

Idiopathic Ventricular Fibrillation The Struggle for Definition, Diagnosis, and Follow-Up

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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.¹ However, SCA/SCD in young patients is mainly caused by congenital disorders of primary arrhythmic or structural origin.² 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.³

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.⁴ 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.⁵ 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.⁶ 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.^{7,8} The differentiation between IVF and other primary arrhythmic 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.⁹ In addition, genetic testing has facilitated the detection of causative mutations for IVF, such as the Dutch *DPP6*-haplotype and *CALMI*.^{10,11}

Early repolarization (ER) is a common electrocardiographic finding that is present in 1% to 5% of the general population.¹² 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.^{5,13} 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.¹⁴ 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.⁵ 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

Received December 3, 2015; accepted February 25, 2016.

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The Data Supplement is available at <http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.115.003817/-/DC1>.

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(*Circ Arrhythm Electrophysiol*. 2016;9:e003817. DOI: 10.1161/CIRCEP.115.003817.)

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Circ Arrhythm Electrophysiol is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.115.003817

familial inheritance of a malign ER pattern have been identified.¹⁵ 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.¹⁶ A subgroup of IVF patients show short-coupled VPBs causing TdP/VF. In these patients, mapping and ablation proved effective to prevent recurrence of short coupled TdP (scTdP)/VF.^{17,18} 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.^{10,19,20} 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.^{10,19,20} Second, the origin could be polygenic. Third, the origin might be multifactorial in which mono- or polygenic 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*.^{10,11,19,20} 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.⁹

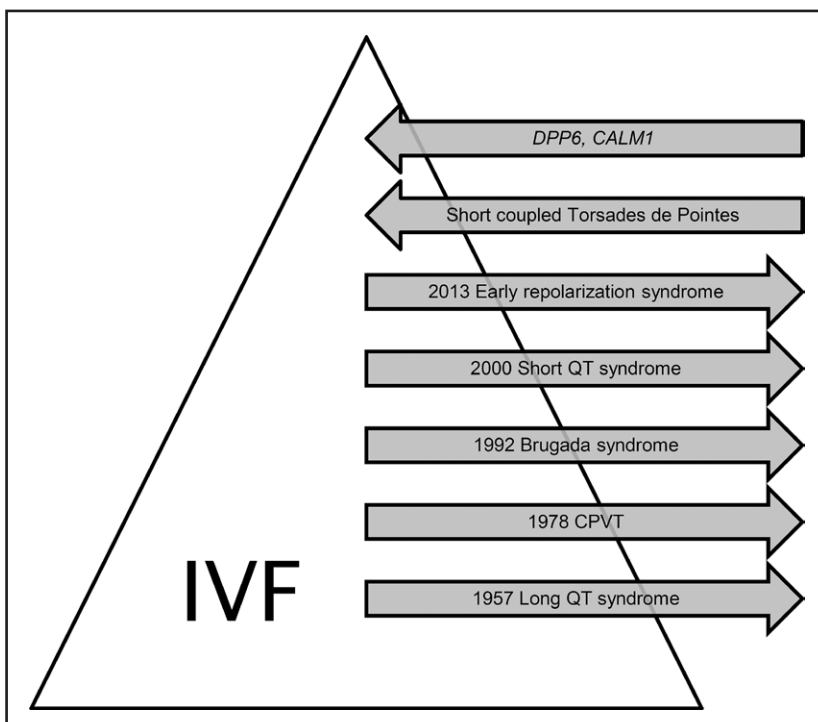


Figure 1. Schematic illustration of the evolution of the diagnosis idiopathic ventricular fibrillation (IVF). In the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus, statement on the diagnosis of patients with inherited primary arrhythmia syndromes early repolarization syndrome was for the first time mentioned as a separate disease entity.⁵ *CALM1* indicates calmodulin 1 gene mutation; CPVT, catecholaminergic polymorphic ventricular tachycardia; and *DPP6*, Dutch *DPP6* risk haplotype associated with sudden cardiac death.

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

Disease	Incidence/Prevalence	SCD as First Manifestation of Disease	Event Rate
CAD/MI	Incidence MI: 785 000/y in the United States ²¹ Prevalence CAD: 17.6 million in the United States ²¹	20% ²²	Death rate CAD: 287–390/100 000/y for males and 201–277/100 000/y for females ²¹
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-years ²⁴ Prevalence: 1/2700 ²⁴	Rarely	Unknown
HCM	Incidence: 1.4–3.6/100 000 person-years ²⁴ Prevalence: 1/500 ²⁵	Unknown Annual death rate SCD 0.7% ²⁶ 35% (44/125) of all HCM-related deaths are sudden and unexpected ²⁶	5%/y ICD discharge rate ²⁶ (skewed toward a more severe phenotype)
ARVD/C	Incidence: unknown Prevalence: 1/5000 ²⁷	13% ²⁸	19% (16/84) of primary prophylactic ICD patients showed recurrence of VF (FU 4.7 y) ²⁹
BrS	Incidence: unknown Prevalence: 50–100/100 000 ⁵	Unknown	Event rate per year per group of presentation ³⁰ : 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 ⁵	Unknown 2% (23/1049) of young athletes with SCD in postmortem studies ²	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: 10/100 000 ⁵	Unknown	Arrhythmic event rate ³² : Probands: 21.7 per 1000 person-years Relatives with <i>RyR2</i> 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% ¹² in patients with IVF: 7% to 31% ^{34,35}	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 sarcoidosis	Incidence: unknown Prevalence: 20–30/100 000 for pulmonary sarcoidosis, of which 5% has cardiac involvement ³⁷	41% (16/42) of patients with myocardial sarcoidosis confirmed on autopsy presented with SCD ³⁸	Unknown
IVF	Incidence: Estimated 4900–47 000 patients/y in the United States Prevalence: unknown	100%	Appropriate ICD therapy in 11% to 43% ^{34,39,40}

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.

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 pilsicainide) 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 are frequently detected. Table 3 shows the yield of genetic testing in patients with IVF.

In summary, acetylcholine and ergonovine have a comparable sensitivity in diagnosing coronary artery spasm.^{43,44} Coronary artery spasm provocation has a potential risk of arrhythmias; however, this risk is acceptable with an overall incidence of $\approx 5\%$ of arrhythmic complications that can usually be treated adequately.^{61,62} The value of diagnosing coronary artery spasm and the subsequent medical treatment and prevention of ischemic and important arrhythmic events outweighs, in our opinion, the risks of the test.

Of the sodium channel blockers, ajmaline and flecainide show a comparable sensitivity in diagnosing BrS; however, when compared to each other flecainide fails to identify 32% of the patients with BrS.^{45–47,63} The exact sensitivity of pilsicainide and procainamide is unknown, but all sodium channel blockers are suitable to diagnose BrS. The choice of sodium channel blocker depends on the availability and differs per country.

Although epinephrine shows a high sensitivity and specificity in diagnosing LQTS, healthy subjects show a high number of false-positive test results.⁶⁴ Therefore, the epinephrine test is of no additive value in the regular evaluation of LQTS. A good alternative is the highly sensitive QTc posture test, in which QT prolongation is provoked by brisk standing.^{55,56} Epinephrine provocation testing is also not

suitable for diagnosing CPVT because of the low sensitivity and specificity.⁵⁷

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 $\approx 25\%$ 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*. Genetic 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.^{66–68}

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 \pm 27 months.⁷⁰

Table 2. Diagnostic Value Additional Tests

Cohort	Population	Cut-Off Values	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	
Intracoronary acetylcholine; Coronary artery spasm							
Okumura et al ⁴³	70 patients with previous chest pain with total occlusion or severe spasm at CAG	Occlusion or severe spasm at CAG	90%	99%	NR	NR	
Intravenous ergonovine; Coronary artery spasm							
Waters et al ⁴⁴	34 patients with CAS (chest pain, relief of chest pain with nitroglycerine and ST elevation on ECG)	ST elevation ≥ 2 mm on surface ECG	90%	NR	NR	NR	
Ajmaline test; BrS							
Veltmann et al ⁴⁵	382 genotyped patients (20% <i>SCN5A</i> carrier)	Type 1 Brugada ECG	76%	43%	24%	88%	
Hong et al ⁴⁶	104 genotyped patients (35 <i>SCN5A</i> carriers) of which 71 received an ajmaline challenge	Type 1 Brugada ECG	80%	94%	93%	83%	
Flecainide test; BrS							
Meregalli et al ⁴⁷	110 genotyped patients (35 <i>SCN5A</i> carriers)	Type 1 Brugada ECG	77%	80%	96%	36%	
Epinephrine test; LQTS							
Vyas et al ⁴⁸	125 genotyped patients (LQT1, 2, and 3)	QTc cut-off NR Epinephrine test abnormal if paradoxical QT prolongation >30 ms occurred	92%	86%	76%	96%	
Shimizu et al ⁴⁹	90 patients (31 LQT1, 23 LQT2, 6 LQT3, and 30 healthy controls)	$\Delta QTc \geq 35$ ms	LQT1	90%	97%	97%	91%
			LQT2	91%	90%	88%	93%
Clur et al ⁵⁰	41 children with clinical suspicion of LQTS	QTc* cutoff >470 ms in asymptomatic individuals QTc* cutoff >450 m in symptomatic individuals	50%	61%	6%	96%	
Krahn et al ⁵¹	170 patients, including 58% SCA survivors, 21% SCA relatives, 18% SCD relatives, and 4% patients with syncope	Absolute QT interval prolonged by ≥ 30 ms	40%†	84%	50%	78%	
Exercise test; LQTS							
Andrsova et al ⁵²	105 patients with <i>KCNQ1</i> or <i>KCNH2</i> mutation	QTc cut-off NR	92%	93%	NR	NR	
Sy et al ⁵³	152 genotyped LQT1 and LQT2 patients	Algorithm rest QTc+exercise-QTc QTc* cutoff >470 ms in males or >480 ms in females Exercise-QTc measured at 4-min recovery	94%	82%	NR	NR	
Krahn et al ⁵⁴	23 patients (14 LQTS score >4 , 9 family members of LQT patients) and 40 healthy controls	$\Delta RT > 25$ ms ($\Delta RT = RT$ interval at 1 min recovery subtracted from RT interval at a similar heart rate during exercise)	73%	92%	79%	90%	
QTc prolongation provocation by QTc posture test; LQTS							
Adler et al ⁵⁵	108 genotyped LQT1, LQT2, and LQT3 patients	QTc* cutoff >490 ms	89%	87%	NR	NR	
Viskin et al ⁵⁶	68 patients (31 LQT1, 28 LQT2, 3 LQT3, and 6 unsuccessful genotyped) and 82 healthy controls	Maximal QT-stretching (not further specified)	90%	86%	NR	NR	
Epinephrine test; CPVT							
Marjamaa et al ⁵⁷	36 patients (25 <i>RyR</i> carriers, 11 genetically undefined CPVT patients) and 45 healthy unaffected family members	≥ 3 consecutive VPBs or recurrent couplets or sustained bigeminal rhythm and >10 single VPBs per minute	28%	98%	88%	75%	

(Continued)

Table 2. Continued

Cohort	Population	Cut-Off Values	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Exercise test; CPVT						
Hayashi et al ⁵⁸	67 genotyped asymptomatic CPVT relatives	Bigeminal VPBs, VPB couplets, or ventricular tachycardia (≥ 3 of successive VPBs)	50%	97%	NR	NR
Blich et al ⁵⁹	16 CPVT patients with <i>CASQ2</i> mutation and 36 healthy subjects	≥ 3 consecutive VPBs at peak exercise	97%	100%	94%	100%

BrS indicates Brugada syndrome; CAG, coronary angiography; CAS, coronary artery spasm; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQT1, long-QT syndrome type 1; LQT2, long-QT syndrome type 2; LQT3, long-QT syndrome type 3; LQTS, long-QT syndrome; QTc, corrected QT interval; NR, not reported; SCA, sudden cardiac arrest; SCD, sudden cardiac death; and VPB, ventricular premature beat.

*QTc measured in lead II and V5 using Bazett formula.

†Sensitivity calculated with positive exercise test or genetic test as a gold standard.

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. 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.⁴ 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 3. Yield of Genetic Testing

Cohort	Population	Selection of Patients for Genetic Screening	Genes That Were Screened	Yield	Detected Pathogenic Mutations
Bai et al ⁶⁰	175 patients with IVF or a family history of unexplained SCD	All patients	LQTS: <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> BrS: <i>SCN5A</i> CPVT: <i>RyR2</i>	9% (15/175)	NR
Herman et al ⁶⁴	200 patients with unexplained cardiac arrest with normal ECG, echocardiography, and CAG	Basis of phenotype detection after systematic clinical testing	LQTS: <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> BrS: <i>SCN5A</i> ARVD/C: <i>PKP2</i> , <i>DSP</i> CPVT: <i>RyR2</i>	8% (13/158)	<i>RyR2</i> (2 patients; CPVT), <i>DSP</i> (2 patients; ARVD/C), <i>PKP2</i> (3 patients; ARVD/C), <i>KCNH2</i> (1; LQT2), <i>SCN5A</i> (2 patients; BrS and LQT3), <i>LMNA</i> (1 patient; no diagnosis specified, has concurrent <i>RyR2</i> mutation), <i>KCNQ1</i> (1 patient; probable diagnosis not specified), <i>TMEM43</i> (1 patient; ARVD/C)
Knecht et al ¹⁷	38 patients with IVF caused by short-coupled VPBs	In patients suspected of channelopathy	NR	0% (0/14)	None
Haissaguerre et al ¹⁸	37 patients with IVF caused by short-coupled VPBs	In patients suspected of channelopathy, including 5 patients with a family history of SCD	BrS: <i>SCN5A</i> LQTS: <i>KCNH2</i>	0% (0/12)	None

ARVD/C indicates arrhythmogenic cardiomyopathy; BrS, Brugada syndrome; CAG, coronary angiography; CPVT, catecholaminergic polymorphic ventricular tachycardia; IVF, idiopathic ventricular fibrillation; LQT2, long-QT syndrome type 2; NR, not reported; SCD, sudden cardiac death; and VPB, ventricular premature beat.

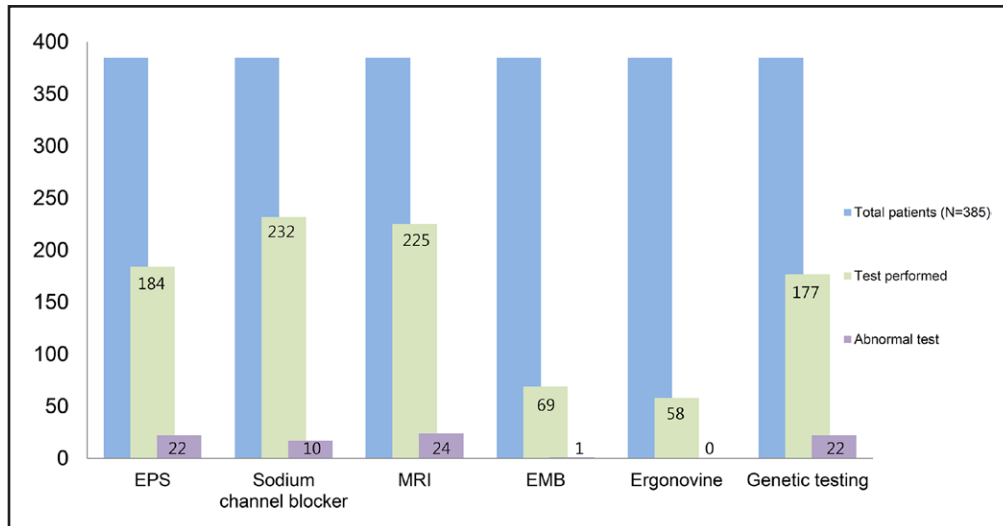


Figure 2. Performed diagnostic tests and yield. EMB indicates endomyocardial biopsy; EPS, electrophysiological study; and MRI, magnetic resonance imaging.

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

Cohort	Year of Publication	No. of Patients Included	Mean FU (mo)	Specific Diagnosis Detected After Additional Diagnostics or During FU; N (%)	Patients With IVF; N (%) Male/Female; N (%)	Mean Age During IVF Event, y	ICD Implantation; N (%)	No. of IVF Patients With Arrhythmia Recurrence; N (%)
Herman et al ³⁴	2016	200 (134 with initial diagnosis IVF)	3.15 \pm 2.34 y	13(7)	119 (90*) 73(61)/46(39)	NR Whole cohort: 48 \pm 14.7	111 (93)	10 (11)
Remme et al ⁶⁹	2001	37	77 \pm 41	4(11)	33 (89) NR/NR Whole cohort: 26(70)/11(30)	35 \pm 17	23 (62)	NR Whole cohort: 16 (43)
Champagne et al ⁷⁰	2005	29	41 \pm 27	11(38)	18 (62) 13 (72)/5 (28)	42 \pm 14	All (100)	7 (39)
Meissner et al ⁷¹	1993	28	30.6	0	28 (100) 15 (54)/13 (46)	42 \pm 14	All (100)	16 (57)
Mewis et al ⁷²	1998	18	45 \pm 29	0	18 (100) 9 (50)/9 (50)	48 \pm 14	1 (6)	2 (11)
Crijns et al ⁷³	1995	10	32	0	10 (100) 8 (80)/2 (20)	37 \pm 11	1 (10)	0 (0)
Total	N/A	385 (254 with initial diagnosis of IVF)	42 mol/L	28(11†)	226 (94) NR/NR	45	193 (80)	NR

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.

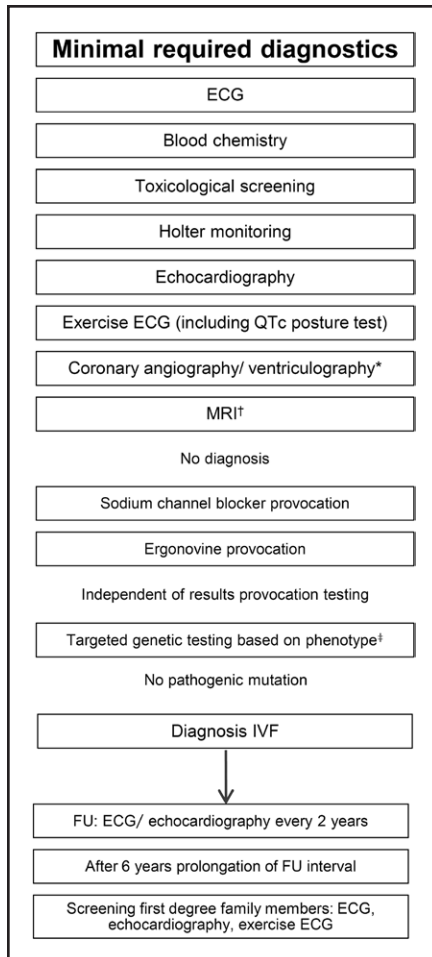


Figure 3. Proposed flowchart for the diagnosis and follow-up of patients with idiopathic ventricular fibrillation (IVF). *In young patients (<45 years) without risk factors for coronary artery disease, coronary computed tomography (CT; or MR) angiography is an alternative diagnostic tool to exclude coronary artery disease. The sensitivity is 85% and 99%, respectively, the specificity is 90% and 64%, respectively, the positive predictive value is 91% and 86%, respectively, and the negative predictive value is 83% and 90%, respectively.^{41,42} Coronary CT angiography has a higher sensitivity compared with magnetic resonance imaging (MRI) in detecting coronary stenosis; therefore, CT is a better alternative for coronary angiography.⁷⁴ †A proposed acquisition protocol for cardiac MRI is available in the Data Supplement and is based on the arrhythmogenic right ventricular dysplasia/cardiomyopathy protocol. ‡Proposed genetic testing consists of a basic panel of *SCN5A*, the most common long-QT genes (*KCNQ1* and *KCNH2*), *RyR2*, and *CALM1* in patients with exercise-induced VF. In patients with a negative phenotype, we recommend *SCN5A*, *KCNQ1*, and *KCNH2* screening. FU indicates follow-up.

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.⁵ 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 $\leq 30\%$ 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.

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KEY WORDS: coronary artery disease ■ incidence ■ sudden cardiac death ■ ventricular fibrillation ■ ventricular tachycardia

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Circ Arrhythm Electrophysiol. 2016;9:

doi: 10.1161/CIRCEP.115.003817

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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SUPPLEMENTARY MATERIAL

Recommended cardiac MRI protocol based on the ARVD/C protocol			
Sequence	Imaging plane	Parameters	Comments
<p><i>Double inversion recovery TSE/FSE</i></p> <p><i>a) Axial: with and without fat suppression</i></p> <p><i>b) short axis: without fat suppression</i></p>	<p>a) Axial: obtain ~6-8 images centered on the left/right ventricle</p> <p>b) Short axis: obtain ~6-8 images centered on the left ventricle</p>	<p>TR = 2 R-R intervals, TE = 5 msec (minimum-full) (GE), TE = 30 msec (Siemens) slice thickness = 5 mm, interslice gap = 5 mm, and field of view (FOV) = 28-34 cm. ETL 16-24</p>	<p>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.</p>
<p><i>SSFP Bright Blood Cine Images</i></p>	<p>Axial, Four chamber and Short Axis. RV 3 chamber (optional)</p>	<p>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</p>	<p>Axial images are best to assess RV wall motion. RV quantitative analysis is performed on the short axis cine images.</p>
<p>Gadolinium is administered according to institutional protocol (usually 0.15-0.2 mmol/kg)</p>			
<p>TI scout</p>	<p>Four chamber</p>		<p>TI scout sequences or trial TI times to suppress normal myocardium for the right</p>

			inversion time.
Delayed Gadolinium Imaging (Phase Sensitive Inversion Recovery recommended)	Axial, Short Axis, Four Chamber and Vertical Long Axis	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)	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.

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;16:50.¹

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