Idiopathic ventricular fibrillation
INTRODUCTION

Cardiac arrest (CA) mostly follows from cardiac disorders that elicit lethal ventricular tachyarrhythmias, primarily ventricular fibrillation (VF).\textsuperscript{1,2} The predominant cause of VF in the general population is considered to be previously silent coronary artery disease resulting in myocardial infarction with VF and CA as its first symptoms.\textsuperscript{3} However, there are many more cardiac and also non-cardiac causes that can result in VF, such as intracranial haemorrhage, pulmonary embolism, myocarditis, cardiomyopathies, valvular heart disease, congenital cardiac anomalies and accessory pathways.\textsuperscript{4-8} Despite the advances in our medical emergency systems we cannot avoid that only 2 to 30% of patients survive VF.\textsuperscript{9-11} The remaining suffer a sudden (cardiac) death (SD/SCD).

In approximately 5% of CAs at all ages, there is no explanation for the event, not even after extensive evaluation (figure 1).\textsuperscript{12} Within this group several categories can be distinguished depending on the initial rhythm and whether or not the patient survived the event. In case of unexplained aborted CA with documented VF, idiopathic VF (IVF) is the terminology that best acknowledges our current inability to identify a plausible cause for the occurrence of VF in these patients who were previously considered healthy.\textsuperscript{12} In cases of unexplained aborted CA with another initial rhythm or unexplained SD, unexplained cardiac arrest or sudden unexplained death are the terms most commonly used. It is important to recognise that the diagnostic workup for these patients and/or their family members is similar and aimed at diagnosing or excluding specific causes of VF and CA.

As the total burden of CA and SD is enormous, the burden of IVF is considerable. In the United States the estimated incidence of SD is 180,000 to 250,000 cases per year, which results in an estimated incidence of IVF up to 9,000 or 12,500 cases per year.\textsuperscript{1,3,13,14} Although

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**Figure 1** Cardiac arrest differential diagnosis

Diagnostic flow-chart in cardiac arrest based on the initial rhythm and whether or not the patient survived the event. Note that if the patient did not survive the event, the presence or absence of ventricular fibrillation is of no value.
IVF constitutes a minority in aborted CA and SD, it is an intriguing and notoriously difficult condition that still affects many. Its cause is unknown, there are no clinical signs that identify individuals at risk and its first symptom may be CA. Aside the possibility of recurrent VF episodes in those individuals who survived IVF, it is clear that there are several hereditary forms of IVF. The latter implicates that whole families may be predisposed to IVF and SCD. As coronary artery disease becomes more prevalent with increasing age, it is comprehensible that the majority of IVF will occur in young patients, i.e. in those less than 40-45 years old. Further, over the last decades many cases that have previously been described as IVF can now be categorised to distinct clinical entities. Therefore the contribution of IVF to CA has declined simultaneously.

Clinical decision making in these patients and/or in their families is seriously hampered by the absence of risk markers for the onset of VF, also after extensive evaluation. Clinical decision making is further complicated by the lack of treatment options in order to make VF in (yet) asymptomatic family members less likely to occur. In the current era of implantable cardioverter defibrillators (ICDs), survivors of a CA due to IVF will often be pragmatically treated with an ICD. This device can restore normal cardiac rhythm in case of recurrent ventricular arrhythmias, but is not without complications and does not prevent VF recurrence.

**CLINICAL DIAGNOSIS**

The difficulties associated with the diagnosis of IVF may be classified in two components: (1) IVF is a diagnosis per exclusionem, and (2) the paucity of IVF survivors. Diagnoses per exclusionem are hard to establish with our current diagnostic tools, and even more so if the patient did not survive the event. The diagnosis IVF is made in those who survived VF (figure 1). In patients with other initial rhythms or in patients who did not survive the event, when further evaluations of the patient or first degree relatives do not result in a diagnosis we will diagnose unexplained cardiac arrest (UCA) or sudden unexplained death (SUD).

In the survivors of CA the first effort in establishing a diagnosis is of course a detailed documentation of the event, medical history, family history, physical examination and blood chemistry. The second effort is non-invasive cardiological evaluation, including resting ECG, exercise ECG and an echocardiogram. Registration of arrhythmias can be extremely helpful, if not the key to a diagnosis. If a diagnosis is still not (fully) established, additional evaluations should be performed, amongst which: Holter-monitoring, coronary angiography (consider intra-coronary ergonovine or equivalents for evaluation of coronary spasm), toxicology screening, cardiac biopsies, cardiac magnetic resonance imaging and drug provocation testing with sodium channel blockers (using e.g. ajmaline or flecainide) and adrenaline. Clearly, there is no established chronological order in which these evaluations
should be performed, e.g., coronary angiography will often be one of the first diagnostic (and possibly therapeutic) investigations in the work-up of a resuscitated patient.

In case of SD, cardiac and genetic examination of first degree relatives is recommended when autopsy did not reveal a cause of death or was not performed. The first step in this approach is to collect detailed information on the event and on the medical history of the SD victim and his or her first degree relatives. A resting ECG in the relatives is made and if autopsy was performed, the autopsy report is reviewed. Ideally the autopsy should have been performed according the histo-pathological guideline which Basso et al. established for post-mortem evaluation of SD victims. Subsequently, depending on the information available, further steps can be taken. These may consist of revision of cardiac autopsy by a specialized pathologist and/or further cardiac examinations in the attending relatives (figure 2). Tan et al. and Behr et al. established the contributions of these modalities in relatives of the SD victim.

![Figure 2: Algorithm for Evaluation of Relatives of Sudden Death Victims](image)

Algorithm for cardiological and genetic examination in relatives of SD victims. *Including revision of autopsy by cardiac pathologists, if possible; †Consider adrenaline provocation; ‡Class I drugs (ajmaline, flecainide or pilocarpine; preferably not procainamide); §Advice to monitor traditional cardiovascular risk factors (e.g. hypertension, diabetes mellitus, hypercholesterolemia, overweight); ||Advice repetition of cardiological examination in 3-5 years; #When not performed yet, consider examinations in one or more of the other pathways; SD indicates sudden death; LQTS, long QT syndrome; BrS, Brugada syndrome; SQTS, short QT syndrome; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; FH, familial hypercholesterolemia; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; CM, cardiomyopathy. Please note that this algorithm is not exhaustive.
idiopathic ventricular fibrillation

victim. In these studies it appeared that the resting and exercise ECG were most valuable as to establish a diagnosis.

Despite the per exclusionem character of the IVF diagnosis, Haissaguerre et al. recently recognized a clinical sign that was positively associated with IVF: the electrocardiographic finding of ‘early repolarization’ was found in a third of IVF victims as opposed to 5% in a control population. Furthermore, those IVF victims with early repolarization had more recurrent episodes of VF than IVF victims without early repolarization. However, as early repolarization is indeed a rather common electrocardiographic finding (present in about 1 to 5% of the population) it can not be used as a risk marker in patients who are not suspected of an increased risk of CA. Further, its value in patients suspected of a CA risk still needs further study.

**HISTORICAL DIAGNOSES**

Medicine has dealt with many cases of unexplained CA in the past centuries. An informative and early case of familial SUD was, for example, composed by the German physician Meissner in 1856. He described a young girl living in an institute for deaf children, who had stolen something from one of her peers. When the offence was discovered she was summoned to clarify her action but at the moment she arrived in front of the director she sank to the floor and died. Meissner could not explain this acute and premature death. He did not entirely exclude a punishment from God, but he considered sudden cardiac failure possibly with some form of pre-existing cardiac pathology more likely. This notwithstanding, he had to inform the parents of the girl about the tragedy. Unexpectedly the SUD of their daughter did not surprise the parents. They had already lost two of their children in similar conditions, one directly following a vigorous fright and one while intense angry.

At present many SUD cases, like the one described by Meissner, can be clarified with our immensely increased knowledge and diagnostic repertoire over the past decades. It is tempting to speculate that Meissner’s case is one of the earliest descriptions of Jervell Lange-Nielsen syndrome (autosomal recessive form of Long-QT syndrome with deafness). However, it may be that even at present we would not have been able to explain these SUDs and would be obliged to diagnose familial SUD.

During the course of the 20th century many more UCA/SUD cases have been published, but now as distinct clinical diagnostic entities which could be recognized and sometimes also effectively treated and/or explained. Primarily this development has become possible with the application of electrocardiography to study abnormal cardiac behaviour. The progress in our understanding of CA and cases previously considered to be IVF, further expanded in the last decades with the development of cardiac imaging techniques such as echocardiography, electrophysiological and molecular research and with the elucidation of
DNA and the human genome. The evolution of genetics has enabled a search for genes underpinning the risk for familial IVF and CA even when phenotypic markers are lacking or difficult to interpret. The increasing insights in cardiac pathophysiology and its relation with ventricular arrhythmias and CA have increased the contribution of known causes of aborted CA and, consistently, decreased the contribution of unknown causes of CA (and thus IVF). The differential diagnosis of CA currently includes multiple different pathologies and, while IVF is a diagnosis per exclusionem, our diagnostic repertoire has increased simultaneously. In Table 1 we describe a limited number of milestone publications in the history of IVF. These publications cover several (familial) causes of VF and SD that previously would probably have been considered IVF. Importantly, this list excludes many causes which may also have (in part) a familial background, such as coronary artery disease (e.g. familial hypercholesterolemia) or muscle disorders (e.g. Duchenne's muscular dystrophy), and more clear non-familial causes such as myocarditis, cardiomyopathies caused by nutritional deficiencies or valvular disease. Furthermore, the authors of most of these publications were not the first to associate a certain observation with VF or SD, rather they were recognized for the collection of several cases into a separate clinical entity.

### Table 1: Historical overview of idiopathic ventricular fibrillation

<table>
<thead>
<tr>
<th>Year</th>
<th>Syndrome</th>
<th>Authors</th>
<th>Diagnosis by:</th>
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<tbody>
<tr>
<td>1951</td>
<td>Long-QT syndrome</td>
<td>Jervell &amp; Lange-Nielsen&lt;sup&gt;66&lt;/sup&gt;</td>
<td>ECG, exercise-ECG, Holter-monitoring</td>
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<tr>
<td>1958</td>
<td>Hypertrophic cardiomyopathy</td>
<td>Teare&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Post-mortem, echocardiography, ECG, biopsy</td>
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<tr>
<td>1978</td>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>Coumel et al.&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Exercise-ECG, Holter-monitoring, adrenaline provocation</td>
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<tr>
<td>1982</td>
<td>Arrhythmogenic right ventricular cardiomyopathy/dysplasia</td>
<td>Marcus et al.&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Post-mortem, ECG, echocardiography, MRI, biopsy, Holter-monitoring</td>
</tr>
<tr>
<td>1992</td>
<td>Brugada syndrome</td>
<td>Brugada et al.&lt;sup&gt;70&lt;/sup&gt;</td>
<td>ECG, sodium channel blocker provocation</td>
</tr>
<tr>
<td>2000</td>
<td>Short-QT syndrome</td>
<td>Gussak et al.&lt;sup&gt;71&lt;/sup&gt;</td>
<td>ECG</td>
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<tr>
<td>2008</td>
<td>IVF associated with early repolarization</td>
<td>Haissaguerre et al.&lt;sup&gt;25&lt;/sup&gt;</td>
<td>ECG</td>
</tr>
<tr>
<td>2009</td>
<td>IVF associated with DPP6</td>
<td>Alders et al.&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Genetic analyses</td>
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Several milestone publications explaining idiopathic ventricular fibrillation (IVF)/sudden cardiac death previously considered idiopathic
GENETIC DIAGNOSIS

As there are familial forms of IVF (in 5 to 20% of cases\textsuperscript{5,36,37}), there must be underlying genetic defects to be transmitted through these IVF families. In solitary cases similar genetic defects or genetic variations vulnerable for interaction with, e.g., drugs, can be expected to be important. The identification of a genetic defect which predisposes to IVF may certainly save lives as this raises the unique possibility to assess the risk status of, and to treat accordingly, presymptomatic individuals with a potentially fatal disease that does not express otherwise. However, the identification of genetic defects involved in IVF is very difficult for the same two reasons that complicate its diagnosis. First, unlike the other arrhythmia syndromes there is no clinical phenotype except aborted CA or SD that reveals an individuals’ risk. For example, in Long-QT syndrome or Brugada syndrome, the typical ECG characteristics can be used to classify family members as affected or unaffected and this is subsequently used to correlate with the genetic data. Second, as many IVF patients die young, this leaves little patients and material available for analysis.

Recently, two breakthroughs in a genetic diagnosis of IVF were established. Alders et al. uncovered a haplotype (a combination of alleles transmitted together) on chromosome 7q36 that harbours the DPP6 gene in 10 distantly related IVF families using a genome-wide haplotype-sharing analysis.\textsuperscript{38} That familial IVF can indeed be an extremely malignant disease was apparent from the poor event-free survival in carriers of this risk-haplotype: before the age of 58 years, 50% of the risk-haplotype carriers had died or had been resuscitated. From expression analyses in heart biopsies it became clear that the risk-haplotype carriers had on average a 22-fold higher expression of DPP6 than controls. This makes overexpression of DPP6 the likely pathogenetic mechanism underlying IVF in these families. Furthermore, DPP6 is probably involved in the transient outward current (I_{to}) in the heart, which is responsible for phase 1 of the cardiac action potential by the Kv4.2 and Kv4.3 subunits.\textsuperscript{39} Because the DPP6 gene had previously not been related to CA or IVF, and at present all detected families constitute a founder population, the importance of this gene in other IVF patients and families still requires further study. Interestingly, affected patients in the DPP6 families present with very short-coupled monomorphic extrasystoles (predominantly from the right ventricular apex/free wall) initiating VF. This finding suggests possible overlap with similar descriptions of IVF\textsuperscript{36} and short-coupled Torsade de pointes.\textsuperscript{40}

A second study into IVF genetics was performed by Haissaguerre et al. concerning IVF associated with early repolarization.\textsuperscript{41} In 157 IVF patients with early repolarization, mutation analysis was conducted by direct sequencing of candidate genes for cardiac arrhythmias. This included genes encoding potassium channels, their subunits and transcriptional regulators (KCNQ1, KCNE1, KCNH2, KCNE2, KCNJ2, KCNJ8, KCNJ11, ABCC9, KCNJ5, KCNJ3, KCND3, IRX3, IRX5), sodium channels (SCN5A, SCN1B), Na+/Ca2+ exchanger (NCX1),
calcium channels (CACNA1C, CACNB2), Ca2+-binding proteins (CALR, CASQ2), and cytoskeletal proteins interacting with ion channels (ANK2). In just one patient, a missense mutation in KCNJ8 encoding the Kir6.1 subunit of the $K_{\text{ATP}}$ channel was identified. Although the function of the $K_{\text{ATP}}$ channel and its Kir6.1 subunit is still not fully elucidated, it could be that the channels act in synergy with the Kv4.2 and Kv4.3 subunits responsible for $I_{\text{to}}$. Clearly, also the importance of KCNJ8 mutations in IVF also demands further study, but judging from this report the quantitative contribution of KCNJ8 to IVF morbidity will be limited. Moreover, it is apparent that a candidate gene approach, even using a population of definitely affected patients, has a low yield of mutations, further establishing the current idiopathic nature of the condition and the difficulties associated with genetic research in this field.

Earlier, a SCN5a mutation had been associated with IVF by Akai et al. without evidence for Brugada syndrome. However, these patients had (as can be expected with loss-of-function SCN5a mutations) severe conduction disease. Therefore they did not meet the strict criteria for IVF used here, as (progressive) conduction disease is already an established entity associated with VF.

**THERAPY, FOLLOW-UP AND PROGNOSIS**

As mentioned, therapeutic decision making in IVF is complicated. First there needs to be a therapeutic strategy for patients who survived IVF. Second, regardless of survival, there needs to be a diagnostic and preventive strategy for their first degree relatives. Unfortunately, risk-stratification in IVF is hardly possible because of its idiopathic nature. Obviously it is extremely important that any cause of VF that would require specific treatment (such as Long-QT syndromes type-1 and type-2 which are primarily treated with beta-blockers), is excluded in these patients and in their family.

In aborted CA patients, a first logical therapeutic option is an ICD for secondary prevention of SD (restoration of normal cardiac rhythm in case of VF recurrence, figure 3) resulting in a near normal life expectancy. One of the first three ICDs implanted world-wide was actually implanted in an IVF patient (the two other implanted patients had recurrent VF after a myocardial infarction and recurrent VF with hypertrophic cardiomyopathy respectively). Importantly, an ICD will not lower the chance of VF recurrence, which is reported in 25-43% of IVF patients. Further, from other arrhythmia syndromes we know that ICDs will not always prove to be life saving, and that complications as a result from the implantation or the device can be severe and may be life-threatening itself. Especially when primary prevention of SCD with an ICD is considered, it is noteworthy that complications of ICD therapy in arrhythmia syndromes such as Long-QT syndrome, Brugada syndrome and IVF, seem to be higher than the ICD complication rates in the large primary and secondary prevention trials in structural heart disease. For example, this becomes apparent when
comparing a study in Brugada syndrome patients with a study in patients with structural heart disease. In an European Brugada syndrome multicenter study with 38±27 months follow-up and the inclusion of both primary (92%) and secondary prevention (8%) ICDs, the potential benefit for the 8% of patients who received appropriate ICD therapy during follow-up was accompanied by 20% of patients with inappropriate ICD shocks. In contrast, in the AVID trial (Antiarrhythmics Versus Implantable Defibrillators) with 31±14 months follow-up and the inclusion of patients with structural heart disease for secondary prevention ICDs, a 12% inappropriate shock rate was documented against 65% of appropriate therapy. Furthermore, as the patients in AVID where on average 65 years old and already had structural heart disease, 16% of patients died during follow-up. Patients with arrhythmia syndromes are much younger, more active, have no gross structural cardiac abnormalities and (thus) have a much longer life expectancy than the AVID patients. Sensibly, the exposure time to ICD complications is thus much longer, inappropriate shocks on supraventricular tachycardias (e.g. during exercise) will be more prevalent, lead-systems are much longer and heavier exposed to physical activity and the many ICD replacements will expose these patients to repeated implantation related complications (e.g. infections, bleeding and pneumothorax).

ICD implantation as primary prevention of SD in family members of IVF victims should therefore not be a decision taken light-heartedly. First, in these patients it should be very clear if there is indeed a familial form of IVF present. Second, socioeconomic results of ICD implantation (e.g. difficulties in obtaining mortgages) and possible psychological effects should be discussed. Third, the possible beneficial and possible harmful effects of an ICD on

![Figure 3: ICD recording of IVF](image-url)
the short and long term should be carefully weighted. Naturally, it would be extremely helpful if a form of risk-stratification could be applied, for example if could be determined which age-categories seem to be at highest risk. In the rare occasion that a genetic cause for IVF can be identified, this can be used in asymptomatic family members for risk-stratification for CA in a disease that does not express otherwise.  

Obviously it would be preferable to lower or eradicate the chance of VF recurrences, rather than to treat them when they arise. This can be potentially achieved in two ways: (1) erasing the arrhythmic substrate by ablation therapy and/or (2) antiarrhythmic drug therapy. Because of the invasive character of option 1, this will only be attempted in (severely) symptomatic patients. But when effective, ablation therapy in particular is an elegant and rewarding treatment for patients who suffer from ICD shock after ICD shock for repeated VF episodes. Electrocardiographic documentation of at least one arrhythmia episode (and preferably its start) will be essential for ablation therapy to be considered. Haissaguerre et al. performed ablations in 27 IVF patients who had experienced 10±12 episodes of recurrent VF; 24 of these patients (89%) had no recurrence of VF after 24±28 months of follow-up, and 4 of the patients were even primarily treated with ablation therapy and did not receive an ICD.  

Although very promising, ablation therapy for IVF (and other arrhythmia syndromes) is only incidentally performed in experienced centres and currently lacks long-term follow-up. Nevertheless, despite possible serious complications, lowering the number of IVF episodes in addition to ICD therapy will obviously be of great benefit to patients. Cardiac transplantation has incidentally been used in other arrhythmia syndromes as a last resort in the treatment of an intolerable high incidence of recurrent VF, and might be of similar value in otherwise uncontrollable IVF patients.

The only antiarrhythmic drug with potential in IVF is quinidine. Other antiarrhythmic drugs have not proven to be beneficial, although some promote the use of beta-blockers anyway. Already in 1929, Dock described a patient with recurrent VF without any evidence of heart disease in whom VF recurrences could be prevented by using quinidine. A comparable IVF case was presented in 1949 by Moe. This patient was recurrence free on quinidine for his remaining 40 years. The mechanism of the favourable effect of quinidine on IVF remains uncertain, but it may be that its blocking properties underlie its success in some cases of IVF (and other arrhythmia syndromes) during the past 80 years. It is therefore injudicious that the large pharmaceutical companies have ceased or lowered its production, making it increasingly difficult to obtain quinidine supplies. However, regardless of the proven value of quinidine in the treatment of several IVF victims, its value for preventive treatment in as yet asymptomatic family members in designated IVF families is certainly not clear.
CONCLUSIONS

IVF is a rather rare but notoriously difficult and malignant condition that affects young patients and sometimes a large number of their family members. IVF is a diagnosis per exclusionem which necessitates detailed and thorough assessments of IVF victims and their first degree relatives in a search of better defined conditions that may require specific treatment. IVF recurrences present in 25-43% of IVF patients and in some IVF families 50% mortality before the age of 60 may exist in predisposed individuals. Stratification of IVF risk is hardly possible, but recently uncovered genetic associations with IVF may prove to be of use in the future. Secondary prevention of SD in IVF may be achieved with ICDs, ablation therapy and/or quinidine treatment. Primary prevention of SD in relatives is seriously hampered by its idiopathic nature, but may still be indicated in selected cases. Importantly, complication rates from ICD therapy in IVF and other arrhythmia syndromes, involving many young patients, will be high.

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