analyses.[80] In conjunction with functional studies, genetic testing appears to enclose the ability of redefining IVF even further in the future. As of now, extensive genetic testing is, however, not recommended in IVF patients because of its low yield and high costs.[18] Nevertheless, the costs of this sort of investigation have decreased, resulting in an increase in its feasibility. Consequently, large custom multigene panels have been created and are rapidly replacing targeted genetic screening based on phenotype. Of course, the yield of these custom multigene panels has yet to be determined. Accordingly, an increasing number of variants of uncertain clinical significance have been detected. The interpretation and clinical use of these minor alterations is challenging. Future research, and more specifically functional studies, have to demonstrate the causality between these variants of uncertain clinical significance and IVF.[16]

Future research should also focus on identifying potential polygenic and non-genetic causes that likely underpin much of IVF. These may actually have wider implications for the comprehension of the mechanisms of VF in other more common scenarios, such as ischemic heart disease. With further improvements in the understanding of the mechanisms responsible for VF, we should aim to predict, for instance, the proportion of patients with PVCs that are at greatest risk of VF or its recurrence, and even define the patient population that is most likely to respond to ablation, which should, in turn, follow a tailored technique selection.[149] In fact, rather than finding the one needle, we need to understand the interaction between the blades of grass in the stack.[28] In addition, through advances in the understanding of primary electrical syndromes, subgroups with a specific underlying disease can be identified, diagnosed and managed appropriately, improving prognosis and preventing recurrent events.[56]

A comprehensive registry of patients with IFV, particularly with international coverage, should also be established. This would allow, for instance, both a better definition of the incidence and a further characterization of the different features of this elusive disease. The

database should include information on the performed diagnostic tests, in order to assess their reliability and to gain even more insight into an eventual underlying disease.

CONCLUSION

IVF patients represent a rare and heterogeneous group, with a largely unknown natural history, in whom both diagnosis and management are challenging. In fact, this nosological entity requires the completion of both extensive and differentiated complementary testing and offers few curative options, due to unknown or even inexistent underlying disease.

Historically, after limited diagnostic testing, all VF patients with an apparently normal heart were diagnosed with IVF, resulting in a too large and dissimilar patient population. However, recently, the incidence of IVF has been showing a diminishing tendency and we expect the number of patients diagnosed with IVF to decline even further, albeit not disappearing altogether. This decrease might be explained by the detection of new well-defined primary arrhythmia syndromes, the improvement in high-resolution imaging modalities and the advance in genetic testing.

Nevertheless, in the real world, a majority of unexplained SCAs remain insufficiently investigated, thus resulting in the diagnosis of IVF to be still probably overused, despite the availability of evidence supporting the yield of exhaustive medical investigations in this specific setting. As a consequence, there is a desperate need for international medical societies to frame management guidelines, so that standardized and systematic approaches could be implemented in order to improve the proportion of definitive diagnosis in otherwise apparently unexplained SCAs and to ensure that opportunities for specific therapies and preventive strategies, including among family members, are not missed.

Of note, presently, IVF is no longer the obscure disease it has been for most of its existence as an individual pathology. In fact, the role of a variety of genetic mutations and even polymorphisms has already been unveiled. These may act individually or represent a distinct pillar of the so-called polygenic manifestation, exerting their influence on a wide variety of tissular mechanisms. In fact, processes as diverse as sympathetic innervation and myocardial electrical repolarization and/or depolarization have already been established as driving sources for the pathophysiology of this condition. A derangement in the latter process may be even easily spotted through the detection of a J wave in the surface ECG. In addition, the term “idiopathic” has been stretched to the limit, given that the existence of a so-called microstructural myocardial substrate, particularly involving the RVOT and the Purkinje network, has been repeatedly testified by a multiplicity of authors.

Given the very intricated nature of IVF diagnosis and management, and the fact that this disease is not at all transitory – that is, it is not over when its paradigmatic event takes place – a specialist-led cardiology follow-up is recommended in all cases. In particular, the diagnosis must constantly be re-evaluated as more diagnostic data is gathered. However, even if it is not, or, even more so, mostly if is not, one must never forget that the risk of ventricular

arrhythmia recurrence, ICD therapy necessity or even mortality is real, thus cementing this disease's reputation as a silent killer.

Abbreviations:
APD-Action potential duration; ARVC/D - arrhythmogenic right ventricular cardiomyopathy/dysplasia; AF - atrial fibrillation; AV-atrioventricular; BrS-Brugada syndrome; CPVT- catecholaminergic polymorphic ventricular tachycardia; CT-computed tomography; CAD-coronary heart disease; DCM-dilated cardiomyopathy; DADs-delayed afterdepolarizations; EADs-early afterdepolarizations; ER-early repolarization; ERP-early repolarization pattern; ERS-early repolarization syndrome; ECG-electrocardiogram; ECGI electrocardiographic imaging; HCM-hypertrophic cardiomyopathy; HF-high frequency; ICD- implantable cardioverter defibrillator; Ica-inward calcium current; 123I-MIBG-Iodine123-metaiodobenzylguanidine; Ito- transient outward potassium current; IVF-idiopathic ventricular fibrillation; JPE-J-point elevation; LBBB-left bundle branch block; LPs-late potentials; LV- left ventricle; LVEF-left ventricle ejection fraction: LQTS-long QT syndrome; LF-low frequency; MRI-magnetic resonance imaging; MVP mitral valve prolapse; MB-moderator band; In HF-natural logarithm of high-frequency components; OHCA-out-of-hospital cardiac arrest; PM-papillary muscle; PVB-premature ventricular beat; PVC-short-coupled premature ventricular complex; RBBB-right bundle branch block; RVOT-right ventricle outflow tract; RYR2-ryanodine receptor gene; scTdP-short-coupled *torsades des pointes;* SQTS-short-QT syndrome; SCA-sudden cardiac arrest; SCD-sudden cardiac death; UCA unexplained cardiac arrest; VUS-variants of uncertain significance; VF-ventricular fibrillation; VT-ventricular tachycardia; WPW-Wolff–Parkinson–White.

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