Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are disastrous outcomes of various predominant cardiac diseases. The leading cause of SCA and SCD is coronary artery disease. However, SCA/SCD in young patients is mainly caused by congenital disorders of primary arrhythmic or structural origin. SCD is defined as death from an unexpected circulatory arrest, usually because of a cardiac arrhythmia occurring within an hour of the onset of symptoms. The definition of SCA is similar, with the addition that a medical intervention (eg, defibrillation) reverses the event.

Idiopathic ventricular fibrillation (IVF) is a rare cause of SCA. Patients with IVF present with a sudden onset of ventricular fibrillation (VF) of unknown origin that is not identified even after extensive diagnostic testing. The exact incidence of IVF is unknown but is declining with the advance of diagnostic testing and the discovery of primary arrhythmia syndromes, such as the Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long-QT syndrome (LQTS), short-QT syndrome, and early repolarization syndrome (ERS).

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 SCA and SCD. In this review, we discuss the definition of IVF, overlap with other primary arrhythmia syndromes, the diagnosis, and follow-up of patients with IVF.

Definition of IVF and Overlap With Other Primary Arrhythmia Syndromes

Two different consensus statements about IVF have been published, and proposed 2 different definitions of IVF. 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 that describes IVF as the terminology that best acknowledges our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia. The second and more recent definition is from the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus statement of inherited primary arrhythmia syndromes and defines IVF as a resuscitated cardiac arrest victim, preferably with documentation of VF, in whom known cardiac, respiratory, metabolic and toxicological causes have been excluded through clinical evaluation. In other words, the diagnosis IVF depends on the absence of a substrate for VF and exclusion of specific diseases, including structural cardiac disease (ie, myocarditis, cardiac sarcoidosis, arrhythmogenic right ventricular, hypertrophic, and dilated cardiomyopathy) and primary arrhythmia syndromes (ie, BrS, CPVT, LQTS, short-QT syndrome, and ERS).

Most primary arrhythmia disorders were regarded as IVF before they were discovered. For example, BrS was described as IVF in a 1998 Nature article. Studies in which careful phenotypic and genetic analysis had been performed showed that these primary arrhythmia syndromes are actually separate disease entities, with a separate pathophysiology.

The differentiation between IVF and other primary arrhythmia syndromes has been facilitated by the advance in genetic testing, for example in CPVT and LQTS patients where the yield of genetic testing is 60% and 75%, respectively. In addition, genetic testing has facilitated the detection of causative mutations for IVF, such as the Dutch DPP6-haploype and CALM1.

Early repolarization (ER) is a common electrocardiographic finding that is present in 1% to 5% of the general population. ER pattern is defined as J-point elevation of ≥0.1 mV in ≥2 contiguous leads of a standard 12-lead ECG, excluding leads V1–V3, with an end-QRS notch or slur on the downslope of the R wave with an onset above the baseline. Although ER historically was regarded as a benign finding, multiple studies have shown that ER, and specifically ER in the inferior and lateral leads is associated with an increased risk of VF and SCD. ER pattern is differentiated from ERS, that 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. 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 ER pattern have been identified. Therefore, ERS is considered a separate disease entity that is distinct from IVF. If a patient shows ER that does not fulfill the criteria as mentioned above than these abnormalities are not explanatory and the diagnosis IVF remains.

Short-coupled ventricular premature beats (VPBs) may elicit Torsades de Pointes (TdP) or immediate VF. A subgroup of IVF patients show short-coupled TdP (scTdP)/VF. The pathogenesis of short-coupled VPBs is largely unknown, although a genetic origin is detected in a limited number of patients with scTdP/VF including the Dutch DPP6-haplotype, a novel RyR mutation that causes scTdP in rest, and a novel IRX3 mutation. Until the pathogenesis is further specified, scTdP/VF remains a subgroup of IVF because no particular phenotype responsible for VF can be detected either on the ECG nor during additional diagnostic testing.

Concerning IVF: when do we classify VF as idiopathic? This is a matter of opinion and open for discussion. In fact, here we publish not a consensus document but a personal opinion that incites debate. In our definition of IVF, we have made a distinction between pathogeneses with a clear (sometimes provoked) phenotype, such as LQTS (nonidiopathic) and those without such an obvious phenotype (idiopathic): for example, CALM1 and DPP6 mutations that are still associated with an unclear phenotype. Future research will possibly link these particular mutations to separate disease entities as happened with BrS and other diagnoses (Figure 1).

Pathophysiological Mechanism of IVF and Overlap With Other Arrhythmia Syndromes

The exact pathogenesis and pathophysiological mechanism of IVF are unknown. We hypothesize that IVF has a heterogeneous pathogenesis that is different for each patient with IVF. First, IVF might have a monogenic origin. Second, the origin could be polygenic. Third, the origin might be multifactorial in which mono- or polygenetic mutations need particular environmental and discrete subclinical structural abnormalities, for example minimal electrolyte disturbances such as a mild hypokalemia or development of small areas of fibrotic myocardial tissue, that are currently undetectable with the available diagnostic modalities. The monogenic hypothesis (ie, the hypothesis that the disease is caused by 1 gene mutation) is supported by the detection of several causative mutations in patients with IVF, including DPP6, CALM1, the novel RyR2 mutation, and IRX3. The detection of candidate genes for IVF has been accelerated by the advance in genetic testing and the greater availability of new techniques, such as whole-exome or whole-genome sequencing. However, these extensive genetic data need a critical appraisal against the background, genetic noise rate, as many variants of uncertain clinical significance are concurrently detected. In addition, functional studies have to further elucidate the underlying mechanism that translates novel candidate genes into arrhythmogenesis. Although the monogenic hypothesis is supported by the available literature, the polygenic hypothesis (ie, the hypothesis that the disease is caused by ≥2 gene mutations) and the second hit hypothesis (ie, the hypothesis that the disease is the result of accumulated mutations to the cell’s DNA) cannot be rejected, as no research has been conducted in these areas.

The pathogenic mutations that are described in inherited primary arrhythmia syndromes and IVF cause changes in the cardiac ion channels. This results in altered ion currents disrupting the normal cardiac action potential morphology. Potentially, any change in action potential morphology might lead to enhanced arrhythmogenesis.
The cellular mechanism of short-coupled VPBs and scTdP is dependent on the transient outward potassium (K⁺) current (also known as \( I_{to} \)) of the His and Purkinje fibers. An increase in \( I_{to} \) causes a deeper phase 1 of the cardiac action potential. Because the \( I_{to} \) only increases in the Purkinje fibers, a strong local repolarization gradient is created with the adjacent ventricular myocardium that results in local ectopy and short-coupled VPBs. VPBs with a short-coupled interval (ie, R-on-T phenomenon) can cause phase 2 reentry and hereby elicit VF.¹⁶

### Differential Diagnosis of Patients With VF
VF has an extensive differential diagnosis consisting of many cardiac and noncardiac causes. As the definition of IVF implies, structural cardiac, primary arrhythmic, respiratory, metabolic, and toxicological causes must be excluded before IVF is diagnosed. Because noncardiac causes of VF are usually easily detected by simple laboratory and toxicological assessment, we exclusively discuss the potential cardiac causes of VF. Table 1 shows, if known, an overview of the incidence and prevalence of the diseases in the cardiac differential diagnosis.

#### Table 1. Differential Diagnosis of IVF

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence/Prevalence</th>
<th>SCD as First Manifestation of Disease</th>
<th>Event Rate</th>
</tr>
</thead>
</table>
| CAD/MI           | Incidence MI: 785 000/yr in the United States²¹  
Prevalence CAD: 17.6 million in the United States²¹ | 20%²²                                      | Death rate CAD: 287–390/100 000/yr for males and 201–277/100 000/yr for females²¹ |
| Coronary artery spasm | Incidence: unknown  
Prevalence: unknown | 2.4% (35/1429)²³ | 14% (2/14) of patients with a secondary prophylactic ICD received appropriate ICD therapy (FU 3.2 y)²³ |
| DCM             | Incidence: 3.6–7.9/100 000 person-years²⁴  
Prevalence: 1/2700²⁴ | Rarely                                      | Unknown                                        |
| HCM             | Incidence: 1.4–3.6/100 000 person-years²⁴  
Prevalence: 1/500²⁵ | Unknown                                      | 5%/y ICD discharge rate²⁶ (skewed toward a more severe phenotype) |
| ARVD/C           | Incidence: unknown  
Prevalence: 1/5000²⁷ | 13%²⁸                                      | 19% (16/84) of primary prophylactic ICD patients showed recurrence of VF (FU 4.7 y)²⁸ |
| BrS              | Incidence: unknown  
Prevalence: 50–100/100 000³ | Unknown                                      | Event rate per year per group of presentation²⁹:  
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 000³ | Unknown                                      | 13% (87/647) of genotyped patients with LQTS 1, 2, or 3 experienced cardiac arrest before the age of 40 years and before initiation of treatment (FU 6.2 y)³¹ |
| CPVT             | Incidence: unknown  
Prevalence: 10/100 000³ | Unknown                                      | Arrhythmic event rate³²:  
Probands: 21.7 per 1000 person-years  
Relatives with \( RYR2 \) mutation: 4.4 per 1000 person-years |
| SQTS             | Incidence: unknown  
Prevalence: unknown | 40% (19/47)³³ | 16% (10/62) of patients experienced VF (FU 60 mo)³³ |
| ERS              | Incidence ERS: unknown  
Prevalence ER: in normal population: 1%  
to 5%³⁴  
in patients with IVF: 7% to 31%³⁴⁵ | 100% (presentation with VF or SCD is part of the definition of ERS) | Unknown |
| Myocarditis      | Incidence: unknown  
Prevalence: unknown | 16% (17/112)³⁶ | Unknown |
| Cardiac sarcoïdosis | Incidence: unknown  
Prevalence: 20–30/100 000 for pulmonary sarcoïdosis, of which 5% has cardiac involvement³⁷ | 41% (16/42) of patients with myocardial sarcoïdosis confirmed on autopsy presented with SCD³⁸ | Unknown |
| IVF             | Incidence: Estimated 4900–47 000 patients/y in the United States  
Prevalence: unknown | 100%                                      | Appropriate ICD therapy in 11% to 43%³⁴³⁵⁴⁶ |

ARDV/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.
of IVF, the percentage of patients presenting with (aborted) SCD as first manifestation, and event rates of recurrences of VT/VF for each specific disease.

Diagnosis of IVF

The correct diagnosis of IVF requires extensive diagnostic testing. Routine testing excludes the most common causes of VF. Routine testing usually comprises blood chemistry (cardiac enzymes, electrolytes, and thyroid function), toxicological screening, ECG, chest x-ray, echocardiography, exercise testing, Holter or telemetry monitoring, coronary angiography with or without ventriculography, and magnetic resonance imaging. In young patients (<45 years) with a low risk for coronary artery disease, coronary CT or MR angiography is an alternative for coronary angiography because the sensitivity, specificity, and especially the negative predictive value are high.41,42 If coronary CT or MR is normal, coronary angiography is not necessary. The mandatory additional diagnostic tests are ergonovine or acetylcholine provocation to exclude coronary artery spasm and administration of a sodium channel blocker (ajmaline, flecainide, procainamide, or pilocarpine) to exclude BrS. 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. Table 2 shows the diagnostic value of the additional provocation tests, specified per disease.

Genetic testing increasingly contributes in diagnosing concealed primary arrhythmia syndromes. The role of extensive genetic testing is, however, controversial in patients with IVF.5 Targeted genetic screening based on phenotype is performed in a limited number of patients with IVF and the yield is heterogeneous. In addition, variants of uncertain clinical significance may lead to unnecessary treatment and anxiety among patients.56–68 Genetic screening is performed in a limited number of patients, and the yield is heterogeneous.17,18,34,60 We recommend genetic screening in IVF patients with a negative phenotype with a basic panel of SCN5A and the most common LQTS genes (KCNQ1 and KCNH2), as half of the patients with BrS who present with SCA have a concealed phenotype, and ≈25% of genotype-positive LQTS patients have a normal QT-interval.30,65 If a patient presents with exercise- or emotion-induced VF, we recommend additional screening of RyR2 and CALM1. Genomic testing is a matter of debate, and caution is warranted as a negative genetic test result does neither exclude concealed primary arrhythmia syndromes nor a genetic origin of IVF. Although the limited available data on targeted exome sequencing of large gene panels in SCD victims <50 years of age show a yield of 21% to 32%, it is not routinely recommended because the finding of variants of unknown clinical significance may lead to unnecessary treatment and anxiety among patients.56–68

Characteristics and Follow-Up of Patients With IVF

Multiple studies that focused on IVF have been published; however, data on the diagnosis and follow-up of patients with IVF are limited.17,18,35 Only one study shows the long-term follow-up of 200 patients with an apparently unexplained cardiac arrest and no evident cardiac disease as cause of the cardiac arrest.34 The other available data on the follow-up of patients with IVF are derived from cohort studies, mostly published before the introduction of magnetic resonance imaging, and report largely incomplete diagnostic data (Figure 2). Structural cardiac diseases and primary arrhythmia syndromes were not systematically excluded; therefore, these cohorts are presumably confounded with patients with unrecognized underlying disease. Nevertheless, these are the best available data on the diagnosis and follow-up of patients with IVF. Table 4 shows the characteristics of these cohorts.

ICD Therapy in Patients With IVF

The only therapeutic option in patients with IVF is secondary prevention with a prophylactic implantable cardiac defibrillator (ICD). ICD implantation in patients with IVF is justified by the high recurrence rate of ventricular arrhythmias, varying from 11% to 45%.34,39,40 A meta-analysis showed recurrences of arrhythmias in 31% of the patients with IVF during a mean follow-up of 5.3 years.40 Another study showed appropriate ICD therapy in 43% in a median follow-up of 8.8 years, but also included patients with ERS.39 A recent study showed a lower rate of appropriate ICD therapy: 11% of patients with IVF received one or multiple appropriate shocks in a mean follow-up of 3.2 years, with a median time to first shock of 2.6 years.34

No predictors for appropriate ICD therapy have been identified in patients with IVF, although patients with ERS show higher recurrence of ventricular arrhythmias.39 The limited available data on inappropriate ICD therapy show a high rate of inappropriate shocks (14% to 44%; mean follow-up, 1.9–8.8 years).34,39,70 The reason for most inappropriate shocks is atrial fibrillation. The limited data on ICD complications show complications in 17% in a mean follow-up of 41±27 months.70
Table 2. Diagnostic Value Additional Tests

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Population</th>
<th>Cut-Off Values</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracoronary acetylcholine; Coronary artery spasm</td>
<td>Okumura et al⁴³ 70 patients with previous chest pain with total occlusion or severe spasm at CAG</td>
<td>Occlusion or severe spasm at CAG</td>
<td>90%</td>
<td>99%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Intravenous ergonovine; Coronary artery spasm</td>
<td>Waters et al⁴⁴ 34 patients with CAS (chest pain, relief of chest pain with nitroglycerine and ST elevation on ECG)</td>
<td>ST elevation ≥2 mm on surface ECG</td>
<td>90%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ajmaline test; BrS</td>
<td>Veitmann et al⁴⁵ 382 genotyped patients (20% SCN5A carrier)</td>
<td>Type 1 Brugada ECG</td>
<td>76%</td>
<td>43%</td>
<td>24%</td>
<td>88%</td>
</tr>
<tr>
<td>Hong et al⁴⁶ 104 genotyped patients (35 SCN5A carriers) of which 71 received an ajmaline challenge</td>
<td>Type 1 Brugada ECG</td>
<td>80%</td>
<td>94%</td>
<td>93%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Flecaïnine test; BrS</td>
<td>Meregalli et al⁴⁷ 110 genotyped patients (35 SCN5A carriers)</td>
<td>Type 1 Brugada ECG</td>
<td>77%</td>
<td>80%</td>
<td>96%</td>
<td>36%</td>
</tr>
<tr>
<td>Epinephrine test; LQTS</td>
<td>Vyas et al⁴⁸ 125 genotyped patients (LQT1, 2, and 3)</td>
<td>QTc cut-off NR Epinephrine test abnormal if paradoxical QT prolongation &gt;30 ms occurred</td>
<td>92%</td>
<td>86%</td>
<td>76%</td>
<td>96%</td>
</tr>
<tr>
<td>Shimizu et al⁴⁹ 90 patients (31 LQT1, 23 LQT2, 6 LQT3, and 30 healthy controls)</td>
<td>∆QTc ≥35 ms</td>
<td>LQT1 90%</td>
<td>97%</td>
<td>97%</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Clur et al⁵⁰ 41 children with clinical suspicion of LQTS</td>
<td>QTc* cutoff &gt;470 ms in asymptomatic individuals QTc* cutoff &gt;450 ms in symptomatic individuals</td>
<td>50%</td>
<td>61%</td>
<td>6%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Krahn et al⁵¹ 170 patients, including 58% SCA survivors, 21% SCA relatives, 18% SCD relatives, and 4% patients with syncope</td>
<td>Absolute QT interval prolonged by ≥30 ms</td>
<td>40%†</td>
<td>84%</td>
<td>50%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Exercise test; LQTS</td>
<td>Andsrova et al⁵² 105 patients with KCNQ1 or KCNH2 mutation</td>
<td>QTc cut-off NR</td>
<td>92%</td>
<td>93%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sy et al⁵³ 152 genotyped LQT1 and LQT2 patients</td>
<td>Algorithm rest QTc+exercise-QTc QTc* cutoff &gt;470 ms in males or &gt;480 ms in females Exercise-QTc measured at 4-min recovery</td>
<td>94%</td>
<td>82%</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Krahn et al⁵⁴ 23 patients (14 LQTS score &gt;4, 9 family members of LQT patients) and 40 healthy controls</td>
<td>∆RT &gt;25 ms (ΔRT=RT interval at 1 min recovery subtracted from RT interval at a similar heart rate during exercise)</td>
<td>73%</td>
<td>92%</td>
<td>79%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>QTc prolongation provocation by QTc posture test; LQTS</td>
<td>Adler et al⁵⁵ 108 genotyped LQT1, LQT2, and LQT3 patients</td>
<td>QTc* cutoff &gt;490 ms</td>
<td>89%</td>
<td>87%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Viskin et al⁵⁶ 68 patients (31 LQT1, 28 LQT2, 3 LQT3, and 6 unsuccessful genotyped) and 82 healthy controls</td>
<td>Maximal QT-stretching (not further specified)</td>
<td>90%</td>
<td>86%</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Epinephrine test; CPVT</td>
<td>Marjamaa et al⁵⁷ 36 patients (25 RyR carriers, 11 genetically undefined CPVT patients) and 45 healthy unaffected family members</td>
<td>≥3 consecutive VPBs or recurrent couplets or sustained bigeminal rhythm and &gt;10 single VPBs per minute</td>
<td>28%</td>
<td>98%</td>
<td>88%</td>
<td>75%</td>
</tr>
</tbody>
</table>

(Continued)
of diagnostic techniques have improved the early detection of specific diseases. High-resolution imaging modalities such as magnetic resonance imaging have been introduced, enhanced the detection of small structural abnormalities, and facilitated diagnosing early-stage cardiomyopathy. New provocation tests and disease algorithms for concealed primary arrhythmia syndromes have been developed, for example ajmaline provocation for the exclusion of BrS and the 1993 Schwartz criteria for LQTS. Genetic testing has become increasingly available and contributed in the early diagnosis of concealed primary arrhythmia syndromes.

The consensus statements provide no or limited advice on the follow-up of patients with IVF. The only advice on follow-up was provided in the 1997 IVF consensus statement that recommended ECG, Holter monitoring, and echocardiograms to be repeated every year.3 We recommend follow-up of patients with IVF because a third of patients initially diagnosed with IVF reveal a specific disease during follow-up. Diagnosis of a specific disease generally requires lifestyle modifications to be repeated every year.3 We recommend follow-up of patients with IVF because a third of patients initially diagnosed with IVF reveal a specific disease during follow-up. Diagnosis of a specific disease generally requires lifestyle

**Table 2. Continued**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Population</th>
<th>Cut-Off Values</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al60</td>
<td>67 genotyped asymptomatic CPVT relatives</td>
<td>Bigeminal VPBs, VPB couplets, or ventricular tachycardia (≥3 of consecutive VPBs)</td>
<td>50%</td>
<td>97%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blich et al59</td>
<td>16 CPVT patients with CASD2 mutation and 36 healthy subjects</td>
<td>≥3 consecutive VPBs at peak exercise</td>
<td>97%</td>
<td>100%</td>
<td>94%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Necessity of Follow-Up and Reassessment of Diagnosis

Today, only 7% of patients reveal a specific diagnosis during follow-up because of comprehensive advanced testing at time of the index event.34 However, historically almost 30% of patients initially diagnosed with IVF qualify for a specific diagnosis during follow-up. This emphasizes the need for follow-up as in current daily practice many patients were diagnosed with IVF after limited diagnostic testing.69,70

The first explanation that many patients qualify for a specific disease is that structural or electric abnormalities were (clinically) absent at time of the index event and developed during follow-up. The second explanation is that the relatively new diagnoses such as BrS were not recognized or described yet at the time of the index event. BrS was first described in 1992, before then patients with BrS were incorrectly regarded as patients with IVF.7 The third explanation is that development of diagnostic techniques have improved the early detection of specific diseases.

**Table 3. Yield of Genetic Testing**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Population</th>
<th>Selection of Patients for Genetic Screening</th>
<th>Genes That Were Screened</th>
<th>Yield</th>
<th>Detected Pathogenic Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai et al60</td>
<td>175 patients with IVF or a family history of unexplained SCD</td>
<td>All patients</td>
<td>LQTS: KCN1, KCN2, SCN5A, KCN1, KCNE2, BrS: SCN5A CPVT: RyR2</td>
<td>9% (15/175)</td>
<td>NR</td>
</tr>
<tr>
<td>Herman et al64</td>
<td>200 patients with unexplained cardiac arrest with normal ECG, echocardiography, and CAG</td>
<td>Basis of phenotype detection after systematic clinical testing</td>
<td>LQTS: KCN1, KCN2, SCN5A, KCN1, KCNE2, BrS: SCN5A CPVT: RyR2</td>
<td>8% (13/158)</td>
<td>RyR2 (2 patients; CPVT), DSP (2 patients; ARVD/C), PKP2 (3 patients; ARVD/C), KCNH2 (1; LQT2), SCN5A (2 patients; BrS and LQT3), LMNA (1 patient; no diagnosis specified, has concurrent RyR2 mutation), KCNQ1 (1 patient; probable diagnosis not specified), TMEM43 (1 patient; ARVD/C)</td>
</tr>
<tr>
<td>Knecht et al17</td>
<td>38 patients with IVF caused by short-coupled VPBs</td>
<td>In patients suspected of channelopathy</td>
<td>NR</td>
<td>0% (0/14)</td>
<td>None</td>
</tr>
<tr>
<td>Haissaguerre et al64</td>
<td>37 patients with IVF caused by short-coupled VPBs</td>
<td>In patients suspected of channelopathy, including 5 patients with a family history of SCD</td>
<td>BrS: SCN5A LQTS: KCNH2</td>
<td>0% (0/12)</td>
<td>None</td>
</tr>
</tbody>
</table>

ARVD/C indicates arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; CAG, coronary angiography; CPVT, catecholaminergic polymorphic ventricular tachycardia; IF, idiopathic ventricular fibrillation; LQT2, long-QT syndrome type 2; NR, not reported; SCD, sudden cardiac death; and VPB, ventricular premature beat.
changes and initiation of pharmacological treatment, for example avoidance of competitive sports in patients with CPVT, HCM, arrhythmogenic right ventricular dysplasia/cardiomyopathy, and LQTS, treatment with β-blockers in CPVT and LQTS patients, specific drug avoidance in patients with LQTS and BrS and prevention or treatment of fever in patients with BrS. Patients incorrectly diagnosed with IVF are deprived of therapy that could prevent recurrence of ventricular arrhythmias. Moreover, detection of inherited disease has implications about family counseling and screening. Family members of patients with inherited disease should undergo phenotypic, and if applicable genetic, screening. Affected family members should receive prophylactic therapy and lifestyle changes if indicated. No particular data are available on the value of screening the family of patients with IVF. We recommend cardiac screening of first degree relatives with ECG, echocardiography, and exercise test. Further cascade family screening is indicated in case either a pathogenic mutation is found (for example DPP6 or CALM1) or a specific diagnosis is revealed.

Table 4. FU of Patients Initially Diagnosed With IVF

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Year of Publication</th>
<th>No. of Patients Included</th>
<th>Mean FU (mo)</th>
<th>Specific Diagnosis Detected After Additional Diagnostics or During FU; N (%)</th>
<th>Mean Age During IVF Event, y</th>
<th>ICD Implantation; N (%)</th>
<th>No. of IVF Patients With Arrhythmia Recurrence; N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman et al34</td>
<td>2016</td>
<td>200 (134 with initial diagnosis IVF)</td>
<td>3.15±2.34 y</td>
<td>13(7)</td>
<td>119 (90*) 73(61)/46(39)</td>
<td>NR Whole cohort: 46±14.7</td>
<td>111 (93)</td>
</tr>
<tr>
<td>Remme et al69</td>
<td>2001</td>
<td>37</td>
<td>77±41</td>
<td>4(11)</td>
<td>33 (89) NR/NR Whole cohort: 26(70)/11(30)</td>
<td>35±17</td>
<td>23 (62)</td>
</tr>
<tr>
<td>Champagne et al70</td>
<td>2005</td>
<td>29</td>
<td>41±27</td>
<td>11(38)</td>
<td>18 (62) 13 (72)/5 (28)</td>
<td>42±14</td>
<td>All (100)</td>
</tr>
<tr>
<td>Meissner et al71</td>
<td>1993</td>
<td>28</td>
<td>30.6</td>
<td>0</td>
<td>28 (100) 15 (54)/13 (46)</td>
<td>42±14</td>
<td>All (100)</td>
</tr>
<tr>
<td>Mewis et al72</td>
<td>1998</td>
<td>18</td>
<td>45±29</td>
<td>0</td>
<td>18 (100) 9 (50)/9 (50)</td>
<td>48±14</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Crijns et al73</td>
<td>1995</td>
<td>10</td>
<td>32</td>
<td>0</td>
<td>10 (100) 8 (60)/2 (20)</td>
<td>37±11</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>N/A</td>
<td>385 (254 with initial diagnosis of IVF)</td>
<td>42 mol/L</td>
<td>28(11†)</td>
<td>226 (94) NR/NR</td>
<td>45</td>
<td>193 (80)</td>
</tr>
</tbody>
</table>

FU indicates follow-up; ICD, implantable cardiac defibrillator; IVF, idiopathic ventricular fibrillation; N/A, not applicable; and NR, not reported.

* Ninety percent of 134 patients with an initial diagnosis of IVF.
† Eleven percent of 254 patients with an initial diagnosis IVF.
Guidelines provide limited guidance in the diagnosis and follow-up of patients with IVF; therefore, a protocol is required. A protocol as shown in Figure 3 may be suggested.

Future Perspectives

The incidence of IVF is declining and we expect the number of patients with IVF to decline further. This decline 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. Historically, after limited diagnostic testing all VF patients with an apparently normal heart were diagnosed with IVF, resulting in a heterogeneous and comprehensive group of patients with IVF. Today, IVF is redefined as a rare primary arrhythmia syndrome of unknown, maybe (mono- or poly-) genetic origin that shows different manifestations including scTdP, which however are not explanatory for the arrhythmic event. Genetic testing including the screening of large multigene panels and exome or genome sequencing, followed by functional studies, might redefine IVF even further in the future.

In the present expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, extensive genetic testing is not recommended in patients with IVF because of the low yield and high costs. However, the costs of genetic testing have decreased, resulting in an increase in the feasibility of genetic testing. Consequently, large custom multigene panels have been created and are rapidly replacing targeted genetic screening based on phenotype. However, the yield of these custom multigene panels has yet to be determined. Moreover, an increasing number of variants of uncertain clinical significance are detected. The interpretation and clinical use of these variants of uncertain clinical significance is challenging. Future research, and more specifically functional studies, have to demonstrate the causality between variants of uncertain clinical significance and IVF.

Conclusions

The diagnosis of IVF depends on exclusion of cardiac, respiratory, metabolic, and toxicological causes. Differentiation from structural cardiac disease and other primary arrhythmia syndromes is critical for targeted therapy, follow-up, and family screening. The present expert consensus statements provide limited guidance on the diagnosis and follow-up of patients with IVF. Therefore, we proposed a protocol for the diagnosis and follow-up of IVF. Follow-up is of utmost importance because ≤30% of patients initially diagnosed with IVF qualify for a specific disease during follow-up. Reassessment of diagnosis is, therefore, always necessary in patients with IVF.

Disclosures

None.

References


IVF: Definition, Diagnosis, and Follow-Up


56. Ryvke IVF: Definition, Diagnosis, and F ollow-Up


Key Words: coronary artery disease ■ incidence ■ sudden cardiac death ■ ventricular fibrillation ■ ventricular tachycardia
Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up
Marloes Visser, Jeroen F. van der Heijden, Pieter A. Doevendans, Peter Loh, Arthur A. Wilde and Rutger J. Hassink

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### Recommended cardiac MRI protocol based on the ARVD/C protocol

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Imaging plane</th>
<th>Parameters</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double inversion recovery TSE/FSE</td>
<td>a) Axial: obtain ~6-8 images centered on the left/right ventricle</td>
<td>TR = 2 R-R intervals, TE = 5 msec (minimum-full) (GE), TE = 30 msec (Siemens)</td>
<td>This sequence provides optimal tissue characterization of the RV free wall. Prescribe from the pulmonary artery to the diaphragm. Fat suppression improves reader confidence in diagnosis of RV fat infiltration.</td>
</tr>
<tr>
<td></td>
<td>b) Short axis: obtain ~6-8 images centered on the left ventricle</td>
<td>slice thickness = 5 mm, interslice gap = 5 mm, and field of view (FOV) = 28–34 cm. ETL 16-24</td>
<td></td>
</tr>
<tr>
<td>SSFP Bright Blood Cine Images</td>
<td>Axial, Four chamber and Short Axis. RV 3 chamber (optional)</td>
<td>TR/TE minimum, flip angle = 45-70°, slice thickness = 8 mm, interslice gap = 2 mm. FOV = 36–40 cm, 16–20 views per segment. Parallel imaging n = 2 is desirable</td>
<td>Axial images are best to assess RV wall motion. RV quantitative analysis is performed on the short axis cine images.</td>
</tr>
<tr>
<td>Gadolinium is administered according to institutional protocol (usually 0.15-0.2 mmol/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TI scout</td>
<td>Four chamber</td>
<td>TI scout sequences or trial TI times to suppress normal myocardium for the right</td>
<td></td>
</tr>
<tr>
<td>Delayed Gadolinium Imaging (Phase Sensitive Inversion Recovery recommended)</td>
<td>Axial, Short Axis, Four Chamber and Vertical Long Axis</td>
<td>TR/TE per manufacturer recommendations flip angle = 20-25°, slice thickness = 8 mm, interslice gap = 2 mm. FOV = 36–40 cm, No parallel imaging. Use phase sensitive inversion recovery if available (PSIR)</td>
<td>PSIR is more robust and independent of TI time. Optimal for imaging fibrosis. LV epicardial enhancement in the infero-lateral wall has been reported in classic ARVC and in left dominant forms.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARVC Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, LV left ventricle, FOV field of view, FSE fast spin echo, PSIR phase sensitive inversion recovery, RV right ventricle, SSFP steady state free precession, TE echo time, TI inversion time, TR repetition time, TSE Turbo spin echo. Adapted from te Riele et al. Journal of Cardiovascular Magnetic Resonance 2014;16:50.