Original Article

Long-Term Outcome of Patients Initially Diagnosed With Idiopathic Ventricular Fibrillation

A Descriptive Study

Marloes Visser, MD; Jeroen F. van der Heijden, MD, PhD; Jasper J. van der Smagt, MD, PhD; Pieter A. Doevendans, MD, PhD; Arthur A. Wilde, MD, PhD; Peter Loh, MD, PhD; Rutger J. Hassink, MD, PhD

Background—Idiopathic ventricular fibrillation (IVF) is a rare cause of sudden cardiac arrest. Limited data are available on the long-term outcome of IVF patients.

Methods and Results—In this retrospective cohort study, 107 consecutive patients with an initial diagnosis of IVF were analyzed (age at index event 40.4 years, 60% male). Missing diagnostic data were acquired during follow-up, including genetic testing, to exclude underlying disease. A specific diagnosis was revealed in 22 of 107 patients (21%) during a median follow-up of 10.2 years. Mortality rate was 9% in IVF patients (8/85). Appropriate implantable cardioverter–defibrillator therapy was delivered in 23 patients (29%) of 78 IVF patients with an implantable cardioverter–defibrillator, with a median of 3 appropriate shocks per patient.

Conclusions—One fifth of the patients initially diagnosed with IVF reveal a specific diagnosis during long-term follow-up. Additional diagnostic testing, including genetic testing, contributes to the detection of specific diseases. The recurrence rate of ventricular arrhythmias in IVF patients is high. Our data show the importance of thorough follow-up and reassessment of diagnosis in IVF patients. (***Circ Arrhythm Electrophysiol*. 2016;9:e004258. DOI: 10.1161/CIRCEP.116.004258.)**

Key Words: follow-up study ■ genetic testing ■ sudden cardiac death ■ ventricular fibrillation

Background

Idiopathic ventricular fibrillation (IVF) is a rare cause of sudden cardiac arrest. IVF is currently defined as a resuscitated cardiac arrest victim, preferably with documentation of ventricular fibrillation (VF), in whom known cardiac, respiratory, metabolic, and toxicological causes have been excluded through clinical evaluation.[1] In other words, IVF is diagnosed after exclusion of specific underlying diseases by comprehensive clinical investigation. However, 7% to 35% of patients initially diagnosed with IVF reveal a specific disease during follow-up.[2–4]

Approximately 5% of sudden cardiac deaths are attributed to IVF.[5,6] The exact incidence of IVF is unknown but has decreased with the detection of new primary arrhythmia syndromes, and the introduction of high-resolution imaging modalities, such as the cardiac magnetic resonance imaging (MRI). Genetic testing has increasingly contributed in diagnosing concealed primary inherited arrhythmia syndromes, thereby excluding IVF.[7] In addition, genetic testing is increasingly important for family screening and counseling.

Limited data are available on the natural history of IVF, the diagnostic findings during long-term follow-up, including distribution of putative pathogenic mutations, and the management of patients with IVF and their family members. Our study analyzed a large cohort of patients initially diagnosed with IVF. The objective of our study was to report the natural history, the long-term follow-up including the detection of specific diseases, the yield of genetic testing, the occurrence of implantable cardioverter–defibrillator (ICD) therapy, and the yield of family screening in patients with an initial diagnosis of IVF.

Methods

Patient Population

We performed a retrospective single-center cohort study of 107 consecutive patients initially diagnosed with IVF, admitted to the University Medical Center Utrecht (UMCU) between 1986 and 2015. Missing diagnostic data, for example genetic data, were obtained in all patients if possible. In other words, all patients were re-evaluated, and missing diagnostic tests were either subsequently performed or repeated during follow-up to exclude all underlying causes of VF.

Received April 14, 2016; accepted September 16, 2016.

From the Departments of Cardiology (M.V., J.F.v.d.H., P.A.D., P.L., R.J.H.) and Clinical Genetics (J.J.v.d.S.), University Medical Centre, Utrecht, The Netherlands; Department of Internal Medicine and Cardiology, Bergman Clinics, Bilthoven, The Netherlands (M.V., R.J.H.); and Department of Clinical and Experimental Cardiology, Heart Centre, AMC, Amsterdam, The Netherlands (A.A.W.).

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.116.004258/-/DC1.

Correspondence to Marloes Visser, MD, Department of Cardiology/Electrophysiology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail m.visser-14@umcutrecht.nl

WHAT IS KNOWN

- IVF is a rare cause of sudden cardiac arrest, and limited data are available on the long-term follow-up of patients.

WHAT THE STUDY ADDS

- Of the patients initially diagnosed with IVF, 21% developed a specific diagnosis during a median follow-up of 10.2 years.
- The yield of genetic testing in patients initially diagnosed with IVF is 15%.
- The recurrence rate of ventricular arrhythmias is high in IVF patients, with 29% receiving appropriate ICD therapy.

We enrolled all patients admitted between 1986 and 2015 with an unexplained cardiac arrest with initial rhythm of VF, in whom known cardiac, respiratory, metabolic, and toxicological causes were excluded at first presentation. Accepted diagnostic criteria were used to exclude specific diseases. Missing inclusions were retrieved by selection from 2612 patients who received an ICD between 1994 and 2015. This study was approved by the local ethics committee of the UMCU. Because of the retrospective nature of the study, informed consent of patients was regarded unnecessary. A small number of included patients were also included in a study that was previously published.[8]

Clinical Investigation

Patient and family history was obtained in all patients. Routine testing was performed in all patients, including blood chemistry (cardiac enzymes, electrolytes, and thyroid function), toxicological screening, ECG, chest x-ray, echocardiography, exercise testing, Holter or telemetry monitoring, and coronary angiography with or without left and right angiogram (or coronary computed tomographic angiography in patients <30 years). ECGs at admission, and, if available, at 1, 5, and 10 years of follow-up were retrospectively evaluated for signs of ischemia, resting corrected QT interval, type 1 Brugada pattern, early repolarization (ER) as defined in the 2015 consensus paper on the definition of ER, and arrhythmogenic right ventricular dysplasia/cardiomyopathy criteria as defined in the 2010 Task Force Criteria.[9,10] Because ER syndrome is described as a separate disease entity in the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes, all patients admitted since 2013 with documented ER detected at the time of the index event were diagnosed with ER syndrome and were, therefore, excluded from analysis.[1] Echocardiography was used to assess left ventricular ejection fraction, valve abnormalities, and signs of cardiomyopathy. Exercise testing was performed with a standard Bruce protocol and evaluated for signs of ischemia, QT prolongation, and arrhythmias. Coronary angiography was normal in a total of 100 patients with the absence of coronary anomalies, coronary artery disease (defined as stenosis ≥50%), and signs of coronary artery spasm defined as typical chest pain or ST-elevation of ≥1 mm on ECG. In 7 patients without coronary angiography, coronary computed tomographic angiography (calcium score) was normal. Left ventricular ejection fraction, defined as ≥50%, was normal in all patients using echocardiography, nuclear imaging, or MRI. MRI became a routine diagnostic tool in 2004. MRI scans were acquired in all 49 patients admitted since 2004 (45% of total) and were evaluated for signs of cardiomyopathy, sarcoidosis, amyloidosis, and myocarditis. Right and left ventricular angiograms were normal in 69 of 107 patients (65%) and in 41 of 58 (71%) of patients in whom no MRI was acquired.

Ergonovine provocation was performed in 52 patients (53%) and was positive for coronary artery spasm if ≥2 mm ST-elevation occurred. Sodium channel blocker challenge (flecainide or ajmaline) was performed in 62 patients (58%) to exclude Brugada syndrome (BrS) and was not performed in patients who revealed a specific diagnosis during follow-up (n=13), patients with a contraindication (n=12, all patients with bundle-branch block), patients who objected (n=9), deceased patients (n=8), and patients who were lost to follow-up (n=3). The test was diagnostic for BrS if a type 1 Brugada pattern appeared. Endomyocardial biopsy was performed in 48 patients (44%) and was evaluated for signs of cardiomyopathy, myocarditis, or sarcoidosis.

Genetic Testing

Targeted genetic testing was performed in 79 of 107 patients (74%). Genetic testing was not performed in patients who deceased before genetic testing could have been performed (n=12), patients who objected (n=12), or were lost to follow-up (n=6). Genetic testing consisted of single-targeted gene testing by Sanger sequencing based on phenotype detection after clinical evaluation showed clues for a specific disease not sufficient for diagnosis (n=25) or next-generation sequencing (NGS) of a panel of 33 genes (n=53) associated with an increased risk of ventricular arrhythmias and sudden cardiac death (Table 1), with addition of the *DPP6* haplotype associated with IVF in Dutch patients.[11] Single-targeted genetic testing was extended to NGS of 33 genes in all patients unless NGS was infeasible (10 patients disclosed a pathogenic mutation with single-targeted testing, 6 patients revealed a specific diagnosis during follow-up, 4 patients did not want to participate in further genetic testing, 3 patients were lost to follow-up, and 2 patients deceased before permission for NGS was obtained).

Gene mutations were classified as pathogenic if they have been confirmed as definitive disease-causing based on existing gene-networks and if they were absent in European control alleles (ExAC database Broadinstitute.org). Variants of uncertain clinical significance were considered nonpathogenic. Pathogenic mutations detected with NGS were confirmed by Sanger sequencing.

Follow-Up

Follow-up was conducted in all patients and consisted of biannual outpatient visits to the cardiologist, with the documentation of symptoms, physical examination, ECG, and ICD interrogation. At least one echocardiography was performed during follow-up.

Statistical Analysis

Patient characteristics were reported as percentages, counts, median (interquartile ranges [IQR]), or mean±SD, as appropriate. Continuous data were compared using the independent Student *t* test or Mann–Whitney *U* test. Categorical data were compared using χ^2 or Fisher exact test. The estimated event-free survival probabilities

Table 1. Genetic Screening

AKAP9	*CASQ2*	*DSP*	*KCNE2*
KCNJ8	*RYR2*	*SNTA1*	*ANK2*
CAV3	*GPD1L*	*KCNE3*	*KCNQ1*
SCN1B	*TGFB3*	*CACNA1C*	*DES*
HCN4	*KCNH2*	*LMNA*	*SCN3B*
TMEM43	*DSC2*	*JUP*	*KCNJ2*
DSG2	*KCNE1*	*KCNJ5*	*PLN*
CACNA2D1	*PKP2*	*SCN4B*	*CACNB2*
SCN5A	*DPP6* (VF risk haplotype only)		

were calculated using Kaplan–Meier analysis in which the follow-up period was calculated from the date of ICD implantation to the outcome event (appropriate ICD therapy) or censoring events (end of follow-up and death) and presented as median and 95% confidence interval. Univariate Cox regression was used to identify significant predictors of appropriate ICD therapy and predictors of developing a specific diagnosis. On the basis of the known or expected clinical relevance, the following predictors were selected for the univariate prediction model of appropriate ICD therapy: sex, age, genetic outcome, symptoms preceding the index event, and level of exercise at time of the index event. To assess factors associated with appropriate ICD shock frequency, we performed Poisson analysis or multivariate negative binomial regression analysis with scale parameter to adjust for overdispersion. The factors that we selected were sex, age at the time of index event, symptoms preceding the index event, level of exercise at the time of the index event, and if VF was induced during EPS. For developing a specific diagnosis, the following predictors were selected for the univariate prediction model: ICD therapy, sex, age at index event, symptoms preceding the index event, level of exercise at the time of the index event, and if VF was induced during EPS. Data were analyzed using IBM SPSS Statistics version 21.0 (IBM, Armonk, NY). A probability (P) <0.05 was considered significant.

Results

Patient Characteristics and Long-Term Clinical Outcomes

A specific diagnosis was revealed in 22 of 107 (21%) patients initially diagnosed with IVF (mean age at index-event 40.4 years; 64 males) during a median follow-up of 10.2 years (IQR: 3.9–17.1 years). The incidence rate of specific diagnoses was 1.9 per 100 person-years (95% confidence interval, 1.2–2.6). The median estimated probability of freedom of a specific disease was 22.1 (95% confidence interval, 21.0–23.1), calculated using Kaplan–Meier analysis. Figure 1 shows an overview of the detected diagnoses (more detailed information in the Data Supplement). Phenotypic family screening was performed in 17 of the 22 patients who revealed a specific diagnosis during follow-up and identified 2 affected family members (1 with BrS detected after ajmaline challenge and 1 with hypertrophic cardiomyopathy detected at MRI).

In 85 patients (79%), no specific diagnosis was revealed during follow-up. Baseline characteristics of the 22 patients who revealed a specific diagnosis and the 85 IVF patients are shown in Table 2. Patients who revealed a specific diagnosis had a significantly longer follow-up duration compared with IVF patients, were more often male, and had a higher incidence of a family history of SCD. Among the 85 IVF patients, 11 patients had short-coupled Torsade de Pointes (3 with the Dutch *DPP6* haplotype). None of the IVF patients showed ER on ECG; therefore, none of the patients were diagnosed with ER syndrome.

Genetic Testing

A pathogenic mutation was detected in 12 of the 79 patients; therefore, the yield of genetic testing was 15%. Of the 12 detected pathogenic mutations, 4 were diagnostic as the mutation revealed a specific diagnosis (catecholaminergic polymorphic ventricular tachycardia in 3 patients who all showed >3 ventricular premature beats at peak exercise during exercise ECG and long QT syndrome type 1 in 1 patient with a normal QT-interval in rest and 460 ms during exercise), 4 mutations were detected in arrhythmogenic right ventricular dysplasia/cardiomyopathy patients, 3 patients carried the Dutch *DPP6* haplotype, and 1 patient revealed an *MYL2* mutation with a corresponding hypertrophic cardiomyopathy phenotype.[9] Concurrently, NGS of 33 genes disclosed variants of uncertain clinical significance in 13 IVF patients. Additional

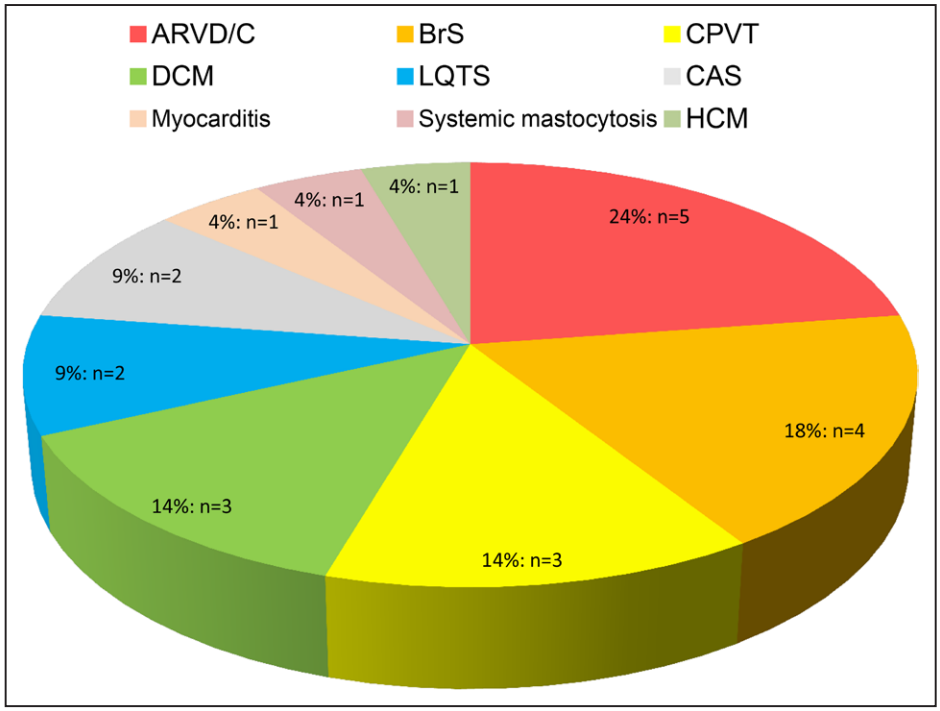

Figure 1. Overview of specific diagnoses that were revealed during follow-up. ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; BrS, Brugada syndrome; CAS, coronary artery spasm; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; and LQTS, long QT syndrome.

Table 2. Baseline Characteristics

	IVF Patients (n=85)		Patients Who Revealed Specific Disease During Follow-Up (n=22)		*P* Value*
Median follow-up	7.9 y (3.4–15.5)		15.6 yr (9.5–22.5)		0.004
Male sex	46 (54%)		17 (77%)		0.049
Median age at event†	40.4 (27.2–54.6)	Male 39.2 Female 42.4	39.8 (27.0–53.9)	Male 39.9 Female 35.4	0.622
Occurrence of VF					0.231
Rest	52 (61%)		9 (41%)		
Mild exercise	15 (18%)		7 (32%)		
Exercise	18 (21%)		6 (27%)		
Symptoms before CA	34 (40%)		11 (50%)		0.397
Palpitations	12 (14%)		5 (23%)		0.325
Syncope	17 (20%)		6 (27%)		0.459
Family history of SCD	5 (6%)		5 (23%)		0.016
ICD	78 (92%)		19 (87%)		0.438

CA indicates cardiac arrest; ICD, implantable cardiac defibrillator; IVF, idiopathic ventricular fibrillation, SCD, sudden cardiac death; and VF, ventricular fibrillation.

*Calculated with Mann–Whitney *U* test or χ^2 test as appropriate.

†Age in years.

clinical assessment and family screening could not establish pathogenicity of these variants. Genetic family screening was performed in 33 family members of the 12 patients with a pathogenic mutation and identified 12 mutation carriers. As a result, the yield of family screening was 36%.

Electrophysiological Testing

EPS was performed in 66 of the 85 IVF patients (78%). VF was induced in 22 patients (33%) with a standard stimulation protocol of a drive train of 8 complexes with an interval of 600 or 430 ms followed by 1 to 3 extrastimuli that were decremented to a coupling interval down to 180 ms. In 6 of the 22 patients, 3 extrastimuli were required to induce VF. In the other patients, 1 or 2 extrastimuli induced VF. EPS was repeated in 6 of the 22 patients after starting antiarrhythmic therapy to evaluate the effect of therapy (quinidine in 4 patients, sotalol in 1 patient, and amiodarone in 1 patient; only 3 of these 6 patients had an ICD, the other 3 patients experienced the index event before 1990 when ICDs were not routinely implanted). In the other 16 patients with inducible VF, an ICD was implanted; therefore, EPS was not repeated.

Ablation of ventricular premature beats was performed in 9 of the 11 patients with short-coupled Torsade de Pointes because of multiple appropriate ICD shocks. After radiofrequency ablation, 7 of the 9 patients were free from appropriate ICD therapy in a median follow-up of 6 years (IQR: 3.0–7.7) after ablation.

IVF Patients

In the IVF patients, age at event, family history of sudden cardiac death, symptoms, or level of exercise preceding the index event were comparable between men and women. Eight of the 85 IVF patients died during follow-up (9%). One patient died of recurrence of VF; he was diagnosed with IVF in 1987 and had no ICD. One patient died of myocardial infarction, 10 years after the index event. Four patients died of noncardiac causes (renal failure, non-Hodgkin lymphoma, pneumonia, and infection of a subdural hematoma). In 2 patients, the cause of death was unknown.

ICD Therapy in IVF Patients

An ICD was implanted in 92% of the IVF patients (78/85). Four patients refused ICD implantation, and 3 patients experienced cardiac arrest before 1990 when ICDs were not routinely implanted. These patients were free of symptoms with quinidine treatment; therefore, no ICD was implanted when ICDs became routinely available. The incidence rate of appropriate ICD therapy was 25.6 per 100 person-years (95% confidence interval, 8.8–42.4). The incidence rate of ≥1 appropriate shock per 100 person-years was 3.1 (95% confidence interval, 2.0–4.2).

Twenty-three patients (30% of the IVF patients with an ICD) received appropriate ICD therapy in a median follow-up of 7.9 years (IQR: 3.8–15.5 years). Eighteen patients received multiple ICD shocks (2 patients experienced only 1 episode with multiple shocks, 5 patients experienced multiple episodes of 1 shock per episode, and 11 patients experienced both single shocks and episodes with multiple shocks). Eleven patients (14%) experienced an electrical storm (defined as >3 shocks in 24 hours). The median number of shocks was 3 per person (IQR: 1.0–9.0). To assess factors of influence on appropriate ICD shock frequency, we performed negative binomial regression (Table 3). Male sex, lower age at the time of index event, and having symptoms preceding the index event were significantly associated with a higher appropriate shock frequency.

Table 3. Factors Associated With Receiving Multiple Appropriate ICD Shocks*

Factor	Rate Ratio	95% CI	*P* Value
Male sex	6.394	1.510–27.072	0.012
Higher age at index event	0.947	0.904–0.991	0.019
No symptoms before cardiac arrest	0.192	0.039–0.961	0.045
Index event during rest	1.293	0.304–5.500	0.728
No VF induced during EPS	0.917	0.250–3.361	0.896

CI indicates confidence interval; EPS, electrophysiological study; ICD, implantable cardiac defibrillator; NB, negative binomial; and VF, ventricular fibrillation.

*Calculated using negative binomial regression.

The underlying arrhythmia that caused the appropriate shock was VF in 18 patients and ventricular tachycardia in 5 patients. The estimated 1, 3, and 5 years free of appropriate ICD therapy probability was 87.8 (95% confidence interval, 80.4–95.2), 72.8 (95% confidence interval, 62.2–83.4), and 69.3 (95% confidence interval, 58.3–80.3) calculated using Kaplan–Meier analysis. In most patients who received appropriate ICD therapy, the first ICD shock occurred within the first 5 years of follow-up (78%; 18/23 IVF patients who received appropriate ICD therapy).

Eighteen patients (23%) received inappropriate ICD therapy because of atrial fibrillation (n=6), supraventricular tachycardia (n=5; 4 AV nodal re-entry tachycardia, 1 supraventricular tachycardia not further specified), sinus tachycardia (n=3), ICD-related reasons (n=2; malsensing and ICD failure), and unknown reasons (n=2). ICD-related complications occurred in 12% (9/78 patients; lead-related complications in 8 patients and a pocket infection in 1 patient). Figure 2 shows the Kaplan–Meier curve of the event-free survival of the IVF patients.

Predictors of Appropriate ICD Therapy and Developing a Specific Diagnosis

Univariate Cox regression analysis was performed to assess the predictors for appropriate ICD therapy and predictors for developing a specific diagnosis. As shown in Tables 4 and 5, none of the possible predictors were statistically significant.

Discussion

We present long-term follow-up of a large population of patients with an initial diagnosis of IVF. Our analysis of 107 patients shows that 21% of the patients reveal a specific diagnosis during follow-up, resulting in family screening and targeted preventive therapy. Most patients who revealed an underlying disease qualified for the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy or BrS. Genetic testing was performed in 74% of all patients and had a yield of 15%. However, only 4 diagnostic mutations were detected, and NGS concurrently disclosed 13 variants of uncertain clinical significance. Genetic family screening identified 12 mutation carriers and had a yield of 36%. Of the IVF

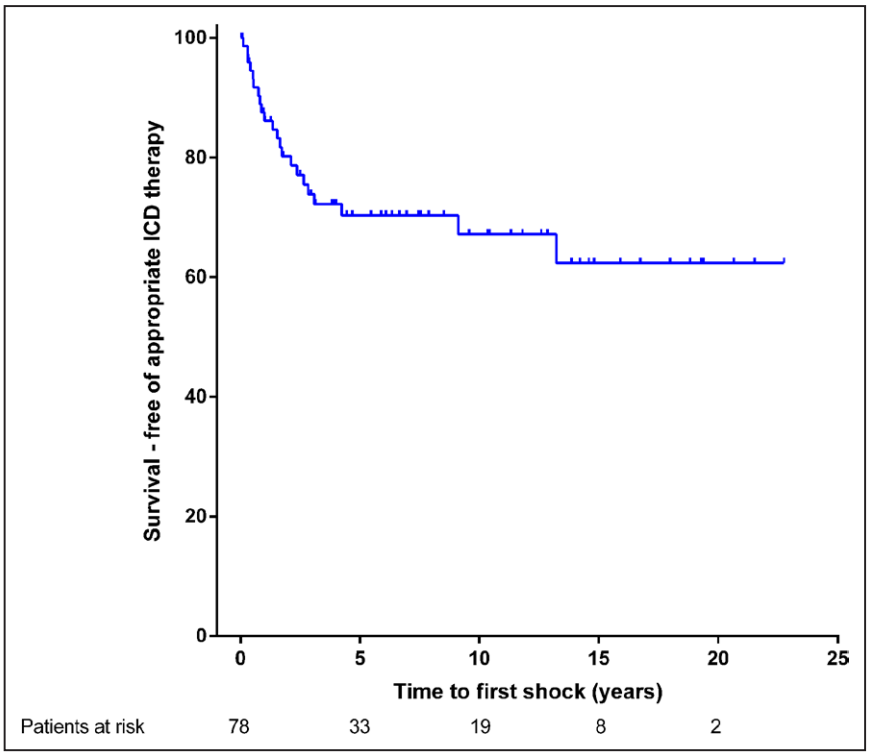

Figure 2. Kaplan–Meier curve of event-free survival in idiopathic ventricular fibrillation patients. ICD indicates implantable cardioverter–defibrillator.

Table 4. Predictors of Appropriate ICD Therapy

Predictor	Univariate HR	95% CI	*P* Value
Alternative diagnosis	1.500	0.679–3.312	0.32
Female sex	0.773	0.362–1.651	0.51
Age at index event	1.014	0.989–1.040	0.27
Symptoms before cardiac arrest	1.118	0.543–2.229	0.76
Index event during exercise	1.358	0.649–2.283	0.41
Pathogenic mutation	1.076	0.450–2.572	0.87
VF induced during EPS	1.265	0.564–2.835	0.57

CI indicates confidence interval; EPS, electrophysiological study; HR, hazard ratio; ICD, implantable cardioverter–defibrillator; and VF, ventricular fibrillation.

patients, 29% received appropriate ICD therapy. Most appropriate ICD shocks occurred in the first 5 years after the index event. Inappropriate ICD therapy occurred in 23% of the IVF patients and ICD-related complications in 13%.

Most previous studies about IVF focused on the presence of ER in IVF patients.[12–15] ER has a high prevalence of ≤30% in IVF patients and is associated with the recurrence of VF and electrical storm.[13,16–18] Initially, ER and ER syndrome were regarded as a subentity of IVF. However, ER syndrome has a distinctive phenotype and has shown to have a separate genetic substrate because several candidate genes for a familial inheritance of a malign ER pattern have been identified.[19,20] Consequently, ER syndrome is described as a separate disease entity in the 2013 consensus statement on the primary arrhythmia syndromes.[1] We also consider ER and ER syndrome as a separate disease entity that is distinct from IVF; therefore, we excluded all patients diagnosed with ER syndrome since 2013.[21] This partly explains the lack of ER in our IVF cohort, with the addition that ER was also simply not present in our cohort as re-evaluation of all available ECGs at 1, 5, and 10 years of follow-up did not show signs of ER.

Specific Diagnoses During Follow-Up

In our study, a specific diagnosis was revealed in one fifth of the patients during follow-up. These results are supported by older studies with small patient cohorts, in which a specific diagnosis emerged in 11% to 38% during follow-up.[3,8] More recent results come from the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER) registry that included all patients with an unexplained cardiac arrest who were free of evidence of coronary artery disease, left ventricular dysfunction, or evident repolarization syndromes.[2] Advanced testing revealed a diagnosis in 34% of patients at baseline. A specific diagnosis was revealed in 7% of patients during follow-up. These findings show that the initial diagnosis of IVF can change during follow-up, despite comprehensive clinical investigation at the time of the index event. In patients who revealed a specific diagnosis, structural or electric abnormalities were subtle or absent at the time of the index event and were, therefore, undetected, sometimes for years. In our cohort, 9 patients with a cardiomyopathy presented with VF as first manifestation, without qualifying for cardiomyopathy at the time of the index event. In these patients, signs of the underlying cardiomyopathy became overt during follow-up. Follow-up is, therefore, of utmost importance in IVF patients. Moreover, the diagnosis IVF must always be re-evaluated in every IVF patient.

Table 5. Predictors of Developing a Specific Diagnosis

Predictor	Univariate HR	95% CI	*P* Value
Appropriate ICD therapy	1.186	0.449–3.133	0.731
Inappropriate ICD therapy	1.236	0.260–5.884	0.790
Female sex	0.464	0.170–1.273	0.136
Age at index event	1.008	0.979–1.037	0.607
Symptoms before cardiac arrest	1.250	0.541–2.888	0.602
Index event during exercise	1.556	0.671–3.607	0.303
VF induced during EPS	1.763	0.723–4.300	0.213

CI indicates confidence interval; EPS, electrophysiological study; HR, hazard ratio; ICD, implantable cardioverter–defibrillator; and VF, ventricular fibrillation.

Patients with the *DPP6* haplotype were regarded as having IVF rather than having a specific diagnosis, according to the Dutch consensus.[21,22] Although an underlying cause is detected in these patients, the exact pathophysiological mechanism is unknown, and clinical abnormalities are absent. Therefore, *DPP6* is still regarded as IVF.

Genetic Testing

We screened a large panel of 33 genes associated with sudden cardiac death. The yield of genetic testing in our cohort was rather limited with pathogenic mutations detected in 15%. Only 4 diagnostic mutations were detected, all revealed a concealed underlying primary arrhythmia syndrome. Importantly, a negative genetic test result does not exclude a genetic origin of IVF because many novel variants associated with IVF have been detected, and not all novel mutations were included in our panel.[23,24]

Because the yield of genetic testing in IVF patients is relatively low and variants of uncertain clinical significance may be found, the current expert consensus statement on primary inherited arrhythmia syndromes does not recommend routine screening of large gene panels.[1] The limited available data that address single-targeted gene testing based on phenotype show a heterogeneous yield of 9% to 47%.[25–27] The yield of genetic testing in the CASPER registry was 8% (13 mutations in 158 patients).[2]

The relatively low yield of genetic testing in IVF patients is not comparable to the high yield in catecholaminergic polymorphic ventricular tachycardia or LQTS (82% and 73%, respectively).[28,29] However, genetic screening in IVF patients is useful in the detection of concealed primary arrhythmia syndromes, which leads to preventive therapy and lifestyle changes. Furthermore, the detection of a pathogenic mutation enables cascade molecular genetic testing, phenotypic screening, and counseling among relatives. In our study, family screening had a yield of 36% (12 detected mutation carriers in 33 screened family members), enabling prophylactic treatment in 58% of mutation carriers. Without genetic testing, the genotype-positive yet phenotype-negative family members

would be deprived of prophylactic therapy, resulting in an increased risk of ventricular arrhythmias.

ICD Therapy

In our study, the rate of appropriate ICD therapy in IVF patients is high: 29% received one or multiple appropriate ICD shocks during follow-up. The available data on appropriate ICD therapy in IVF patients show a high recurrence rate of ventricular arrhythmias, with appropriate ICD therapy in 11% to 45% in a mean follow-up of 3.2 to 5.3 years.[2,3,8,30,31] These results are comparable to our study and justify ICD implantation. In patients who experienced appropriate ICD therapy, a higher appropriate shock frequency was demonstrated in males, younger patients at the time of the index event, and patients who experienced symptoms before the index event.

The rate of inappropriate ICD shocks and ICD complications in our study is also high: 23% of the IVF patients received inappropriate ICD shocks, and ICD-related complications occurred in 13%. The limited available data show inappropriate ICD shocks in 14% to 44% of IVF patients, and ICD-related complications are reported in 17%. In the CASPER registry, the rate of inappropriate ICD is lower with 14% (12/89 IVF patients).[2] The rate of inappropriate therapy in the CASPER registry is probably lower because of the improvement of current state-of-the-art device generation and the development of sophisticated features, such as supraventricular tachycardia discrimination.

Limitations

A limitation of our study is the incompleteness of data. First, cardiac MRI was introduced in our center in 2004 and since then, all patients underwent MRI. The majority of patients diagnosed before 2004 received (non-MRI compatible) ICDs; therefore, MRI could not be performed during follow-up. In these patients, imaging follow-up was performed by echocardiography and revealed no structural heart disease during >10 years of follow-up. Second, BrS was not systematically ruled out in our population. Sodium channel provocation could not be performed in all patients because of contraindications, such as bundle branch block, because patients refused the provocation test, and because some patients were lost to follow-up or deceased.

Strengths

Although our data are incomplete, they represent real-world data in which we have to deal with such limitations. The IVF population described, including its inhomogeneities, represents the patients that we see during clinical practice. Moreover, we present data of one the largest cohorts of patients initially diagnosed with IVF, with the longest follow-up, thus, far reported. Our data give important insight in the evolution in diagnosis of IVF patients because of comprehensive additional diagnostic testing during follow-up, including genetic analysis.

Conclusions

One fifth of the patients initially diagnosed with IVF reveal a specific diagnosis during the long-term follow-up, illustrating that VF frequently occurs as the first manifestation of concealed or undetected underlying disease. Comprehensive clinical investigation, including genetic screening, contributes to the detection of these specific diseases. The recurrence rate of ventricular arrhythmias in IVF patients is high with almost a quarter of patients who received one or multiple appropriate ICD shocks. Our data show the importance of follow-up of patients initially diagnosed with IVF and suggest re-evaluation of diagnosis in every IVF patient. Diagnosis of a specific disease enables cascade family screening and initiation of prophylactic treatment in affected family members to prevent sudden cardiac death.

Disclosures

Dr Wilde is a member of the Scientific Advisory board of LilaNova. The other authors report no conflicts.

References

1. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014.
2. Herman AR, Cheung C, Gerull B, Simpson CS, Birnie DH, Klein GJ, Champagne J, Healey JS, Gibbs K, Talajic M, Gardner M, Bennett MT, Steinberg C, Janzen M, Gollob MH, Angaran P, Yee R, Leather R, Chakrabarti S, Sanatani S, Chauhan VS, Krahn AD. Response to Letter Regarding Article, "Outcome of apparently unexplained cardiac arrest: results from investigation and follow-up of the prospective cardiac arrest survivors with preserved ejection fraction registry". *Circ Arrhythm Electrophysiol*. 2016;9:e004012. doi: 10.1161/CIRCEP.116.004012.
3. Champagne J, Geelen P, Philippon F, Brugada P. Recurrent cardiac events in patients with idiopathic ventricular fibrillation, excluding patients with the Brugada syndrome. *BMC Med*. 2005;3:1. doi: 10.1186/1741-7015-3-1.
4. Vittoria Matassini M, Krahn AD, Gardner M, Champagne J, Sanatani S, Birnie DH, Gollob MH, Chauhan V, Simpson CS, Hamilton RM, Talajic M, Ahmad K, Gerull B, Chakrabarti S, Healey JS. Evolution of clinical diagnosis in patients presenting with unexplained cardiac arrest or syncope due to polymorphic ventricular tachycardia. *Heart Rhythm*. 2014;11:274–281. doi: 10.1016/j.hrthm.2013.11.008.
5. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation*. 1998;98:2334–2351.
6. Survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation. Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. *Circulation*. 1997;95:265–272.
7. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8:1308–1339. doi: 10.1016/j.hrthm.2011.05.020.
8. Remme CA, Wever EF, Wilde AA, Derksen R, Hauer RN. Diagnosis and long-term follow-up of the Brugada syndrome in patients with idiopathic ventricular fibrillation. *Eur Heart J*. 2001;22:400–409. doi: 10.1053/euhj.2000.2366.
9. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533–1541. doi: 10.1161/CIRCULATIONAHA.108.840827.

10. Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan GX. The Early Repolarization Pattern: A Consensus Paper. *J Am Coll Cardiol*. 2015;66:470–477. doi: 10.1016/j.jacc.2015.05.033.
11. Alders M, Koopmann TT, Christiaans I, Postema PG, Beekman L, Tanck MW, Zeppenfeld K, Loh P, Koch KT, Demolombe S, Mannens MM, Bezzina CR, Wilde AA. Haplotype-sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation. *Am J Hum Genet*. 2009;84:468–476. doi: 10.1016/j.ajhg.2009.02.009.
12. Haïssaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clémenty J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol*. 2009;53:612–619. doi: 10.1016/j.jacc.2008.10.044.
13. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med*. 2008;358:2016–2023. doi: 10.1056/NEJMoa071968.
14. Derval N, Lim HS, Haïssaguerre M. Dynamic electrocardiographic recordings in patients with idiopathic ventricular fibrillation. *J Electrocardiol*. 2013;46:451–455. doi: 10.1016/j.jelectrocard.2013.06.023.
15. Aizawa Y, Sato A, Watanabe H, Chinushi M, Furushima H, Horie M, Kaneko Y, Imaizumi T, Okubo K, Watanabe I, Shinozaki T, Aizawa Y, Fukuda K, Joo K, Haissaguerre M. Dynamicity of the J-wave in idiopathic ventricular fibrillation with a special reference to pause-dependent augmentation of the J-wave. *J Am Coll Cardiol*. 2012;59:1948–1953. doi: 10.1016/j.jacc.2012.02.028.
16. Derval N, Simpson CS, Birnie DH, Healey JS, Chauhan V, Champagne J, Gardner M, Sanatani S, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Ahmad K, Gollob MH, Haïssaguerre M, Klein GJ, Krahn AD. Prevalence and characteristics of early repolarization in the CASPER registry: cardiac arrest survivors with preserved ejection fraction registry. *J Am Coll Cardiol*. 2011;58:722–728. doi: 10.1016/j.jacc.2011.04.022.
17. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med*. 2009;361:2529–2537. doi: 10.1056/NEJMoa0907589.
18. Aizawa Y, Chinushi M, Hasegawa K, Naiki N, Horie M, Kaneko Y, Kurabayashi M, Ito S, Imaizumi T, Aizawa Y, Takatsuki S, Joo K, Sato M, Ebe K, Hosaka Y, Haissaguerre M, Fukuda K. Electrical storm in idiopathic ventricular fibrillation is associated with early repolarization. *J Am Coll Cardiol*. 2013;62:1015–1019. doi: 10.1016/j.jacc.2013.05.030.
19. Medeiros-Domingo A, Tan BH, Crotti L, Tester DJ, Eckhardt L, Cuoretti A, Kroboth SL, Song C, Zhou Q, Kopp D, Schwartz PJ, Makielski JC, Ackerman MJ. Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes. *Heart Rhythm*. 2010;7:1466–1471. doi: 10.1016/j.hrthm.2010.06.016.
20. Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpón E, Hu D, Desai M, Borggrefe M, Häissaguerre M, Kanter R, Pollevick GD, Guerchicoff A, Laiño R, Marieb M, Nademanee K, Nam GB, Robles R, Schimpf R, Stapleton DD, Viskin S, Winters S, Wolpert C, Zimmern S, Veltmann C, Antzelevitch C. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm*. 2010;7:1872–1882. doi: 10.1016/j.hrthm.2010.08.026.
21. Visser M, van der Heijden JF, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic ventricular fibrillation: the struggle for definition, diagnosis, and follow-up. *Circ Arrhythm Electrophysiol*. 2016;9:003817. doi: 10.1161/CIRCEP.115.003817.
22. Ten Sande JN, Postema PG, Boekholdt SM, Tan HL, van der Heijden JF, de Groot NM, Volders PG, Zeppenfeld K, Boersma LV, Nannenberg EA, Christiaans I, Wilde AA. Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13:905–912. doi: 10.1016/j.hrthm.2015.12.006.
23. Nakano Y, Chayama K, Ochi H, Toshishige M, Hayashida Y, Miki D, Hayes CN, Suzuki H, Tokuyama T, Oda N, Suenari K, Uchimura-Makita Y, Kajihara K, Sairaku A, Motoda C, Fujiwara M, Watanabe Y, Yoshida Y, Ohkubo K, Watanabe I, Nogami A, Hasegawa K, Watanabe H, Endo N, Aiba T, Shimizu W, Ohno S, Horie M, Arihiro K, Tashiro S, Makita N, Kihara Y. A nonsynonymous polymorphism in semaphorin 3A as a risk factor for human unexplained cardiac arrest with documented ventricular fibrillation. *PLoS Genet*. 2013;9:e1003364. doi: 10.1371/journal.pgen.1003364.
24. Marsman RF, Barc J, Beekman L, Alders M, Dooijes D, van den Wijngaard A, Ratbi I, Sefiani A, Bhuiyan ZA, Wilde AA, Bezzina CR. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. *J Am Coll Cardiol*. 2014;63:259–266. doi: 10.1016/j.jacc.2013.07.091.
25. Bai R, Napolitano C, Bloise R, Monteforte N, Priori SG. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. *Circ Arrhythm Electrophysiol*. 2009;2:6–15. doi: 10.1161/CIRCEP.108.782888.
26. Krahn AD, Healey JS, Chauhan V, Birnie DH, Simpson CS, Champagne J, Gardner M, Sanatani S, Exner DV, Klein GJ, Yee R, Skanes AC, Gula LJ, Gollob MH. Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). *Circulation*. 2009;120:278–285. doi: 10.1161/CIRCULATIONAHA.109.853143.
27. Haïssaguerre M, Shoda M, Jaïs P, Nogami A, Shah DC, Kautzner J, Arentz T, Kalushe D, Lamaison D, Griffith M, Cruz F, de Paola A, Gaïta F, Hocini M, Garrigue S, Macle L, Weerasooriya R, Clémenty J. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation*. 2002;106:962–967.
28. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106:69–74.
29. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, Lombardi MP, Dit Deprez RH, van Langen I, Wilde AA. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. *Circulation*. 2013;128:1513–1521. doi: 10.1161/CIRCULATIONAHA.112.000091.
30. Meissner MD, Lehmann MH, Steinman RT, Mosteller RD, Akhtar M, Calkins H, Cannom DS, Epstein AE, Fogoros RN, Liem LB. Ventricular fibrillation in patients without significant structural heart disease: a multicenter experience with implantable cardioverter-defibrillator therapy. *J Am Coll Cardiol*. 1993;21:1406–1412.
31. Ozaydin M, Moazzami K, Kalantarian S, Lee H, Mansour M, Ruskin JN. Long-Term Outcome of Patients With Idiopathic Ventricular Fibrillation: A Meta-Analysis. *J Cardiovasc Electrophysiol*. 2015;26:1095–1104. doi: 10.1111/jce.12737.

Long-Term Outcome of Patients Initially Diagnosed With Idiopathic Ventricular Fibrillation: A Descriptive Study

Marloes Visser, Jeroen F. van der Heijden, Jasper J. van der Smagt, Pieter A. Doevendans, Arthur A. Wilde, Peter Loh and Rutger J. Hassink

Circ Arrhythm Electrophysiol. 2016;9:
doi: 10.1161/CIRCEP.116.004258
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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

SUPPLEMENTAL MATERIAL

Overview of patients with a specific diagnosis detected during follow-up				
Patient	**Specific diagnosis**	**Time to detection of specific diagnosis (in years)**	**Diagnostic test that revealed specific diagnosis**	**Consequences specific diagnosis**
1	ARVD/C	5.9	ECG/ echocardiography	Patient already received pharmacological therapy, eventually heart transplantation because of end-stage heart failure. *Phenotypic family screening:* normal.
2	ARVD/C	12.5	Autopsy	None, patient deceased. *Phenotypic family screening:* not performed.
3	ARVD/C	21.3	ECG, RV angiography, genetic test > pathogenic *SCN5A* mutation*	Patient already received pharmacological therapy. *Phenotypic family screening:* normal. *Genetic family screening:* 4 of 5 siblings index patient; carriers of pathogenic mutation. Both children index patient; normal genotype. 1 of 3 tested nieces/nephews index patient; carrier pathogenic mutation. All carriers pathogenic mutation receive cardiological screening every 3 years with MRI, echocardiography, Holter monitoring, and exercise-ECG.
4	ARVD/C	3.7	Echocardiography, MRI, genetic test > pathogenic *DSG2* mutation	Beta-blocker and ACE-inhibitor therapy. *Phenotypic family screening:* both sons normal ECG, echocardiography, and MRI. *Genetic family screening:* not performed

				on both sons' request.
5	ARVD/C	10.4	ECG, echocardiography, genetic test > pathogenic *PKP2* mutation	Patient already received pharmacological therapy. *Phenotypic family screening*: father and brother normal. *Genetic family screening:* father normal genotype, brother no genetic screening performed.
6	BrS	22.4	Sodium channel blocker challenge (ajmaline)	Medication advice, *SCN5A* genetic test (negative). *Phenotypic family screening:* daughter has BrS (type 1 BrS ECG after ajmaline provocation).
7	BrS	15.4	Sodium channel blocker challenge (flecainide)	Medication advice, *SCN5A* genetic test (negative). *Phenotypic family screening:* 1 daughter deceased of unknown cause, 1 daughter normal phenotype, flecainide test normal.
8	BrS	7.5	ECG with spontaneous type 1 BrS during FU	Medication advice, *SCN5A* genetic test (negative). *Phenotypic and genetic family screening:* both children and both brothers; normal pheno- and genotype.
9	BrS	15.1	ECG with spontaneous type 1 BrS during FU	Medication advice, no genetic test performed. *Phenotypic family screening*: 2 daughters normal rest-ECG at young age.
10	CPVT	22.1	Genetic test > 1 pathogenic *RYR2* mutation, 1 variant of uncertain clinical significance in *RYR2*	Beta-blocker therapy, avoidance of peak exercise. *Phenotypic family screening:* normal. *Genetic family screening:* father; carrier pathogenic mutation , mother; carrier VUS, brother index patient; carrier VUS,

				both children index patient; normal genotype.
11	CPVT	21.8	Genetic test > pathogenic *RYR2* mutation	Beta-blocker therapy, avoidance of peak exercise, ICD removal, stellectomy. *Phenotypic and genetic family screening:* sister carrier mutation; both daughters are in the phenotypic and genetic screening process.
12	CPVT	1.1	Genetic test > pathogenic *RYR2* mutation	Beta-blocker therapy, avoidance of peak exercise. *Genetic family screening:* 1 daughter tested; normal genotype.
13	DCM	12.2	Echocardiography	Diuretic and ACE-inhibitor therapy. *Phenotypic family screening:* all screened family members normal phenotype.
14	DCM	8.6	Echocardiography	Diuretic, ACE-inhibitor and beta-blocker therapy. *Phenotypic and genetic family screening*: not reported.
15	DCM	8.7	Echocardiography, genetic test > *PLN* mutation	Patient already received pharmacological therapy. *Phenotypic family screening*: normal (both children; normal ECG, echocardiography, and Holter monitoring). *Genetic family screening:* not yet performed.
16	LQTS	2.4	ECG with spontaneous QT prolongation	Medication advice, on patients' request no genetic test. *Phenotypic family screening:* 1 daughter, normal rest-ECG.
17	LQTS type 1	7.1	Genetic test > pathogenic *KCNQ1* mutation	Medication advice, avoidance of competitive and peak exercise, beta-

				blocker therapy. *Genetic family screening:* sister; normal genotype, brother; refuses genetic screening.
18	CAS	1	Recurrence of VF during CAS	Quinidine, sintrom, nitrostat therapy, no calcium-antagonist, reason not reported
19	CAS	2.3	Careful evaluation of patient history and performed diagnostic tests	None, patient already received calcium-antagonist, statin and ascal therapy.
20	Myocarditis	15.1	Careful retrospective evaluation of patient history and performed diagnostic tests (clinical presentation, viral serology)	None
21	Systemic mastocytosis †	4.7	Careful retrospective evaluation of patient history and performed diagnostic tests, and documentation of recurrence of VF during an exacerbation of the mastocytosis	None
22	HCM	0.8	MRI, Genetic test > pathogenic *MYL2* mutation	Avoidance of competitive sports. *Phenotypic and genetic family screening:* father; carrier pathogenic mutation and HCM on MRI (no primary prophylactic ICD implanted because of low 5-year risk of SCD), mother and both brothers; normal genotype and normal MRI.

ARVD/C: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, BrS: Brugada Syndrome, CAS: Coronary Artery Spasm, CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia, DCM: Dilated Cardiomyopathy, DPP6: Dipetidyl-peptidase 6 gene, DSG2: Desmoglein-2 gene, ECG: Electrocardiography, FU; Follow-up, HCM: Hypertrophic Cardiomyopathy, ICD: Implantable Cardiac Defibrillator, LQTS: Long-QT Syndrome, MRI: Magnetic Resonance Imaging, MYL2: Myosin Light Chain-2 gene, PKP2: Plakophilin-2 gene, PLN: Phospholamban gene, RYR2: Ryanodine-2 gene, RV: Right Ventricle, SCD: Sudden

Cardiac Death, SCN5A: Sodium Channel Voltage Gated Type V Alpha gene, VUS: Variant of uncertain clinical significance, VF: Ventricular Fibrillation.

*The SCN5A mutation was a c2184-2186del (p.Leu729del), that is associated with ARVD/C.(te Riele AS, James CA, Agullo-Pascua El, Cerron M, Zhang M, Lin X, Sobreira NL, Amat, N, Marsman RF,. Groeneweg JA, Murray B, Tichnell C, Tandri H, Fowler SJ, Hauer RN, Bu L,. Bezzina CR, Calkins H, van Tintelen P, Delmar M, Judge DP. Exome Sequencing, Functional Analysis, and Super-Resolution Imaging Identify A Pathogenic Role for SCN5A Mutations in ARVD/C. HRS may 15 2015. Available via http://www.abstractsonline.com/pp8/#!/3647/presentation/12449 and Yu J, Hu J, Dai X, Cao Q, Xiong Q, Liu X, Liu X, Shen Y, Chen Q, Hua W, Hong K. SCN5A mutation in Chinese patients with arrhythmogenic right ventricular dysplasia. Herz 2014;39:271-275). Of note: comprehensive evidence of a relation between SCN5A mutations and ARVC is not available and subject to further research.

†Cases with VF as first manifestation of systemic mastocytosis have been reported.(Ridolo E, Triggiani M, Montagni M, Olivieri E, Ticinesi A, Nouvenne A, Magliacane D, de Crescenzo G, Meschi T. Mastocytosis presenting as cardiac emergency. Intern Emerg Med 2013;8:749-752).