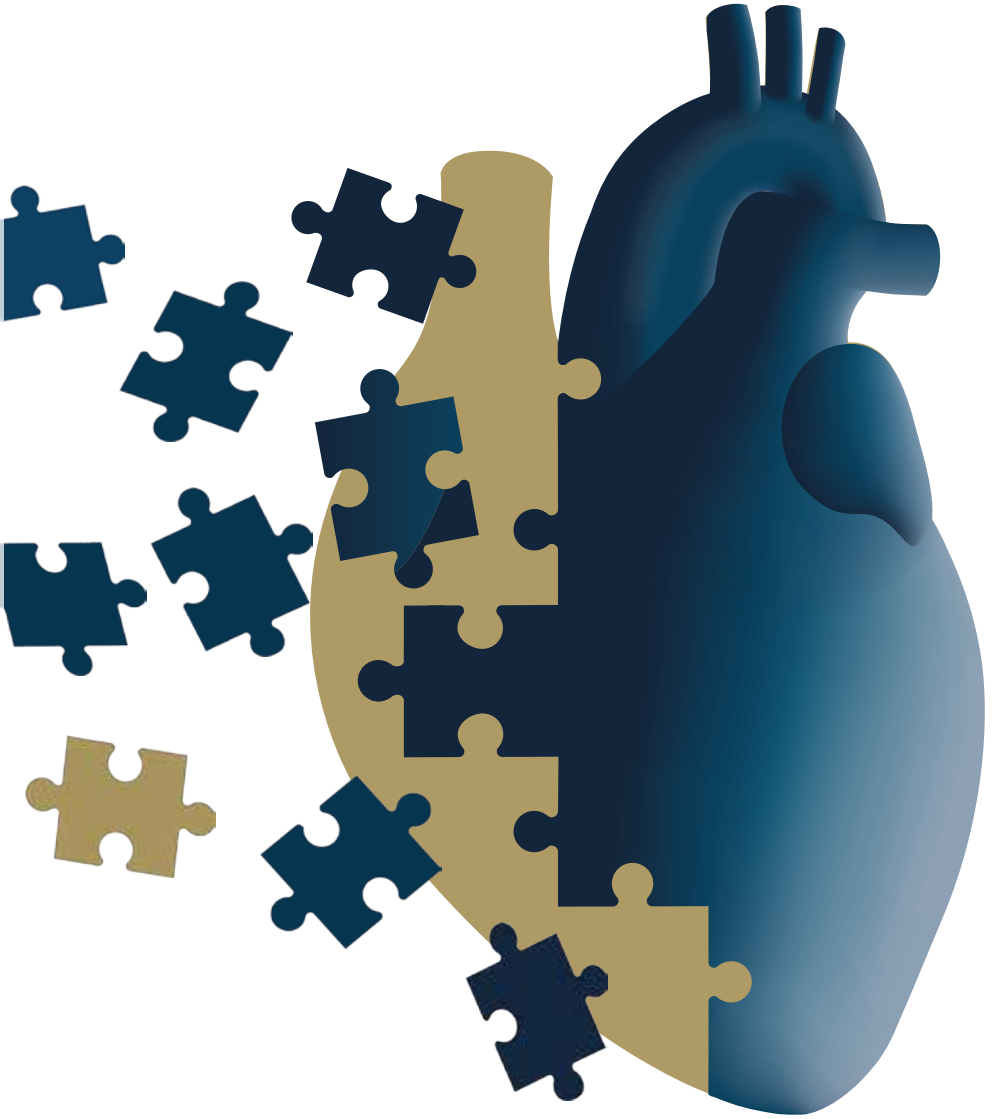
IDIOPATHIC VENTRICULAR FIBRILLATION

Absence of evidence is not evidence of absence



S.A. GROENEVELD

Idiopathic ventricular fibrillation

Absence of evidence is not evidence of absence

S.A. Groeneveld

Colophon

Idiopathic ventricular fibrillation. PhD Thesis with a summary in Dutch. Utrecht University.

Cover design: Chris van Kesteren
Lay-out: Erwin Rutgers
Print: Gildeprint
ISBN: 978-94-6419-611-5

The research described in this thesis was supported by a grant of the Dutch Heart Foundation (CVON 2017-13-VIGILANCE).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Publication of this thesis was additionally supported by Abbott Medical Nederland and Chipsoft.

Idiopathic ventricular fibrillation

Absence of evidence is not evidence of absence

Idiopathisch ventrikelfibrilleren

Afwezigheid van bewijs is geen bewijs van afwezigheid

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

donderdag 1 december 2022 des middags te 2.15 uur

door

Sanne Alies Groeneveld

geboren op 9 september 1994

te Voorburg

Promotoren

Prof. dr. P.A.F.M. Doevendans

Prof. dr. P.G.A. Volders

Copromotor

Dr. R.J. Hassink

Beoordelingscommissie

Prof. dr. B.K. Velthuis

Prof. dr. M.P. van den Berg

Prof. dr. J.P. van Tintelen

Prof. dr. ir. H.M. den Ruijter

Prof. dr. J.R. de Groot

Paranimfen

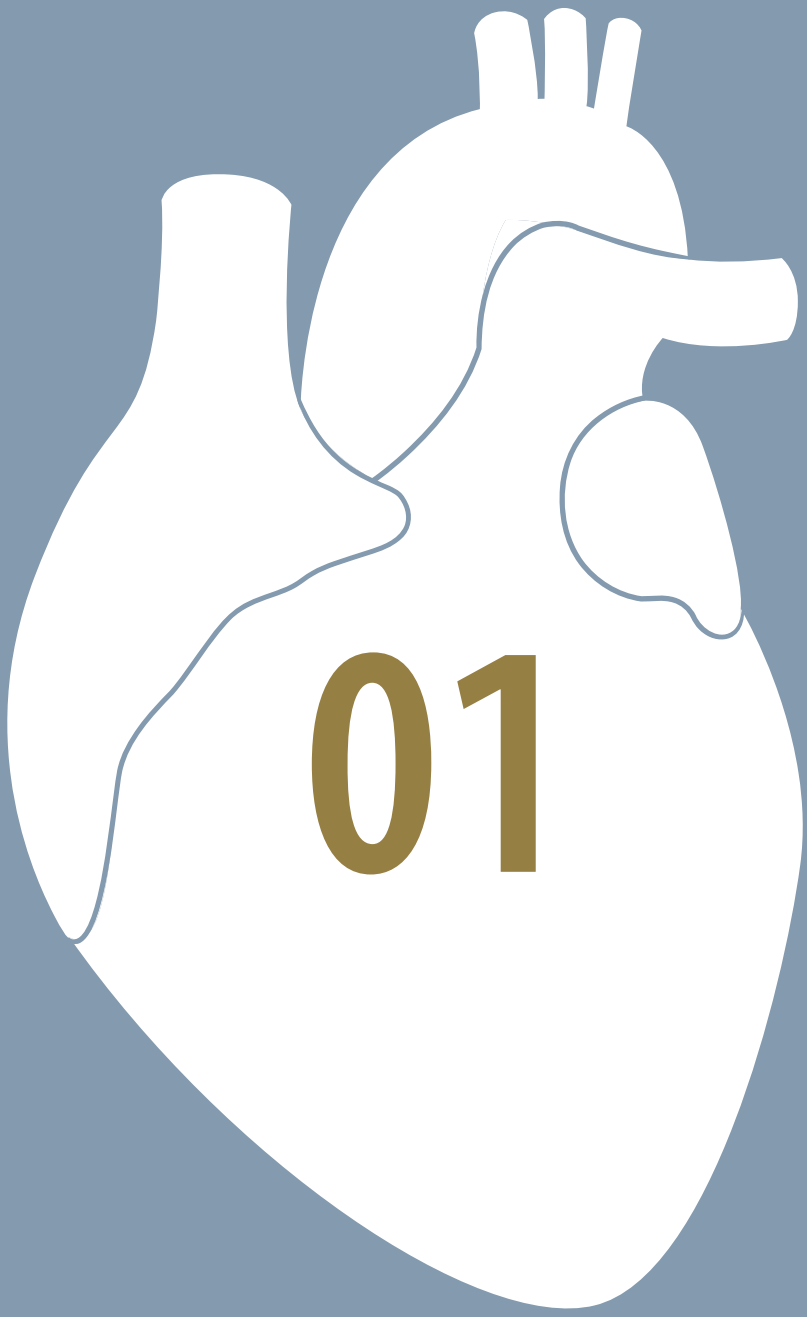
Dr. Marijn H.A. Groen

Drs. Lisa M. Verheul

Table of contents

PART IV | Discussion and Summary

PART V | Appendices


01

General introduction

General introduction

The human heart is a fascinating organ. With its ability to beat consistently every second, it provides the body with blood and oxygen which allows us to breath, move and function. Our heart beats approximately 3600 times per hour, 600,000 times per week and around 34,000,000 times per year. In order to do so, the heart is regulated by a complex electrical conduction system that coordinates the contraction of the various chambers of the heart. The sinus node (located in the right atrium of the heart) creates an electrical stimulus around 60-100 times per minute under normal conditions. This stimulus travels down through the atria into the conduction pathways and causes the ventricles to contract and pump blood into the body. These regular ventricular contractions generate a stable blood pressure to provide all other organs with oxygen.

Arrhythmogenesis

Usually, the heart is capable of generating a regular heart rhythm from the sinus node. However, sometimes the electrical signals get disturbed and an arrhythmia might arise. When an arrhythmia leads to a complete loss of cardiac output it is referred to as sudden cardiac arrest (SCA).[1] SCA is a major health problem in the Western world.[2] In young SCA victims, the arrest is most frequently caused by ventricular fibrillation (VF).[3] VF is a chaotic heart rhythm in which the electrical signals of the ventricles are suddenly disturbed.

During VF, the electrical activation of the ventricles is highly irregular and chaotic which causes the ventricles to "quiver" instead of contract (Figure 1). This leads to a loss of output and consequently also a loss of consciousness. If patients with VF do not receive rapid and adequate resuscitation, the arrhythmia will likely become lethal. It is therefore of utmost importance to understand the underlying factors that lead to this devastating event.

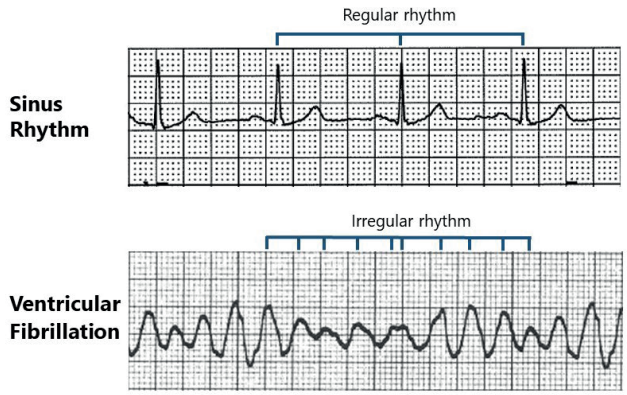


Figure 1 | Sinus rhythm compared to ventricular fibrillation.

An important concept in VF and ventricular tachycardia (VT) is the "triangle of arrhythmogenesis" of Philippe Coumel, one of the founding fathers of electrophysiology. He stated that *"there are always three main ingredients required for the production of a clinical arrhythmia, the arrhythmogenic substrate, the trigger factor and the modulating factors"*.[4,5] Many myocardial changes that facilitate VF are already known (Figure 2) and some of them are well studied. One of the most important and well-studied substrates for VF is myocardial fibrosis. Fibrotic tissue can be caused by different underlying diseases such as coronary artery disease, inflammatory cardiac disease or cardiomyopathies.[3] Besides myocardial fibrosis, also fatty tissue replacement and myocardial stretch are known substrates for VF.[3,6]

Known triggers for VF are short-coupled premature ventricular complexes,[7,8] and supraventricular tachycardias, such as rapid atrial fibrillation.[9,10] Modulating factors include electrolyte disturbances, bradycardia, fever or changes in the autonomic nervous system. These three factors tend to interact with and show interdependence to each other. To understand this concept better, one might compare the rise of an arrhythmia with the start of a wildfire. To facilitate a wildfire, multiple ingredients are necessary. If the climate has been dry and it is a windy day, a burning match may well cause a wildfire. However, on a windy and rainy day, the same burning match will not lead to ignition. This counterplay between the different ingredients plays a pivotal role in understanding arrhythmogenesis.

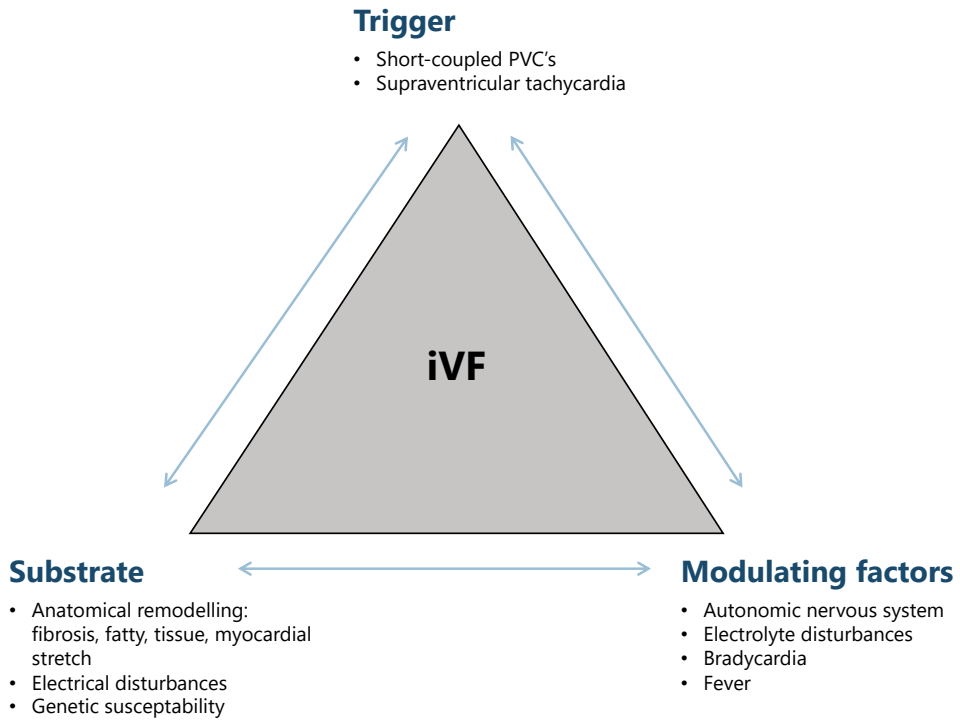


Figure 2 | Triangle of Coumel in idiopathic ventricular fibrillation (IVF).

Idiopathic ventricular fibrillation

Diagnosing a patient comes down to identifying the nature of an illness. The word diagnosis originates from the Greek word '*diagignöskein*', meaning 'to distinguish' or 'to establish'. To diagnose a patient with a disease, we need to distinguish his or her characteristics from those who are healthy. In the medical field this basically comes down to a simple concept: we try to distinguish "pathological" from "physiological" or "abnormal" from "normal". In modern medicine, we use both simple and advanced diagnostic methods to do so. With our current diagnostic possibilities, in most patients with VF a cause for the event can be found. The leading cause for SCA is coronary artery disease, especially in the elderly.[1] In younger patients, SCA is mainly caused by congenital cardiomyopathies and primary arrhythmia syndromes.[3] However, in 2-7% of patients with VF, the underlying cause cannot be found.[11,12] These patients are diagnosed with "idiopathic ventricular fibrillation" (IVF).

IVF is a diagnosis '*per exclusionem*' (by exclusion). That means that the diagnosis fully depends on the absence of an evident cause for VF. To diagnose IVF, it is of great importance to exclude possible underlying causes for VF. Systematic diagnostic assessment is therefore the cornerstone in IVF.

Diagnosing the absent

The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus statement defines IVF as 'resuscitated cardiac arrest, preferably with documentation of VF, for which known cardiac, respiratory, metabolic, and toxicological aetiologies have been excluded through clinical evaluation'. Or, as also stated 'the terminology that best acknowledges our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia'.[13,14] The broad differential diagnosis that needs exclusion before diagnosing a patient with IVF asks for a thorough and systematic diagnostic approach. Different guidelines seem to agree on the need for diagnostic evaluation in patients with unexplained SCA.[13,15–17] Visser et al. proposed a step-by-step diagnostic flowchart (Figure 3).[18] Routine testing comprises of an electrocardiogram (ECG), laboratory testing (cardiac enzymes, electrolytes and thyroid function), toxicology screening, echocardiography, exercise testing, Holter monitoring, coronary angiography and cardiac magnetic resonance imaging (CMR). When these tests reveal no abnormalities, provocation tests for Brugada syndrome and coronary artery spasm should be considered. In addition, targeted genetic testing based on the clinical phenotype may be performed.

Despite the importance of diagnostic testing, previous studies showed that the diagnostic work-up in IVF-patients is incomplete.[11,12,19–21] For instance, CMR was only performed in 37%, 62% and 77% of IVF patients, respectively, amongst different large cohorts.[19–21] The same accounts for sodium channel blocker provocation (SCBP), which was only performed in respectively 34%, 57% and 66% of IVF patients. This makes the absence of an underlying disease in these patients less certain. It remains unclear what reasons lie behind the overall lack of systematic diagnostic testing in IVF patients. However, as the IVF diagnosis fully depends on the absence of a substrate, this is an important issue. In literature, IVF is often referred to as a SCA victim that remained idiopathic despite extensive diagnostic testing. In the real-world, however, IVF seems to be rather a mixed-bag population with both patients who appear to be truly idiopathic versus patients who did not undergo complete diagnostic assessment. Bearing this in mind, it is of importance to 1) further investigate the current diagnostic status of patients in the IVF registry and 2) investigate new diagnostic possibilities.

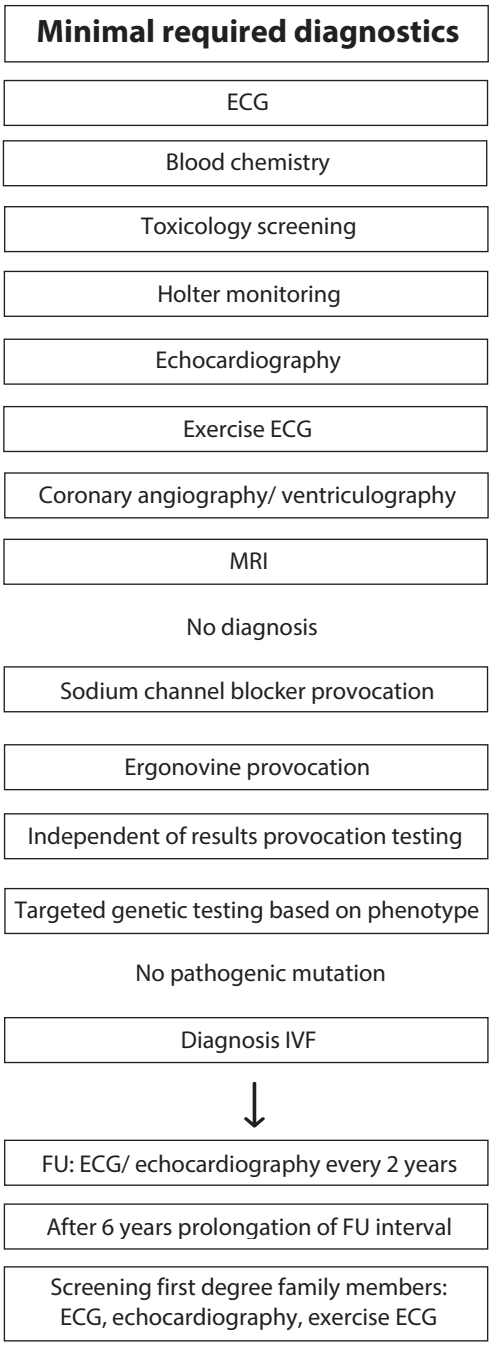


Figure 3 | Minimal required diagnostics.

Treating the unknown

As the cause for VF is unknown in patients with IVF, there are no targeted treatment strategies available. All current guidelines recommend implantable cardioverter defibrillator (ICD) implantation to prevent sudden cardiac death (SCD).[15,16,22] Previous studies showed that ventricular arrhythmia (VA) recurrences occur relatively frequent in IVF patients, ranging from 17-31%.[12,19,21,23] Although ICD therapy proved to be an effective treatment for VA recurrence, ICD shocks are a serious burden in the daily life of these patients.[21] This calls for more individualized treatment strategies in the future.

In a recent paper, a specific IVF-subtype has been described and referred to as short-coupled VF (SCVF).[7] In SCVF-patients, short-coupled premature ventricular complexes (PVC) with a coupling interval <350ms initiate polymorphic VT/VF. Literature data suggests that SCVF is prevalent in approximately 7% of IVF patients, and that they have a higher recurrence risk than other IVF patients.[7,21,24] The exact etiology of SCVF in the context of IVF remains unsettled to date. However, it is a highly interesting subgroup, especially for the Dutch IVF population as a hereditary subset of IVF-patients exists in the Netherlands. In these patients, a link between familial IVF and a risk haplotype on chromosome 7q36 (involving the DPP6 gene) was found.[8,24] In these patients, recordings show that the arrhythmias are elicited by very short-coupled (right) ventricular extrasystoles. Treatment with quinidine seems to be highly effective in SCVF patients.[7,24] However, data on the prevalence and the phenotype of SCVF in other IVF cohorts is scarce.

Prevention of sudden cardiac death

SCD is still a problem in the Western world. A large recent study estimated that 249.538 persons experience SCD in the European Union every year.[2] Despite improvements in the prevention and management of cardiovascular diseases, surprisingly, the incidence of SCA and SCD did not decrease over the years. In patients who survive SCA, specific measures, such as ICD implantation, can be taken to prevent SCD in that patient in the future. However, one has to bear in mind that a significant number of the SCA patients does not survive the arrest. And even if patients survive the arrest, many patients remain with serious cognitive problems. It is therefore of utmost importance to prevent SCA and SCD.

Familial cascade screening

An important tool to prevent SCA in the general population is family screening. As mentioned above, there is currently no minimum of diagnostic tests that need to be performed before IVF is diagnosed.[13] Patients labelled with IVF may represent a variety of underlying pathologies including concealed forms of primary arrhythmia syndromes or cardiomyopathies. Family screening is well-established in patients with SCD.[25,26] Yet, the benefit of family cascade screening in IVF is unknown.

Postmortem testing

Unfortunately, most SCA victims do not survive the arrest. In a SCA survivor, different diagnostic tests are available to diagnose any underlying disease. Catecholaminergic polymorphic VT and Brugada syndrome are important to exclude in SCA survivors. However, in the deceased there are fewer diagnostic possibilities, which complicates the identification of underlying heritable cardiac diseases. As mentioned before, there is a difference in underlying pathologies for SCD in different age groups.[27] In approximately 1 in 3 young SCD victims, no clear underlying cause for the arrest can be found.[27] When the cause of the event remains unexplained after autopsy, this is referred to as sudden unexplained death (SUD). In these patients there is a strong suspicion for an (often heritable) primary arrhythmia syndrome. Cardiogenetic screening for family members of the deceased is therefore strongly recommended.[17,28]

Although both autopsy and family screening are strongly recommended in SCD patients[17], the adherence to this advice in the Netherlands is low.[29] A large community-based study in the Netherlands showed that autopsy was only performed in 43% of young SCD victims aged 1-44 years.[29] Strikingly, cardiogenetic evaluation of relatives was only performed in 8% of the families, while it was indicated in 76% of them. That means that most patients with an indication for cardiogenetic screening do not attend a cardiogenetics clinic. This is a major problem as the risk of inherited cardiac disease is high in these patients and they might be at risk for SCD. Multiple reasons have been proposed, including high autopsy costs, logistical problems and insufficient knowledge of general practitioners about the causes of SCD in the young and preventive options for risk carriers.[29]

Outline of this thesis

The general aim of this thesis is to further unravel the mystery of IVF. In part I and II, we investigate the clinical characteristics of IVF patients and we study promising new diagnostic possibilities. In part III, we focus on the prevention of SCA and SCD.

Part I *Characteristics of idiopathic ventricular fibrillation*

As diagnostic testing is the cornerstone in IVF, we provide an overview of the current diagnostic status of patients that are included in the Dutch national IVF registry in Chapter 2. We also looked into the effect of the number of diagnostic tests performed on the probability to obtain an alternative diagnosis during follow-up. In Chapter 3 we study the prevalence of SCVF in a large cohort of Dutch IVF patients. We also focus on the pitfalls of the definition for SCVF.

Part II *Progress in diagnostic testing*

Despite our current diagnostic abilities, some VF patients still remain undiagnosed. New diagnostic tools are needed to detect subtle signs of underlying disease. One of those promising techniques is echocardiographic deformation imaging, which has shown to provide

unique information on regional and global myocardial mechanical function. In Chapter 4 we explore echocardiographic deformation characteristics amongst IVF patients. Another region of interest that associates with ventricular arrhythmias is the mitral valve. Both mitral valve prolapse (MVP) and mitral annulus disjunction (MAD) have been associated with ventricular arrhythmias and SCA. In Chapter 5, we describe the prevalence and morphology of MAD and MVP in a multicentre cohort of IVF patients compared to matched controls.

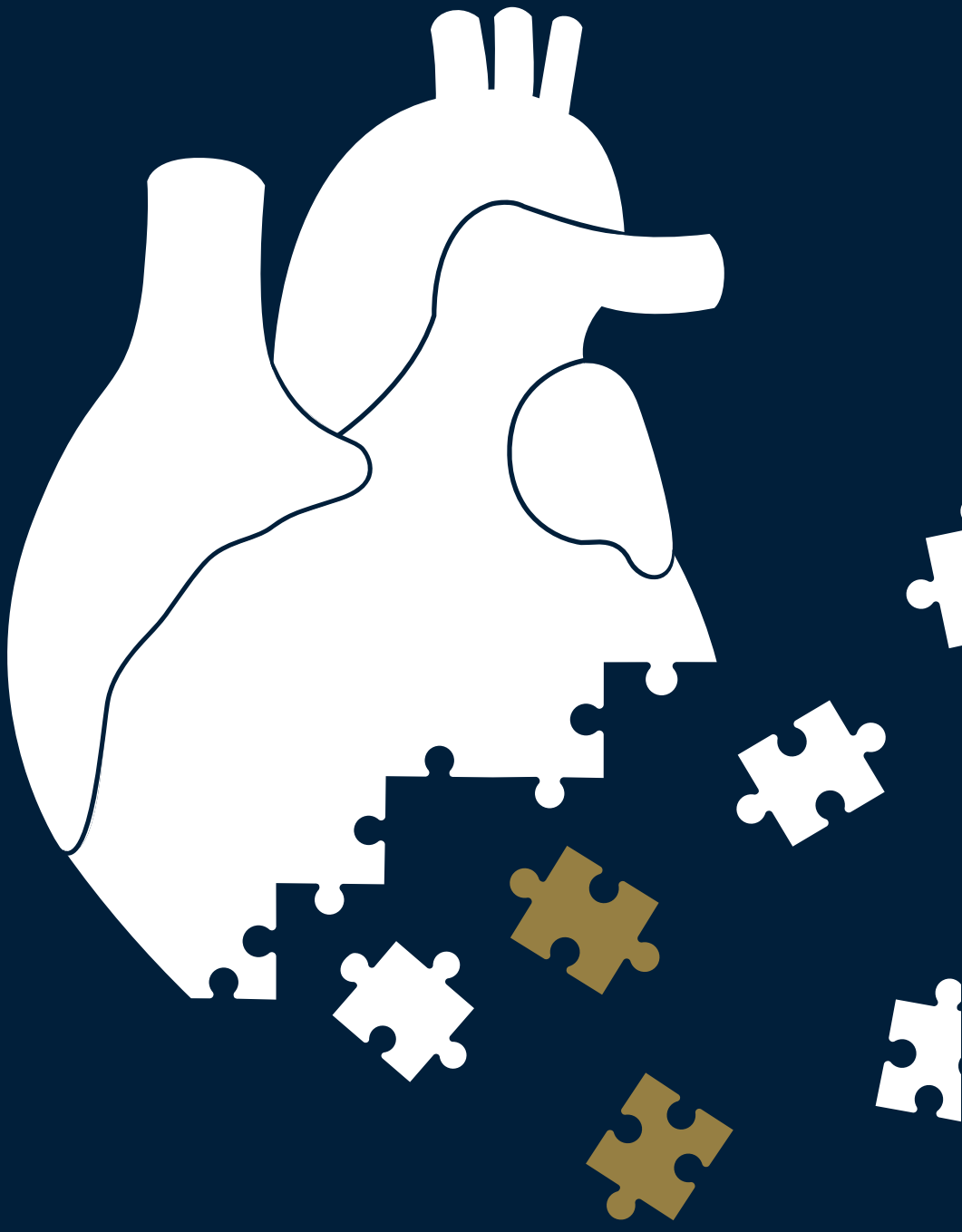
Part III *To prevent sudden cardiac death*
ICD implantation is recommended in IVF patients to prevent SCD. But, we also need strategies to prevent SCA in the general population. There are different tools available to do so, but major knowledge gaps and practical issues regarding family screening and post-mortem testing in SCA and SCD remain. To explore the need for family screening, we study the yield of family screening in IVF in Chapter 6. In Chapter 7, we review current challenges in the diagnostic approach of young SCD victims and we created a roadmap to guide general practitioners.

Part IV *Discussion and Summary*
Chapter 8 presents a general discussion and future perspectives based on the content of this thesis. A summary of the chapters in this thesis is provided in Dutch in Chapter 9.

References

1. Zipes D, Wellens H. Sudden Cardiac Death. *Circulation*. 1998;97(12):1107.
2. Jean-Philippe E, Lerner I, Valentin E, Folke F, Böttiger B, Gislason G, *et al.* Incidence of Sudden Cardiac Death in the European Union. *J Am Coll Cardiol*. 2022;79(18):1818–27.
3. Ackerman M, Atkins DL, Triedman JK. Sudden cardiac death in the young. *Circulation*. 2016;133(10):1006–26.
4. Coumel P. Cardiac Arrhythmias and the Autonomic Nervous System. *J Cardiovasc Electrophysiol*. 1993;4(3):338–55.
5. Farre J, Wellens HJ. Philippe Coumel: a founding father of modern arrhythmology. *Europace*. 2004;6(5):464–5.
6. Hayashi M, Shimizu W, Albert CM. The Spectrum of Epidemiology Underlying Sudden Cardiac Death. *Circ Res*. 2015;116(12):1887–906.
7. Steinberg C, Davies B, Mellor G, Tadros R, Laksman ZW, Roberts JD, *et al.* Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report from the CASPER registry. *Eur Heart J*. 2021;42(29):2827–38.
8. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13(4):905–12.
9. Wang Y, Scheinman MM, Chien WW, Cohen TJ, Lesh MD, Griffin JC. Patients with supraventricular tachycardia presenting with aborted sudden death: Incidence, mechanism and long-term follow-up. *J Am Coll Cardiol*. 1991;18(7):1711–9.
10. Mendoza IJ, Medina-ravell V, Myerburg RJ. One to One Atrioventricular Conduction During Atrial Pacing at Rates of 300/min in Absence of Wolff-Parkinson-White syndrome. *Am J Cardiol*. 1980;48:789–96.
11. Waldmann V, Bougouin W, Karam N, Dumas F, Sharifzadehgan A, Gandjbakhch E, *et al.* Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: Focus on idiopathic ventricular fibrillation. *Eur Heart J*. 2018;39(21):1981–7.
12. Conte G, Belhassen B, Lambiase P, Ciconte G, Asmundis C De, Arbelo E, *et al.* Out-of-hospital cardiac arrest due to idiopathic ventricular fibrillation in patients with normal electrocardiograms: Results from a multicentre long-term registry. *Europace*. 2019;21(11):1670–7.
13. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* 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(12):1932–63.
14. Survivors of Out-of-Hospital Cardiac Arrest With Apparently Normal Heart. 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 State. *Circulation*. 1997;95(1):265–72.
15. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, *et al.* 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Hea. *J Am Coll Cardiol*. 2018;72(14):e91–220.
16. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, *et al.* EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias. *Heart Rhythm*. 2014;11(10):e166–96.
17. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, *et al.* 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm*. 2021;18(1):e1–50.
18. Visser M, Heijden JF Van Der, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up. *Circ Arrhythmia Electrophysiol*. 2016;9(5):1–11.

19. Herman ARM, Cheung C, Gerull B, Simpson CS, Birnie DH, Klein GJ, *et al.* Outcome of Apparently Unexplained Cardiac Arrest: Results From Investigation and Follow-Up of the Prospective Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythmia Electrophysiol*. 2016;9(1):e003619.
20. Siebermair J, Sinner MF, Beckmann B-M, Laubender RP, Martens E, Sattler S, *et al.* Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18(5):718–25.
21. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace*. 2019;21(10):1519–26.
22. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europea. *Eur Heart J*. 2015;36(41):2793–867.
23. Visser M, Heijden JF Van Der, Smagt JJ Van Der, Doevendans PA, Wilde AA, Loh P, *et al.* Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. *Circ Arrhythmia Electrophysiol*. 2016;9(10):e004258.
24. Postema PG, Christiaans I, Hofman N, Alders M, Koopmann TT, Bezzina CR, *et al.* Founder mutations in the Netherlands: Familial idiopathic ventricular fibrillation and DPP6. Netherlands Hear. J. 2011. p. 290–6.
25. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, *et al.* Familial cardiological and targeted genetic evaluation: Low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm*. 2013;10(11):1653–60.
26. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, *et al.* Sudden arrhythmic death syndrome: Familial evaluation identifies inheritable heart disease in the majority of families. *Eur Heart J*. 2008;29(13):1670–80.
27. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, *et al.* Burden of sudden cardiac death in persons aged 1 to 49 years nationwide study in denmark. *Circ Arrhythmia Electrophysiol*. 2014;7(2):205–11.
28. Werf C Van Der, Hofman N, Tan HL, Dessel PF Van, Alders M, Wal AC Van Der, *et al.* Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: The experience of a tertiary referral center in the Netherlands. *Heart Rhythm*. 2010;7(10):1383–9.
29. Werf C van der, Hendrix A, Birnie E, Bots ML, Vink A, Bardai A, *et al.* Improving usual care after sudden death in the young with focus on inherited cardiac diseases (the CAREFUL study): a community-based intervention study. *Europace*. 2016;18(4):592–601.



PART I

Characteristics of idiopathic ventricular fibrillation


02

The importance of systematic diagnostic testing in idiopathic ventricular fibrillation: results from the Dutch IVF registry.

JACC: Clinical Electrophysiology. In press.

Sanne A. Groeneveld
Lisa M. Verheul
Martijn H. van der Ree
Bart A. Mulder
Marcoen F. Scholten
Marco Alings
Pepijn van der Voort
Marianne Bootsma
Reinder Evertz
Jippe Balt
Sing-Chien Yap
Pieter. A.F.M. Doevendans
Pieter G. Postema
Arthur A. Wilde
Paul G. A. Volders
Rutger J. Hassink

Abstract

Background | Idiopathic ventricular fibrillation (IVF) is a diagnosis "per exclusionem". Systematic diagnostic testing is important to exclude alternative causes for VF. Especially the "high yield" of cardiac magnetic resonance imaging (CMR), exercise testing and sodium channel blocker provocation (SCBP) has been increasingly recognized.

Objectives | To investigate the importance and consistency of systematic diagnostic testing in IVF.

Methods | IVF patients from 11 large secondary and tertiary hospitals in the Netherlands were included. Clinical characteristics and diagnostic testing data were derived from medical records.

Results | In total, 423 patients were included with a median age at time of the index event of 40 [28-52] years old, 61% was male. The median follow-up time was 6 [2-12] years. Over the years, "high yield" diagnostic tests were increasingly performed (mean 68% in 2000-2010 vs. 75% in 2011-2021, $p<0.001$). During follow-up, 38 patients (9%) originally labeled as IVF received an alternative diagnosis. Patients in whom "high yield" diagnostic tests were consistently performed during the initial work-up received an alternative diagnosis less frequently during follow-up (HR: 0.439, 95%CI: 0.219-0.878, $p=0.020$). Patients who received an alternative diagnosis during follow-up were associated with a worse prognosis in terms of cardiac death ($p=0.012$) with a trend towards more ICD therapy ($p=0.055$).

Conclusion | Although adherence to (near-)complete diagnostic testing in this population of IVF patients increased over the years, patients with IVF still undergo varying levels of diagnostic evaluation. The latter leads to underdiagnosing of alternative diseases and is associated with a worse prognosis. Our results underscore the importance of systematic diagnostic assessment in patients with apparent IVF.

Introduction

Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with ventricular fibrillation (VF) of which the origin is not identified despite extensive diagnostic testing.[1] The IVF diagnosis thus depends on the absence of an evident substrate for VF by exclusion of coronary artery disease, structural cardiac diseases and primary arrhythmia syndromes.[2] Extensive diagnostic testing is therefore the cornerstone in IVF patients. An electrocardiogram, echocardiogram, laboratory testing and coronary evaluation are standardly performed to identify a cause for the arrest. If no cause can be identified for the arrest, this is referred to as unexplained cardiac arrest (UCA). Current guidelines recommend comprehensive diagnostic testing in UCA survivors.[3,4]

Identifying the cause of ventricular fibrillation is important as it has therapeutic consequences and might guide targeted family screening. Several primary arrhythmia syndromes, such as Brugada syndrome (BrS), were previously considered idiopathic as well.[5] With the help of several diagnostic tools, such as drug provocation tests and cardiac imaging, the prevalence of IVF has decreased significantly.[1] A recent systematic review showed that the yield of comprehensive diagnostic testing in IVF is consistently high.[6] Especially cardiac magnetic resonance imaging (CMR), exercise treadmill testing (ETT) and sodium channel blocker provocation (SCBP) showed to be of importance in the diagnostic work-up of UCA survivors as they have a relatively high diagnostic yield of respectively 10%, 9% and 8%.[6–11] Holter monitoring, electrophysiology study and epinephrine challenge appear to have either a lower diagnostic yield (<5%) or a high false-positive or -negative rate and their diagnostic value is therefore under debate.[6] Genetic testing proved to be of value in UCA victims, however, there are conflicting results on its value in IVF when the patient is comprehensively assessed.[12,13]

Despite the importance of diagnostic testing, previous studies showed that the diagnostic work-up in IVF is consistently incomplete.[7,8,14–16] In these studies, the number of patients undergoing "high yield" diagnostic tests such as SCBP, CMR or ETT ranged widely between 10-80%. The exact reasons behind and the impact of this incomplete adherence to the diagnostic work-up remain unknown. In this study, we aimed to investigate the consistency and importance of systematic diagnostic testing in a large cohort of Dutch IVF patients.

Methods

Study population

The Dutch national IVF registry comprises patients from eleven large secondary and tertiary hospitals in the Netherlands. This study was approved by the local ethics committee of the participating centers. The study was in accordance with the declaration of Helsinki. Patients were included in this registry if they had experienced a cardiac arrest, with documented VF, and no diagnosis had been made after comprehensive clinical assessment, as explained below. Study parameters were collected retrospectively and prospectively. IVF was defined as a resuscitated cardiac arrest victim, with documented VF and/or polymorphic VT, in whom known cardiac, respiratory, metabolic and toxicological etiologies were excluded through clinical evaluation, in accordance with the 2013 consensus criteria.[3] Diagnostic criteria used to exclude specific diseases are shown in supplementary table 1.

Clinical investigations

Enrolled patients underwent a detailed investigation of the medical history, physical examination and standard investigations including laboratory testing, resting 12-lead ECG, coronary angiography (or CT angiography in patients under 40 years old), ETT and cardiac imaging with echocardiography and/or CMR. Additional investigations, such as Holter monitoring, SCBP, endomyocardial biopsy and genetic testing were performed at the treating physician's discretion during initial hospitalization or outpatient follow-up. SCBP was performed with either Ajmaline (maximum dosage 1mg/kg), Flecainide (maximum dosage 2 mg/kg), or longer ago procainamide (maximum dosage 10mg/kg) to exclude Brugada syndrome. Provocation testing with ergonovine or acetylcholine was performed in a subgroup of patients to exclude coronary artery spasm, upon suspicion. Endomyocardial biopsy was performed in a subgroup of patients to evaluate signs of cardiomyopathy, myocarditis, sarcoidosis or storage disease. In patients with a suspicion of toxic or illicit drug use a toxicological screening was performed to potentially detect cocaine, cannabis, benzodiazepines, amphetamines and barbiturates. Electrophysiology study was performed at the clinician's discretion, using standard stimulation protocols. DNA analysis was performed in most patients for Next Generation Sequencing (NGS) of a large panel of genes associated with ventricular arrhythmias (34-212 genes) and/or cardiomyopathies depending on the center where the genetic testing was performed. In some cases, single targeted gene testing by Sanger sequencing was performed based on the phenotype. Patients with the previously described *DPP6* haplotype, a genetic variant associated with short-coupled polymorphic VT/IVF, were also included as IVF patients.[1,17] All patients received cardiac follow-up in centers with electrophysiological expertise where the IVF diagnosis is continuously evaluated and reconsidered. Additional diagnostic tests were performed when deemed appropriate. The diagnostic- and outcome data in the registry were updated yearly. In addition, participating hospitals receive information on the diagnostic status of their patients regularly and are encouraged to perform additional diagnostic tests when missing.

Arrhythmia recurrence during follow-up

To assess recurrence of ventricular arrhythmias, all available medical records and ICD recordings were used. ICD read-outs were used to determine whether ICD therapy was appropriate. Appropriate therapy was defined as anti-tachycardia pacing or shocks delivered for ventricular tachyarrhythmias. Inappropriate therapy was defined as shocks delivered in the absence of ventricular arrhythmias. Due to the retrospective nature of this study, recordings from various generations of ICDs were obtained and analyzed. Therefore, ICD types and programming varied over time according to available recommendations and was adjusted during follow-up based on the patient's individual clinical history to avoid inappropriate interventions.

Statistical analysis

Data were analyzed using SPSS version 26.0.0.1. We present continuous variables as mean ± standard deviation (SD) or median (interquartile range), and discrete data as frequencies and percentage. Comparisons were performed using a Student's t-test, Mann-Whitney U test, or Fisher exact test as appropriate. Predictors to obtain an alternative diagnosis were determined using multivariate Cox proportional hazards regression models. The amount of "high yield" tests performed, age at index event, year of index event and the circumstances in which the event occurred were included as predictors in the model. We estimated event-free survival by the Kaplan–Meier method and compared differences by log-rank tests. A p-value <0.05 was considered significant.

Results

Baseline characteristics

Between 1988 and 2021, 423 patients initially diagnosed with IVF were included in the registry (61% male). The median age at time of the index event was 40 [28-52] years. In most cases, the event occurred at rest (59%). The clinical baseline characteristics of the cohort are presented in Table 1.

Diagnostic testing rate

In all 423 patients, a 12-lead electrocardiogram, laboratory testing and an echocardiogram were performed. Coronary angiography or CT angiography was performed in 407 patients (96%). CMR was performed in 315 patients (75%). Exercise stress testing and SCBP were performed in 298 (70%) and 266 (63%) patients, respectively. DNA analysis was performed in 367 of 423 patients (87%). An overview of the genetic test results can be found in supplementary table 2, supplementary table 3 shows pathogenic or likely pathogenic variants found. Electrophysiology study was performed in 171 patients (40%), the results of which can be found in supplementary table 4. Table 2 shows an overview of all performed diagnostic tests. Over the last years, the total percentage of diagnostic tests performed became significantly higher (mean 69% in 1980-2000 vs. 68% in 2000-2010 vs. 75% in 2011-2021, $p<0.001$) (figure 1).

Table 1 | Baseline characteristics of 423 patients initially diagnosed with IVF

Characteristics	All (n=423)
Male sex (%)	259 (61%)
Median age at event (years)	40 [28-52]
Circumstances during occurrence of VF (%)	
Exercise	84 (21%)
Emotions	19 (5%)
Rest	247 (60%)
Asleep	51 (12%)
Other	9 (2%)
Symptoms before cardiac arrest (%)	
Any symptoms†	155 (37%)
Palpitations	50 (12%)
Syncope	49 (12%)
Family history of sudden cardiac death* (%)	65 (15%)
DPP6 risk haplotype, n (%)¥	37 (9%)

**History of SCD defined as 1 first degree family member with SCD <45 years, or multiple second-degree family members with SCD. †Any symptoms defined as chest-pain, syncope, near-syncope or palpitations. ¥DPP6 haplotype on chromosome 7q36, a genetic variant associated with short-coupled polymorphic VT/iVF.*[17]

Table 2 | Diagnostic tests performed during the diagnostic work-up in 423 patients initially diagnosed with IVF

Diagnostic test	N (%)
Laboratory testing	423 (100%)
Toxicological screening	63 (15%)
12-lead ECG	423 (100%)
Cardiac Imaging	423 (100%)
Echocardiography	415 (100%)
MRI	315 (75%)
Coronary angiography or CT angiography	407 (96%)
Exercise stress test	298 (70%)
Holter monitoring	274 (65%)
Sodium channel blocker provocation	266 (63%)
Coronary spasm provocation	78 (18%)
DNA analysis	367 (87%)
Electrophysiology study	171 (40%)

CMR: cardiac magnetic resonance, CT: computed tomography, DNA: deoxyribonucleic acid

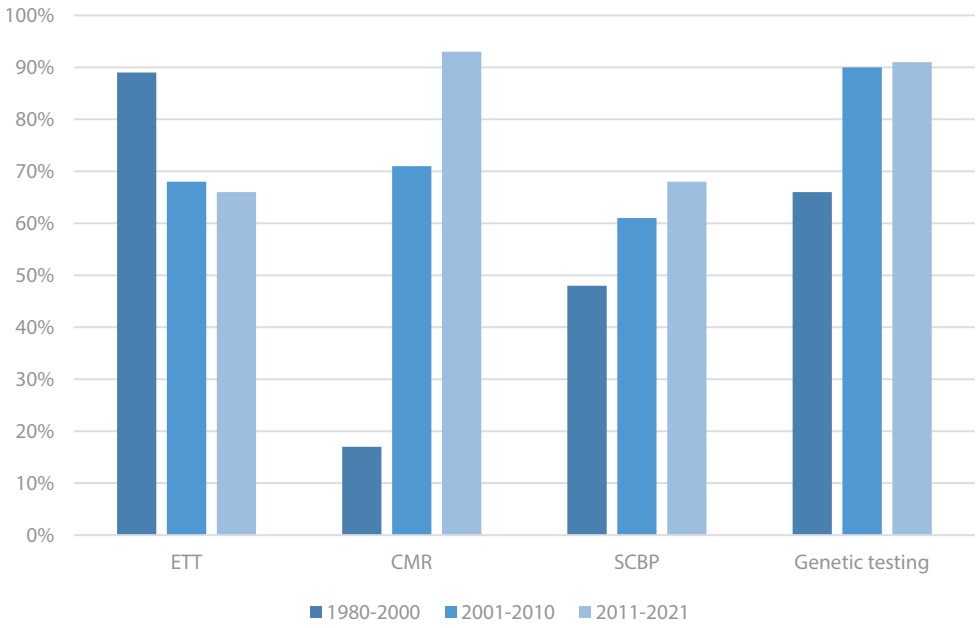


Figure 1 | Percentage of different diagnostic tests performed over time. CMR: cardiac magnetic resonance, ETT: exercise treadmill test, SCBP: sodium channel blocker provocation.

High yield diagnostic tests

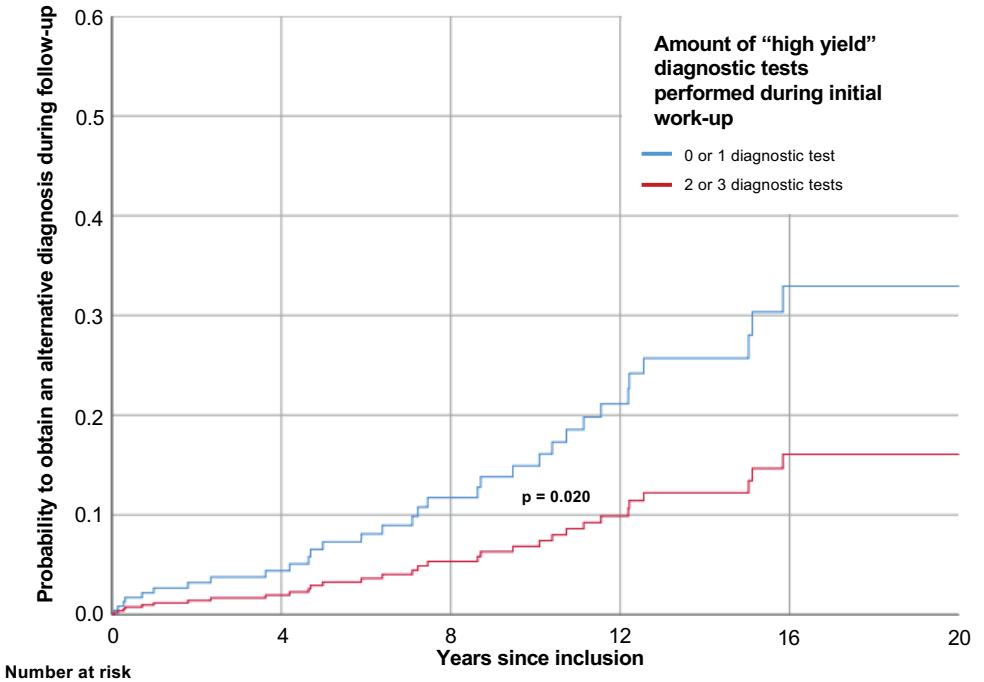
Compared to patients with a high number of "high yield" diagnostic tests performed during initial work-up, patients with a low number of "high yield" diagnostic tests were significantly older (47 vs. 38 years old, $p<0.001$) and more frequently experienced their index event before 2010 (39% vs. 64%, $p<0.001$)). In patients with a low number of "high yield" diagnostic tests, the event more frequently occurred during emotions ($p<0.001$) (table 3). In patients with a low number of "high yield" diagnostic tests, the event more frequently occurred during emotions (table 3).

Multivariate analysis was performed to assess predictors to obtain an alternative diagnosis during follow-up in patients initially diagnosed with IVF (supplementary table 2). Obtaining an alternative diagnosis was independently associated with the consistency at which "high yield" diagnostic tests were performed. Patients with a high number of "high yield" diagnostic tests performed less frequently obtained an alternative diagnosis during follow-up (HR: 0.439, 95% CI: 0.219-0.878, $p=0.020$) (figure 2).

Table 3 | Comparison between patients with low amount (zero or one) of "high yield" diagnostic tests versus a high amount (two or three) of "high yield" diagnostic tests.

Characteristics	0 or 1 n=104	2 or 3 n=319	P-value
Male sex, n(%)	62 (60%)	197 (62%)	0.729
Median age at event (years)	47 [33-57]	38 [27-49]	<0.001
Year of index event before 2010, n (%)	67 (64%)	124 (39%)	<0.001
DPP6 risk haplotype, n(%)	12 (12%)	25 (8%)	0.237
First hospitalization in academic center, n(%)	89 (86%)	265 (83%)	0.647
Circumstances event, n(%)			
Exercise	18 (18%)	66 (21%)	0.483
Emotions	12 (12%)	7 (2%)	<0.001
Rest	59 (60%)	188 (61%)	0.732
Asleep	8 (8%)	43 (14%)	0.164
Other	2 (2%)	7 (2%)	1.000
Family member with SCD, n (%)	15 (16%)	50 (16%)	1.000
ECG characteristics, n(%)			
T-wave abnormalities†	21 (22%)	45 (15%)	0.114
Type 2 or 3 Brugada pattern	2 (2%)	7 (2%)	0.853
Alternative diagnosis detected during follow-up	18 (17%)	20 (6%)	0.001

**History of SCD defined as 1 first degree family member with SCD <45 years, or multiple second degree family members with SCD. †T-wave abnormalities were defined as negative, biphasic or flat T-waves. "High yield" diagnostic tests were defined as an exercise test, CMR or SCB.*



Number at risk						
Total	423	257	163	102	54	31
0 or 1	104	69	50	31	16	11
2 or 3	319	188	113	71	38	20

Figure 2 | Cox regression analysis to assess the effect of a low amount (zero or one) of "high yield" diagnostic tests versus a high amount (two or three) of "high yield" diagnostic tests performed on the probability to obtain an alternative diagnosis during follow-up. "High yield" diagnostic tests were defined as ETT, CMR or SCB. Variables were adjusted for age at index event, year of index event and circumstances of the event (supplementary table 5). Patients with a high amount of "high yield" diagnostic tests performed less frequently obtained an alternative diagnosis during follow-up (HR: 0.439, 95% CI: 0.219-0.878, p=0.020)

Follow-up

Median follow-up duration was 6 [2-12] years. During follow-up, 38 of 423 patients (9%) initially diagnosed with IVF received an alternative diagnosis (Figure 3). The median time to diagnosis was 9 [4-14] years. Patients who received an alternative diagnosis during follow-up tended to receive appropriate ICD therapy more frequently than patients who retained the IVF diagnosis, although this did not reach statistical significance (p=0.055). Survival free of cardiac death was significantly lower in patients who received an alternative diagnosis compared to patients who retained the IVF diagnosis (p=0.012) (Figure 4). Two patients who were diagnosed with arrhythmogenic cardiomyopathy (ACM) died of recurrent VF, one patient with coronary artery spasm died due to end-stage ischemic heart failure and one patient with dilated cardiomyopathy (DCM) also died as a consequence of heart failure. Follow-up of patients who retained the IVF diagnosis and who received ICD implantation is summarized in table 4.

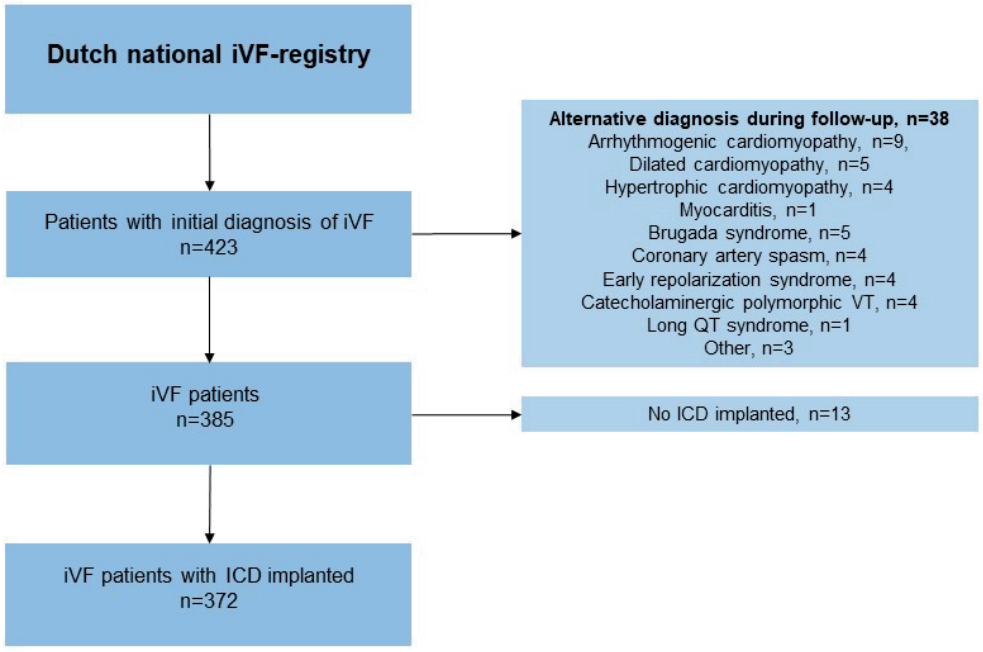
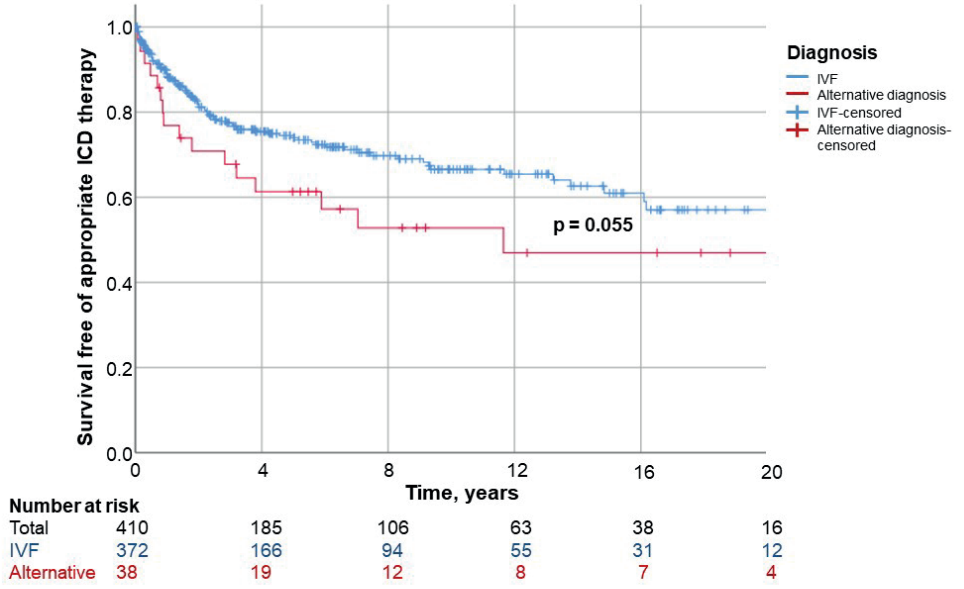


Figure 3 | Alternative diagnosis detected in patients initially diagnosed with IVF during follow-up. ICD: implantable cardioverter defibrillator.



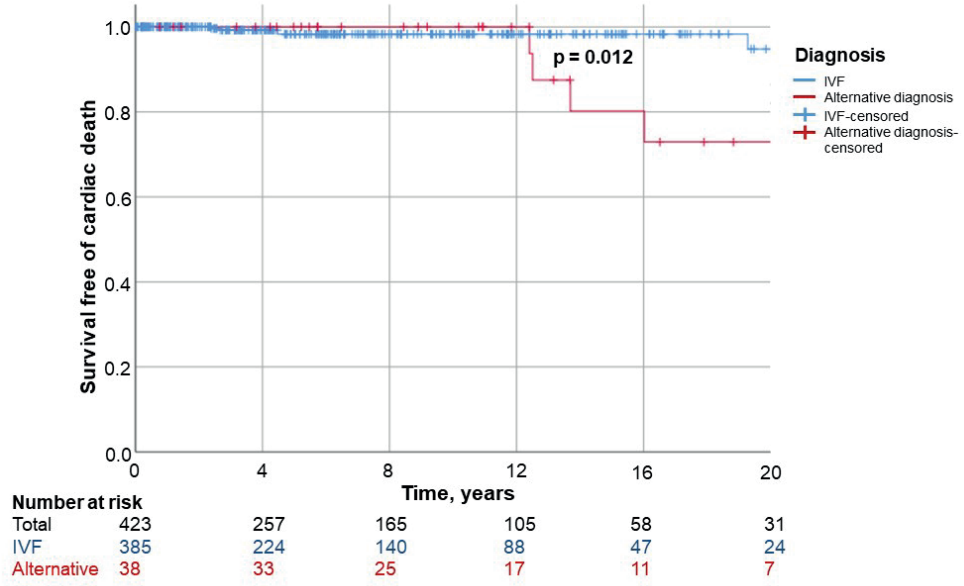


Figure 4 | Kaplan-Meier survival curves for appropriate ICD therapy and cardiac death in patients who retained the IVF diagnosis compared to patients who obtained an alternative diagnosis during follow-up.

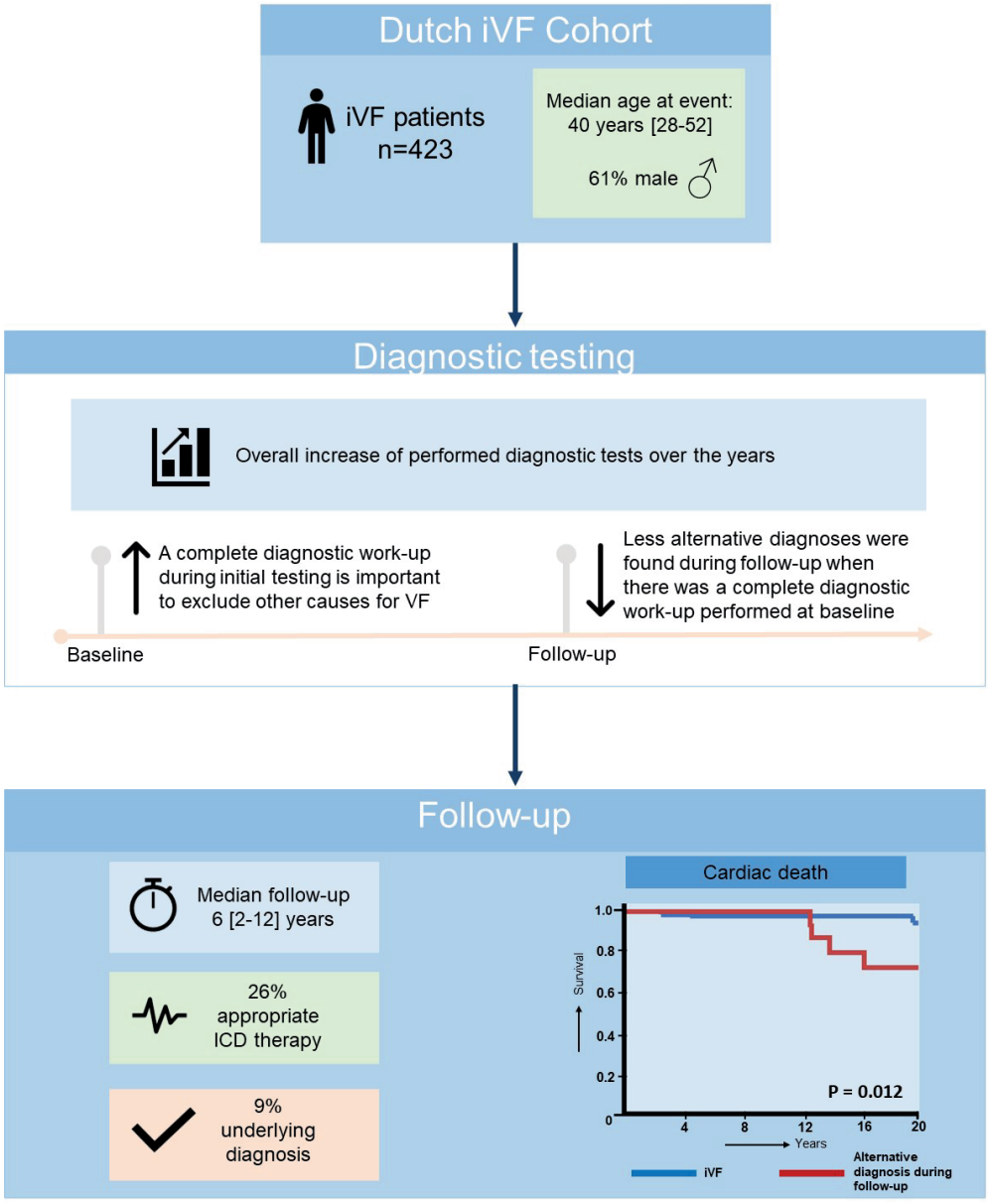
Table 4 | Follow-up of 374 IVF patients with an ICD.

Characteristics	IVF patients n=372
Median follow-up duration (years)	6 [2-12]
Implantable cardioverter defibrillator	372 (100%)
Transvenous	255 (69%)
Subcutaneous	100 (27%)
Unknown	17 (5%)
Appropriate ICD therapy (%)	96 (26%)
Shock	94 (25%)
Anti tachycardia pacing	2 (1%)
Inappropriate ICD therapy (%)	64 (17%)
Supraventricular tachycardia	44 (12%)
T-wave oversensing or ICD/lead malfunction	20 (5%)
Other ICD complications (%)	57 (15%)
Death (%)	12 (4%)
Arrhythmic	2 (1%)
Cardiac	2 (1%)
Other	8 (2%)

Median time duration to first shock: 1 (0-3) years. ICD: implantable cardioverter defibrillator.

Discussion

The aim of this study was to investigate the prevalence and importance of diagnostic testing in a large cohort of Dutch IVF patients. To the best of our knowledge, this is currently the largest consecutive IVF cohort worldwide. This multicenter cohort study extends the findings of our previous study in 217 patients initially diagnosed with IVF.[16] In total, 38 of 423 patients (9%) initially diagnosed with IVF received an alternative diagnosis during follow-up. Although adherence to (near-)complete diagnostic testing in IVF patients increased over the years, patients with IVF still undergo varying degrees of diagnostic evaluation. Patients in whom "high yield" diagnostic tests were consistently performed during the initial work-up, received an alternative diagnosis less frequently during follow-up (HR: 0.439, 95%CI: 0.219-0.878, p=0.020). Our results confirm the importance of systematic use of CMR, exercise testing and SCBP in the diagnostic work-up of IVF to exclude other possible diseases before diagnosing a patient with IVF. Patients with a concealed disease who, in retrospect, erroneously received the IVF diagnosis were associated with a worse prognosis in terms of ICD therapy and survival (Central illustration).



Central illustration | The importance of systematic diagnostic testing in idiopathic ventricular fibrillation (iVF). Cardiac magnetic resonance (CMR), exercise treadmill test (ETT), and sodium channel blocker provocation (SCBP) are considered 'high yield' diagnostic tests. A complete diagnosic work-up with more 'high yield' diagnostic tests during the initial presentation, results in less alternative diagnoses during follow-up. ICD: implantable cardioverter defibrillator.

In clinical practice, there is a delicate balance between optimal clinical care and overuse of diagnostic tools. Identifying a cause for the VF is important as it allows for specific lifestyle interventions (such as avoiding high risk drugs in Brugada syndrome or avoiding excessive sport activities in CPVT[3]) and targeted therapy (such as heart failure medication in patients with a cardiomyopathy with preserved ejection fraction[18]). Although ICD implantation is included in the standard clinical care for IVF patients, recurrence of ventricular arrhythmias proved to be a serious burden in IVF patients.[14,16,19] Our study shows that patients who receive an alternative diagnosis during follow-up were associated with a worse prognosis in terms of ICD therapy and survival. This is understandable since some diseases such as ACM and DCM are known to have a poor prognosis, especially in the absence of adequate lifestyle interventions or treatment to prevent recurrent arrhythmias or heart failure.[18,20] For instance, calcium channel blockers are an effective treatment for patients with coronary artery spasms, and evidence has shown that their absence is an independent determinant of cardiovascular events.[21] One could argue that if IVF patients with a concealed underlying disease benefit from early targeted treatment, this might affect their prognosis

Over the years, the overall percentage of diagnostic tests performed significantly increased. Interestingly, the adherence to diagnostic testing did not increase in the early years (mean 69% in 1980-2000 vs. 68% in 2000-2010). However, the diagnostic testing rate did increase in the years between 2011-2021 to 75%. Different trends were visible between different diagnostic tests (figure 1). For instance, the use of SCBP did not only increase from 1980-2000 to 2000-2010, which can be explained by the discovery of the role of sodium channel blockers to diagnose Brugada Syndrome in the late nineties[22,23], but continued to increase in the time frame of 2011-2021. This indicates that its importance is still increasingly recognized. On the other hand, the use of ETT substantially decreased from 89% to 68% between 1980-2000 to 2001-2010, which cannot be explained by any lower availability of the test. Perhaps, with the rise of new diagnostic possibilities (CMR, CT, nuclear scans), ETT was urged into the background and its value was less recognized.

As the diagnostic yield of SCBP, ETT and CMR appear to be respectively 8%, 9% and 10%[6] in SCA patients, one could argue that a concealed underlying disease was missed in a significant number of patients in our cohort. For instance, Brugada Syndrome might have been missed in 12 patients (8% of 156 patients without SCBP test). However, given the concern about the specificity of SCBP[10,24], one could speculate that some of these tests might be false-positive. Given the lack of a good alternative to diagnose BrS and the importance to recognize the disease, SCBP should be considered in all UCA survivors before diagnosing IVF.[10] Second, also LQTS and CPVT might have been missed in some patients, however, it is unknown if patients without ETT remain undiagnosed after genetic testing.[25] As genetic testing occurred frequently in our cohort (87%), at least a part of these patients should have been identified.

It is important and proven to be of value, to interpret all the diagnostic results in a multidisciplinary team in combination with other clinical and diagnostic information.[26] Our results show that SCBP, ETT and CMR all tend to have a diagnostic value in IVF, although this did not reach statistical significance for all three diagnostic tests alone (supplementary table 2). However, when combined, they showed to have a significant impact on the probability to obtain an alternative diagnosis. After the event, regular follow-up and repeat diagnostic testing is important as new abnormalities may develop over time.[1,27] With advancing possibilities in imaging, there might be a role for repeat CMR in some IVF patients, although this is not routinely established yet. In addition, systematic documentation of arrhythmia recurrences on Holter or ICD readouts are important to assess the presence of short-coupled ventricular fibrillation (SCVF). Recent research indicates that SCVF is a common phenotype in IVF with frequent arrhythmia recurrences.[28,29] Class IA anti arrhythmic drugs showed to be an effective treatment option, which makes the detection of SCVF highly relevant.

It remains unclear what reasons lie behind the overall lack of diagnostic testing in IVF patients amongst different cohorts. Previous studies showed that younger patients and patients admitted to university medical centers are more thoroughly investigated.[7,30] These findings indicate that there is a gap in diagnostic work-up between academic centers and non-academic centers. Interestingly, in our cohort there was no significant difference between academic centers and non-academic centers concerning the adherence to "high yield" diagnostic testing. We consider that these findings might be influenced by collaboration of the investigators of the national IVF registry which intensifies the contact between academic and non-academic hospitals in the Netherlands.

Limitations

An important limitation of this study is the potential survival bias, as only patients who survived the event could be included in the registry. This is also an important limitation for the survival analyses, as these were defined on the basis of a change in diagnosis post-baseline. However, it is likely that the disease was already present at baseline but left unrecognized due to a lack of diagnostic testing or limited clinical features. The results of these analyses should thus be interpreted with these limitations in mind. Due to the observational nature of this study, patients did not undergo systematic diagnostic assessment and treatment strategies, and ICD settings differed between hospitals and cardiologists. As the data is collected in a registry, research is confined to the available parameters in the registry. A major limitation is the lack of detailed data on the efforts that led to an alternative diagnosis in IVF patients. As a result, it is unknown if additional diagnostic testing, progression of disease or re-evaluation in a multidisciplinary team led to an alternative diagnosis. At last, patients from different time eras were included, which complicates any comparison between diagnostic testing in different time periods.

Conclusions

We studied the prevalence and importance of diagnostic testing in a large cohort of 423 Dutch IVF patients. Only in the minority of IVF patients (9%), an alternative diagnosis was found during follow-up. Although adherence to (near-)complete diagnostic testing in IVF patients increased over the years, patients with IVF still undergo varying degrees of diagnostic evaluation. Incomplete diagnostic testing at baseline was an independent predictor to obtain an alternative diagnosis during follow-up. Patients with a concealed underlying disease who, in retrospect, erroneously received the IVF diagnosis were associated with a worse prognosis in terms of ICD therapy and survival. Our results confirm the importance of systematic use of CMR, exercise testing and SCBP in the diagnostic work-up of IVF to exclude an underlying disease in IVF.

References

1. Visser M, Heijden JF Van Der, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up. *Circ Arrhythmia Electrophysiol* 2016;9:1–11.
2. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europea. *Eur Heart J* 2015;36:2793–867.
3. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* 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;10:1932–63.
4. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, *et al.* 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm* 2021;18:e1–50.
5. Ree MH Van Der, Postema PG. What's in a name? further classification of patients with apparent idiopathic ventricular fibrillation. *Eur Heart J* 2021;1–3.
6. Alqarawi W, Dewidar O, Tadros R, Roberts JD, Steinberg C, MacIntyre CJ, *et al.* Defining idiopathic ventricular fibrillation: A systematic review of diagnostic testing yield in apparently unexplained cardiac arrest. *Heart Rhythm* 2021;18:1178–85.
7. Waldmann V, Bougouin W, Karam N, Dumas F, Sharifzadehgan A, Gandjbakhch E, *et al.* Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: Focus on idiopathic ventricular fibrillation. *Eur Heart J* 2018;39:1981–7.
8. Herman ARM, Cheung C, Gerull B, Simpson CS, Birnie DH, Klein GJ, *et al.* Outcome of Apparently Unexplained Cardiac Arrest: Results From Investigation and Follow-Up of the Prospective Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythmia Electrophysiol* 2016;9:e003619.
9. Stępień-Wojno M, Ponińska J, Rydzanicz M, Bilińska M, Truszkowska G, Baranowski R, *et al.* Sudden cardiac arrest in patients without overt heart disease: A limited value of next generation sequencing. *Polish Arch Intern Med* 2018;128:721–30.
10. Tadros R, Nannenberg EA, Lieve K V., Škorić-Milosavljević D, Lahrouchi N, Lekanne Deprez RH, *et al.* Yield and Pitfalls of Ajmaline Testing in the Evaluation of Unexplained Cardiac Arrest and Sudden Unexplained Death: Single-Center Experience With 482 Families. *JACC Clin Electrophysiol* 2017;3:1400–8.
11. Jiménez-Jáimez J, Peinado R, Grima EZ, Segura F, Moriña P, Sánchez Muñoz JJ, *et al.* Diagnostic Approach to Unexplained Cardiac Arrest (from the FIVI-Gen Study). *Am J Cardiol* Elsevier Inc.; 2015;116:894–9.
12. Visser M, Dooijes D, Smagt JJ van der, Heijden JF van der, Doevendans PA, Loh P, *et al.* Next-generation sequencing of a large gene panel in patients initially diagnosed with idiopathic ventricular fibrillation. *Heart Rhythm* Elsevier; 2017;14:1035–40.
13. Grondin S, Davies B, Cadrin-Tourigny J, Steinberg C, Cheung CC, Jorda P, *et al.* Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J* 2022;1–11.
14. Conte G, Belhassen B, Lambiase P, Ciconte G, Asmundis C De, Arbelo E, *et al.* Out-of-hospital cardiac arrest due to idiopathic ventricular fibrillation in patients with normal electrocardiograms: Results from a multicentre long-term registry. *Europace* 2019;21:1670–7.
15. Siebermair J, Sinner MF, Beckmann B-M, Laubender RP, Martens E, Sattler S, *et al.* Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace* 2016;18:718–25.
16. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace* 2019;21:1519–26.

17. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm* 2016;13:905–12.
18. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017;136:2068–82.
19. Herman ARM, Cheung C, Gerull B, Simpson CS, Birnie DH, Klein GJ, *et al.* Outcome of apparently unexplained cardiac arrest: Results from investigation and follow-up of the prospective cardiac arrest survivors with preserved ejection fraction registry. *Circ Arrhythmia Electrophysiol* 2016;9:1–10.
20. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
21. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, *et al.* Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation* 2019;139:E891–908.
22. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061–70.
23. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;101:510–5.
24. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AAM. Everybody has Brugada syndrome until proven otherwise? *Heart Rhythm* Elsevier; 2015;12:1595–8.
25. Leinonen JT, Crotti L, Djupsjöbacka A, Castelletti S, Junna N, Ghidoni A, *et al.* The genetics underlying idiopathic ventricular fibrillation: A special role for catecholaminergic polymorphic ventricular tachycardia? *Int J Cardiol* 2018;250:139–45.
26. Merghani A, Monkhouse C, Kirkby C, Savvatis K, Mohiddin SA, Elliott P, *et al.* Diagnostic impact of repeated expert review & long-term follow-up in determining etiology of idiopathic cardiac arrest. *J Am Heart Assoc* 2021;10:1–10.
27. Visser M, Heijden JF Van Der, Smagt JJ Van Der, Doevendans PA, Wilde AA, Loh P, *et al.* Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. *Circ Arrhythmia Electrophysiol* 2016;9:e004258.
28. Steinberg C, Davies B, Mellor G, Tadros R, Laksman ZW, Roberts JD, *et al.* Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report from the CASPER registry. *Eur Heart J* 2021;42:2827–38.
29. Groeneveld SA, Ree MH van der, Mulder BA, Balt J, Wilde AAM, Postema PG, *et al.* Prevalence of Short-Coupled Ventricular Fibrillation in a Large Cohort of Dutch Patients With Idiopathic Ventricular Fibrillation. *Circulation* 2022;145:1437–9.
30. Stampe NK, Jespersen CB, Glinge C, Bundgaard H, Tfelt-Hansen J, Winkel BG. Clinical characteristics and risk factors of arrhythmia during follow-up of patients with idiopathic ventricular fibrillation. *J Cardiovasc Electrophysiol* 2020;31:2677–86.

Supplemental material

Supplementary table 1 | Tests used for exclusion of disease.

Diagnosis	Tests used for exclusion	Criteria used
Coronary heart disease	electrocardiogram, blood chemistry, coronary CT/angiography	Roffi et al[1]
Coronary artery spasm	ergonovine provocation	Montalescot et al[2]
Long QT syndrome	electrocardiogram, exercise stress test, DNA analysis	Schwartz et al[3]
Brugada syndrome	electrocardiogram, sodium channel blocker provocation, DNA analysis	Antzelevitch et al[4]
Catecholaminergic polymorphic ventricular tachycardia	electrocardiogram, Holter, exercise stress test, DNA analysis	Priori et al[5]
Short QT syndrome	electrocardiogram, DNA analysis	Mazzanti et al[6]
Early repolarization syndrome	electrocardiogram	Macfarlane et al[7]
Hypertrophic cardiomyopathy	Cardiac imaging, DNA analysis	Elliot et al[8]
Dilated cardiomyopathy	Cardiac imaging, DNA analysis	Pinto et al[9]
Arrhythmogenic cardiomyopathy	ECG, Holter, Cardiac imaging, endomyocardial biopsy, DNA analysis	Marcus et al[10]
Myocarditis	Cardiac imaging, blood chemistry, endomyocardial biopsy	Caforio et al[11], Friedrich et al[12]

1. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016;37(3):267–315.
2. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013;34(38):2949–3003.
3. Schwartz PJ, Ackerman MJ. The long QT syndrome: A transatlantic clinical approach to diagnosis and therapy. Eur Heart J. 2013;34(40):3109–16.
4. Antzelevitch C, Yan G-X. J-wave syndromes: Brugada and early repolarization syndromes. Antzelevitch C, Yan G-X, editors. Heart Rhythm 2015;12(8):1852–66.
5. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. Heart Rhythm 2013;10(12):1932–63.
6. Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol. 2014;63(13):1300–8.
7. MacFarlane PW, Antzelevitch C, Haissaguerre M, Huikuri H V., Potse M, Rosso R, et al. The early repolarization pattern: A consensus paper. J Am Coll Cardiol. 2015;66(4):470–7.
8. Task A, Elliott PM, Uk C, Anastasakis A, Germany MAB, Germany MB, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35(39):2733–79.
9. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: A position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J. 2016;37(23):1850–8.

10. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/Dysplasia: Proposed modification of the task force criteria. Circulation 2010;121(13):1533–41.
11. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636–48.
12. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009;53(17):1475–87

Supplementary table 2 | Overview of genetic tests results.

Genetic testing	IVF patients
Performed	N = 367
Any variant found	158 (43%)
Pathogenic/likely pathogenic	46 (29%)
Pathogenic/likely pathogenic and VUS	8 (5%)
VUS	103 (65%)
Unknown	1 (1%)

Supplementary table 3 | Overview of pathogenic or likely pathogenic variants

Patient	Gene	Nucleotide	Peptide	Classification
1	DPP6			Pathogenic
2	DPP6			Pathogenic
3	DPP6			Pathogenic
4	DPP6			Pathogenic
5	DPP6			Pathogenic
6	DPP6			Pathogenic
7	DPP6			Pathogenic
8	DPP6			Pathogenic
9	DPP6			Pathogenic
10	DPP6			Pathogenic
11	DPP6			Pathogenic
12	DPP6			Pathogenic
13	DPP6			Pathogenic
14	DPP6			Pathogenic
15	DPP6			Pathogenic
16	DPP6			Pathogenic
17	DPP6			Pathogenic
18	DPP6			Pathogenic
19	DPP6			Pathogenic
20	DPP6			Pathogenic
21	DPP6			Pathogenic
22	DPP6			Pathogenic
23	DPP6			Pathogenic
24	DPP6			Pathogenic
25	DPP6			Pathogenic

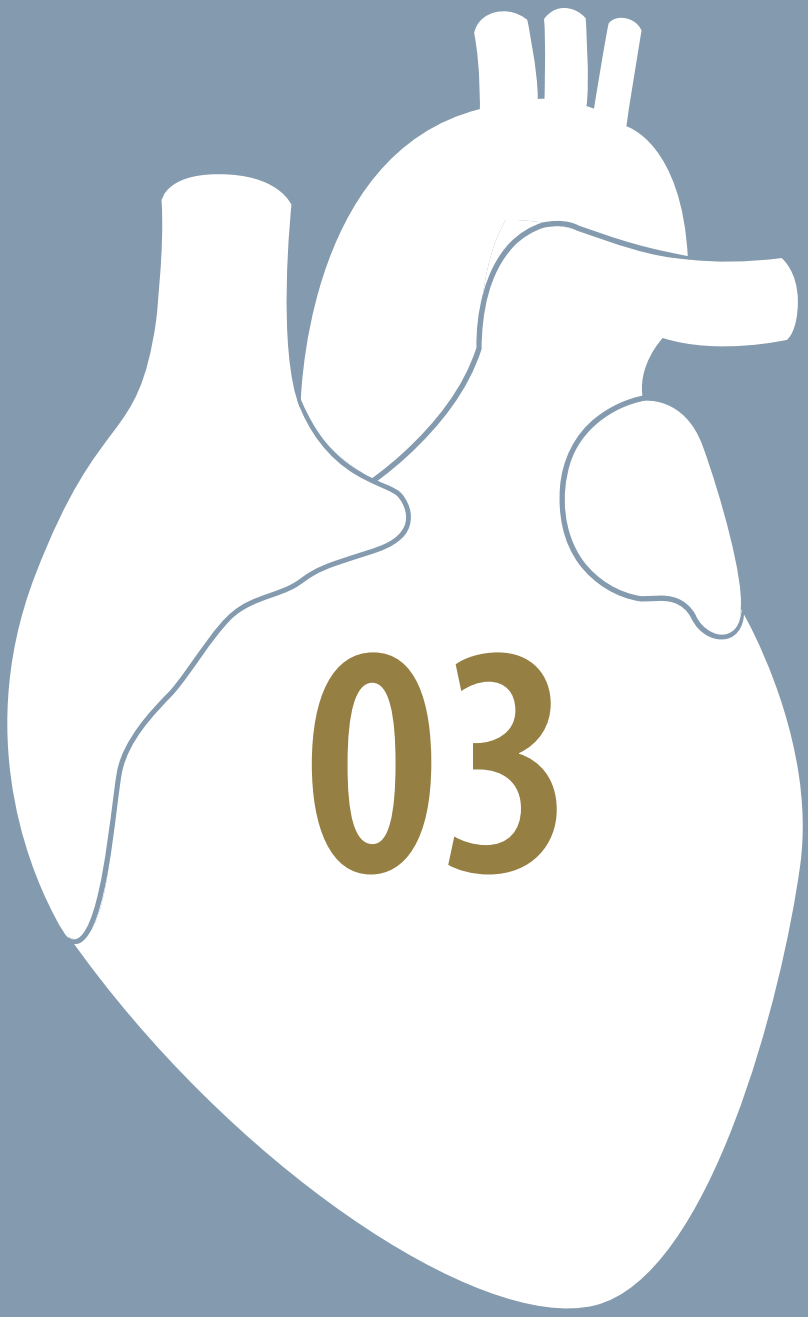
26	DPP6			Pathogenic
27	DPP6			Pathogenic
28	DPP6			Pathogenic
29	DPP6			Pathogenic
30	DPP6			Pathogenic
31	DPP6			Pathogenic
32	DPP6			Pathogenic
33	DPP6			Pathogenic
34	DPP6			Pathogenic
35	DPP6			Pathogenic
36	DPP6			Pathogenic
37	SCN5A	Unknown	Unknown	Pathogenic
38	PLN	Unknown	Unknown	Pathogenic
39	RYR2	Unknown	Unknown	Pathogenic
40	MYH7	Unknown	Unknown	Pathogenic
41	RYR2	c.14173T>C	p.(Tyr4725His)	Possible pathogeni
42	CPT2	c.338C>T	p.(Ser113Leu)	Pathogenic
43	SCN5A	Unknown	Leu729del	Pathogenic
44	RYR2	c.11368T>C	(p.Phe3790Leu)	Pathogenic
45	RYR2	c.1244C>G	p.Thr415Arg	Pathogenic
46	PLN	c.40.42delAGA,	p.Arg14del	Pathogenic
47	LMNA	c.1517A>C	p.(His506Pro)	Likely pathogenic
48	PKP2	c.1550A>G	(p.Asn517Ser)	Pathogenic
49	TTN	c.52198G>T	p.(Glu17400*)	Likely pathogenic
50	KCNQ1	c.1066C>T	p.(Gln356*)	Pathogenic
51	NEB	c.25288C>T	p(Arg8430*)	Pathogenic
52	MYL2	c.64G>A	p.Glu22Lys	Pathogenic
53	TTN	c.76352dupC	p. (Pro25452fs)	Likely Pathogenic
54	TTN	Unknown	Unknown	Pathogenic

Supplementary table 4 | Electrophysiological studies and ablation results

Electrophysiological study	IVF patients N=423
Performed	171 (40%)
VT or SVT inducible?	
Ventricular tachycardia inducible	11 (6%)
Ventricular fibrillation inducible	25 (15%)
Ventricular tachycardia and ventricular fibrillation inducible	19 (11%)
SVT inducible	10 (6%)
Ablation Performed	51 (12%)
Successful	35 (68%)

Supplementary table 5 | Multivariate analysis to assess predictors to obtain an alternative diagnosis during follow-up in 423 patients initially diagnosed with IVF.

Predictors to obtain an alternative diagnosis	HR	Lower limit	Upper limit	P-value
2 or 3 "high yield" tests performed at baseline	0.439	0.219	0.878	0.020
CMR performed at baseline	0.579	0.237	1.141	0.230
SCB provocation performed at baseline	0.612	0.306	1.222	0.164
Exercise test performed at baseline	0.864	0.386	1.935	0.722
Age at event	0.988	0.975	1.022	0.899
Year of index event	1.018	0.967	1.073	0.495
Index event during emotions	1.292	0.449	3.715	0.634


03

Prevalence of short-coupled ventricular fibrillation in a large cohort of Dutch patients with idiopathic ventricular fibrillation.

Circulation. 2022; 145; 1437-1439.

Sanne A. Groeneveld*
Martijn H. van der Ree*
Bart A. Mulder
Jippe Balt
Arthur A.M. Wilde
Pieter G. Postema
Rutger J. Hassink

*Both authors contributed equally

In patients with idiopathic ventricular fibrillation (IVF), the cause of VF remains unknown after extensive diagnostic testing. With increased knowledge, several disease entities have been identified over the past decades resulting in targeted treatment options.

In a recent paper from Canada,[1] a specific IVF-subtype was described and referred to as short-coupled IVF (SCVF) – resembling earlier reports[2] and also known as short-coupled variant of torsade de pointes. The correct terminology is still a matter of debate. Since we report on IVF patients, we adhere to SCVF. In SCVF-patients, short-coupled premature ventricular complexes (PVC) with a coupling interval <350ms initiate polymorphic VT/VF. SCVF is malignant with frequent arrhythmia recurrences. In the Canadian IVF cohort, a SCVF-prevalence of only 6.6% was reported. However, data on the percentage of patients with documentation of the VF onset was not provided. We aimed to investigate (1) the prevalence and (2) the SCVF-phenotype in our Dutch IVF-registry.

Patients were included in our IVF-registry following cardiac arrest, with documented VF, when no etiology was identified after comprehensive assessment.[3] We assessed SCVF by retrospectively reviewing telemetry, Holters, electrocardiograms and ICD-interrogations, using the proposed definition of VF or polymorphic VT/VF initiated by a PVC with a coupling interval <350ms.[1] As by IVF-definition, patients with QTc-prolongation, pause-dependent torsades, structural heart disease or primary electrical disorders were excluded. The study data is available from the corresponding author upon reasonable request. The study was approved by the institutional review committee and the subjects gave informed consent. Comparisons between continuous variables were performed using independent samples t-test or Mann-Whitney-U test, categorical variables were compared using the Fisher-exact test, incidence rates were compared using an exact-Poisson test.

In total, 228 IVF patients were included. Median follow-up duration was 6.4 [IQR: 2.6;12.5] years. Altogether, 57/228 (25%) patients experienced VF-recurrence (including 9 during hospitalization and 48 during follow-up). In 34/57 (60%) of these patients, the initiation of VF was documented. Importantly, in 31/34 (91%) patients with documented VF-onset, the arrhythmia was triggered by a short-coupled PVC, resulting in a SCVF prevalence of 14% (31/228) for the entire cohort and 91% (31/34) for those with documented arrhythmia initiation (figure 1). There were no significant differences between SCVF-patients and IVF-patients regarding age (51±10 versus 53±17 years) or gender distribution (55% versus 60% male). The occurrence of the *DPP6* IVF-haplotype[4] was higher in SCVF-patients compared to IVF-patients (n=15[48%] versus n=15[8%], p<0.0001). The median VF-initiating coupling interval in SCVF-patients was 288ms [IQR 251;316]. SCVF-patients showed a higher shock burden (median 8 versus 3 shocks in patients with at least 1 recurrence, p<0.0001) and a higher incidence of electrical storm (32% versus 4%, p<0.0001) than in IVF-patients. Quinidine was frequently prescribed to SCVF-patients (n=19/31[61%]; median dose 733mg). The incidence of VF-recurrence on-quinidine was significantly lower than off-quinidine (0.1 versus 1.2 event/year, p<0.0001). Quinidine was effective in patients with and without DPP6. Interestingly, six SCVF

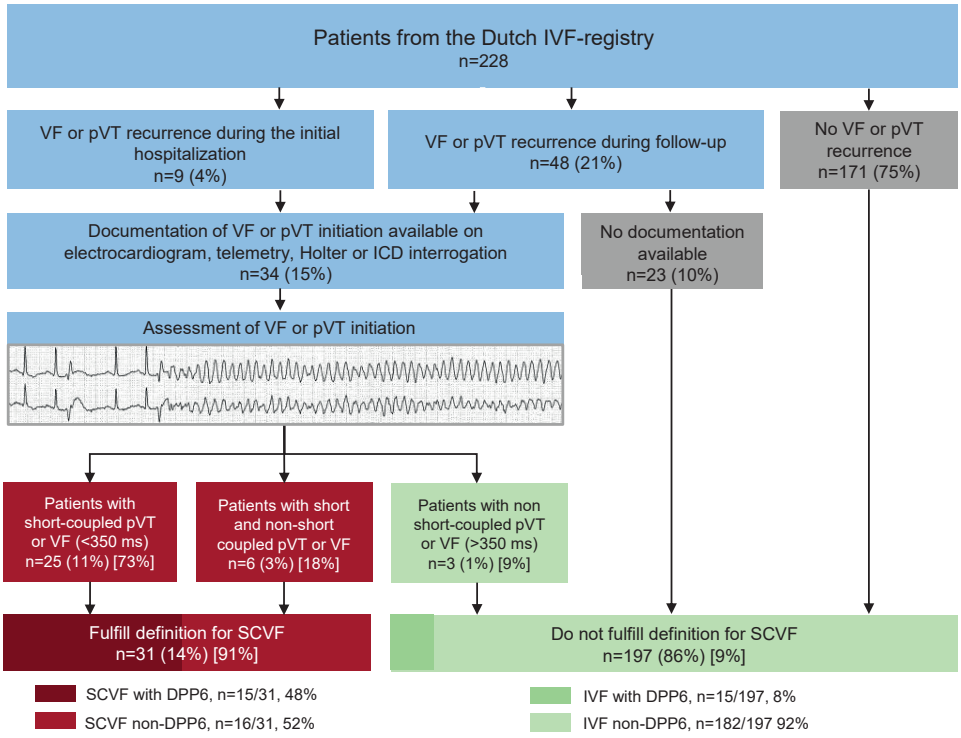


Figure 1 | Flowchart of the diagnostic assessment for SCVF. Parentheses show percentages for the entire cohort (n=228) and square brackets show percentages for those with documented initiations of VF [n=34]. Abbreviations: DPP6 = DPP6 IVF risk-haplotype (a genetic subset of IVF-patients with arrhythmias initiated by short-coupled PVCs), ICD = implantable cardioverter defibrillator, IVF = idiopathic ventricular fibrillation, PVC = premature ventricular complex, pVT = polymorphic VT, SCVF = short coupled ventricular fibrillation, VT = ventricular tachycardia, VF = ventricular fibrillation.

patients also had VF-episodes initiated by PVCs with a coupling interval >350ms. In only three patients, VF-initiating PVCs always had a coupling interval >350ms (range: 360-560).

Quinidine was effective in patients with and without DPP6. Interestingly, six SCVF patients also had VF-episodes initiated by PVCs with a coupling interval >350ms. In only three patients, VF-initiating PVCs always had a coupling interval >350ms (range: 360-560).

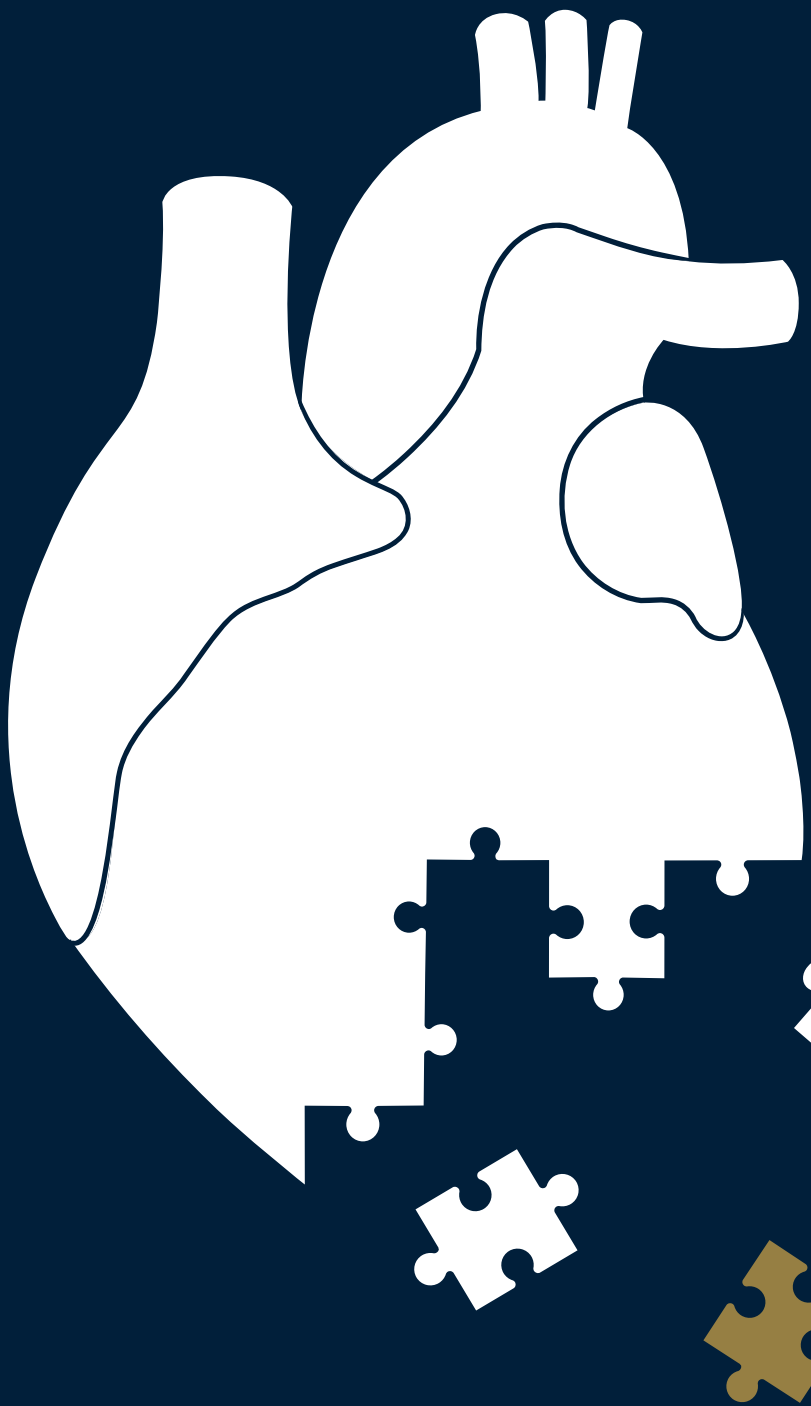
In this contribution we report a high prevalence of SCVF, of 91% for IVF patients with documented arrhythmia-onset and 14% for the entire IVF-cohort. We confirm the malignant phenotype of this subset of IVF-patients. A limitation of the proposed definition for SCVF is the arbitrary and circular-thinking nature of the description. Our data confirms that SCVF is a distinct phenotype in IVF, but we believe that it is too early to recognize SCVF as a distinct primary arrhythmia syndrome. One could argue that if the vast majority (91%) of documented

VF-recurrences have short-coupled initiations, then, SCVF might not be a 'subtype' of IVF but rather the common phenotype in true IVF. Furthermore, in our cohort we found IVF-patients with *both* short and longer VF-initiating coupling intervals. As the cut-off value for SCVF is debatable, it is unclear if these patients should be classified as IVF- or SCVF-patients.[5] Secondly, the SCVF-diagnosis is fully dependent on documenting initiating PVCs. For this reason, SCVF can only be diagnosed in patients with arrhythmia recurrences as the initiation of VF during the index event is typically not documented, potentially introducing bias towards a more malignant phenotype. Lastly, in the Netherlands, a hereditary subset of IVF-patients with arrhythmias initiated by short-coupled PVCs exists (the *DPP6*-haplotype)[4], which contributes to our higher SCVF-prevalence. The appropriate terminology for arrhythmias triggered by short-coupled PVCs also remains unsettled as different terms are used interchangeably.

To conclude, our data confirms that short-coupled idiopathic ventricular fibrillation (SCVF) is a malignant phenotype but also indicates that its prevalence may be higher than recently reported, depending on the study population, the cut-off value for SCVF and availability of VF documentation. As such, the incidence, underlying mechanisms, heritability, and SCVF-treatment requires further scrutiny. As quinidine and verapamil have been reported to be effective in SCVF, a future randomized trial is needed to evaluate these findings.

References

1. Steinberg C, Davies B, Mellor G, Tadros R, Laksman ZW, Roberts JD, *et al.* Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report from the CASPER registry. *Eur Heart J*. 2021;42(29):2827–38.
2. Viskin S, Belhassen B. Idiopathic ventricular fibrillation. *Am Heart J*. 1990;120(3):661–71.
3. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace*. 2019;21(10):1519–26.
4. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13(4):905–12.
5. Haïssaguerre M, Shoda M, Jaïs P, Nogami A, Shah DC, Kautzner J, *et al.* Mapping and ablation of idiopathic ventricular fibrillation. *Circulation*. 2002;106(8):962–7.



PART II

Progress in diagnostic testing


04

Echocardiographic deformation imaging unmasks global and regional mechanical dysfunction in patients with idiopathic ventricular fibrillation: a multicenter case-control study.

Heart Rhythm. 2021; 18(10): 1666-1672.

Sanne A. Groeneveld*
Martijn H. van der Ree*
Karim Taha*
Rianne H.A. de Bruin-Bon
Maarten J. Cramer
Arco J. Teske
Berto J. Bouma
Ahmad S. Amin
Arthur A.M. Wilde
Pieter G. Postema
Rutger J. Hassink

*Authors contributed equally

Abstract

Background | Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with sudden onset of ventricular fibrillation of which the origin is not identified. New diagnostic tools which are able to detect subtle abnormalities are needed to diagnose and treat patients with an underlying substrate.

Objective | The purpose of this study was to explore echocardiographic deformation characteristics in IVF patients.

Methods | Echocardiograms were analyzed with deformation imaging by 2D speckle tracking. Global and regional measurements were performed of the left and right ventricle (LV/RV). Regional LV deformation patterns were evaluated for presence of post-systolic shortening. Regional RV deformation patterns were classified as type I (normal) or type II/III (abnormal).

Results | In total, 47 IVF patients (mean age 45 years, LVEF 56%) and 47 healthy controls (mean age 41 years, LVEF 60%) were included. IVF patients showed more global deformation abnormalities as indicated by lower LV global longitudinal strain (18.5±2.6% vs. 21.6±1.8%, $p<0.001$), and higher LV mechanical dispersion (41±12ms vs. 26±6ms, $p<0.001$). In addition, IVF patients showed more regional LV post-systolic shortening as compared to healthy controls (50% vs. 11%, $p<0.001$). Abnormal RV deformation patterns were observed in 16% of IVF patients and in none of the control subjects ($p<0.001$).

Conclusion | We were able to show both regional and global echocardiographic deformation abnormalities in IVF patients. This study provides evidence that localized myocardial disease is present in a subset of IVF patients.

Introduction

Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with a sudden onset of ventricular fibrillation (VF) of which the origin is not identified after extensive diagnostic testing.[1] The IVF diagnosis thus depends on the absence of an evident substrate for VF by exclusion of coronary artery disease, structural cardiac diseases and primary arrhythmia syndromes.[2] Importantly, IVF may be an inheritable condition which thus also infers risk of VF in currently asymptomatic family members.[3] With continuous sophistication of diagnostic modalities, the presence of several disease entities have been identified in VF patients previously considered idiopathic.[1]

Imaging modalities such as echocardiography and cardiovascular magnetic resonance imaging (CMR) play an important role in the standard diagnostic work-up for IVF patients. By definition, IVF is characterized by a lack of overt structural and functional abnormalities detected by conventional imaging by fulfilling current cut-off values for cardiomyopathies (CMP). However, detailed endo- and epicardial mapping in IVF patients revealed that localized structural alterations underlie a significant subset of patients.[4] Even in these patients, conventional imaging lacks sensitivity for detection of these subtle changes. Therefore, application of novel imaging techniques could be of added value in IVF patients.

Echocardiographic deformation imaging is an advanced and widely available imaging technique that has shown to provide unique information on regional and global myocardial function.[5] This technique is already being applied in the field of (inherited) arrhythmia syndromes. For example, right ventricular (RV) deformation imaging has been shown to enable detection of an early electro-mechanical substrate in arrhythmogenic cardiomyopathy (ACM) patients, which was proven to have prognostic value in relatives who are in a subclinical stage of disease.[6,7] But also in primary arrhythmia syndromes, such as long QT syndrome and Brugada Syndrome, deformation imaging revealed abnormal myocardial contraction patterns, which have previously been linked to ventricular arrhythmias.[8,9] Echocardiographic deformation imaging may therefore potentially play a role in the search for an arrhythmogenic substrate in IVF patients or to define subsets of IVF patients with distinct underlying pathophysiological mechanisms.

In this study, we aimed to explore echocardiographic deformation characteristics in IVF patients. Our hypothesis is that deformation abnormalities precede signs of disease on conventional imaging in IVF patients and may therefore eventually help classify and stratify patients and their family members at risk.

Methods

Study population

Patients were selected from a Dutch registry of IVF patients between 1996 and 2020.[10,11] Patients were included in this registry if they had experienced a cardiac arrest, with an initial

shockable rhythm, and no diagnosis had been made after comprehensive clinical assessment, as explained below. Patients from two tertiary referral centers (Amsterdam University Medical Centers and University Medical Center Utrecht) in the Netherlands with an echocardiogram of sufficient image quality were included for analysis. Echocardiograms within the first two weeks after the cardiac event were excluded from analysis due to potential cardiac stunning. The subsequent follow-up echocardiogram with the highest image quality was included. Patients with cardiac pathology at the time of echocardiography were excluded (figure 1). In addition to subjects with idiopathic VF, we included a group of age- and sex-matched control subjects. The control group consisted of a mixed group of (1) healthy, non-athlete volunteers[12] and (2) patients who visited the outpatient clinic but were found to be free of cardiac disease (for example non-cardiac chest pain or genotype elusive family members who visited the outpatient clinic for screening). This study was approved by the local ethics committee of the participating centers. The study was in accordance with the declaration of Helsinki.

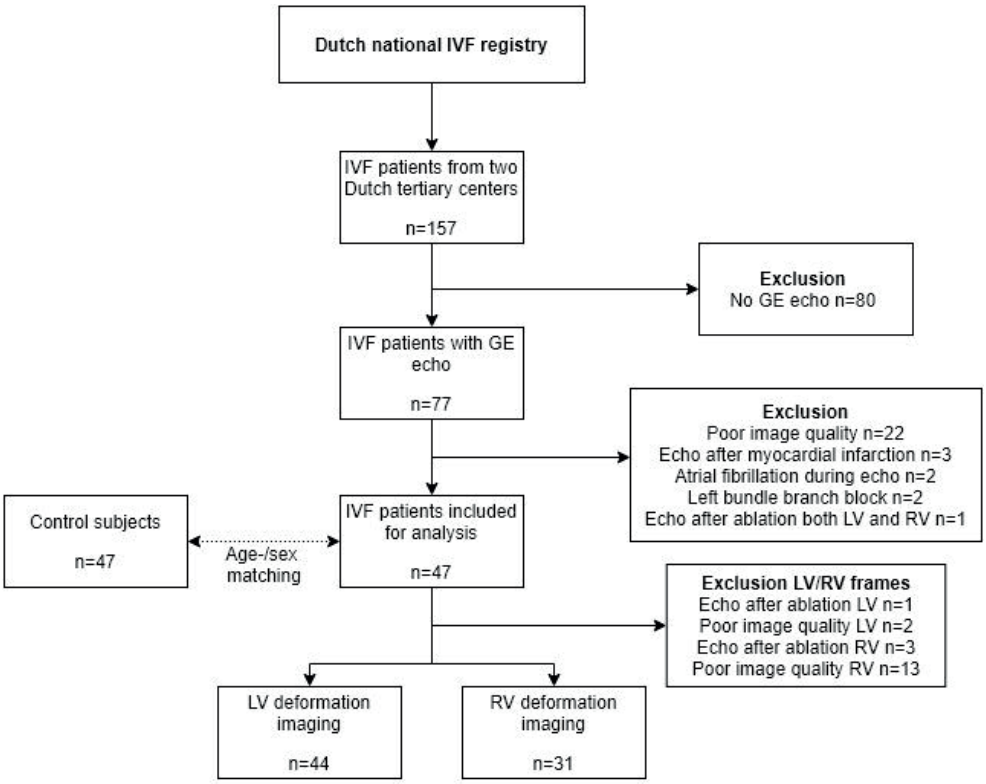


Figure 1 | Patient selection. Patients were derived from a large Dutch national registry. For this study, only echocardiograms performed with GE healthcare machines were included. IVF = idiopathic ventricular fibrillation, GE = GE healthcare, LV = left ventricle, RV = right ventricle.

Clinical investigations

Enrolled patients underwent a detailed investigation of the medical history, physical examination and standard investigations including resting 12-lead ECG and cardiac imaging with echocardiography and/or CMR. Additional investigations, such as coronary artery imaging, holter monitoring, exercise test, sodium channel blocker provocation and endomyocardial biopsy and genetic testing were performed at the treating physician's discretion. Patients with the previously described *DPP6* haplotype, a genetic variant associated with short-coupled Torsade de Pointes/IVF, were also included as IVF patients.[1,3] All patients received cardiac follow-up in a large tertiary center with electrophysiological expertise where the IVF diagnosis is continuously evaluated and reconsidered. Additional diagnostic tests were performed when deemed appropriate. The diagnostic- and outcome data in the registry are updated in a yearly manner.

Conventional echocardiography

All echocardiograms were performed as part of routine clinical care. Only echocardiograms performed with Vivid 7, E9 and E95 machines (GE Healthcare, Horten, Norway) were included. Measurements were performed by two operators (KT and HB). Blinding was not possible, since IVF patients typically have an implantable cardioverter defibrillator (ICD), in contrast to control subjects. The two operators were unfamiliar with the patients' clinical characteristics. Conventional echocardiographic measurements were performed in accordance with current recommendations.[13] Measurement of left ventricular ejection fraction (LVEF) was either performed by 2D-Simpson's Biplane method or by 3D volume measurements.

Deformation imaging methods

Longitudinal strain analysis was performed by 2D-speckle tracking with EchoPAC version 203 (GE Healthcare, Horten, Norway). All analyses were performed in accordance with current recommendations.[5,14] Post-processing methods have previously been described.[15]

For left ventricular (LV) deformation imaging, apical 4-, 2- and 3-chamber views were analyzed. Images were excluded for analysis in case of a low frame rate (<50/s), in case of foreshortening and in cases where more than one segment required exclusion (e.g. due to insufficient window). Timing of aortic valve closure was derived from 2D-recordings in the apical 3-chamber view. Right ventricular (RV) deformation imaging was only performed if there was a RV-focused apical 4-chamber view available of sufficient quality. Single wall-analysis was performed on the RV free wall. Timing of pulmonic valve closure was derived from spectral Doppler recordings in the RV outflow tract. LV or RV deformation imaging were not performed in subjects who had a history of catheter ablation in the LV or RV respectively.

Global deformation imaging parameters

All global deformation imaging parameters are reported as absolute values. LV global longitudinal strain (GLS) was defined as the average global peak strain (in %) from the three apical views. LV mechanical dispersion (MD) was defined as the standard deviation of time to peak longitudinal strain (in ms) from the 18 LV segmental deformation curves. LV GLS <18%

and LV MD>45 ms, as used at our center, were considered abnormal. RV free wall strain (RVFWS) was defined as the average systolic peak strain (in %) from the three RV free wall segments.

Regional deformation imaging parameters

The 18 regional LV deformation curves were evaluated for presence of post-systolic shortening. Post-systolic shortening was defined as longitudinal myocardial shortening after aortic valve closure. Post-systolic shortening was considered present in case the post-systolic index was ≥10%.[16] The post-systolic index was calculated as follows:

$$\frac{\text{peak strain} - \text{systolic peak strain}}{\text{peak strain}} * 100\%.$$

The three regional RV free wall deformation curves (basal, mid, and apical) were evaluated according to the classification of Mast et al.[7] The deformation patterns were consequently classified as follows:

Type I Normal deformation pattern

Type II Delayed onset of shortening, decreased systolic peak strain, post-systolic shortening

Type III Systolic stretching and large post-systolic shortening

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics version 25.0 for windows (IBM Corporation, Armonk, New York). Continuous variables are expressed as mean±standard deviation or median [interquartile range]. Comparisons between continuous variables were performed using independent samples t-test or Mann-Whitney U test. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher-exact test, as appropriate. A p-value <0.05 was accepted as level of statistical significance.

Results

Baseline characteristics and diagnostic testing

Table 1 shows the baseline characteristics of the IVF patients. Echocardiograms with highest image quality performed after the initial cardiac arrest, were included (median timeframe 56 [29;133] months). IVF patients were aged 45±12.9 years at the time of the echocardiography and 51.1% were males. Control subjects were aged 41±12.1 at the time of the echocardiography and 34.0% were males. Table 2 shows the diagnostic tests performed.

Table 1 | Baseline characteristics of 47 idiopathic ventricular fibrillation patients

IVF patients	n=47
Age at the moment of echocardiography, years	45±12.9
Male sex	24 (51.1)
Age at cardiac arrest	38.0 ±12.1
Circumstances during occurrence of VF	
Sleep	11 (23.4)
Rest	19 (40.4)
Exercise	13 (27.7)
Other	4 (8.5)
Witnessed event	38 (84.4)
Post-anoxic encephalopathy	11 (23.4)
ICD implanted	47 (100)
Outcome of DNA analysis	
Variant of uncertain significance	7 (14.9)
Pathogenic *DPP6* haplotype	12 (25.5)

Values are given as mean ± SD or n (%). ICD = implantable cardioverter-defibrillator; IVF = idiopathic ventricular fibrillation; VF = ventricular fibrillation.

Table 2 | Diagnostic tests performed

IVF patients	n (%)
12-lead electrocardiography	47 (100)
Cardiac imaging	47 (100)
Echocardiography	47 (100)
Cardiac MR	35 (76.1)
Coronary angiography or CT angiography	42 (89.4)
Exercise stress test	42 (89.4)
Holter monitoring	26 (55.3)
Sodium channel blocker provocation	34 (72.3)
Ergonovine provocation	15 (31.9)
Signal-averaged ECG	5 (10.6)
Endomyocardial biopsy	8 (17.0)
DNA analysis	44 (93.6)

Values are given as n (%). CT = computed tomography; ECG = electrocardiography; MR = magnetic resonance; IVF = idiopathic ventricular fibrillation.

Conventional echocardiography

Table 3 shows the echocardiographic measurements of the IVF and the control cohort. For conventional measurements, only LVEF differed significantly between groups, being lower in IVF patients than in control subjects (56±6% vs. 60±5%, respectively, p<0.001). Global RV function was not different between IVF patients and control subjects, and neither were LV and RV dimensions.

Deformation imaging

Deformation imaging measurements are shown in table 3 and figure 2. LV deformation imaging was performed in 44 IVF subjects (94%) and 47 control subjects (100%), whereas RV deformation imaging could be reliably performed in 31 IVF subjects (66%) and 29 control subjects (62%).

With regard to global deformation imaging, LV GLS was lower in IVF patients than in control subjects (18.5±2.6% vs. 21.6±1.8%, p<0.001). LV MD was higher in IVF patients than in control subjects (41±12 ms vs. 26±6 ms, p<0.001). Abnormal GLS and MD according to our center-specific cut-off values were significantly more prevalent in IVF patients than in controls (table 3).

With regard to regional deformation imaging, 22 IVF subjects (50%) showed regional LV post-systolic shortening in at least one segment, which was more frequent than in control subjects (5(11%), p<0.001). Ten IVF subjects (23%) had post-systolic shortening in ≥2 segments, which was only seen in one of the control subjects. With regard to RV deformation imaging, six IVF subjects (19%) had an abnormal deformation pattern, which was not seen in any of the control subjects (table 3, figure 2).

Patients with an MD above 45 ms more frequently received ICD therapy than patients with MD below 45 ms (50% vs 32%, p=0,242). IVF patients with ICD therapy also showed slightly lower GLS values than patients without ICD therapy (mean GLS 18 vs 19, p=0,352). These observations however, were non-significant.

Table 3 | Echocardiographic characteristics

	IVF subjects (n=47)	Control subjects (n=47)	p-value
Conventional echocardiography			
LVEDD, mm	50 [47;53]	48 [45;51]	0.062
LVESD, mm	32 [30;35]	30 [29;33]	0.126
LVEF, %	56±6	60±5	<0.001
RVEDD, mm	37±5	36±4	0.799
TAPSE, mm	24±4	25±3	0.278
RV S' velocity, cm/s	13 [11;15]	13 [12;15]	0.278
Deformation imaging			
LV GLS, %	18.5±2.6	21.6±1.8	<0.001
LV GLS <18%, n	16/44 (36)	0/44 (0)	<0.001
LV MD, ms	41±12	26±6	<0.001
LV MD >45 ms, n	17/44 (39)	0/44 (0)	<0.001
PSS in ≥1 segment	22/44 (50)	5/47 (11)	<0.001
PSS in ≥2 segments	10/44 (23)	1/47 (2)	0.003
RVFWS	26.1±5.5	27.7±3.6	0.200
RV strain pattern abnormal	6/31 (16)	0/29 (0)	0.024
Type I (normal)	26	29	
Type II (abnormal)	5	0	
Type III (abnormal)	1	0	

Values are given as mean ± SD, median [IQR] or n (%). GLS = global longitudinal strain; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MD = mechanical dispersion; PSS = postsystolic shortening; RV = right ventricle; RVEDD = right ventricular end-diastolic diameter; RVFWS = right ventricular free-wall strain; TAPSE = tricuspid annular plane systolic excursion.

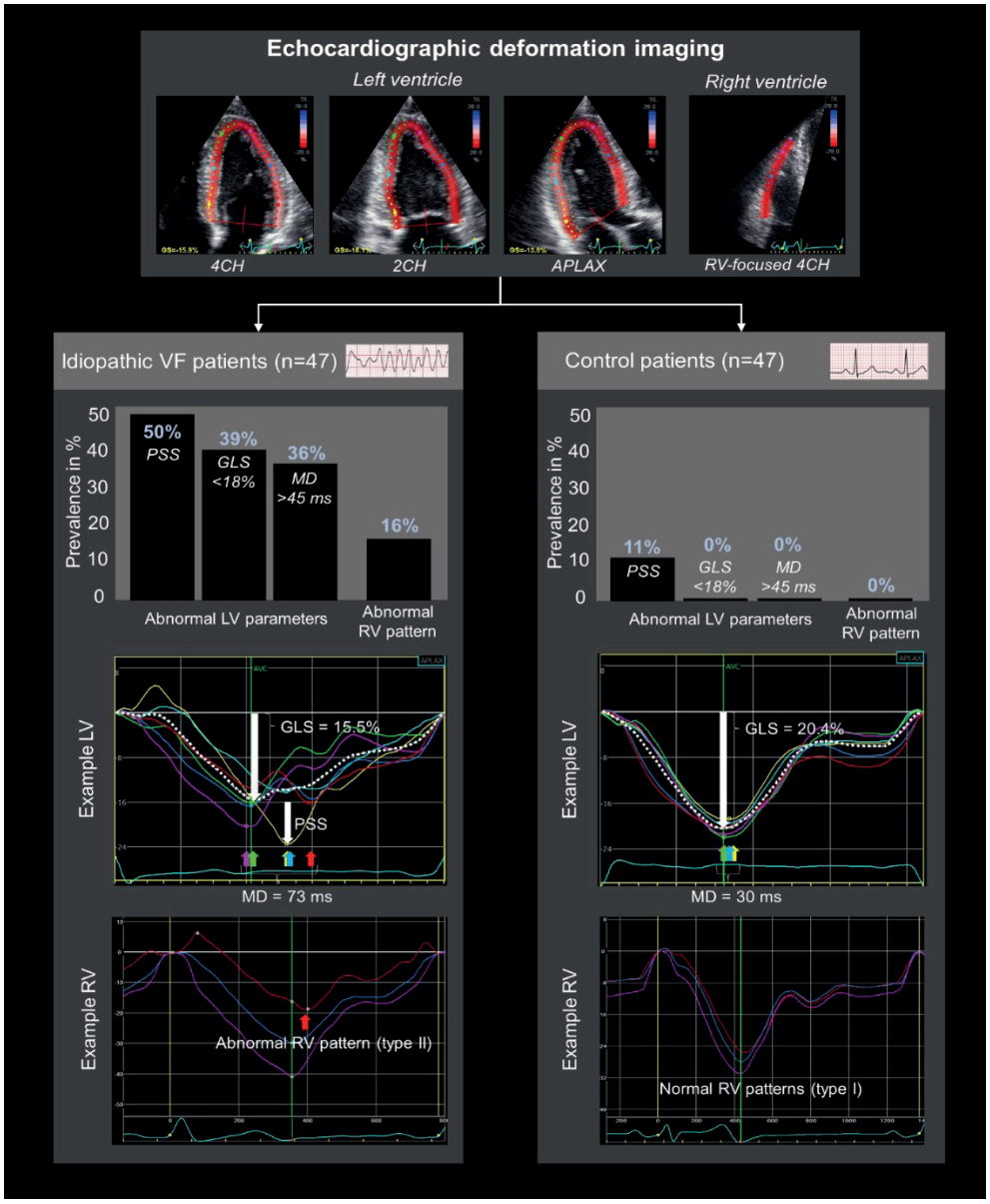


Figure 2 | Central illustration. Deformation imaging was performed in 47 IVF patients and 47 healthy controls. LV deformation abnormalities such as post systolic shortening (PSS), mechanical dispersion (MD) >45 ms and global longitudinal strain (GLS) <18% were significantly more prevalent in IVF patients versus controls. Abnormal RV patterns according to Mast et al.[7] were also more frequently seen in IVF patients. The example of LV deformation imaging of an IVF patient (mid left) shows low GLS values (large white arrow), pronounced MD (colored arrows) and PSS (small white arrow). The example of LV deformation imaging in a control patient (mid right) shows normal values and patterns. The example of RV deformation imaging in an IVF patient (bottom left) shows an abnormal type 2 pattern (red arrow) in the basal segment, while the control patient (bottom right) shows normal patterns in all segments.

Discussion

In the present explorative study we investigated echocardiographic deformation characteristics in IVF patients. We found that deformation imaging has the ability to reveal both global and regional mechanical alterations in IVF patients, compared to findings on deformation characteristics in age- and sex-matched control subjects (figure 2). These results suggest that 'idiopathic VF' may be less associated with a completely structurally normal heart than previously appreciated, which is compatible with the significant subset of IVF patients with localized structural alterations demonstrated by detailed endo and epicardial mapping.[4,17]

Global deformation abnormalities

Conventional imaging already showed that LVEF was slightly lower in patients compared to healthy controls (56% vs 60%), but these values are still within normal range. To characterize myocardial function beyond conventional echocardiographic techniques we applied 2D-speckle tracking software which allows assessment of myocardial tissue deformation. Deformation imaging also revealed significant systolic dysfunction in IVF patients. Although this is a novel finding, it is conceivable that IVF patients who have been resuscitated might have suffered from global cardiac ischemia to some degree during their circulatory arrest, which could have resulted in a slightly lower systolic function. However, since GLS seems to be able to detect subtle changes preceding deterioration of LVEF in several cardiomyopathies, it is also possible that these global deformation abnormalities are the result of an early stage cardiac disease. This has, for instance, been demonstrated in patients with familial dilated cardiomyopathy.[18] However, it remains unknown whether decreased GLS in these subjects is the cause of VF, or rather a consequence of the circulatory arrest.

IVF patients also showed higher LV MD compared to controls. LV MD, which represents heterogeneity in LV contraction, has been associated with malignant ventricular arrhythmias in several cardiac diseases, such as prior myocardial infarction,[19] ACM,[20] and long QT syndrome.[21] The pronounced LV MD in our IVF cohort might reflect subtle (interstitial) fibrosis in myocardial tissue, which may be caused either by the cardiac arrest or, by a yet undiscovered underlying disease. Considering that MD is also seen in primary electrical diseases in which fibrosis is assumed to be completely absent, MD in IVF may also be a sign of disturbed electrical conduction of the myocardium. A recent population-based study showed that a longer duration of repolarization on the surface ECG is associated with higher LV MD values, which supports the hypothesis that LV MD represents not only mechanical properties of the myocardium, but also electrical properties.[22] In our cohort, the sample size was too small to determine the value of LV MD as a prognostic factor in IVF patients. Thus, this should be further explored in a larger prospective study.

Regional deformation abnormalities

In addition, we observed significantly more regional deformation abnormalities in IVF patients versus controls. Whereas the global deformation abnormalities could possibly be explained by the cardiac ischemia caused by global hypoperfusion during circulatory arrest, this is less likely for regional deformation abnormalities as coronary artery disease was ruled out in every patient.

Previous literature showed that a significant subset of previously unexplained sudden cardiac arrest patients show localized electrical alterations during endocardial and epicardial mapping.[4] Prior experimental studies have shown that small ventricular lesions are able to promote VF inducibility.[23,24] Endo-epicardial mapping results in IVF patients revealed that the pathology in most cases only involved a part of the ventricular wall rather than being transmural and only covered a limited surface area.[4] This might explain why these subtle abnormalities cannot be perceived by conventional imaging but can be revealed by deformation imaging.

The RV deformation patterns of 6 patients in our cohort share similarities with previously described RV abnormalities in ACM patients.[6,7,25] Previous literature showed that a right ventricular electro-mechanical substrate as detected by deformation imaging may already be present in desmosomal mutation carriers who are in subclinical disease stage.[7] In addition, in IVF patients, high density endo-epicardial mapping showed a high prevalence of structural abnormalities in the RV.[4] There have been previous cases reported where IVF patients were diagnosed with ACM during follow-up.[26] Previous literature confirms that IVF does not necessarily infer a complete absence of any disease and that some early stage ACM patients might not be recognized as such. Also, in IVF and particularly DPP6 related IVF, the Purkinje system appears to play a pivotal role, and particularly so in the RV free wall, which might also result in changed regional deformation.[27]

Limitations

Due to the retrospective nature of this study, availability of echocardiographic imaging and its quality was limited. Of 47 (29.9%) patients in our IVF registry an echocardiogram performed with Vivid 7 E9 and E95 machines and appropriate quality was available, potentially leading to selection bias. Not all patients underwent systematic diagnostic assessment, however this is common in IVF studies in a real-world setting and is partly explained by the inclusion of patients with the Dutch *DPP6* risk-haplotype where the amount of diagnostic tests performed is typically lower than in other IVF patients.[28,29] As an ICD is implanted in all IVF patients after the event for secondary prevention, observers cannot be fully blinded when performing measurements and this is deemed an inevitable limitation. Lastly, due to the small sample size of this study, the correlation between clinical follow-up data and echocardiographic deformation abnormalities was merely exploratory.

Future perspective

The exact mechanism of these global and regional echocardiographic deformation abnormalities remains to be elucidated. In future research it would be interesting to correlate these deformation abnormalities with T1 mapping in IVF patients to further explore a potential underlying substrate. A large prospective study is needed to confirm, and further explore these deformation abnormalities – as well as correlating these echocardiographic findings with CMR and prognostic outcome measures. Furthermore, it would be relevant to study the subgroup of IVF patients with a clear inheritable nature, as in these families we currently often lack the possibilities to define currently asymptomatic family members at risk for future VF.

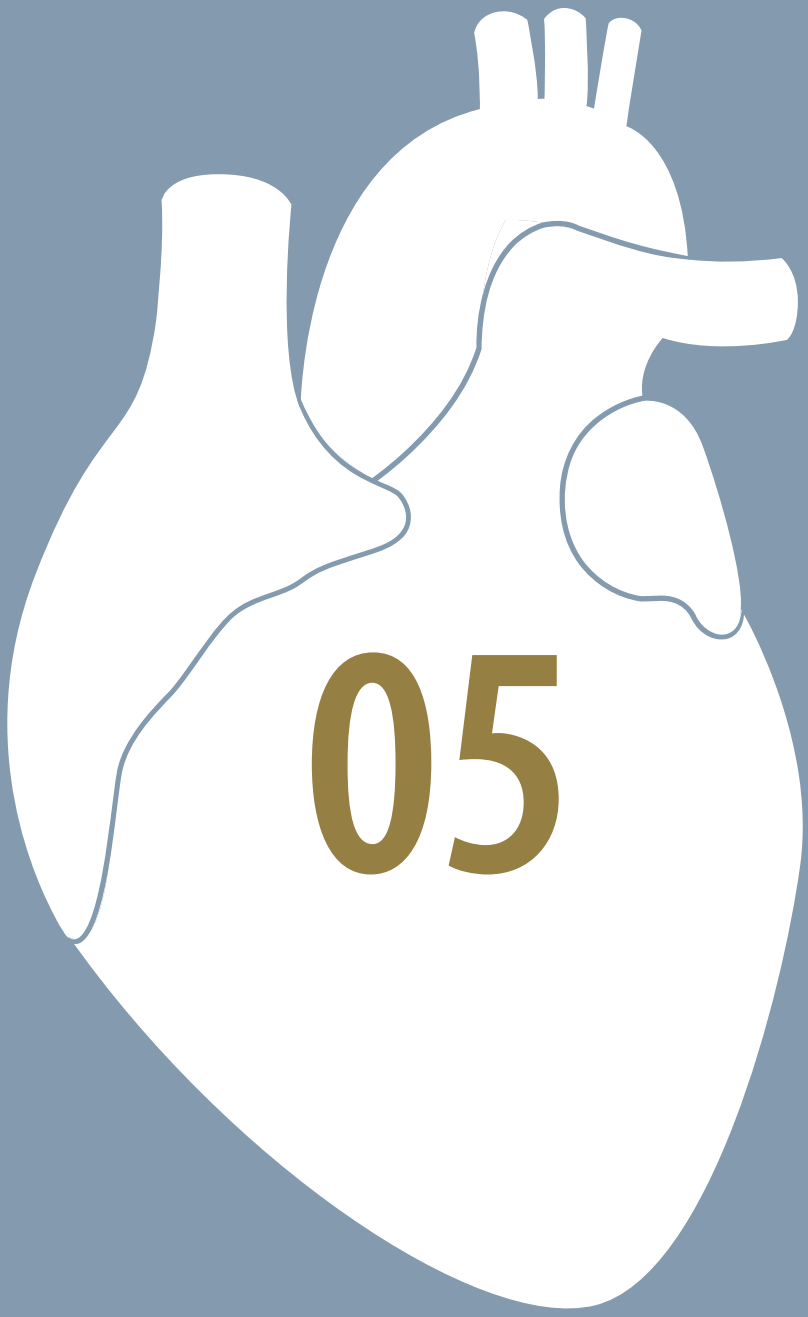
Conclusion

In patients with IVF we were able to show both global and regional echocardiographic deformation abnormalities. This study provides evidence that localized myocardial disease is present in a subset of IVF patients. Future prospective studies are needed to confirm, and further explore the clinical value of our findings.

References

1. Visser M, Heijden JF Van Der, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up. *Circ Arrhythmia Electrophysiol*. 2016;9(5):1–11.
2. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europea. *Eur Heart J*. 2015;36(41):2793–867.
3. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13(4):905–12.
4. Haïssaguerre M, Hocini M, Cheniti G, Duchateau J, Sacher F, Puyo S, *et al.* Localized Structural Alterations Underlying a Subset of Unexplained Sudden Cardiac Death. *Circ Arrhythmia Electrophysiol*. 2018;11(7):e006120.
5. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, *et al.* Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(1):1–11.
6. Mast TP, Taha K, Cramer MJ, Lumens J, Heijden JF van der, Bouma BJ, *et al.* The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy. *JACC Cardiovasc Imaging*. 2019;12(3):446–55.
7. Mast TP, Teske AJ, Walmsley J, Heijden JF van der, Es R van, Prinzen FW, *et al.* Right Ventricular Imaging and Computer Simulation for Electromechanical Substrate Characterization in Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Coll Cardiol*. 2016;68(20):2185–97.
8. Haugaa KH, Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. *Eur Heart J*. 2008;30(3):330–7.
9. Scheirlynck E, Malderen S Van, Motoc A, Lie ØH, Asmundis C de, Sieira J, *et al.* Contraction alterations in Brugada syndrome; association with life-threatening ventricular arrhythmias. *Int J Cardiol*. 2020;299:147–52.
10. Visser M, Heijden JF Van Der, Smagt JJ Van Der, Doevendans PA, Wilde AA, Loh P, *et al.* Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. *Circ Arrhythmia Electrophysiol*. 2016;9(10):e004258.
11. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace*. 2019;21(10):1519–26.
12. Teske AJ, Prakken NH, Boeck BW De, Velthuis BK, Martens EP, Doevendans PA, *et al.* Echocardiographic tissue deformation imaging of right ventricular systolic function in endurance athletes. *Eur Heart J*. 2009;30(8):969–77.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Hear J – Cardiovasc Imaging*. 2015;16(3):233–71.
14. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, *et al.* Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: A consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018;19(6):591–600.
15. Teske AJ, Boeck BW De, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound*. 2007;5(1):27.

16. Voigt JU, Lindenmeier G, Exner B, Regenfus M, Werner D, Reulbach U, *et al.* Incidence and characteristics of segmental postsystolic longitudinal shortening in normal, acutely ischemic, and scarred myocardium. *J Am Soc Echocardiogr*. 2003;16(5):415–23.
17. Haïssaguerre M, Nademanee W, Hocini M, Duchateau J, André C, Lavergne T, *et al.* The Spectrum of Idiopathic Ventricular Fibrillation and J-Wave Syndromes: Novel Mapping Insights. *Card Electrophysiol Clin*. 2019;11(4):699–709.
18. Verdonschot JAJ, Merken JJ, Brunner-La Rocca HP, Hazebroek MR, Eurlings CGMJ, Thijssen E, *et al.* Value of Speckle Tracking–Based Deformation Analysis in Screening Relatives of Patients With Asymptomatic Dilated Cardiomyopathy. *JACC Cardiovasc Imaging*. 2020;13(2P2):549–58.
19. Haugaa KH, Grenne BL, Eek CH, Ersbøll M, Valeur N, Svendsen JH, *et al.* Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging*. 2013;6(8):841–50.
20. Sarvari SI, Haugaa KH, Anfinsen O-G, Leren TP, Smiseth OA, Kongsgaard E, *et al.* Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *Eur Heart J*. 2011;32(9):1089–96.
21. Haugaa KH, Amlie JP, Berge KE, Leren TP, Smiseth OA, Edvardsen T. Transmural Differences in Myocardial Contraction in Long-QT Syndrome. *Circulation*. 2010;122(14):1355–63.
22. Verdugo-Marchese M, Coiro S, Selton-Suty C, Kobayashi M, Bozec E, Lamiral Z, *et al.* Left ventricular myocardial deformation pattern, mechanical dispersion, and their relation with electrocardiogram markers in the large population-based STANISLAS cohort: Insights into electromechanical coupling. *Eur Heart J Cardiovasc Imaging*. 2020;21(11):1237–45.
23. Janse MJ, Kléber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. *Circ Res*. 1981;49(5):1069–81.
24. Kubota I, Lux RL, Burgess MJ, Abildskov JA. Activation sequence at the onset of arrhythmias induced by localized myocardial warming and programmed premature stimulation in dogs. *J Electrocardiol*. 1988;21(4):345–54.
25. Taha K, Mast TP, Cramer MJ, Heijden JF van der, Asselbergs FW, Doevendans PA, *et al.* Evaluation of Disease Progression in Arrhythmogenic Cardiomyopathy. *JACC Cardiovasc Imaging*. 2020;13(2):631–4.
26. Blom LJ, Riele ASJM Te, Vink A, Hauer RNW, Hassink RJ. Late evolution of arrhythmogenic cardiomyopathy in patients with initial presentation as idiopathic ventricular fibrillation. *Hear Case Reports*. 2019;5(1):25–30.
27. Xiao L, Koopmann TT, Ördög B, Postema PG, Verkerk AO, Iyer V, *et al.* Unique cardiac Purkinje fiber transient outward current β-subunit composition: A potential molecular link to idiopathic ventricular fibrillation. *Circ Res*. 2013;112(10):1310–22.
28. Conte G, Belhassen B, Lambiase P, Ciconte G, Asmundis C De, Arbelo E, *et al.* Out-of-hospital cardiac arrest due to idiopathic ventricular fibrillation in patients with normal electrocardiograms: Results from a multicentre long-term registry. *Europace*. 2019;21(11):1670–7.
29. Siebermair J, Sinner MF, Beckmann B-M, Laubender RP, Martens E, Sattler S, *et al.* Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18(5):718–25.


05

Prevalence of mitral annulus disjunction and mitral valve prolapse in patients with idiopathic ventricular fibrillation.

Journal of the American Heart Association. 2022;11:e025364.

Sanne A. Groeneveld*
Feddo P. Kirkels*
Maarten J. Cramer
Reinder Evertz
Kristina H. Haugaa
Pieter G. Postema
Niek H.J. Prakken
Arco J. Teske
Arthur A.M. Wilde
Birgitta K. Velthuis
Robin Nijveldt
Rutger J. Hassink

*Both authors contributed equally

Abstract

Background | Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with ventricular fibrillation of which the origin is not identified after extensive evaluations. Recent studies suggest an association between mitral annulus disjunction (MAD), mitral valve prolapse (MVP) and ventricular arrhythmias. The prevalence of MAD and MVP in IVF patients in this regard, is not well established. We aimed to explore the prevalence of MAD and MVP in a consecutive cohort of IVF patients compared to matched controls.

Methods | In this retrospective multicenter cohort study, cardiac magnetic resonance images from IVF patients (i.e., negative for ischemia, cardiomyopathy and channelopathies) and age- and sex-matched control subjects were analyzed for the presence of MAD (≥2mm) and MVP (>2mm).

Results | In total, 72 patients (mean age 39±14 years, 42% female) and 72 control subjects (mean age 41±11 years, 42% female) were included. MAD in the inferolateral wall was more prevalent in IVF patients versus healthy controls (7 [11%] vs. 1 [1%], p=0.024). MVP was only seen in IVF patients and not in controls (5 [7%] vs. 0 [0%], p=0.016). MAD was observed in both patients with (n=4) and without (n=3) MVP.

Conclusions | Inferolateral MAD and MVP were significantly more prevalent in IVF patients compared to healthy controls. The authors advocate that evaluation of the mitral valve region deserves extra attention in the extensive screening of patients with unexplained cardiac arrest. These findings support further exploration of the pathophysiological mechanisms underlying a subset of IVF that associates with MAD and MVP.

Introduction

Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with ventricular fibrillation of unknown origin that remains unidentified after extensive diagnostic testing.[1,2] The diagnosis IVF depends on the absence of a substrate for VF by exclusion of both structural cardiac diseases and primary arrhythmia syndromes. In the follow-up of these patients, a continuing search for previously unknown pro-arrhythmic factors is driven by the evolution of medical knowledge and diagnostic techniques.[3]

Decades ago, mitral valve prolapse (MVP) and mitral annulus disjunction (MAD) have already been associated with ventricular arrhythmias and sudden cardiac arrest (SCA) in young patients.[4–13] In recent years, MAD regained attention in association with MVP and ventricular arrhythmias.[8,14–17] MAD is defined as an abnormal atrial displacement of the mitral valve leaflet hinge point, away from the ventricular myocardium. Close relation has been shown to MVP and SCA but recent studies also showed an association with ventricular arrhythmias independently of MVP.[8–10]

Imaging with cardiac magnetic resonance imaging (CMR) and echocardiography is included in the standard work-up for IVF patients. Previous studies have reported a high prevalence of MVP in patients with aborted cardiac arrest of unexplained etiology[9], but until now no specific attention has been given to the presence of MAD in IVF patients. We hypothesize that this abnormality might often have been overlooked in the routine clinical work up of IVF patients. The aim of this study was to describe MAD and MVP prevalence and morphology in a multicenter cohort of IVF patients and matched controls.

Methods

Study population

Patients were derived from a large Dutch registry of IVF patients. Details of the cohort have been published in previous studies.[2,18] In summary, we enrolled patients with an unexplained cardiac arrest with an initial rhythm of ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicological causes were excluded at first presentation. Comprehensive clinical investigation was performed, and accepted diagnostic criteria were used to exclude specific disease.[19]

For this multicenter retrospective cohort study, we included IVF patients who were evaluated in three tertiary referral centers in the Netherlands (University Medical Center Utrecht, Amsterdam University Medical Center and Radboud University Medical Center) between September 2004 and December 2020 and underwent CMR imaging of sufficient image quality (figure 1). Age- and sex-matched controls with no history of cardiovascular disease were selected from a previous prospectively included cohort of healthy non-athletes.[20,21] The study complied with the Declaration of Helsinki and was approved by the Regional Committee for

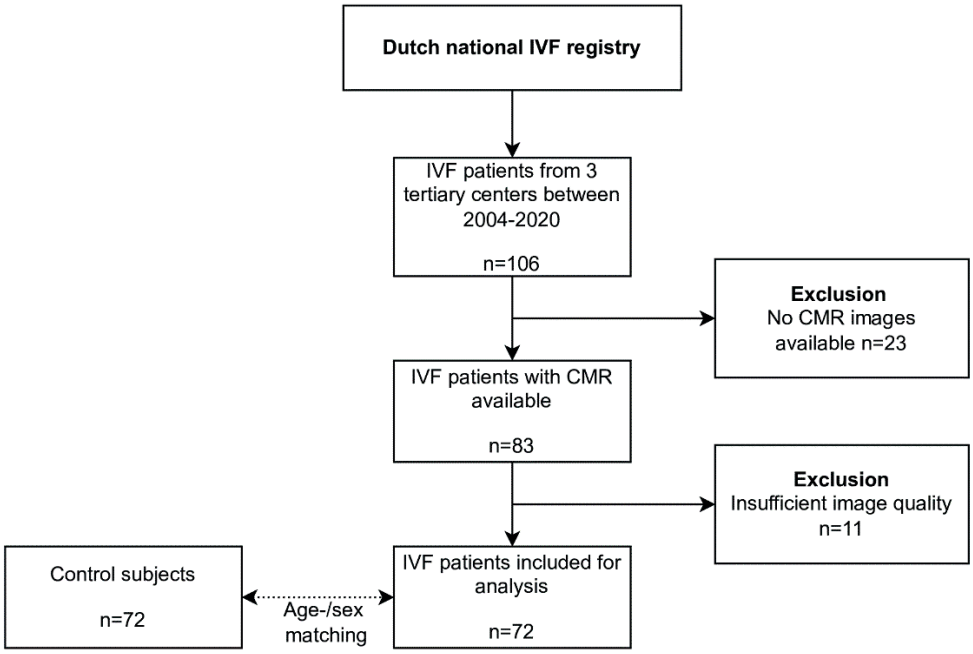


Figure 1 | Inclusion flowchart. IVF patients included in a large national registry from three tertiary centers were included. Abbreviations: CMR = cardiac magnetic resonance, IVF = idiopathic ventricular fibrillation.

Medical Research Ethics in all participating centers and the subjects gave informed consent when appropriate. The data that support the findings of this study are available from the corresponding author upon reasonable request.

CMR imaging

All included subjects underwent CMR examination on a clinical 1.5T or 3T MR scanner using electrocardiographic gating and a phased array cardiac receiver coil according to standardized cardiac protocols.[22] Breath-hold balanced steady-state free-precession (bSSFP) cine images covering both the ventricles and atria were acquired (4-chamber long-axis view, 2- and 3-chamber long-axis LV views and multi-slice full coverage of the LV in short axis orientation). The voxel size of the cine sequences used was dependent on the local clinical scan protocol and was typically around 1.5 x 1.5 x 5-8 mm^3. In addition, late gadolinium enhancement (LGE) imaging was performed at least 10 minutes after intravenous administration of a gadolinium-based contrast agent in identical views. LGE imaging was not performed in control subjects.

Ventricular metrics and ejection fraction (EF) were measured in a standardized way using semi-automated contour tracing software.[23] Ventricular end-diastolic volumes were indexed for body surface area (EDVi). Patients with major LGE (sufficient for a specific diagnosis) were not included in the IVF registry, while patients with minor LGE of uncertain pathogenicity were

included in this study. The LGE images were re-evaluated for any myocardial fibrosis in the left ventricle and papillary muscles by an experienced cardiac radiologist. Mild insertion fibrosis was deemed insignificant for this study.

Two blinded observers analyzed CMR images for presence and longitudinal distance of MAD and MVP. Longitudinal MAD distance was measured on all three long-axis cine views from the left atrial wall mitral valve leaflet junction to the top of the left ventricular wall at end-systole. Presence of MAD was defined as a longitudinal displacement of >1 mm (figure 2). Presence of MVP was defined as displacement of >2 mm of one or both leaflets beyond the annular hinge points at end-systole, measured perpendicular to the annular plane in the 3-chamber view (figure 2).[24] Presence of the curling sign, defined as an unusual systolic motion of the inferior mitral annulus on the adjacent ventricular wall, was identified by visual assessment (online video A).[8,25]

Clinical characteristics

Clinical data was derived from the IVF registry. Enrolled patients all underwent detailed investigation of the medical history, physical examination, 12-lead ECG, laboratory testing, echocardiography, coronary angiography (or CT angiography) and CMR. All patients underwent echocardiographic imaging according to the standard clinical protocol.[26,27] Additional investigations such as exercise ECG, sodium channel blocker provocation, endomyocardial biopsy and genetic testing were performed at the treating physician's discretion.[2,18] T-wave abnormalities were defined as inverted or biphasic T-waves. Genetic testing consisted of single targeted gene testing or next generation sequencing of a larger panel of genes, depending on the center where the genetic testing was performed. In line with previous studies, we also included patients with the DPP6 haplotype, a genetic variant associated with short-coupled Torsade de Pointes/IVF.[1,28] Although we previously proposed

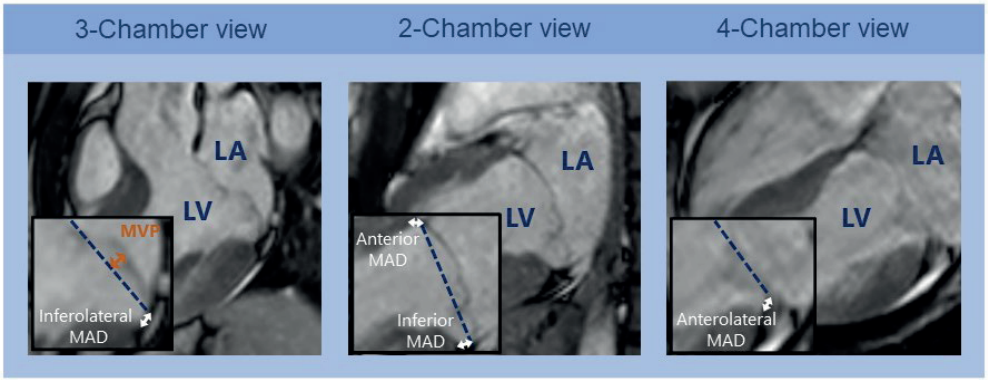


Figure 2 | Measurements of longitudinal MAD and MVP distance on CMR imaging. All images are obtained at end-systole. The blue line connects the annular hinge points of the mitral valve, the white arrows are longitudinal MAD measurements, the orange arrow is the MVP measurement. Abbreviations: CMR = cardiac magnetic resonance, LA = left atrium, LV = left ventricle, MAD = mitral annulus disjunction, MVP = mitral valve prolapse.

that Ito overexpression particularly in Purkinje plays an essential role in these patients[29], the underlying pathophysiological mechanism for VF remains uncertain.

Follow-up data was retrospectively collected from all patients. All electrocardiographic data on ECGs, cardiac telemetry during admission, exercise ECG and Holter monitoring was analyzed for the occurrence of PVCs. A high PVC burden was defined as more than 1000 PVCs per 24 hours on Holter monitoring. In patients without Holter monitoring, a high PVC burden was defined as more than 20 PVCs during an exercise test or bigeminy or trigeminy on ECG or cardiac telemetry. Non sustained ventricular tachycardia was defined as three or more ventricular beats with a maximum duration of 30 seconds.[30] Appropriate ICD therapy was defined as anti-tachycardia pacing or shock during a ventricular tachycardia or ventricular fibrillation.

Statistical analysis

Parametric data were presented as mean ± standard deviation, median [interquartile range] or number (%). Comparisons were performed using a Student's t-test, Mann-Whitney U test, or Fisher exact test as appropriate. Analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, Illinois). Intra- and inter-observer variability was expressed by intraclass correlation coefficients (ICC). Two-sided p values <0.05 were considered significant.

Results

Study population

After screening 106 IVF patients from three centers, a total of 72 patients (mean age 39 ± 14 years, 42% female) and 72 age- and sex-matched control subjects (mean age 41 ± 11 years, 42% female) were included (figure 1). In total, 23 patients were excluded due to CMR unavailability and 11 patients were excluded due to insufficient image quality. An ICD for secondary prevention was implanted in all but one of the IVF patients (99%) (table 1).

Prevalence of mitral valve disease

MAD was commonly measured in the anterior, inferior and anterolateral wall in both IVF patients and healthy controls (table 2). The inferolateral wall was the only distinctive location for the presence of MAD between IVF patients and controls (7 [11%] vs. 1 [1%], p=0.024). In addition, IVF patients showed a higher prevalence of MVP (5 [8%] vs. 0 [0%], p=0.016). A curling sign of the inferior wall was observed in three IVF patients with MAD and not in controls. One control subject showed MAD in the inferolateral wall of 2 mm, without signs of other mitral valve disease. In seven IVF patients with inferolateral MAD, other mitral valve disease was prevalent; four (57%) also had MVP, of which three females with bi-leaflet MVP, and four patients (57%) showed signs of mitral regurgitation. One patient with MVP did not have inferolateral MAD. Characteristics of subjects with MAD and/or MVP are described in table 3. In two subjects with MAD/MVP, a variant of uncertain significance was found with genetic testing (table S1). Three subjects with MAD/MVP underwent electrophysiology study. Voltage

mapping of the LV was not performed. One subject underwent radiofrequency ablation due to frequent PVCs in the anterolateral RVOT. Seven subjects with MAD/MVP underwent exercise stress testing, zero showed NSVT or multifocal PVCs.

Table 1 | Baseline characteristics of idiopathic ventricular fibrillation patients.

Characteristics	All (n=72)
Age, yrs	39 ± 14
Female, n (%)	30 (42)
Circumstances event, n (%)	
- Rest	43 (60)
- Exercise	16 (22)
- Asleep	9 (12)
- Emotions	4 (6)
Genetic testing	
- DPP6 haplotype	9 (13)
Electrocardiogram	
- Heart rate, bpm	69 ± 13
ICD implantation	71 (99)

Values are, n (%), mean ± standard deviation. Abbreviations: bpm = beats per minute, ICD = implantable cardioverter defibrillator.

Table 2 | Comparison between idiopathic ventricular fibrillation (IVF) patients and matched controls.

Characteristics	IVF patients (n=72)	Controls (n=72)	p-value
Age, yrs	39 ± 14	41 ± 11	0.290
Female, n(%)	30 (42)	30 (42)	1.000
BSA, m^2	2.0 ± 0.2	1.9 ± 0.2	0.571
Cardiac magnetic resonance			
LVEF, %	57 ± 15	60 ± 7	0.180
LVEDVi, ml/m^2	85 ± 16	93 ± 14	0.005
Late gadolinium enhancement, n (%)	8 (13)	n/a	n/a
Mitral annulus disjunction, n (%)	40 (56)	44 (61)	0.612
- Anterolateral wall (n=141*)	17 (24)	13 (18)	0.417
- Anterior wall (n=132*)	21 (33)	32 (46)	0.156
- Inferior wall (n=135*)	26 (40)	29 (41)	1.000
- Inferolateral wall (n=133*)	7 (11)	1 (1)	0.024
Mitral valve prolapse, n (%)	5 (8)	0 (0)	0.016
Bi-leaflet mitral valve prolapse, n (%)	3 (5)	0 (0)	0.096
Curling sign, n (%)	3 (5)	0 (0)	0.096

*Values are, n (%), mean ± standard deviation. Abbreviations: BSA = body surface area, LVEF = left ventricular ejection fraction, LVEDVi = indexed left ventricular end diastolic volume. *Missing values due to unavailable views or insufficient image quality.*

Table 3 | Characteristics of 8 subjects with MVP and/or MAD in the inferolateral wall on CMR.

Subject N=7	Sex	MAD (mm) AL	ANT	INF	IL	MVP (mm)	Bi-leaflet MVP	Curling sign	MR*	LGE	ECG T-wave Abnormalities	Ventricular ectopy
Control	M	2	2	3	2	0	No	No	No	n/a	n/a	n/a
IVF 1	F	3	0	0	2	5	Yes	No	Moderate	Basal septal LV	Yes (inferior)	No
IVF 2	M	3	0	5	3	3	No	No	Mild	No	No	Yes (basal LV)
IVF 3	M	3	0	8	3	0	No	No	Mild	No	No	No
IVF 4	F	3	3	2	2	0	No	Yes	No	No	No	Yes (RVOT)
IVF 5	F	1	2	5	3	6	Yes	Yes	No	No	Yes (inferior)	Yes (basal LV)
IVF 6	M	2	5	1	2	0	No	No	No	No	Yes (inferior)	Yes (RVOT)
IVF 7	F	2	2	2	2	7	Yes	Yes	Mild	No	No	Yes (LV apex)
IVF 8	M	0	0	4	0	4	No	No	No	No	No	Yes (RVOT)

*Abbreviations: AL = anterolateral wall, ANT = anterior wall, INF = inferior wall, IL = inferolateral wall, MAD = mitral annulus disjunction, MVP = mitral valve prolapse, CMR = cardiac magnetic resonance, ECG = electrocardiogram, LGE = late gadolinium enhancement, MR = mitral regurgitation. n/a = not available. MAD, MVP and the curling sign were assessed on CMR. * Mitral regurgitation was determined on echocardiography.*

Comparison between IVF patients with and without mitral valve disease

Mitral regurgitation was more prevalent in patients with MAD and/or MVP compared to patients without (4 [50%] vs. 7 [14%], p=0.024) (table 4). In addition, inverted or biphasic T-waves were more frequently observed in IVF patients with MAD/MVP compared to patients without (3 [38%] vs. 2 [3%], p=0.009). LGE imaging was available for analysis in the majority of IVF patients (n=61). In eight (13%) IVF patients, small LGE spots of uncertain pathogenicity were reported (table 4). There was no difference in the occurrence of LGE between patients with MAD/MVP compared to patients without (1 [13%] vs. 7 [13%], p=1.000). One patient with inferolateral MAD showed midwall LGE in the LV basal inferoseptal myocardium (figure S1) LGE was seen in seven patients without MAD: location and pattern of LGE ranged from small mid-wall or epicardial foci in 3 patients (basal inferolateral twice and basal inferior wall); three patients had a small subendocardial scar in the respectively basal inferior, apical septal and apical inferior segments, and one patient had a small transmural scar in the basal inferolateral segment. The patient with possible basal subendocardial LGE could also be slow flow in a basal crypt (figure S1). The four patients with subendocardial to transmural LGE had no coronary artery disease on catheter angiography or coronary CT angiography.

Table 4 | Comparison between IVF patients with and without MAD and/or MVP.

Characteristics	IVF with MAD/MVP (n=8)	IVF without MAD/MVP (n=64)	p-value
Age, yrs	38 ± 17	39 ± 14	0.890
LVEF, %	54 ± 15	56 ± 8	0.430
Female, n (%)	4 (50)	25 (39)	0.706
Late gadolinium enhancement, n(%)	1 (13)	7 (13)	1.000
Mitral regurgitation, n (%)	4 (50%)	7 (14%)	0.024
Inverted/biphasic T waves, n (%)	3 (38%)	2 (3%)	0.009
Follow-up data			
Follow-up duration, yrs	7 [4-11]	7 [2-12]	0.886
PVC count per hour on Holter monitoring, n	228 [71-676]	1 [0-18]	0.016
High PVC burden on ECG, telemetry, exercise test or Holter	6 (75%)	8 (16%)	0.001
LV basal	2 (25%)	0 (0%)	n/a
RVOT	3 (38%)	3 (6%)	n/a
Other	0 (0%)	5 (10%)	n/a
Multiform	1 (12%)	0 (0%)	n/a
Non-sustained ventricular tachycardia	4 (50%)	17 (31%)	0.423
Appropriate ICD therapy, n (%)	1 (13%)	15 (24%)	0.670
Ventricular tachycardia	1 (13%)	5 (8%)	n/a
Ventricular fibrillation	0 (0%)	10 (16%)	n/a
Atrial fibrillation, n (%)	1 (13%)	5 (9%)	0.567

Values are, n (%), mean ± standard deviation or median [interquartile range]. Abbreviations: BSA = body surface area, ECG = electrocardiogram, ICD = implantable cardioverter defibrillator, LV = left ventricle, LVEF = left ventricular ejection fraction, PVC = premature ventricular complex, RVOT = right ventricular outflow tract.

Follow-up

The mean follow-up duration of the IVF cohort was seven (IQR 2-12) years. Patients with MAD/MVP more frequently showed a high PVC burden (6 [75%] vs 7 [13%], p=0.001). In patients with MAD/MVP the PVCs more frequently originated from the basal LV or RVOT (table S2 and figure S2). There were no significant differences between IVF patients with MAD/MVP compared to patients without MAD/MVP with regard to the occurrence of non-sustained VTs or appropriate ICD therapy during follow-up (table 4).

Intra- and interobserver agreement

We showed excellent reproducibility of longitudinal MAD distance measurements. The intra-observer agreement on 80 segments from 20 patients was 0.92, 95% CI (0.88 - 0.95), p<0.001 and the inter-observer agreement was also 0.92, 95% CI (0.88 - 0.95), p<0.001.

Discussion

Our study is the first to compare prevalence of MAD and MVP in a consecutive multicenter cohort of IVF patients to a healthy control population. The most important finding was the increased prevalence of MAD in the inferolateral wall and MVP compared to controls (figure 3). Subjects with MAD in the inferolateral wall also showed high prevalence of other mitral valve disease and ventricular ectopy. This is in line with previous studies suggesting a correlation between mitral valve disease and IVF. MAD in the anterior, inferior and anterolateral wall was commonly measured in both IVF patients and healthy controls.

Location of mitral annulus disjunction

Previous studies showed that MAD distance can vary considerably along the annulus circumference. This was shown with an extensive CMR protocol design assessing the mitral annulus every 30 degrees.[8] Although we did not assess the mitral annulus every 30 degrees due to unavailability of these acquisitions or 3D CMR data in this retrospective study, we also observed considerable differences in longitudinal MAD distance over the mitral annulus (table 3). The aforementioned study showed that MAD located in the inferolateral wall assessed by CMR was an independent risk marker for ventricular arrhythmias.[8] In our cohort, the inferolateral wall visualized in the 3-chamber long-axis view was found to be the only distinctive location for MAD between IVF patients and controls. In the other walls, gaps of 1-3 mm between the LV myocardium and the mitral annulus hinge points were frequently seen in both patients and controls. Where the 3-chamber view (or parasternal long-axis view in echo) is generally considered to be the most standardized for measurements of the mitral valve, the other views are less reproducible when it comes to measurements on the saddle shaped valve and might therefore be more subjected to errors.[24,31] This might have contributed to our finding that the inferolateral wall was the only distinctive location for MAD between IVF patients and controls, which is in line with previous studies.[8,9,25,32] Additionally, a recent study applying a comprehensive 3D analysis on cardiac computed tomography images of 98 structurally normal hearts also showed high prevalence of MAD in the anterior to anterolateral and inferior to inferoseptal segments (77.5% and 87.8%, respectively), while inferolateral MAD was less common in healthy subjects (11.2%).[33]

The cut-off to determine presence of MAD on CMR is another point of discussion. We considered longitudinal distances of >1 mm significant, given the spatial resolution of CMR[18], but general consensus is lacking. The voxel size of cine sequences acquired in routine clinical care limits reliability of measurements below 1.5 mm. Besides, longitudinal distances measured by CMR and echocardiography cannot be used interchangeably, as shown by differences in measured distances by the two modalities in a previous study.[8] Larger CMR based population studies are needed to determine the upper limit of normal.

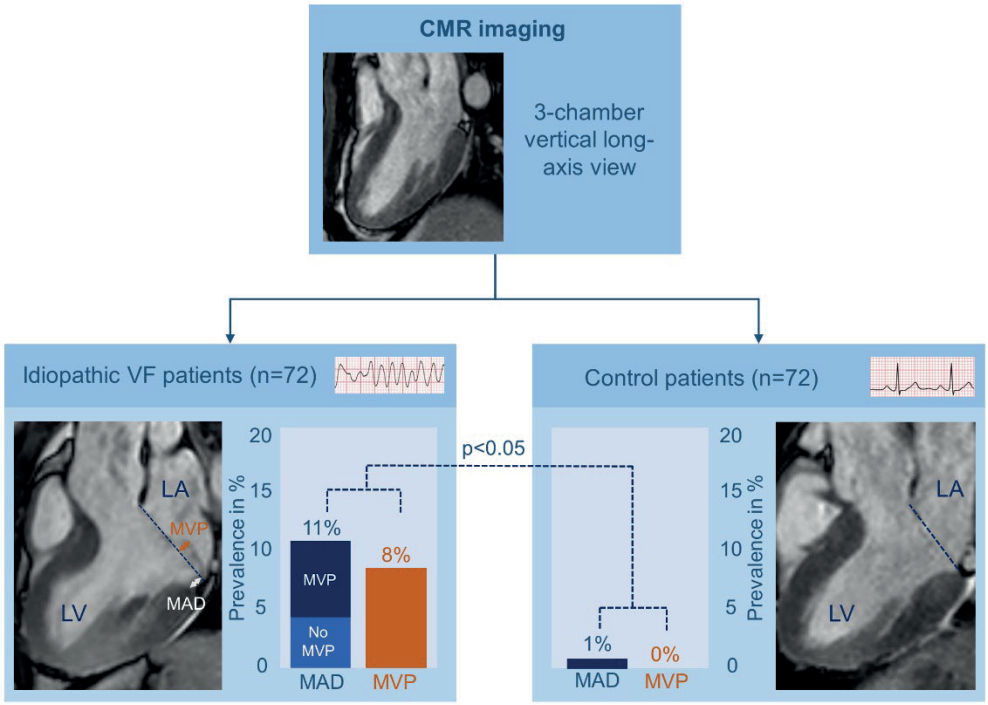


Figure 3 | Prevalence of MAD and MVP in IVF patients compared to healthy controls. In total, 144 patients were enrolled in the study; 72 idiopathic ventricular fibrillation (IVF) patients and 72 healthy controls. All patients were screened for presence of mitral annulus disjunction (MAD) and mitral valve prolapse (MVP) on CMR by two blinded observers. MAD in the inferolateral wall was more prevalent in IVF patients compared to controls (p = 0.024). MVP was also more prevalent in IVF patients compared to controls (p = 0.016).

Mitral annulus disjunction and the relation to mitral valve prolapse

The concept of MAD as an arrhythmic factor was introduced for the first time around the 1980s.[11,12,34] Since then, it has been closely linked to MVP and other mitral valve disease.[25] During the last years, MAD has regained interest and multiple reports indicate that MAD may also be present without MVP.[8,35] This is in line with our findings, as 43% of IVF patients with MAD did not show MVP. The distinction between MAD and MVP can however be difficult, especially when determining the exact hinge point of a prolapsed mitral valve that parallels the atrial wall. If the prolapse distance is measured from the myocardial edge, MVP will always be found in presence of MAD.[25] We measured longitudinal MAD distance from the myocardial edge to the annular hinge point and MVP beyond the annular hinge point, allowing a distinction between the two.[8] Although the distinction between MAD and MVP can be challenging, the increased prevalence of both entities in IVF that was found in this study is remarkable.

The pro-arrhythmic substrate

The exact proarrhythmic mechanism of MAD is unknown. It has been hypothesized that hypermobility of the mitral valve causes mechanical stretch on the myocardial wall. This may directly induce ventricular ectopy which can potentially trigger VF. On the long term, mechanical stretch may also result in myocyte hypertrophy and fibrosis, creating another potential cause for myocardial electrical instability and arrhythmias.[9,25] Previous studies related papillary muscle fibrosis to arrhythmic events in the presence of MAD and MVP, but severe arrhythmias were also observed in patients without visible papillary muscle fibrosis on CMR.[8,14,25] In this study, we did not observe any papillary muscle fibrosis in IVF patients with MAD. However, we did observe more frequently ventricular ectopy and T-wave abnormalities in the inferolateral leads in MAD/MVP patients, which was also observed in previous studies.[9,25] While PVCs from the basal LV correspond with the anatomical location of MAD, this relation is less clear for PVCs from the RVOT. The latter were previously reported in MAD, but mainly with concurrent LVOT PVCs.[9] Ventricular ectopy from areas in close proximity to the mitral annular region and papillary muscles has been attributed to mechanical traction in a subgroup of IVF patients with bi-leaflet MVP[9] and the same mechanism of traction induced ectopy may be present in MAD.[36] Bi-leaflet MVP was present in three female IVF patients in our cohort, in consistence with the previous description of the 'malignant bi-leaflet MVP syndrome', which was characterized by bi-leaflet MVP, frequent ventricular ectopy and female sex.[9]

Clinical implications

A previous report demonstrated a case of unexplained cardiac arrest in an otherwise healthy patient, whereby clear MAD was found upon secondary evaluation of cardiac imaging data.[37] We confirm that in 11% of our IVF cohort, MAD and/or MVP can be observed during focused analysis of CMR images, while it was previously left unrecognized in a thorough diagnostic process. In a matched cohort of healthy controls, MAD and MVP were rarely found. Overt MVP in combination with extensive myocardial fibrosis in the annular region and papillary muscles was not observed in our IVF cohort. These subjects were most likely already diagnosed with an arrhythmic mitral valve prolapse according to current clinical standards and did not end up in the IVF cohort.[9,38] Our findings suggest that mitral valve disease may still contribute as pro-arrhythmic factor in a subset of IVF patients. However, one could still argue that minor degrees of MAD are a bystander in IVF. A future, larger prospective study is needed to further evaluate our findings. We advocate that evaluation of the mitral valve region deserves extra attention in the extensive screening of patients with unexplained sudden cardiac arrest. The direct therapeutic consequences for IVF patients may be limited as they generally have a clear indication for secondary prevention ICD implantation. However, knowledge about the correlation between MAD and arrhythmias may yield prognostic value for IVF patients and might especially be important to identify a possible arrhythmogenic risk in family members.

Limitations

Although this is one of the largest IVF cohorts worldwide, the number of patients included is relatively small due to the rarity of the disease. Due to the retrospective nature of this study,

image plane acquisition was already performed. Therefore, MAD measurements were confined to available CMR views. In addition, LGE imaging was not standardly performed in the older CMRs and in some cases could not be interpreted due to artefacts. Other studies suggest that MAD is also easily detectable on echocardiography, but the quality and focus of the images acquired are of great importance.[8,35] We did not use echocardiography because we concluded that measurement of MAD distance on retrospective exams without focused images was not feasible. Holter monitoring was not routinely performed due to the retrospective set-up of the study. In addition, the number of patients with MAD or MVP was relatively small, hampering strong conclusions on clinical follow-up data. Larger prospective follow-up studies are needed to determine the potential impact of MAD/MVP on the prognosis of IVF patients.

Conclusions

Inferolateral mitral annulus disjunction (MAD) and mitral valve prolapse (MVP) were significantly more prevalent in a large multicenter cohort of IVF patients compared to healthy controls. Our findings support further exploration of the pathophysiological mechanisms underlying a subset of IVF that associates with MAD and MVP. The clinical implications of the presence of MAD for recurrences of ventricular arrhythmias and treatment strategies remain to be elucidated.

References

1. Visser M, Heijden JF Van Der, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up. *Circ Arrhythmia Electrophysiol*. 2016;9(5):1–11.
2. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace*. 2019;21(10):1519–26.
3. Groeneveld SA, Ree MH van der, Taha K, Bruin-Bon RHA de, Cramer MJ, Teske AJ, *et al.* Echocardiographic deformation imaging unmasks global and regional mechanical dysfunction in patients with idiopathic ventricular fibrillation: A multicenter case-control study. *Heart Rhythm*. 2021;18(10):1666–72.
4. Vohra J, Sathe S, Warren R, Tatoulis J, Hunt D. Malignant Ventricular Arrhythmias in Patients with Mitral Valve Prolapse and Mild Mitral Regurgitation. *Pacing Clin Electrophysiol*. 1993;16(3):387–93.
5. Dollar AL, Roberts WC. Morphologic comparison of patients with mitral valve prolapse who died suddenly with patients who died from severe valvular dysfunction or other conditions. *J Am Coll Cardiol*. 1991;17(4):921–31.
6. Pocock WA, Bosman CK, Chesler E, Barlow JB, Edwards JE. Sudden death in primary mitral valve prolapse. *Am Heart J*. 1984;107(2):378–82.
7. Kleid JJ. Sudden Death and the Floppy Mitral Valve Syndrome. *Angiology*. 1976;27(12):734–7.
8. Dejgaard LA, Skjølsvik ET, Lie ØH, Ribe M, Stokke MK, Hegbom F, *et al.* The Mitral Annulus Disjunction Arrhythmic Syndrome. *J Am Coll Cardiol*. 2018;72(14):1600–9.
9. Sriram CS, Syed FF, Ferguson ME, Johnson JN, Enriquez-Sarano M, Cetta F, *et al.* Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2013;62(3):222–30.
10. Essayagh B, Sabbag A, Antoine C, Benfari G, Yang LT, Maalouf J, *et al.* Presentation and Outcome of Arrhythmic Mitral Valve Prolapse. *J Am Coll Cardiol*. 2020;76(6):637–49.
11. Hutchins GM, Moore GW, Skoog DK. The association of floppy mitral valve with disjunction of the mitral annulus fibrosus. *N Engl J Med*. 1986;314(9):535–40.
12. Angelini A, Ho SY, Anderson RH, Becker AE, Davies MJ. Disjunction of the mitral annulus in floppy mitral valve. *N Engl J Med*. 1988;318(3):188–9.
13. Bharati S, Granston AS, Liebson PR, Loeb HS, Rosen KM, Lev M. The conduction system in mitral valve prolapse syndrome with sudden death. *Am Heart J*. 1981;101(5):667–70.
14. Bennett S, Thamman R, Griffiths T, Oxley C, Khan JN, Phan T, *et al.* Mitral annular disjunction: A systematic review of the literature. *Echocardiography*. 2019;36(8):1549–58.
15. Basso C, Perazzolo Marra M. Mitral Annulus Disjunction: Emerging Role of Myocardial Mechanical Stretch in Arrhythmogenesis. *J Am Coll Cardiol*. 2018;72(14):1610–2.
16. Haugaa KH, Aabel EW. Mitral Annulus Disjunction. *JACC Cardiovasc Imaging*. 2021;14(11):2088–90.
17. Muthukumar L, Jahangir A, Jan MF, Perez Moreno AC, Khandheria BK, Tajik AJ. Association Between Malignant Mitral Valve Prolapse and Sudden Cardiac Death. *JAMA Cardiol*. 2020;5(9):1053.
18. Visser M, Heijden JF Van Der, Smagt JJ Van Der, Doevendans PA, Wilde AA, Loh P, *et al.* Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. *Circ Arrhythmia Electrophysiol*. 2016;9(10):e004258.
19. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace*. 2013;15(10):1389–406.
20. Prakken NH, Velthuis BK, Teske AJ, Mosterd A, Mali WP, Cramer MJ. Cardiac MRI reference values for athletes and nonathletes corrected for body surface area, training hours/week and sex. *Eur J Cardiovasc Prev Rehabil*. 2010;17(2):198–203.
21. Prakken NH, Cramer MJ, Teske AJ, Arend M, Mali WP, Velthuis BK. The effect of age in the cardiac MRI evaluation of the athlete's heart. *Int J Cardiol*. 2011;149(1):68–73.

22. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22(1):17.
23. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, *et al.* Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update. *J Cardiovasc Magn Reson*. 2020;22(1):19.
24. Han Y, Peters DC, Salton CJ, Bzymek D, Nezafat R, Goddu B, *et al.* Cardiovascular Magnetic Resonance Characterization of Mitral Valve Prolapse. *JACC Cardiovasc Imaging*. 2008;1(3):294–303.
25. Perazzolo Marra M, Basso C, Lazzari M De, Rizzo S, Cipriani A, Giorgi B, *et al.* Morphofunctional Abnormalities of Mitral Annulus and Arrhythmic Mitral Valve Prolapse. *Circ Cardiovasc Imaging*. 2016;9(8).
26. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Hear J – Cardiovasc Imaging*. 2015;16(3):233–71.
27. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, *et al.* European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *Eur J Echocardiogr*. 2008;9(4):438–48.
28. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13(4):905–12.
29. Xiao L, Koopmann TT, Ördög B, Postema PG, Verkerk AO, Iyer V, *et al.* Unique cardiac Purkinje fiber transient outward current β-subunit composition: A potential molecular link to idiopathic ventricular fibrillation. *Circ Res*. 2013;112(10):1310–22.
30. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, *et al.* EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias. *Heart Rhythm*. 2014;11(10):e166–96.
31. Parwani P, Avierinos J-F, Levine RA, Delling FN. Mitral Valve Prolapse: Multimodality Imaging and Genetic Insights. *Prog Cardiovasc Dis*. 2017;60(3):361–9.
32. Essayagh B, Sabbag A, Antoine C, Benfari G, Batista R, Yang L-T, *et al.* The Mitral Annular Disjunction of Mitral Valve Prolapse. *JACC Cardiovasc Imaging*. 2021;14(11):2073–87.
33. Toh H, Mori S, Izawa Y, Fujita H, Miwa K, Suzuki M, *et al.* Prevalence and extent of mitral annular disjunction in structurally normal hearts: comprehensive 3D analysis using cardiac computed tomography. *Eur Hear J - Cardiovasc Imaging*. 2021;00:1–9.
34. Bharati S, Bauernfiend R, Scheinman M, Wu D, Lev M, Rosen KM. Congenital Abnormalities of the Conduction System in Two Patients with Tachyarrhythmias. *Circulation*. 1979;59:593–606.
35. Konda T, Tani T, Suganuma N, Nakamura H, Sumida T, Fujii Y, *et al.* The analysis of mitral annular disjunction detected by echocardiography and comparison with previously reported pathological data. *J Echocardiogr*. 2017;15(4):176–85.
36. Thamman R. A New Malignant MVP Phenotype? *JACC Case Reports*. 2021;3(2):247–9.
37. Bennett S, Phan T, Patwala A, Thamman R, Kwok CS. Surviving cardiac arrest from mitral annular disjunction: A case report. *Echocardiography*. 2019;36(7):1405–8.
38. Basso C, Perazzolo Marra M, Rizzo S, Lazzari M De, Giorgi B, Cipriani A, *et al.* Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death. *Circulation*. 2015;132(7):556–66.

Supplemental material

Table S1 | Variants of uncertain significance found in patients with MAD/MVP

Patient	Mutation	Gene		
IVF survivor 3	VUS	TMEM43	c.428C>T	p.(Thr143Met)
	VUS	DSP	c.3230C>A	p.(Ala1077Glu)
IVF survivor 4	VUS	TTN	c.76352dupC	Pro25452fs

Table S2 | Morphologic PVC criteria in patients with MAD/MVP.

Patient	VE	BBB pattern	Precordial transition	Axis	Estimated origin
IVF survivor 1	No	N/A	N/A	N/A	N/A
IVF survivor 2	Yes	RBBB	V4	Superior	LV inferoseptal
		LBBB	V5	Inferior	RVOT
IVF survivor 3	No	N/A	N/A	N/A	N/A
IVF survivor 4	Yes	LBBB	V3	Inferior	RVOT (distal)
IVF survivor 5	Yes	RBBB	Positive conc.	Intermediair/ superior	LV mid posterior
IVF survivor 6	Yes	LBBB	V4	Inferior	RVOT (distal)
IVF survivor 7	Yes	RBBB	V5	Superior	LV apex
IVF survivor 8	Yes	LBBB	V4	Inferior	RVOT distal lateral DD LVOT RCC

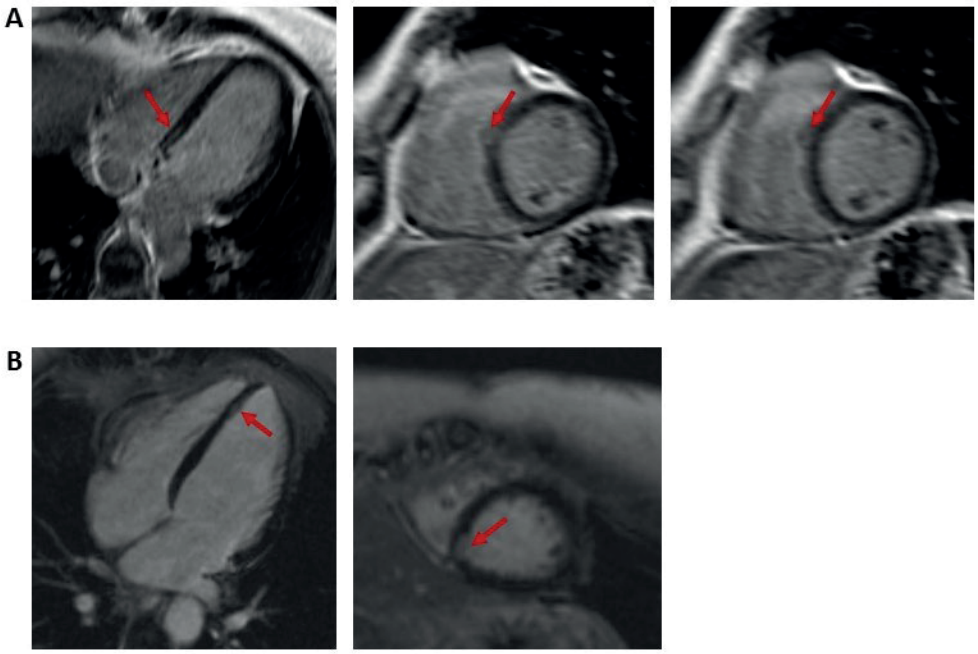


Figure S1 | Example of two IVF patients with LGE. A: One patient with inferolateral MAD showed midwall LGE in the LV basal inferoseptal myocardium. B: One patient without MAD/MVP showed possible basal subendocardial LGE. However, this could also be due to slow flow in a basal crypt.

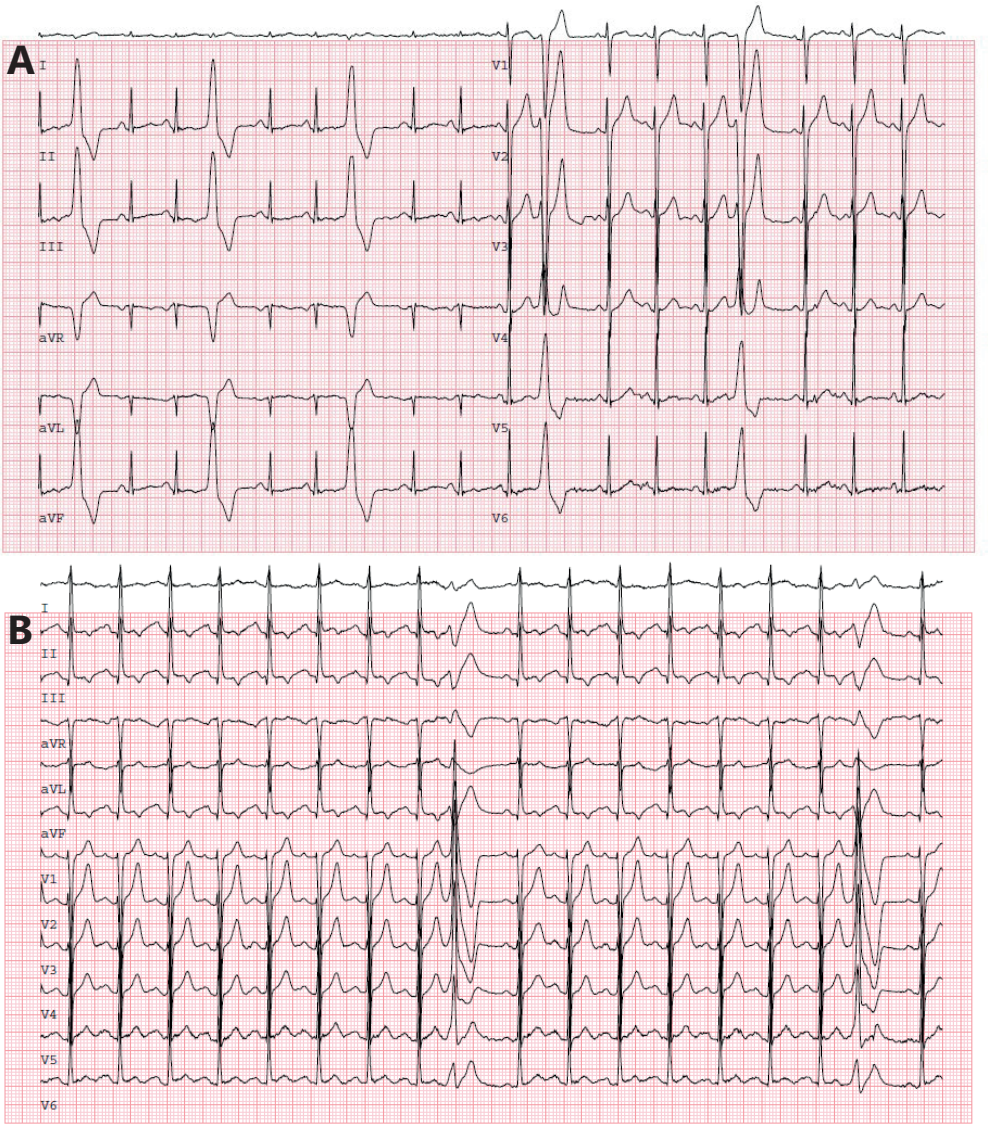


Figure S2 | Example of two patients with MAD/MVP and PVCs. A: The electrocardiogram shows PVCs with a LBBB morphology and an inferior axis of an IVF patient with MAD/MVP. B: The electrocardiogram shows PVCs with an RBBB morphology and a horizontal axis of an IVF patient with MAD/MVP.

PART III

To prevent sudden cardiac death


06

Familial Evaluation in Idiopathic Ventricular Fibrillation: Diagnostic Yield and Significance of J Wave Syndromes.

Circulation Arrhythmia and Electrophysiology. 2021 Mar; 14(3):e009089.

*Greg J Mellor**
*Lennart J Blom**
Sanne A Groeneveld
Bo G Winkel
Bode Ensam
Johannes Bargehr
Bianca van Rees
Chiara Scrocco
Ingrid P C Krapels
Paul G A Volders
Jacob Tfelt-Hansen
Andrew D Krahn
Rutger J Hassink
Elijah R Behr

** Authors contributed equally.*

Abstract

Background | Familial cascade screening is well established in patients with heritable cardiac disease and in cases of sudden arrhythmic death syndrome. The clinical benefit of family screening in idiopathic ventricular fibrillation (IVF) is unknown.

Methods | Patients with IVF were identified from national and institutional registries. All underwent systematic and comprehensive clinical evaluation to exclude identifiable causes of cardiac arrest with a minimum requirement of ECG, cardiac (echocardiogram or magnetic resonance imaging) and coronary imaging, exercise ECG, and sodium channel blocker provocation. Additional investigations including genetic testing were performed at the physician's discretion. First-degree relatives who were assessed with at least a 12-lead ECG were included in the final cohort. Results of additional investigations, performed at the physician's discretion, were also recorded. Results were coded as normal, abnormal, or minor findings.

Results | We identified 201 first-degree relatives of 96 IVF patients. In addition to a 12-lead ECG, echocardiography was performed in 159 (79%) and ≥1 additional investigation in 162 (80%) relatives. An inherited arrhythmia syndrome was diagnosed in 5 (3%) individuals from 4 (4%) families. Two relatives hosted the DPP6 risk haplotype identified in a single proband, one of whom received a primary prevention implantable cardioverter defibrillator. In 3 separate families, an asymptomatic parent of the IVF proband developed a type 1 Brugada ECG pattern during sodium channel blocker provocation. All were managed with lifestyle measures only. The early repolarization (ER) ECG pattern was present in 16% probands and was more common in relatives in those families than those where the proband did not have early repolarization (25% versus 8%, P=0.04).

Conclusions | The yield of family screening in relatives of IVF probands is low when the proband is comprehensively investigated. The significance of J wave syndromes in relatives and the role for systematic sodium channel blocker provocation are, however, uncertain and require further research.

Introduction

Cardiac arrest due to ventricular fibrillation is a common presentation and important cause of death.[1] The majority of cases are due to ischemic heart disease. Alternatively, manifest cardiomyopathy or ion channel disease may be evident. In a significant minority, initial investigation with ECG, transthoracic echocardiogram, and coronary imaging will be nondiagnostic.[2] Systematic clinical investigation of such unexplained cardiac arrest (UCA)[3] may reveal a diagnosis in approximately one-third of cases.[4] Frequently, the diagnosis made will be an inherited arrhythmia syndrome or cardiomyopathy which will lead to a recommendation to perform cascade screening of immediate family members.[5,6]

If no diagnosis is made, a label of idiopathic ventricular fibrillation (IVF) is used although there is currently no consensus on which investigations are required before IVF is diagnosed.[7] Therefore, those patients labeled with IVF may represent a variety of underlying pathologies including concealed forms of established arrhythmia syndromes or cardiomyopathies, short-coupled ventricular fibrillation (VF) without documentation of the initiating premature ventricular contraction (PVC), or unidentified environmental triggers in otherwise normal hearts.

Heritability in sudden death[8] is recognized and familial evaluation in sudden unexplained death is well established with evidence of inherited heart disease identified in around one-third of families.[9] However, the benefit of family cascade screening in idiopathic VF is not known. Long-term follow-up has revealed a heritable diagnosis in a fifth of idiopathic VF patients[10] and incomplete penetrance and variable expressivity are well recognized in the inherited arrhythmia syndromes.[11,12] We hypothesized that familial screening may reveal heritable diagnoses in first-degree relatives that were not apparent in the IVF proband.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Cohort Identification

Eligible patients were identified through a 2-step process. Initially, cardiac arrest patients meeting the criteria for IVF, as outlined below, were identified. Next, first-degree relatives of these patients who had undergone assessment with at least a 12-lead ECG were identified, with further evaluation of relatives being performed at the discretion of the treating physician. Families with an IVF proband and ≥1 relative assessed were included in the final cohort (Figure 1).

Cases were identified from national and institutional registries in Canada, Denmark, the Netherlands, and the United Kingdom. The breakdown of the cohort by registry is described in the Data Supplement. Individuals were diagnosed with IVF if they had been resuscitated from

cardiac arrest with documentation of VF and no diagnosis had been made after comprehensive clinical assessment comprising a minimum of resting 12-lead ECG, cardiac imaging with echocardiogram or magnetic resonance imaging (MRI), coronary artery imaging, exercise ECG, and sodium channel blocker (SCB) provocation. Further investigations were performed at the treating physician's discretion. Cases with positive toxicology were excluded. Genetic testing was not required for inclusion although results were recorded where performed. In addition, minor or nondiagnostic findings from clinical investigations were recorded. Presence of the early repolarization (ER) ECG pattern and documented short-coupled PVC initiating VF were considered part of the spectrum of IVF and therefore individuals with these diagnoses were included. ER pattern was defined as ≥0.1 mV J-point elevation in 2 contiguous inferior or lateral leads.[7,13] The study was approved by the relevant institutional review boards and subjects gave informed consent as required. A summary of the minimum required clinical assessment is shown in Figure 1.

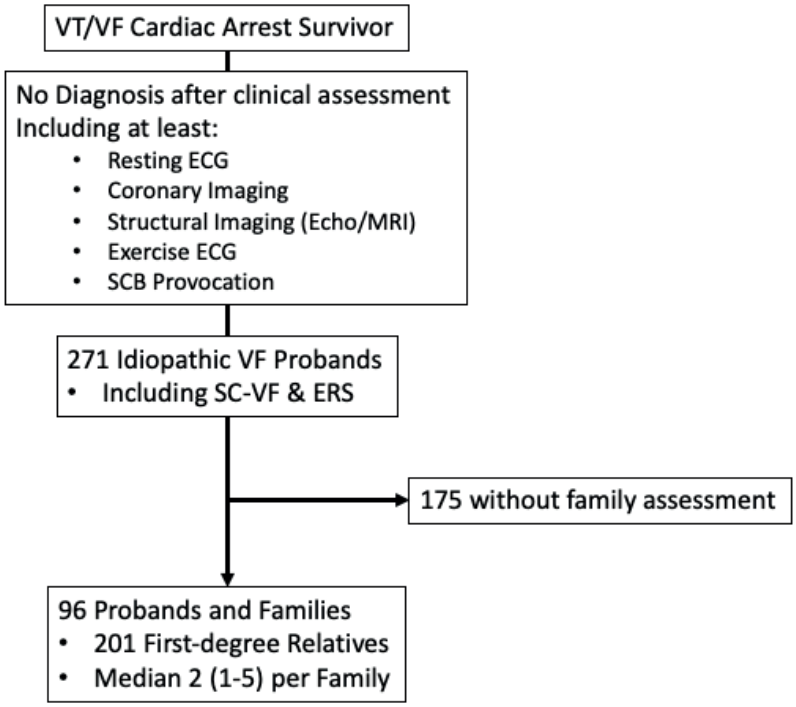


Figure 1 | Cohort selection. Idiopathic ventricular fibrillation (VF) probands were identified after comprehensive clinical evaluation. Families where ≥1 first-degree relatives were assessed with at least a resting ECG were included. Echo indicates echocardiogram; ERS, early repolarization syndrome; MRI, magnetic resonance imaging; SCB, sodium channel blocker; SC-VF, short-coupled ventricular fibrillation; and VT, ventricular tachycardia

Data Collection

Clinical characteristics of cardiac arrest patients and relatives were collected. Results of investigations performed were recorded and coded by study investigators at each site as normal, abnormal (meeting recognized disease-specific diagnostic criteria), or minor findings (outside of recognized normal limits but not diagnostic). Investigations with positive results were noted and associations with proband's and relatives' characteristics were sought. A familial diagnosis was recorded when ≥1 first-degree relatives had investigation findings compatible with a diagnosis of a recognized inherited cardiac condition as per guidelines.[5,14,15]

Statistical Methods

Continuous data are presented as median (interquartile range) and were compared using the Mann-Whitney *U* test. Categorical variables are presented as n (%) and were compared with Fisher exact test. A $P<0.05$ was considered significant. Statistical analysis was performed with SPSS 24 (SPSS, Inc, Chicago, IL).

Results

We included 96 families of IVF probands where cascade screening with at least a 12-lead ECG was performed. The final cohort comprised 201 first-degree relatives of these 96 idiopathic VF probands.

Proband Characteristics

The clinical characteristics of probands are summarized in Table 1. The mean age was 39±12 years, 51 (53%) were male. Self-reported ethnicities were White (91%), South-East Asian (n=3), African-Caribbean (n=3), Chinese (n=1), and Middle Eastern (n=1). One individual self-reported as other ethnicity. The circumstance of cardiac arrest was recorded in 81 (84%). The majority occurred at rest (45, 56%). Prior suspected arrhythmic syncope was reported in 17 (18%). A prior familial history of sudden death was reported in 12 (13%). Additional investigations performed above those required for inclusion are listed in Table 1.

Minor investigation findings were common (specific findings are listed in the Data Supplement). The inferolateral ER pattern was seen in 17% of probands. A type 2 Brugada ECG pattern that did not convert to a type 1 pattern with SCB provocation (including high right ventricular [RV] leads) was seen in 2 probands. Other minor ECG findings including minor conduction delay, repolarization changes, and PVCs were seen in 20%. Minor imaging findings were present in 18% on echocardiography and 16% on MRI with significant overlap of findings between modality. Minor changes in RV dimension or contractility (echocardiography 59%, MRI 80%) were most common. Minor findings, most commonly isolated PVCs (65%), were present in 18% of exercise tests.

Table 1 | Clinical Characteristics and Summary of Investigation Findings in Idiopathic VF Probands.

Characteristic, n (%)	All probands (n=96)	Negative family screening (n=92)	Positive family screening (n=4)	p-value
Age, mean±SD	39±12	39±12	28±17	0.08
Male Sex (%)	51 (53)	47 (51)	3 (75)	0.35
Caucasian (%)*	87 (91)	83 (90)	4 (100)	0.33
Circumstance of cardiac arrest				
Sleep (%)	12 (15)	10 (13)	2 (50)	0.12
Rest (%)	45 (56)	44 (57)	1 (25)	
Exercise (%)	24 (30)	23 (30)	1 (25)	
Prior syncope (%)	17 (18)	16 (17)	1 (25)	0.70
Other FH SD (%)	12 (13)	12 (13)	0 (0)	0.44
Investigations				
ECG (n=96, 100%)				
Normal	61 (64)	58 (63)	3 (75)	0.63
Early Repolarisation	16 (17)	15 (16)	1 (25)	
Other Minor findings	19 (20)	19 (21)	0 (0)	
High lead ECG (n=84, 85%)				
Normal	82 (98)	78 (98)	4 (100)	0.75
Type 2 Brugada pattern	2 (2)	2 (2)	0 (0)	
SAECG (n=48, 52%)				
Normal (0/3)	36 (75)	35 (74)	1 (100)	1.0
Abnormal (≥2/3)	7 (15)	7 (15)	0 (0)	
Equivocal (1/3)	5 (10)	5 (11)	0 (0)	
Echo cardiogram (n=96, 100%)				
Normal	79 (82)	76 (83)	3 (75)	0.70
Minor finding	17 (18)	16 (17)	1 (25)	
Cardiac MRI (n=81, 85%)				
Normal	68 (84)	66 (86)	2 (50)	0.06
Minor finding	13 (16)	11 (14)	2 (50)	
Exercise ECG (n=96, 100%)				
Normal	79 (82)	75 (82%)	4 (100)	0.34
Minor finding	17 (18)	17 (18%)	0 (0)	
Adrenaline provocation (n=33, 34%)				
Negative	23 (70)	21 (68)	2 (100)	0.35
QT prolongation >30ms	1 (3)	1 (3)	0 (0)	
QT prolongation 1-30ms	9 (26)	9 (28)	0 (0)	
Sodium channel blocker provocation (n=96, 100%)				
Negative	96 (100)	92 (100)	4 (100)	-
Type 1 Brugada ECG	0 (0)	0 (0)	0 (0)	
Genetics (n=73, 77%)				
Negative inc. VUS	71 (97)	68 (99)	3 (75)	0.01
P/LP variant	2 (3)	1 (1)	1 (25)	

*Stratified by presence of a positive finding during evaluation in a first-degree relative. FH SD indicates family history of sudden cardiac death; MRI, magnetic resonance imaging; P/LP, pathogenic or likely pathogenic; SAECG, signal-averaged ECG; VF, ventricular fibrillation; and VUS: variant of uncertain significance. *The self-reported ethnicities of the remaining 9% were South-East Asian (n=3), African-Caribbean (n=3), Chinese (n=1), and Middle Eastern (n=1). One individual self-reported as other ethnicity.*

Relative Characteristics

The clinical characteristics of relatives are displayed in Table 2. The mean age was 39±20 years and 114 (57%) were male. Sixty (30%) were parents, 69 (34%) were siblings, and 72 (36%) were offspring of the proband. Prior syncope was reported in 12 (6%). A prior familial history of sudden death (other than the proband) was reported in 7 (4%).

As per the protocol, all relatives had a resting 12-lead ECG, with additional high RV leads performed in 52 (26%). Further investigations included an echocardiogram in 159 (79%), echocardiogram and cardiac MRI in 22 (11%), exercise ECG in 124 (62%), SAECG in 59 (29%), SCB provocation in 20 (10%), and adrenaline provocation in 6 (3%) relatives.

Table 2 | Clinical characteristics and investigations performed in relatives.

	All relatives (n=201)	No familial diagnosis (n=185)	Familial diagnosis (n=16)	p-value
Age, mean±SD	37 (23-57)	36 (23-56)	48 (23-61)	0.80
Male (%)	114 (57)	107 (58)	7 (44)	0.28
Relationship to proband (%)				
Child	72 (36)		72 (36)	0.08
Sibling	69 (34)		69 (34)	0.08
Parent	60 (30)	70 (38)	60 (30)	0.08
Syncope %	12 (6)	12 (7)	0 (0)	0.29
Other FH SD (%)	7 (4)	6 (4)	1 (6)	0.53
Investigations performed				
ECG (%)	201 (100)	185 (100)	16 (100)	-
High lead ECG (%)	52 (26)	44 (24)	8 (50)	0.02
SAECG (%)	59 (29)	53 (29)	6 (38)	0.46
Echocardiogram (%)	159 (79)	149 (81)	10 (63)	0.09
MRI (%)	22 (11)	21 (11)	1 (6)	0.53
Exercise ECG (%)	124 (62)	117 (63)	7 (44)	0.13
Adrenaline provocation %	6 (3)	6 (3)	0 (0)	0.46
Na channel blocker provocation (%)	20 (10)	15 (8)	5 (31)	0.01

Stratified by presence of positive findings during familial evaluation. FH SD indicates family history of sudden cardiac death; MRI, magnetic resonance imaging; and SAECG, signal-averaged ECG.

Diagnostic Yield in Relatives

Five (3%) relatives from 4 (4%) families had a positive test result in keeping with a heritable condition (See Figure 2). There were no significant differences between the clinical characteristics of probands where a familial diagnosis was made in first-degree relatives compared to those where no familial diagnosis was made, although the proband age tended to be lower (28±17 years versus 39±13 years, *P*=0.08). High RV lead ECG and SCB provocation were both performed more often in relatives where a heritable diagnosis was made (*P*=0.02, 0.01, respectively). The finding of a pathogenic/likely pathogenic variant on genetic testing

was associated with a familial diagnosis (*P*=0.01). The families with positive findings are summarized below.

Family 1

A 54-year-old male of Dutch heritage suffered VF during sleep. Clinical assessment revealed only dyskinesia of the RV lateral wall and an RV ejection fraction of 44%. There was no ER pattern. Genetic testing with a 34 gene panel identified the *DPP6* risk haplotype. Six relatives (4 siblings and 2 children) underwent cascade genetic testing. The patient's brother and daughter were found to carry the haplotype. A primary prevention subcutaneous implantable cardioverter defibrillator was implanted in the daughter.

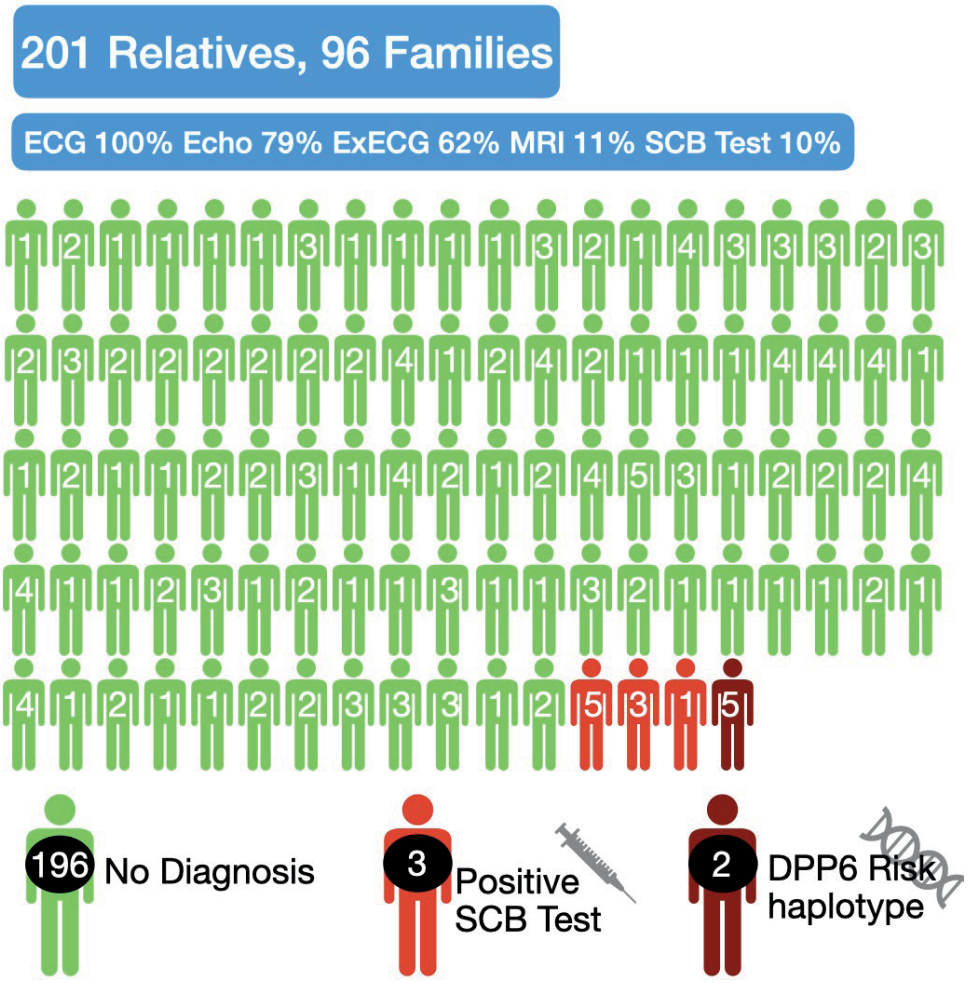


Figure 2 | Outcomes of family assessment in idiopathic ventricular fibrillation. Each person icon represents one family with the number of relatives assessed noted inside the icon. ExECG indicates exercise ECG; MRI, magnetic resonance imaging; and SCB, sodium channel blocker.

Family 2

A 21-year-old male suffered VF during sleep. He had a history of prior syncope. There was an inferior ER pattern on the resting ECG and further clinical assessment revealed no positive findings. Three relatives underwent clinical assessment. His 62-year-old father was found to have a type 2 Brugada ECG pattern at rest which converted to a type 1 pattern with ajmaline provocation. Genetic testing in both proband and father was negative. The father was asymptomatic and received lifestyle advice only. Ajmaline provocation in the patient's sister was negative and was not performed in his mother (Figure 3).

Family 3

An 18-year-old male suffered VF during exercise. Clinical assessment revealed only basal septal hypokinesia on echocardiogram and MRI. There was no ER pattern. Five relatives underwent clinical assessment. The patient's 49-year-old father was found to have a type 2 Brugada ECG pattern which converted to a type 1 pattern with ajmaline provocation. During exercise testing, changes in RV conduction approaching a type 1 Brugada ECG pattern were also noted. Genetic testing in both proband and father was negative. The father was asymptomatic and received lifestyle advice only. The ECG of the patient's 16-year-old brother showed partial right bundle branch block. Ajmaline provocation was negative. Ajmaline provocation was not performed in the patient's mother or 2 other siblings with normal resting ECGs.

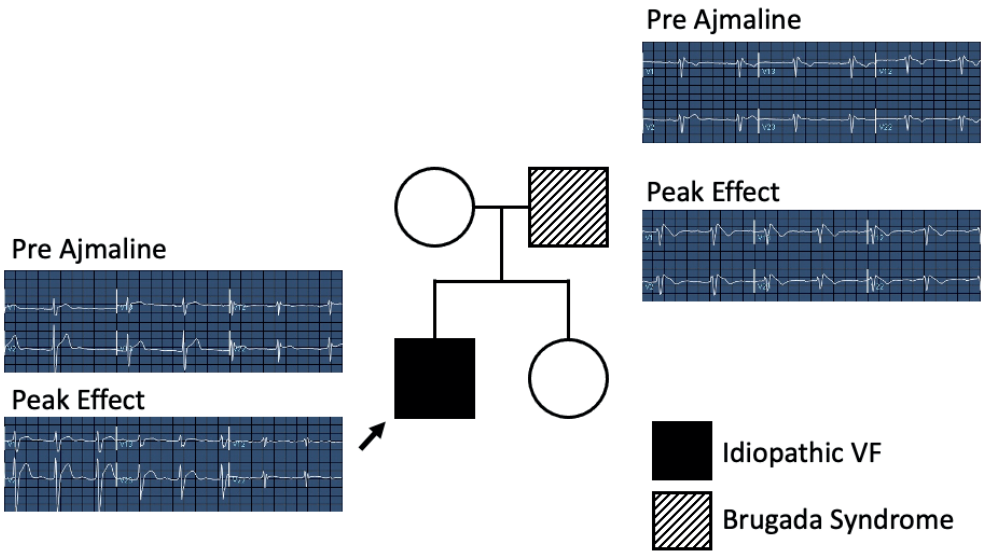


Figure 3 | Sodium channel blocker provocation results in family 2. An 18-y-old male idiopathic ventricular fibrillation (VF) proband had a negative ajmaline provocation. The patient's father had a positive test with a type 1 Brugada ECG pattern seen. 1 mg/kg Ajmaline was infused over 5 min. Continuous digital ECGs were recorded with V_1 and V_2 in the standard and high lead positions (labeled V_{12}/V_{22} for second intercostal space, V_{13}/V_{23} for third intercostal space).

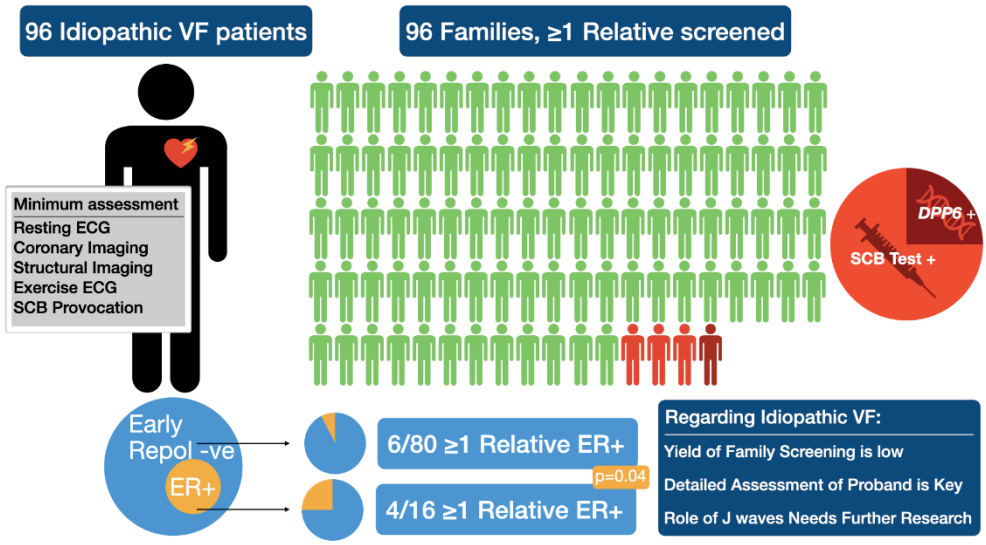
Family 4
A 19-year-old female suffered VF at rest. Clinical assessment revealed no positive findings. There was no ER pattern. Genetic testing with a 212 gene panel revealed a variant of uncertain significance in *CACNA1C* (c.6637G>A, *P*.Asp2213Asn). Her 61-year-old mother received intravenous flecainide for treatment of atrial fibrillation. During the infusion, she developed a type 1 Brugada ECG pattern. She was found to carry the same variant in *CACNA1C*. She was asymptomatic and received lifestyle advice only.

Other Findings in Relatives
ECG abnormalities were present in 22% of relatives. The ER pattern was seen in 11 (5%) relatives from 10 families. Where the proband had ER (n=16), ≥1 relative also had ER in 4 families (25%). ER was less common in families where the proband did not have ER (6/80, 8%, *P*=0.04). Minor findings were reported on echocardiogram (9%) and exercise ECG (11%). Two relatives were diagnosed with left ventricular hypertrophy secondary to hypertension and a single relative was found to have a significant atrial septal defect which was subsequently closed.

Genetic Testing
Genetic testing was performed in 77 (77%) probands. Testing strategies varied from single phenotype panels to broad multiphenotype panels of up to 212 genes. A pathogenic/likely pathogenic variant was identified in 2 (2%). A male proband of Dutch ancestry was found to carry the *DPP6* risk haplotype. A truncating *PKP2* (Arg79Ter) variant was identified in a single proband who experienced VF at rest. His ECG and cardiac imaging were unremarkable both at the time of arrest and when repeated several years later, although a small number of PVCs were seen during exercise ECG at repeat assessment. Predictive testing was carried out in families of the probands with the *DPP6* risk haplotype (2 relatives positive, 4 negative) and the pathogenic *PKP2* variant (one relative negative). In relatives where Brugada syndrome (BrS) was diagnosed, 2 had negative panel testing, and 1 was found to carry a variant of uncertain significance in *CACNA1C* previously identified in the familial proband.

Discussion

This study provides a unique insight into the heritability and genetic risk in idiopathic VF. We describe a large multicentre international cohort of IVF probands fulfilling stringent and strict negative investigative criteria, designed to ensure that acquired disease and expressed genetic disorders have been excluded as fully as possible. We then assessed the yield of genetic disease following evaluation of relatives with at least an ECG performed. We identified a 3% yield of families with a drug-induced type 1 Brugada pattern in first-degree relatives, a higher prevalence of the ER pattern in relatives of probands with preexisting ER pattern, and a role for targeted *DPP6* haplotype testing in Dutch families (graphic abstract).



Graphic abstract: Familial Evaluation in Idiopathic Ventricular Fibrillation: Diagnostic Yield and Significance of J Wave Syndromes.

Stringency of IVF Patient Investigation

A recent study has found that 6.9% of all cardiac arrest patients were described as IVF, although there was significant variability in clinical assessment carried out before arriving at the diagnosis.[2] Indeed, although IVF is a diagnosis of exclusion, there remains no consensus on the minimum clinical evaluation required before a diagnosis can be made. Previous studies of IVF have contained heterogeneous cohorts of patients with investigations carried out in varying depth.[16] The inclusion criteria for this study were therefore strict to arrive at as homogenous a population as possible.

Diagnostic Yield of Familial Evaluation

The yield of clinical familial evaluation was low with only 5 (3%) relatives from 4 (4%) families with a heritable diagnosis. This is in contrast to previous studies of familial evaluation in autopsy-negative and toxicology-negative sudden unexplained death (also known as sudden arrhythmic death syndrome [SADS][17]) which have reported diagnoses of an inherited cardiac condition in 18% to 53% of families.[17–23] Furthermore, postmortem genetic testing (molecular autopsy) series in SADS have reported potentially disease-causing variants in genes associated with ion channel disease and cardiomyopathy in 13% to 30% cases.[24–26]

Clinical assessment of SADS probands is very limited by default as most deaths are unheralded and therefore very few would have had antemortem cardiac assessment.[27,28] Comparison between sudden death and cardiac arrest survivors is not straightforward and fundamental differences between cardiac arrest survivors and those who die suddenly cannot be

excluded.[20,29] However, it is probable that, if SADS cases survived clinical evaluation, a proportion would have an identifiable heritable phenotype and that testing in these families would account for much of the expected positive diagnostic yield. The remainder would presumably, therefore, overlap phenotypically with the IVF cohort described here and be expected to have a lower yield from family evaluation.

Studies of familial evaluation in cardiac arrest survivors are fewer with varying yields. Kumar et al[22] reported a 62% yield of familial evaluation in UCA, although relatives were only assessed if a heritable diagnosis was made in the proband. Familial evaluation in the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry) included relatives of UCA patients with and without a diagnosis after clinical evaluation. This led to a definite diagnosis in 5.4% of first-degree relatives and a probable diagnosis in a further 11.8%.[30] A single study of idiopathic VF probands with similar inclusion criteria to our study found no familial diagnosis in 72 relatives of 33 probands.[31]

The low yield in this current cohort, therefore, reflects that probands with identifiable phenotypes where cardiac screening would be expected to have the highest yield have been actively excluded through extensive evaluation of the patients with VF. Therefore, the original hypothesis that a significant proportion of idiopathic VF may be due to concealed forms of inherited heart disease is only weakly supported by our data. Since relatives were investigated at a single time point, we are unable to comment on whether further serial evaluation would have revealed additional diagnoses over time.

Diagnostic Yield of Genetic Testing

Genetic testing of the proband was not required for inclusion in the study and was performed at the discretion of the treating physician. One proband of Dutch heritage was identified with the *DPP6* risk haplotype.[32] Four family members were tested with 2 positive and one receiving a primary prevention implantable cardioverter defibrillator. A second proband had a pathogenic truncating *PKP2* variant identified through whole-genome sequencing. A single-family member was negative for the variant thus providing welcome reassurance.

The *DPP6* risk haplotype is currently the only well-established genetic culprit associated with familial IVF.[32] However, identified cases have been limited to a recognized founder effect in Dutch families.[33] The yield of pathogenic and likely pathogenic variants in other studies of IVF and UCA is higher than ours at 9% to 17%.[16,34,35] Established genes associated with both ion channel disease and cardiomyopathy are frequently implicated. However, clinical investigation in these studies was not as systematic and comprehensive in excluding these disorders as in our cohort.

The low yield of genetic testing in this and previous studies may be seen as evidence of significant nongenetic risk factors in idiopathic VF. More comprehensive genetic testing in probands may have led to an increased number of diagnoses in relatives. However, this study

was not designed to be able to dissect what is likely to be a highly complex interaction between many potential nongenetic as well as genetic contributing factors.

BrS and Early Repolarization

The sole familial condition identified through clinical assessment (n=3) was BrS following positive SCB provocation testing, that is, >2 mm J-point elevation (or J wave) in the right precordial leads with coved ST elevation and T wave inversion. Overall, SCB provocation was performed in 20 relatives from 12 families giving a positive rate of 15% and 25% at the family level. Use of SCB provocation and high lead ECGs was, however, highly selected and the absolute numbers of positive tests may have been higher if they were undertaken more systematically. Nonetheless, this yield is similar to reported yields of 14-20% in recent large studies of ajmaline use in families with a history SADS, sudden unexpected death, and UCA.[36,37]

The diagnosis of BrS by SCB provocation in asymptomatic patients has been a matter of debate due to low rates of arrhythmic events[38] and positive test results in patients with apparently unrelated conditions.[39] Accordingly, recently adopted diagnostic criteria for BrS classifies the combination of positive SCB provocation and history of UCA in a first-degree relative only as possible BrS unless the cardiac arrest event itself was suspicious for BrS.[14]

However, the complex nature of heritability of BrS must also be considered. Although traditionally considered a Mendelian autosomal dominant trait, common genetic variation has also been shown to influence disease susceptibility with cumulative effects on overall disease expression[40] and the type 1 ECG pattern response to SCB.[41] It is therefore possible that some shared genetic predisposition is responsible, at least in part, for idiopathic VF in one family member and a positive SCB provocation test in another.

Another form of J wave, the inferior ER pattern, is over-represented in IVF probands[42] which has led to the proposed diagnosis of Early Repolarization Syndrome (ERS)[7] as a further J wave syndrome alongside BrS.[14] Previous reports have demonstrated heritability of the ER pattern, and it is more common in relatives of SADS cases than control groups.[43,44] ER was present in a significant number of probands in this study and was more common in their relatives than relatives of probands without ER, supporting previous findings in a similar small cohort.[31] As in BrS, recent data support that common genetic variation associates with the ER pattern,[45] and there is little evidence of autosomal dominant disorders underlying ERS.[14]

Our data, therefore, suggest a genetic predisposition to ER or ERS in some IVF patients and their families, as well as a genetic predisposition to the drug-induced type 1 pattern or BrS in others. Future systematic ECG, electrophysiological and genomic research of ER and Brugada ECG patterns in IVF probands and their relatives, coupled with long-term follow-up, will be required to determine their true significance as predisposition for unexpected cardiac arrest in this setting.

Clinical Implications

The comprehensive evaluation of the cardiac arrest patient should be a priority to ensure exclusion of well-established genetic causes. We advocate a similar approach to our inclusion criteria (Figure 1). Although the current study was not designed to assess the utility of genetic testing in the proband, the impact of positive findings on familial cascade testing can support its inclusion albeit with a focus on established genes.

However, given the low yield of family screening in our study, the justification of routine comprehensive testing of relatives of idiopathic VF cases is weak. And yet, ER pattern and drug-induced type 1 Brugada ECG patterns suggest that J wave syndromes form an important sub-group of heritable risk in IVF families. Based upon current understanding routine, SCB provocation in asymptomatic relatives of IVF probands is not indicated unless there is a strong prior suspicion of BrS such as the type 2 Brugada patterns seen in our families. The long-term management will usually be with lifestyle measures to avoid arrhythmic triggers together with monitoring for any evolution of risk.[36] No clinical action can be taken in relatives with ER given the low absolute risk of arrhythmia in asymptomatic individuals with ER. Cardiac syncope or a strong family history for premature SCD would otherwise be indications for intervention.[7]

Limitations

The study was a retrospective analysis; evaluation of family members and genetic testing in probands was not standardized. Therefore, bias cannot be excluded. Although the cohort is large in terms of a rare disease, its size limits the analysis of clinical predictors for familial diagnosis. The majority of individuals were of white European ethnicity and so application of the results to other groups may not be possible. Furthermore, as these findings were generated from tertiary services with variable catchment areas, they may not be generalizable to a nontertiary population and should be investigated prospectively.

Future Studies

A prospective study with systematic and standardized genetic testing in probands and routine use of SCB provocation in relatives would be important to further develop the conclusions drawn from this study.

Conclusions

The yield of family screening in relatives of IVF probands is low. Comprehensive clinical evaluation of the UCA proband is the cornerstone of management in these families. The significance of J wave Syndromes in relatives of IVF cases, and the role for SCB provocation testing, require further systematic research.

References

1. Zipes DP, Wellens H. Sudden Cardiac Death. Circulation. 1998;98:2334–2351.
2. Waldmann V, Bougouin W, Karam N, Dumas F, Sharifzadehgan A, Gandjbakhch E, Algalarrondo V, Narayanan K, Zhao A, Amet D, et. al. Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: Focus on idiopathic ventricular fibrillation. Eur Heart J. 2018;39:1981–1987.
3. Krahn AD, Healey JS, Chauhan V, Birnie DH, Simpson CS, Champagne J, Gardner M, Sanatani S, Exner D V., Klein GJ, et. al. Systematic assessment of patients with unexplained cardiac arrest: Cardiac arrest survivors with preserved ejection fraction registry (CASPER). Circulation. 2009;120:278–285.
4. Herman ARM, Cheung CC, Gerull B, Simpson CS, Birnie DH, Klein GJ, Champagne J, Healey JS, Gibbs K, Talajic M, et. al. 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:e003619
5. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europea. Eur Heart J. 2015;36:2793-2867l.
6. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, Chugh SS, Cornel MC, Gardner K, Ingles J, et. al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Hear Rhythm. 2021;18:E1-50.
7. Priori SG, Wilde AAM, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang C-E, Huikuri H V., et. al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15:1389–406.
8. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population. The Paris prospective study I. Circulation. 1999;99:1978–1983.
9. Raju H, Behr ER. Unexplained sudden death, focussing on genetics and family phenotyping. Curr Opin Cardiol. 2013;28:19–25.
10. Visser M, Van Der Heijden JF, Van Der Smagt JJ, Doevendans PA, Wilde AAM, Loh P, Hassink RJ. Long-Term Outcome of Patients Initially Diagnosed with Idiopathic Ventricular Fibrillation. Circ Arrhythmia Electrophysiol. 2016;9:e004258.
11. Probst V, Wilde AAM, Barc J, Sacher F, Babuty D, Mabo P, Mansourati J, Le Scouarnec S, Kyndt F, Le Caignec C, et. al. SCN5A Mutations and the role of genetic background in the pathophysiology of brugada syndrome. Circ Cardiovasc Genet. 2009;2:552–557.
12. Mazzanti A, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M, Braghieri L, Gambelli P, Memmi M, Pagan E, et. al. Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome. J Am Coll Cardiol. 2018;71:1663–1671.
13. Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri H V., Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan G-X. The Early Repolarization Pattern: A Consenus Paper. J Am Coll Cardiol. 2015;66:470–477.
14. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, et. al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Hear. Rhythm. 2016;13:e295–e324.
15. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke D a, Calkins H, Corrado D, Cox MGPJ, Daubert JP, et. al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121:1533–41.
16. Leinonen JT, Crotti L, Djupsjöbacka A, Castelletti S, Junna N, Ghidoni A, Tuiskula AM, Spazzolini C, Dagradi F, Viitasalo M, et. al. The genetics underlying idiopathic ventricular fibrillation: A special role for catecholaminergic polymorphic ventricular tachycardia? Int J Cardiol. 2018;250:139–145.

17. Behr ER, Wood D a, Wright M, Syrris P, Sheppard MN, Casey a, Davies MJ, McKenna W. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet. 2003;362:1457–9.
18. Tan HL, Hofman N, van Langen IM, van der Wal AC, Wilde AAM. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation. 2005;112:207–13.
19. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, Rowland E, Jeffery S, McKenna WJ. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J. 2008;29:1670– 80.
20. van der Werf C, Hofman N, Tan HL, van Dessel PF, Alders M, van der Wal AC, van Langen IM, Wilde AAM. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in The Netherlands. Heart Rhythm. 2010;7:1383–9.
21. McGorrian C, Constant O, Harper N, O'Donnell C, Codd M, Keelan E, Green A, O'Neill J, Galvin J, Mahon NG. Family-based cardiac screening in relatives of victims of sudden arrhythmic death syndrome. Europace. 2013;15:1050–8.
22. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, Zentner D, Kalman JM, Winship I, Vohra JK. Familial cardiological and targeted genetic evaluation: Low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. Hear Rhythm. 2013;10:1653–1660.
23. Hansen BL, Jacobsen EM, Kjerrumgaard A, Tfelt-hansen J, Winkel BG, Bundgaard H, Christensen AH. Diagnostic yield in victims of sudden cardiac death and their relatives. Europace. 2020;1–8.
24. Bagnall RD, Weintraub R, Ingles J, Duflou J, Yeates L, Lam L, Davis A, Thompson T, Connell V, Wallace J, et. al. A Prospective Study of Sudden Cardiac Death among Children and Young Adults. N Engl J Med. 2016;374:2441–2452.
25. Lahrouchi N, Raju H, Lodder EM, Papatheodorou E, Ware JS, Papadakis M, Tadros R, Cole D, Skinner JR, Crawford J, et. al. Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. J Am Coll Cardiol. 2017;69:2134–2145.
26. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. J Am Coll Cardiol. 2007;49:240–6.
27. Mellor G, Raju H, de Noronha S V, Papadakis M, Sharma S, Behr ER, Sheppard MN. Clinical Characteristics and Circumstances of Death in the Sudden Arrhythmic Death Syndrome. Circ Arrhythm Electrophysiol. 2014;7:1078–1083.
28. Raju H, Papadakis M, Govindan M, Bastiaenen R, Chandra N, O'Sullivan A, Baines G, Sharma S, Behr ER. Low prevalence of risk markers in cases of sudden death due to Brugada syndrome relevance to risk stratification in Brugada syndrome. J Am Coll Cardiol. 2011;57:2340–5.
29. Semsarian C, Wilde AAM. Genetic Causes in Cardiac Arrest Survivors: Fake News or the Real Deal? Circ Cardiovasc Genet. 2017;10:8–10.
30. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, Roberts JD, Healey JS, Chauhan VS, Birnie DH, J et. al. Cardiac Abnormalities in First-Degree Relatives of Unexplained Cardiac Arrest Victims. Circ Arrhythmia Electrophysiol. 2016;9:e004274.
31. Honarbakhsh S, Srinivasan N, Kirkby C, Firman E, Tobin L, Finlay M, Hunter RJ, Murphy C, Lowe MD, Schilling RJ, Lambiase PD. Medium-term outcomes of idiopathic ventricular fibrillation survivors and family screening: A multicentre experience. Europace. 2017;19:1874–1880.
32. Alders M, Koopmann TT, Christiaans I, Postema PG, Beekman L, Tanck MWT, Zeppenfeld K, Loh P, Koch KT, Demolombe S, et. al. Haplotype-Sharing Analysis Implicates Chromosome 7q36 Harboring DPP6 in Familial Idiopathic Ventricular Fibrillation. Am J Hum Genet. 2009;84:468–476.
33. Postema PG, Christiaans I, Hofman N, Alders M, Koopmann TT, Bezzina CR, Loh P, Zeppenfeld K, Volders PGA, Wilde AAM. Founder mutations in the Netherlands: Familial idiopathic ventricular fibrillation and DPP6. Netherlands Hear J. 2011;19:290–296.
34. Visser M, Dooijes D, van der Smagt JJ, Van Der Heijden JF, Doevendans PA, Loh P, Asselbergs FW, Hassink RJ. Next Generation Sequencing of a large panel in patients initially diagnosed with idiopathic ventricular fibrillation. Hear Rhythm. 2017;14:1035- 1040

35. Mellor G, Laksman ZWM, Tadros R, Roberts JD, Gerull B, Simpson CS, Klein GJ, Champagne J, Talajic M, Gardner M, et. al. Genetic Testing in the Evaluation of Unexplained Cardiac Arrest: From the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry). Circ Cardiovasc Genet. 2017;10:1–8.
36. Papadakis M, Papatheodorou E, Mellor G, Raju H, Bastiaenen R, Wijeyeratne YD, Wasim S, Ensam B, Finocchiaro G, Gray B, et. al. The Diagnostic Yield of Brugada Syndrome After Sudden Death With Normal Autopsy. J Am Coll Cardiol. 2018;71:1204–1214.
37. Tadros R, Nannenberg EA, Lieve K V., Škorić-Milosavljević D, Lahrouchi N, Lekanne Deprez RH, Vendrik J, Reckman YJ, Postema PG, et. al. Yield and Pitfalls of Ajmaline Testing in the Evaluation of Unexplained Cardiac Arrest and Sudden Unexplained Death: Single-Center Experience With 482 Families. JACC Clin Electrophysiol. 2017;3:1400–1408.
38. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, et. al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121:635–43.
39. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, Aydin M, Pfeiffer R. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. Hear Rhythm. 2015;12:1584–1594.
40. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud J-B, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, et. al. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013;45:1044–9.
41. Tadros R, Tan HL, Mathari S el, Kors JA, Postema PG, Lahrouchi N, Beekman L, Radivojkov-Blagojevic M, Amin AS, Meitinger T, et. al. Predicting cardiac electrical response to sodium channel blockade and Brugada syndrome using polygenic risk scores. Eur Heart J. 2019;1–12.
42. Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié J-L, Nogami A, Babuty D, Yli-Mayry S,. Sudden cardiac arrest associated with early repolarization. N Engl J Med. 2008;358:2016–23.
43. Nunn LM, Bhar-Amato J, Lowe MD, Macfarlane PW, Rogers P, McKenna WJ, Elliott PM, Lambiase PD. Prevalence of J-point elevation in sudden arrhythmic death syndrome families. J Am Coll Cardiol. 2011;58:286–90.
44. Mellor G, Nelson CP, Robb C, Raju H, Wijeyeratne YD, Hengstenberg C, Reinhard W, Papadakis M, Sharma S, Samani NJ, Behr ER. The Prevalence and Significance of the Early Repolarization Pattern in Sudden Arrhythmic Death Syndrome Families. Circ Arrhythmia Electrophysiol. 2016;9:e003960
45. Teumer A, Trenkwalder T, Kessler T, Jamshidi Y, van den Berg ME, Kaess B, Nelson CP, Bastiaenen R, de Bortoli M, Rossini A, et. al. KCND3 potassium channel gene variant confers susceptibility to electrocardiographic early repolarization pattern. JCI Insight. 2019;4:e131156.

Supplemental Material

Table S1 | Breakdown between contributing centres. FDR=First-Degree Relative.

Centre	Recruitment since	Probands included	Probands excluded; no FDR seen	FDRs included	FDR:proband	% available FDRs seen
CASPER	2004	32	70	50	1.6	32
Copenhagen	2005	10	42	14	1.4	33
London	2010	17	14	46	2.7	74
Utrecht	2014	25	40	70	2.8	67
Maastricht	2016	6	4	11	1.8	34
Cambridge	2018	6	5	10	1.7	40
Overall		96	175	201	2.1	47

The study represents a collaboration between six established regional or institutional registries of unexplained cardiac arrest. Contributing centres were asked to identify those probands who met the study definition of idiopathic VF as described in the main manuscript. Since the criteria for inclusion in each contributing registry are variable, it is not possible to comment on the overall frequency of idiopathic VF in the respective source populations or what proportion of all cardiac arrests were ultimately classified as idiopathic VF. The relative contribution of each registry generally reflected the number of years the registry had been recruited and the size of the sample population although accurate figures on population sizes were not available. Overall, 271 probands were identified meeting the inclusion criteria. 175 were excluded from the study as there no first-degree relatives in whom assessment with at least a 12-lead ECG was available. For the 96 families in the final cohort, 47% of all first degree relatives were included. This varied from 32-67% between centres reflecting differences in local practice.


07

Sudden death in the young: the importance of autopsy and DNA testing.

Nederlands Tijdschrift voor Geneeskunde. 2020 May 20; 164: D4342.

Sanne A Groeneveld
Lennart J Blom
Rutger J Hassink

English abstract

When a young person suddenly dies, there is a real chance that this was caused by genetic heart disease. Autopsy plays an important role in determining the cause of death, but the autopsy rate in the Netherlands is relatively low. Practical problems and a lack of information on autopsy play a role. It is important to inform the family on the importance of autopsy and DNA testing. If the family refuses autopsy, consent can be given for removal of material for DNA testing. If no autopsy and no DNA test were done, cardiological screening of family members remains highly recommended. New guidelines and procedures for diagnostics after sudden death are very important. For that reason, we developed a step-by-step plan to support healthcare providers. Early detection of genetic heart disease may prevent sudden death of family members, for example, by using preventive medication or internal defibrillators (ICD).

Nederlandse samenvatting

Wanneer een jong persoon plotseling overlijdt, bestaat er een reële kans dat een erfelijke hartziekte de oorzaak was. Obductie speelt een belangrijke rol bij het vaststellen van de doodsoorzaak, maar het percentage obducties in Nederland ligt relatief laag. Praktische problemen en insufficiënte informatievoorziening over obductie spelen een rol. Het is belangrijk om de familie in te lichten over het belang van obductie en DNA-onderzoek. Als de familie obductie weigert, kan zij wel toestemming geven om materiaal voor DNA-onderzoek af te nemen. Als er geen obductie en evenmin DNA-diagnostiek is gedaan, wordt cardiologische screening van familieleden alsnog sterk geadviseerd. Nieuwe richtlijnen en procedures voor diagnostiek na plotseling overlijden zijn van groot belang. Daarom ontwikkelden wij een stappenplan om zorgverleners te ondersteunen. Het vroegtijdig opsporen van erfelijke hartziekten kan plotseling overlijden van familieleden voorkomen door bijvoorbeeld preventieve medicatie of een inwendige defibrillator (ICD).

Casus

U bent huisarts en heeft avonddienst. U wordt gebeld door de centrale. Een van de patiënten uit de praktijk van uw collega is plotseling overleden. Het gaat om een voorheen gezonde man van 33 jaar. De ambulance was als eerste ter plaatse maar is niet gestart met reanimatie, de dood was reeds ingetreden. U wordt gevraagd om een schouw te verrichten en met de familie te spreken. Eenmaal aangekomen bij het huis vindt u een zeer aangeslagen familie. Volgens de familie is de overledene vier uur geleden voor het laatst levend gezien; de man werd door zijn vrouw thuis aangetroffen. U schouwt de patiënt en stelt de dood vast. U loopt naar de huiskamer om de verdere gang van zaken met de familie te bespreken. Maar wat vertelt u eigenlijk aan de familie? En welk advies geeft u hen?

Plotselinge hartdood wordt gedefinieerd als plotseling en onverwachts overlijden binnen een korte tijd na het ontstaan van eventuele klachten. Plotselinge hartdood is een reëel probleem in de westerse wereld. Jaarlijks krijgt 1 op de 1000 Nederlanders tussen de 20-75 jaar buiten het ziekenhuis plotseling een hartstilstand.[1,2] Ongeveer driekwart van de mensen overleeft een reanimatie buiten het ziekenhuis niet.[3]

Een hartstilstand kan veel verschillende oorzaken hebben. Bij het merendeel van de oudere patiënten wordt een plotselinge hartstilstand veroorzaakt door coronairlijden. Bij jongere patiënten ligt er vaker een erfelijke hartziekte aan ten grondslag.[4] Uitgebreide diagnostiek bij de overledene en screening van familieleden is belangrijk om een eventuele erfelijke hartziekte op te sporen en wordt door meerdere internationale richtlijnen aanbevolen.[5,6]

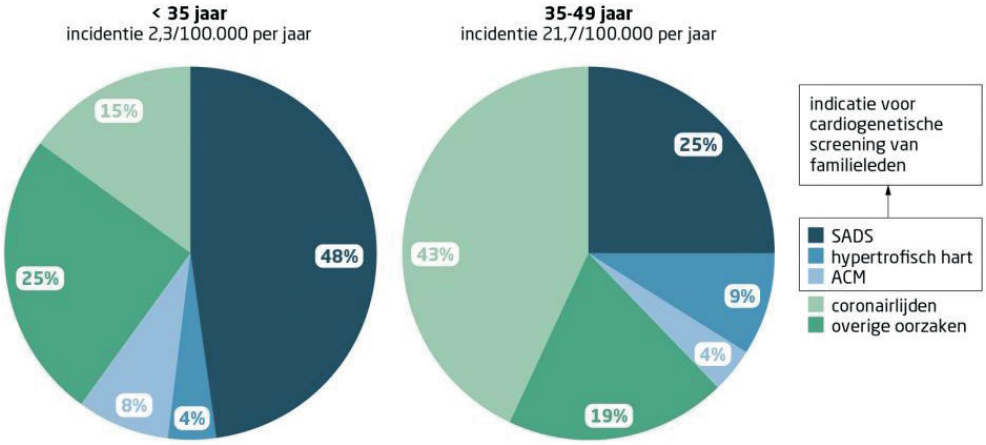
In de praktijk blijken er echter diverse knelpunten te zijn rond de diagnostiek na plotseling overlijden. In dit artikel beschrijven wij de huidige stand van zaken op het gebied van de epidemiologie, etiologie en diagnostiek van plotseling overlijden. Welke onderzoeken zijn geïndiceerd wanneer iemand plotseling is overleden? En wat is de opbrengst van deze onderzoeken? Om deze vragen te beantwoorden raadpleegden wij de huidige internationale richtlijnen, inclusief aanvullende achtergrondliteratuur. Daarnaast introduceren wij een nieuw stappenplan om zorgverleners meer informatie te bieden over de noodzaak van vervolgonderzoek, de gewenste werkwijze en kosten van obductie en DNA-onderzoek.

Plotseling overlijden bij jonge mensen

Waar coronairlijden in de oudere bevolking de meest voorkomende oorzaak van plotse dood is, komt dit bij jong volwassenen weinig voor (figuur 1). Bij slechts 15% van de personen jonger dan 35 jaar die plotseling overleden zijn, wordt coronairlijden geconstateerd. Dit loopt op tot 44% bij personen van 35-49 jaar oud.[7] Het plotseling overlijden van een kind of jongvolwassene – vooral mensen onder de 45 jaar – is dus een signaal dat er mogelijk sprake is van een erfelijke hartziekte. Bij een plotse dood van een patiënt boven de 45 jaar is een erfelijke oorzaak alsnog reëel als ischemisch hartlijden uitgesloten is.

Erfelijke hartziekten kunnen worden onderverdeeld in cardiomyopathieën en elektrische hartziekten. Een cardiomyopathie veroorzaakt structurele veranderingen in het hart, bijvoorbeeld hypertrofie of dilatatie van de hartspier. Bij obductie kunnen deze afwijkingen vaak vastgesteld worden. Het vaststellen van deze afwijkingen is belangrijk. Als er bijvoorbeeld aanwijzingen zijn voor een hypertrofische cardiomyopathie, kan gericht gezocht worden naar genetische afwijkingen binnen de familie.

Bij een elektrische hartziekte is er sprake van een defect in een van de ionkanalen van de cardiomyocyten, waardoor ritmestoornissen kunnen optreden. Voorbeelden hiervan zijn het Brugada-syndroom en het lange-QT-syndroom. Deze afwijkingen zijn niet zichtbaar bij obductie. Bij 1 op de 3 jonge mensen wordt tijdens obductie geen oorzaak gevonden voor het plotseling overlijden.[7,8] Bij personen jonger dan 35 loopt dit aantal op tot wel 48%.[7] Als er geen oorzaak voor het overlijden wordt vastgesteld bij obductie, spreekt men ook wel van het 'sudden arrhythmic death syndrome' (SADS). Bij deze overledenen is er een sterke verdenking op een –waarschijnlijk erfelijke – elektrische hartziekte en wordt cardiogenetische screening van eerstegraads familieleden sterk geadviseerd (zie figuur 1).[5,6]



Figuur 1 | Oorzaken van plotseling overlijden. Deze gegevens zijn gebaseerd op een Deense studie waarin bij 439 plotseling overleden patiënten jonger dan 50 jaar obductie werd uitgevoerd om de doodsoorzaak te achterhalen.7 De omlijnde oorzaken zijn een indicatie voor cardiogenetische screening van familieleden. SADS = 'sudden arrhythmic death syndrome' (geen oorzaak voor het overlijden vastgesteld bij obductie); ACM = aritmogene cardiomyopathie.

Vervolg casus

U spreekt met de familie over de overledene. Uit het gesprek komt naar voren dat patiënt geheel gezond was en geen duidelijke klachten had vóór het overlijden. U herinnert zich dat het vaststellen van een oorzaak in dit geval belangrijke gevolgen kan hebben voor de familieleden en bespreekt de mogelijkheid tot obductie. De familie heeft veel vragen over de noodzaak van obductie en wat er precies gebeurt tijdens een obductie.

Obductie

Praktische zaken

Als er geen duidelijke oorzaak voor het overlijden is bestaat er een reële kans op een erfelijke hartziekte. Om de oorzaak van overlijden te achterhalen wordt obductie sterk aanbevolen.[5,6,9] Het bespreken van obductie met familieleden blijkt in de praktijk lastig door verdriet en onbegrip. Een informatiefolder voor familieleden over obductie kan zorgverleners helpen om familieleden in begrijpelijke taal uit te leggen wat er wel en niet gebeurt tijdens een obductie; er zijn ook websites met informatie (www.umcutrecht.nl/acuutoverlijden).

Naast het emotionele aspect is er ook een financieel aspect. Vanaf het tijdstip van overlijden is er namelijk geen sprake meer van een verzekerde. De kosten voor obductie en transport komen dus voor rekening van de familie. Obductie kost gemiddeld 300 euro, maar wordt in de meeste gevallen niet in rekening gebracht.[10] Het transport van de overledene naar de obductieruimte (kosten gemiddeld 400 euro) komt echter altijd voor rekening van de familie.[10] Dit betekent dat de totale kosten zullen variëren tussen de 400 en 700 euro. Deze financiële drempel kan in de praktijk een bezwaar zijn voor de familie.

Procedure bij kinderen

De procedure voor obductie van minderjarigen verschilt van die voor volwassenen. In het geval van onverwacht en onverklaard overlijden van een minderjarige gaat in principe de NODOK-procedure in (NODOK staat voor 'Nader Onderzoek naar de DoodsOorzaak bij Kinderen').[11] Deze regeling bestaat sinds 2016. De NODOK-procedure draagt bij aan het achterhalen van de doodsoorzaak en het in kaart brengen van de omstandigheden die bijgedragen hebben aan het overlijden. Deze procedure maakt laagdrempelig overleg tussen de forensisch arts en een gespecialiseerde kinderarts van het UMC mogelijk. Als de ouders toestemming geven, wordt er obductie en DNA-diagnostiek uitgevoerd om de doodsoorzaak te achterhalen. Gegevens over het kind, toegepaste onderzoeken en uitslagen worden opgeslagen in een landelijke database. Volgens een evaluatierapport was er na de NODOK-procedure in 34% van de gevallen een indicatie voor genetische counseling van familieleden van het overleden kind.[12] De NODOK-procedure lijkt dus een bijdrage te leveren aan het opsporen van genetische aandoeningen.

Procedure bij jongvolwassenen

In het geval van onverwacht en onverklaard overlijden van een jongvolwassene bestaat zo'n protocol echter niet. In Nederland wordt alleen een gerechtelijke obductie uitgevoerd als de schouwend arts een niet-natuurlijke dood niet kan uitsluiten. Een klinische obductie moet geïnitieerd en besproken worden door de schouwend arts, bijvoorbeeld de huisarts. Dit betekent dat deze arts op de hoogte moet zijn van deze mogelijkheid, hoe dit in zijn werk gaat en wat de voor- en nadelen voor de familie zijn.

In bepaalde landen, bijvoorbeeld Denemarken, is een gerechtelijke obductie inclusief toxicologische screening verplicht in alle gevallen van plotseling onverklaard overlijden waarbij de doodsoorzaak niet vastgesteld kan worden tijdens de lijkschouw. Dit resulteert in een hoog percentage obducties bij jonge mensen die plotseling overlijden, namelijk wel 75%.[13]

Opbrengst van de obductie

Een grote Nederlandse studie laat zien dat obductie bij slechts 43% van de plotseling overleden personen onder de 45 jaar wordt verricht. Bij mensen zonder relevante voorgeschiedenis ligt het percentage obducties iets hoger, namelijk op een bescheiden 60%, terwijl er volgens sommige publicaties na obductie vaak – bij wel 64% van de plotseling overleden personen – reden is om een erfelijke hartziekte te vermoeden.[7,14] Obductie wordt dus maar relatief weinig uitgevoerd ondanks het grote belang ervan.

Interventies uit een grote Nederlandse studie, zoals het opzetten van een 24/7-informatielijn, een website en extra onderwijs aan huisartsen, hadden geen effect op het percentage obducties.[14] Meerdere factoren spelen een rol, waaronder eerder genoemde financiële en logistieke problemen. Tevens blijken sommige huisartsen niet overtuigd van de diagnostische waarde van een obductie.[14] De huidige Nederlandse richtlijnen bieden weinig ondersteuning op dit gebied.[15,16] Een duidelijk stappenplan voor behandelend artsen bij onverwacht overlijden van jongvolwassen is noodzakelijk; figuur 2 toont een stroomdiagram dat artsen informeert over de mogelijkheden voor diagnostiek en verwijzing naar de juiste informatiebronnen in de desbetreffende regio.

Vervolg casus

De familie heeft persoonlijke bezwaren tegen obductie en besluit hier toch vanaf te zien. In dit gesprek haalt u aan dat er ook nog optie is tot het afnemen van materiaal voor DNA-onderzoek. U heeft dit zelf nooit eerder meegemaakt en gaat online op zoek naar informatie.

Postmortaal genetisch onderzoek

Praktische zaken

Tegenwoordig bestaat ook de mogelijkheid om na het overlijden genetische diagnostiek uit te voeren. Bij de obductie neemt de patholoog tijdens het onderzoek wat DNA-materiaal af. Als er geen toestemming voor obductie wordt verkregen, kan buiten het ziekenhuis alsnog DNA veilig gesteld worden met een huidbiopt. Hier zijn alleen een biopteur of mesje, pincet, schaar, alcohol en een steriel potje voor nodig. Het huidbiopt wordt vervolgens kosteloos door een koerier opgehaald. Als de behandeling van een persoon met een hartstilstand binnen het ziekenhuis wordt gestaakt, is het van belang om bloed af te nemen voor DNA-isolatie. Het DNA-materiaal wordt kosteloos opgeslagen bij de afdeling Genetica en onderzocht zodra het eerste familielid zich meldt voor screening.

Opbrengst

Wanneer na de obductie verdenking op een erfelijke hartziekte is gerezen, kan de patholoog adviseren om de familieleden te verwijzen voor cardiogenetische screening.[9] Als er geen obductie is gedaan maar wel DNA-materiaal is opgeslagen, kan de huisarts familieleden doorverwijzen. Postmortaal genetisch onderzoek bij een jong overledene geeft een bescheiden opbrengst aan opgespoorde erfelijke hartziekten van ongeveer 13-32%.[17,18] In combinatie met cardiogenetische screening van familieleden kan de diagnostische opbrengst echter oplopen tot ongeveer 40-50%.[18] De interpretatie van genetische varianten is vaak moeilijk als er geen obductie heeft plaatsgevonden en het fenotype dus onbekend is. Het afnemen van DNA is dus géén goede vervanging voor obductie, maar kan in sommige gevallen wel bijdragen aan het stellen van een diagnose bij familieleden.

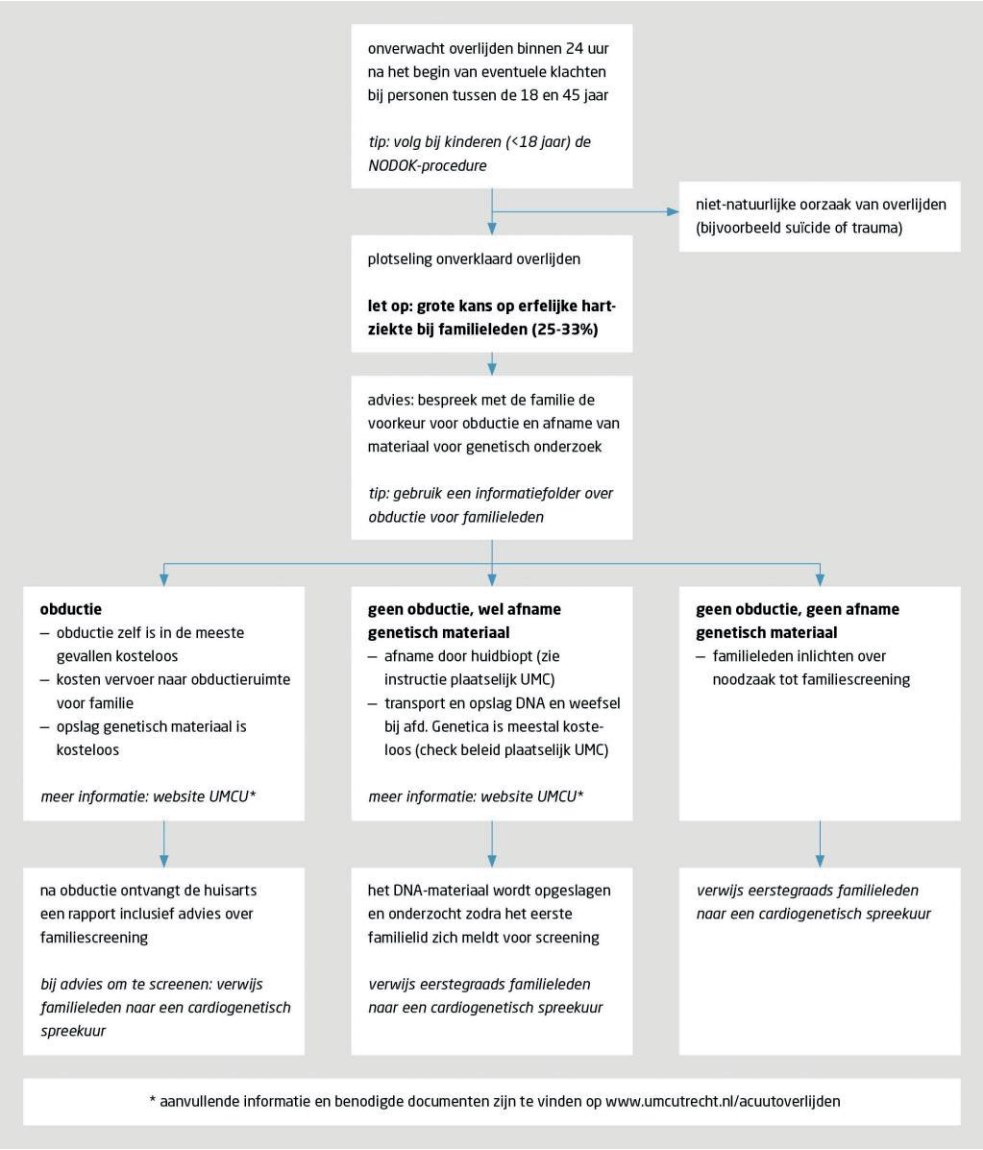
Vervolg casus

Een jaar na het overlijden meldt de zus van het slachtoffer zich in uw praktijk. Zij heeft een kinderwens en maakt zich nu na het overlijden van haar broer zorgen dat er iets in de familie voorkomt waardoor zij of haar toekomstige kinderen mogelijk ook risico lopen. Ze vraagt uw advies.

Cardiogenetische screening familieleden

Praktische zaken

In de meeste gevallen van plotseling overlijden is klinische screening van familieleden geïndiceerd (zie figuur 2). De uitgebreidheid van deze screening is afhankelijk van de bevindingen bij de overledene. Als bij de overledene geen obductie werd verricht en ook geen DNA-materiaal werd afgenomen, wordt cardiologische – en eventueel genetische – screening van familieleden alsnog geadviseerd.



Figuur 2 | Stappenplan voor behandelend artsen bij onverwacht plotseling overlijden.

Klinische screening van eerstegraadsfamilieleden kan het beste plaatsvinden volgens een standaardaanpak in een cardiogenetische kliniek.[19] Deze spreekuren vinden plaats in academische ziekenhuizen; daarbij wordt gebruikgemaakt van een multidisciplinaire aanpak.[6,20] Het onderzoek bestaat minimaal uit een uitgebreide familieanamnese, lichamelijk onderzoek, ecg, echografie en een inspanningstest. Wanneer er een verdenking is op een specifieke hartziekte kan verder aanvullend onderzoek gedaan worden. Alle bevindingen worden uiteindelijk gebruikt om gericht genetisch onderzoek te verrichten bij familieleden en – als er DNA-materiaal beschikbaar is – van de overledene.

Opbrengst

De opbrengst van cardiogenetische screening bij familieleden van plotseling overleden jonge mensen is hoog. Bij 33% van de plotseling overleden personen bij wie obductie geen duidelijke oorzaak aan het licht brengt, wordt een erfelijke hartziekte in de familie gevonden.[21] De opbrengst is het hoogste als er eerst obductie en DNA-onderzoek gedaan wordt, maar ook met alleen screening van familieleden kunnen veel erfelijke hartziekten opgespoord worden. In Nederland echter bedraagt het percentage familieleden dat zich laat onderzoeken naar aanleiding van het plotseling overlijden van een jong familielid momenteel slechts 14%.[14] Mogelijke barrières voor verwijzing zijn ontbrekende of incomplete adviezen voor screening van de patholoog, lastig te traceren familieleden en onvoldoende expertise van lokale cardiologen, waardoor sommige erfelijke hartziektes mogelijk gemist worden.

Het belang van vroegtijdige opsporing

Het opsporen van familieleden met een erfelijke hartziekte is van groot belang. In sommige gevallen kan medicamenteuze behandeling of een implanteerbare defibrillator plotseling overlijden voorkomen. Mensen met het lange-QT-syndroom kunnen lang asymptomatisch blijven, maar hebben wel een verhoogd risico op plotseling overlijden door ritmestoornissen. Behandeling met bètablokkers bij deze patiënten wordt sterk aanbevolen, omdat dat de kans op ritmestoornissen verlaagd.[22]

Ook patiënten met een hypertrofische cardiomyopathie hebben een verhoogd risico op hartritmestoornissen, maar zijn vaak asymptomatisch.[23,24] Het opsporen en onderzoeken van deze patiënten is belangrijk. Een ernstig verdikte hartspier, ventriculaire tachycardieën bij een holteronderzoek en een positieve familieanamnese voor plotseling overlijden zijn belangrijke risicofactoren voor ritmestoornissen. Patiënten met meerdere risicofactoren hebben een reële kans op plotseling overlijden door ritmestoornissen.[24] Plotseling overlijden kan bij deze patiënten voorkomen worden door een implanteerbare defibrillator.

Toekomstmuziek

Er lijkt een hoop verbetering mogelijk. Nieuwe richtlijnen en procedures voor diagnostiek na plotseling overlijden voor volwassenen – in het bijzonder jongvolwassenen – zijn van groot belang. Een recent rapport van de 'Taskforce lijkschouw en gerechtelijke sectie' benadrukte dat het uitvoeren van obductie bij overlijden op jonge leeftijd zinvol is.[25] Volgens hen geldt: 'ja, tenzij op grond van de omstandigheden van obductie kan worden afgezien'.

De huidige inrichting van het wettelijk systeem en de financiële last voor familieleden is echter een probleem en verandering van dit systeem lijkt noodzakelijk. Daarnaast ontbreekt een laagdrempelig instrument om behandelend artsen snel te voorzien van de benodigde informatie.[25] Een duidelijk stappenplan met eenvoudige toegang tot de benodigde documenten is ons inziens essentieel (zie figuur 2). Gezien de huidige technologische vooruitgang in de zorg kan bijvoorbeeld een elektronische applicatie (app) een goede optie zijn.

Conclusie

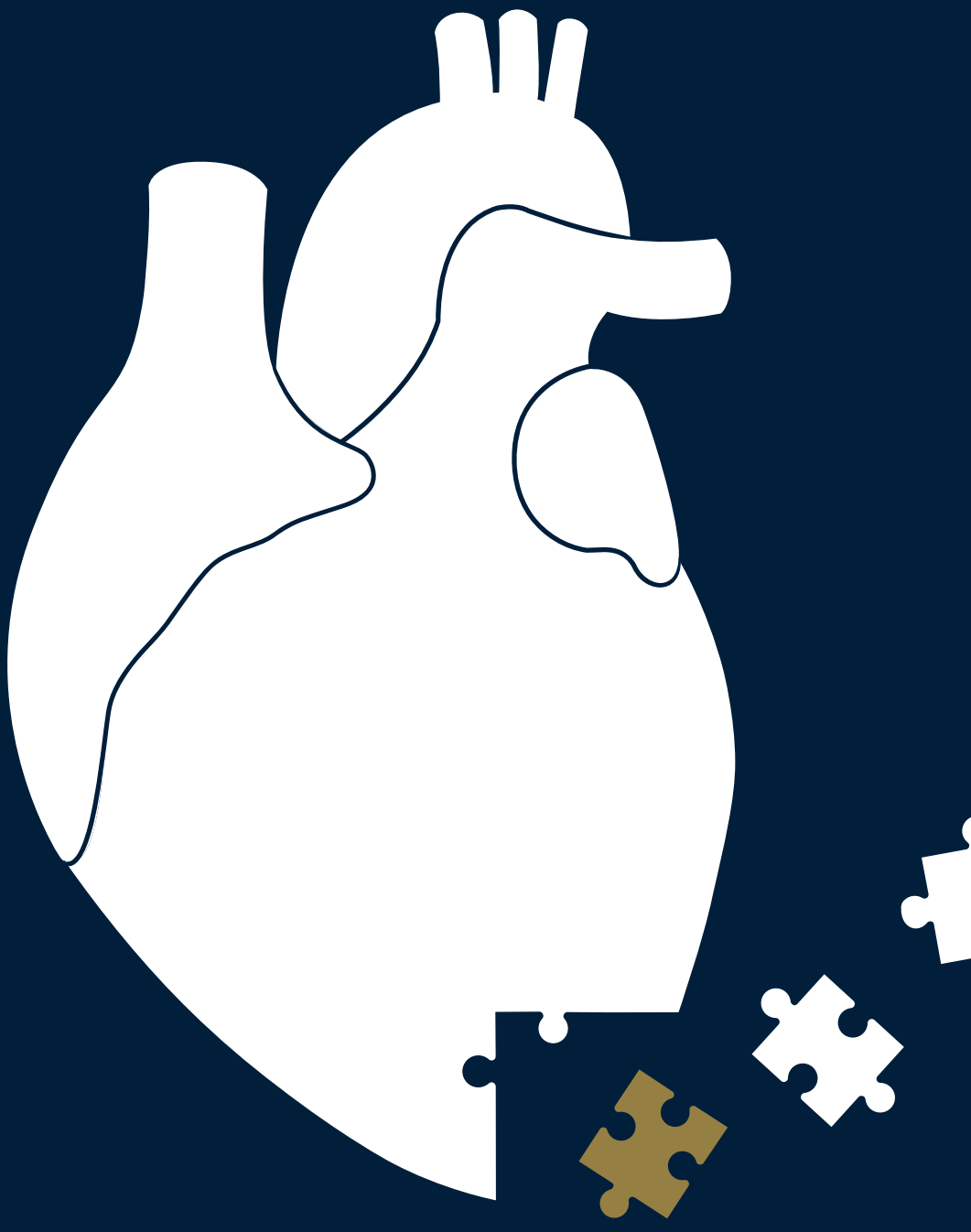
Wanneer een jong persoon plotseling overlijdt bestaat er een reële kans dat een erfelijke hartziekte de oorzaak was. De kans om een oorzaak te vinden is het grootst wanneer er uitgebreid onderzoek wordt gedaan bij zowel de overledene als de familieleden. Diagnostiek na plotseling overlijden bij kinderen is duidelijk vastgelegd in de NODOK-procedure, maar voor plotseling overleden volwassenen ontbreekt vooralsnog een duidelijke werkwijze.

Obductie en DNA-onderzoek zijn bij zowel kinderen als volwassenen in het geval van plotseling overlijden van groot belang om de doodsoorzaak op te sporen. Nieuwe richtlijnen en procedures voor diagnostiek na plotseling overlijden van volwassenen zijn noodzakelijk om artsen te voorzien van de benodigde informatie. Door erfelijke hartziekten vroegtijdig op te sporen kan plotseling overlijden van familieleden namelijk voorkómen worden.

Literatuur

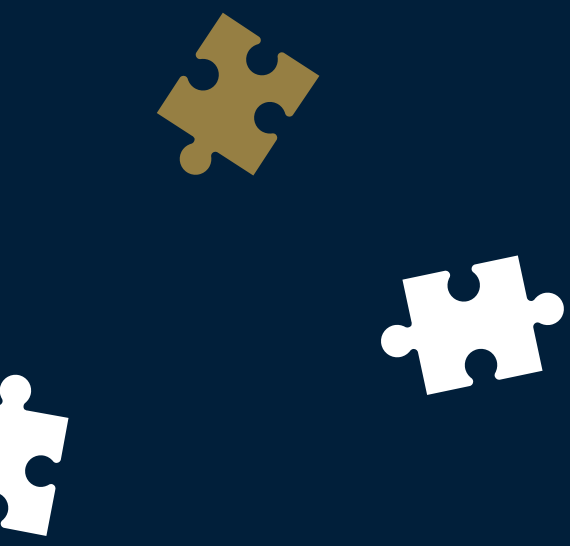
1. De Vreede-Swagemakers JJM, Gorgels APM, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol. 1997;30:1500-5.
2. Wellens HJJ, Schwartz PJ, Lindemans FW, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J. 2014;35:1642-51.
3. Reanimatie in Nederland, 2016. Den Haag: Hartstichting; oktober 2016.
4. Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation. 1998;98:2334-51.
5. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary. Heart Rhythm. 2018;15:e190-e252.
6. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36:2793-867.
7. Risgaard B, Winkel BG, Jabbari R, et al. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. Circ Arrhythm Electrophysiol. 2014;7:205-11.
8. Eckart RE, Shry EA, Burke AP, et al; Department of Defense Cardiovascular Death Registry Group. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol. 2011;58:1254-61.
9. Basso C, Aguilera B, Banner J, et al; Association for European Cardiovascular Pathology. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017;471:691-705.
10. Van Zwieten J. Sparen voor de obductie. Medisch Contact. 2006;61:1418-9.
11. Handelingsprotocol "Nader Onderzoek naar de DoodsOorzaak bij Kinderen" (NODOK). Versie 1.0. Utrecht: Nederlandse Vereniging voor Kindergeneeskunde; 2015.
12. Van de Putte EM, Rudolph MW. Evaluatierapport NODOK-procedure ten behoeve van het Ministerie van Volksgezondheid, Welzijn en Sport. Nader Onderzoek naar de DoodsOorzaak bij Kinderen. Utrecht: Universitair Medisch Centrum Utrecht; 2018.
13. Winkel BG, Holst AG, Theilade J, et al. Nationwide study of sudden cardiac death in persons aged 1-35 years. Eur Heart J. 2011;32:983-90.
14. Van der Werf C, Hendrix A, Birnie E, et al. Improving usual care after sudden death in the young with focus on inherited cardiac diseases (the CAREFUL study): a community-based intervention study. Europace. 2016;18:592-601.
15. Richtlijn Lijkschouw voor behandelend artsen. Utrecht: Nederlands Huisartsen Genootschap; juni 2016.
16. Richtlijn Forensische Geneeskunde Lijkschouw. Forensisch Medisch Genootschap; april 2016.
17. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. J Am Coll Cardiol. 2017;69:2134-45.
18. Kumar S, Peters S, Thompson T, et al. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. Heart Rhythm. 2013;10:1653-60.
19. Ackerman MJ, Priori SG, Willems S, et al. Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace. 2011;13:1077-109.
20. Semsarian C, Ingles J, Wilde AAM. Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives. Eur Heart J. 2015;36:1290-6.

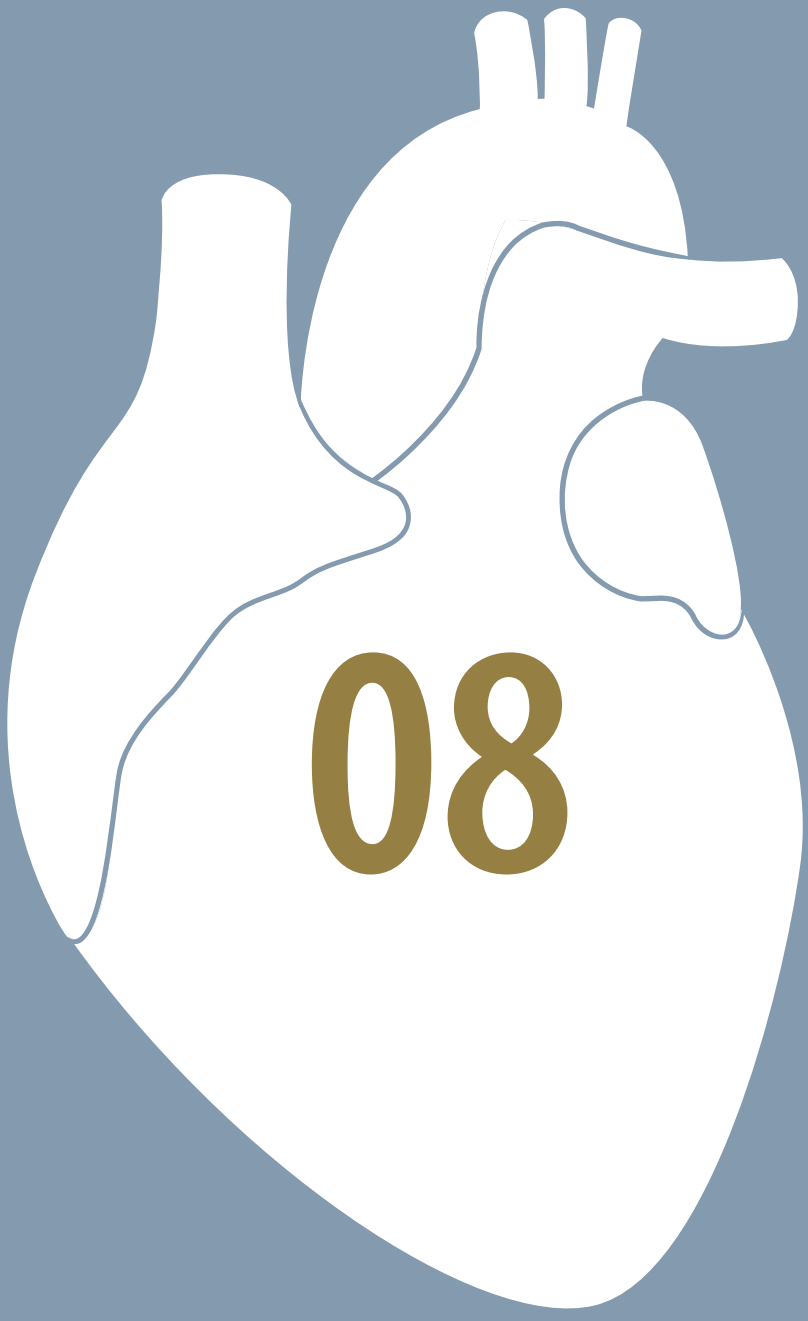
21. Van der Werf C, Hofman N, Tan HL, et al. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in The Netherlands. Heart Rhythm. 2010;7:1383-9.
22. Priori SG, Wilde AA, Horie M, et al; Document Reviewers; Heart Rhythm Society; European Heart Rhythm Association; Asia Pacific Heart Rhythm Society. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. 2013;15:1389-406.
23. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation. 2006;114:2232-9.
24. Elliott PM, Anastasakis A, Borger MA, et al; Authors/Task Force members. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35:2733-79.
25. De dood als startpunt: een onderzoek naar de keten van lijkschouw en gerechtelijke sectie. Taskforce lijkschouw en gerechtelijke sectie; 2018.



PART IV

Discussion and Summary




08

Discussion

Idiopathic ventricular fibrillation (IVF) is diagnosed in sudden cardiac arrest survivors in whom known etiologies have been excluded. In other words, the term IVF reflects our current inability to identify a causal relationship between the clinical circumstance and the arrhythmia.[1,2] Some diseases of which we now know their ability to cause VF were previously considered idiopathic as well.[3] With improving knowledge and increased sophistication of diagnostic tools, the prevalence of IVF has decreased over the past decades.[3,4] However, despite our efforts, some patients remain idiopathic to date. In these patients there is a need for new diagnostic possibilities to search for an underlying cause for the event. After all, absence of evidence is not evidence of absence.

In this chapter, we discuss how future studies should progress with 1) the uncertainties of diagnosing IVF, 2) further attempts to classify subforms of IVF and 3) prevention of sudden cardiac death.

Challenges of the IVF diagnosis

As the IVF diagnosis fully depends on the absence of a demonstrable substrate for VF, systematic diagnostic assessment is essential. Over the past years, several attempts have been made to standardize the minimal diagnostic tests required to diagnose IVF.[3,5–7] A recent systematic review showed that the yield of comprehensive diagnostic testing in unexplained cardiac arrest (UCA) is consistently high.[8] Especially cardiac magnetic resonance imaging (CMR), exercise testing and sodium channel blocker provocation (SCBP) showed to be of importance in the diagnostic work-up as they have a relatively high diagnostic yield of respectively 10%, 9% and 8%.[6,8–11] Holter monitoring, electrophysiology study (EPS) and epinephrine challenge appear to have either a low diagnostic yield (<5%) or a high false-positive rate and their diagnostic value is therefore under debate. Genetic testing proved to be of value in UCA victims, however, there are conflicting results on its value in IVF when the patient is comprehensively assessed.[12,13] Despite the importance of diagnostic testing, previous studies showed that the diagnostic work-up in IVF in general is heterogeneous and incomplete.[9,14–17] The exact reasons behind and the effect of this incomplete adherence to the diagnostic work-up remain unknown.

In **Chapter 2**, we studied the diagnostic characteristics of 423 patients from the Dutch national IVF registry. In total, 38 of 423 patients (9%) initially diagnosed with IVF obtained an alternative diagnosis during follow-up. Although adherence to (near-)complete diagnostic testing in IVF patients increased over the years, patients with IVF still undergo varying degrees of diagnostic evaluation. An important clinical finding was that a low amount (zero or one) of "high yield" diagnostic tests performed during work-up was an independent predictor of an alternative diagnosis during follow-up (HR 2.55, 95% CI: 1.30-5.03, p=0.007). Our results confirm the importance of systematic testing and especially the use of CMR, exercise testing and SCB in the diagnostic work-up of IVF. Based on these results and current literature results, we advocate that a minimal diagnostic evaluation should comprise of a 12-lead electrocardiogram,

laboratory testing, echocardiography, coronary angiography (or computed tomography angiography), CMR, exercise testing, SCBP and targeted genetic testing based on the clinical phenotype.[3,7,8,13,18,19] International guidelines should promote a standardized and systematic diagnostic approach for IVF patients, but this is not yet adopted by most societies or consensus groups. Interestingly, patients with a concealed underlying disease who erroneously received the IVF diagnosis also appeared to have a worse prognosis in terms of survival in our cohort. One could argue that if IVF patients had benefit from targeted lifestyle interventions (such as avoiding excessive sports in arrhythmogenic cardiomyopathy[20]) or earlier initiation of treatment, this might affect their prognosis.

Challenges in treatment options

Without an identifiable cause for VF, treatment options are limited. Class IA drugs and ablation therapy have shown benefit in some subgroups of IVF patients.[21,22] Yet, most patients do not receive any targeted treatment despite ICD implantation. Even though ICD implantation is effective in terminating ventricular tachyarrhythmias, it is also associated with risk of conscious shocks and complications.[17] It is therefore of utmost importance to perform subclassification of IVF patients to provide targeted management options. An interesting IVF subset are patients with short-coupled ventricular fibrillation (SCVF).[23,24] In these patients, ventricular arrhythmias are elicited by short-coupled premature ventricular complexes (PVCs).[24–26] In a recent study, a SCVF prevalence of 6.6% was reported in a cohort of IVF patients. The authors concluded that SCVF is a malignant phenotype with a higher recurrence rate than in IVF. Treatment with quinidine showed to be effective, also in earlier reports.[27,28] It is, however, important to bear in mind that the SCVF-diagnosis is fully dependent on documentation of the initiating PVC. For this reason, a major limitation of the proposed definition for SCVF is the arbitrary and circular-thinking nature of the description. SCVF can only be diagnosed in patients with arrhythmia recurrences as the initiation of VF during the index event is typically not documented, potentially introducing bias towards a more malignant phenotype.

On the quest to further unravel SCVF, we studied the prevalence and phenotype of SCVF in our Dutch cohort of IVF patients in **Chapter 3**. This is particularly interesting in our cohort, as a hereditary subset of IVF patients exists in the Netherlands, called the chromosome 7q36 risk haplotype, harbouring the dipeptidyl peptidase like 6 (DPP6) gene.[29,30] These patients have a high risk for SCVF and current evidence indicates that quinidine is effective.[17,30] We found a SCVF prevalence in our Dutch IVF cohort of 14%.[31] In this cohort, 57/228 (25%) IVF patients experienced VF recurrence. In 34/57 (60%) of these patients, the initiation of VF was documented. Strikingly, in 31/34 (91%) patients of which the VF-onset was documented, the arrhythmia was triggered by a short-coupled PVC. One could argue that if the vast majority (91%) of documented VF-recurrences have short-coupled initiations, SCVF might not be a 'subtype' of IVF but rather the common phenotype in true IVF. As SCVF reacts well to treatment with quinidine, this is an important finding and might create a new and effective treatment option for a significant part of the IVF patients. Interestingly, patients with the DPP6 haplotype

seem to be treated with quinidine more frequently than other SCVF patients. This is shown by a prevalence of 93% of DPP6 positive SCVF patients treated with quinidine compared to 31% without the DPP6 risk haplotype. This is interesting since our research indicates that quinidine is effective for the prevention of arrhythmia recurrence in SCVF patients with and without the DPP6 risk haplotype.[31] It is crucial that all recurrences in IVF patients are documented and stored to assess the coupling interval of the initiating PVC. Without documentation, the diagnosis SCVF cannot be made and patients are withheld from possible treatment with quinidine. Future research should focus on the incidence, underlying mechanisms and heritability of SCVF. In addition, prospective studies are needed to evaluate the effectivity of quinidine in patients with SCVF.[32]

The quest for an arrhythmogenic substrate

To make progress in diagnostic testing, it is important to reflect on possible mechanisms for VF that cannot be detected with conventional diagnostic tools. Imaging modalities such as echocardiography and CMR play an important role in the standard diagnostic work-up for IVF patients. However, by definition, IVF is characterized by a lack of overt structural and functional abnormalities detected by these conventional imaging methods. If we simplify this, we currently cannot provide any evidence of underlying abnormalities. The question is, does this mean that there are no abnormalities, or are we simply unable to identify them (yet)?

Important factors in IVF include premature triggers (mostly from the Purkinje system), microstructural alterations and heterogeneity in repolarization.[33,34] Non-invasive mapping data showed that co-occurrence of these different factors determines the inducibility of an arrhythmia.[34] Although short-coupled triggers occur frequently in IVF[23,31], these alone might not have the ability to induce an arrhythmia. However, early triggers combined with structural abnormalities or repolarization abnormalities might create the optimal condition to promote VF. Previous research showed that repolarization abnormalities are indeed more prevalent in IVF patients than in controls.[34] In addition, endocardial and epicardial mapping data showed that most IVF patients have localized electrical alterations.[35] Prior experimental studies have shown that small ventricular lesions can promote VF inducibility.[36,37] Endo-epicardial mapping in IVF patients revealed that the pathology, in most cases, only involved a part of the ventricular wall rather than being transmural and only covered a limited surface area.[35] This might explain why these small structural alterations cannot be perceived by conventional imaging techniques. Implicating the need for new techniques that are able to detect subtle myocardial changes.

The field of structural and functional cardiac imaging is continuously advancing. New promising techniques to detect or visualize subtle myocardial changes are currently in development, such as 3D CMR and dark-blood late gadolinium enhancement (LGE) CMR. Dark-blood LGE provides a superior visualization and quantification of ischemic scar due to a higher scar-to-blood contrast.[38] Another promising technique is echocardiographic deformation

imaging. This technique provides unique information on regional and global myocardial mechanical function.[39] For example, right-ventricular deformation imaging has shown to enable detection of an early electromechanical substrate in patients with arrhythmogenic cardiomyopathy (ACM) and proved of prognostic value in relatives, who were in a subclinical stage of disease.[40,41] Cases of IVF patients diagnosed with ACM during follow-up have been reported.[42] But also in primary arrhythmia syndromes such as Brugada syndrome and long-QT syndrome, deformation imaging revealed abnormal myocardial contraction patterns. [43,44] In **chapter 4** we studied echocardiographic deformation characteristics in IVF patients. We found both global and regional echocardiographic deformation abnormalities in patients with IVF.[45] IVF patients showed more global deformation abnormalities as indicated by lower mean LV global longitudinal strain, and higher LV mechanical dispersion. In addition, IVF patients showed more regional LV post-systolic shortening as compared to healthy controls (50% vs. 11%, $p<0.001$). Abnormal RV deformation patterns were observed in 16% of IVF patients and in none of the control subjects ($p<0.001$). One could argue that global deformation abnormalities might be explained by cardiac ischemia caused by global hypoperfusion during the circulatory arrest, but this is less likely for regional deformation abnormalities. Our study therefore confirms that localized myocardial disease is present in a subset of IVF patients. It remains, however, unclear which etiology lays behind these alternations.

Both electrical mapping and deformation imaging results provide us with evidence for the existence of (small) myocardial alterations in patients with IVF. One could say that current diagnostic modalities are unable to reveal these abnormalities. But could it be possible that we are simply not paying attention to some important information that is already there? Already decades ago, mitral valve disease has been associated with ventricular arrhythmias and sudden cardiac arrest (SCA) in young patients. [46–53] Especially mitral valve prolapse (MVP) has been shown to be closely related to SCA and ventricular arrhythmias. However, recent studies suggest that there is also an association between mitral annulus disjunction (MAD) and ventricular arrhythmias, independently of MVP. [49–51] MAD is defined as an abnormal atrial displacement of the mitral valve leaflet hingepoint, away from the ventricular myocardium. The exact mechanisms of MAD are unknown, but is has been hypothesized that hypermobility of the mitral valve causes mechanical stretch on the myocardial wall.[54] This may result in myocyte hypertrophy and fibrosis, creating a potential substrate for VF.[50,54] Previous studies have reported a high prevalence of MVP in patients with aborted cardiac arrest of unexplained etiology[50], but until now no specific attention has been given to the presence of MAD in IVF patients.

In **chapter 5**, we described the prevalence and morphology of MAD and MVP on CMR in a multicenter cohort of IVF patients compared to matched controls. We found that inferolateral MAD and MVP were significantly more prevalent in IVF patients compared to healthy controls. Subjects with MAD in the inferolateral wall also showed a high prevalence of other mitral valve disease and ventricular ectopy. Our findings suggest that mitral valve disease may still contribute as proarrhythmic factor in a subset of IVF patients. However, there are some major

knowledge gaps that require further research. First, the cut-off value to determine the presence of MAD on CMR is a point of discussion, as general consensus is lacking. In addition, longitudinal distances measured by different modalities such as echocardiography and CMR cannot be used interchangeably, as shown by differences in measured distances by the two modalities in a previous study.[49] Future prospective studies are needed to study the prevalence, morphology and prognosis of MAD and its relation to arrhythmogenesis. We believe that MAD deserves special attention in the extensive diagnostic work-up of IVF.

Management of family members of SCA victims

Heritability plays an important role in SCD.[1,55,56] In one-third of the families with a SCD victim, evidence is found of an inherited cardiac disease.[56,57] However, the benefit of family screening in patients with IVF was unknown. In **chapter 6**, we studied the yield of familial cascade screening in IVF.[58] Interestingly, we found that the yield of family screening to detect an inherited arrhythmia syndrome in relatives of IVF patients was only 3%. These findings are in contrast to the evidence currently available on family screening in unexplained cardiac arrest victims, where higher yields were reported.[56,59] We believe that this is the result of strict inclusion criteria for our study, focusing exclusively on the IVF victims among those with SCA. IVF patients were only eligible for inclusion after comprehensive clinical assessment including a 12-lead ECG, cardiac imaging with echocardiogram or magnetic resonance imaging, coronary artery imaging, exercise testing and SCBP. This means that most known heritable cardiac diseases were probably excluded in the proband. Our study showed that the yield of family screening is low when the proband is comprehensively investigated and deemed to have IVF. Which again underlines that comprehensive diagnostic evaluation of the cardiac arrest victim should be the priority to ensure exclusion of well-established genetic causes.

When we looked into the family members who did obtain a cardiac diagnosis due to family screening, we observed something interesting. In three family members, Brugada syndrome was diagnosed following a positive SCBP test. However, both SCBP and genetic testing were negative in the proband of all three family members. In one of three family members, the diagnosis was made after infusion of flecainide for treatment of atrial fibrillation, and coincidentally a type-1 Brugada pattern was observed. The interpretation of these positive tests are challenging, mainly because there are serious concerns about the specificity of the SCBP test.[11,60] Moreover, evidence suggests that Brugada syndrome is not caused by a single mutation but has a complex genetic background.[61] It is thus unclear whether these positive tests were false-positive or might have been the result of some shared genetic predisposition for ventricular arrhythmias or Brugada Syndrome. As the significance of a positive SCBP test in these patients is uncertain[62], we advise against SCBP testing in asymptomatic family members of IVF patients. Given the overall low yield of family screening in our study, the justification of routine family screening is weak and should be re-evaluated in current guidelines.

While the benefit of family screening in IVF seems to be low, the benefit of family screening in SCD victims has proven to be high.[56] Especially when the cause for the arrest remains unknown after autopsy, there is a high chance of approximately 33% on a heritable cardiac disease.[63] Although both autopsy and family screening are strongly recommended in SCD patients[18], the adherence to this advice in the Netherlands is low.[64] This is a major problem as it puts family members of SCD victims at an unanticipated risk for SCA or SCD. To provide more attention to this important subject, we looked into the current challenges in **chapter 7**. With regard to the low autopsy rates in young SCD victims in the Netherlands, we observed multiple problems. In contrast to some other countries, such as Denmark, autopsy is not mandated in young SCD victims in the Netherlands.[65] This indicates an important role for the general practitioner, who has to propose and explain the importance of autopsy. In clinical practice, many problems seem to be encountered, such as a lack of knowledge and logistical problems arranging the autopsy.[64] Moreover, both family members and caregivers seem to be unaware of the importance of referring family members to specialized cardiogenetic clinics. In addition, the costs of transporting the corpse to the coroner's office must be paid by the family, which can also be a problem in some families. The combination of these issues may explain the low autopsy rate of 43% with an even lower rate of 8% of family members attending family screening.[64]

To provide Dutch general practitioners with more information and guidance for the management of a young SCD victim, we created a roadmap. This roadmap emphasizes the importance of autopsy and family screening and provides specific information on the logistical steps that need to be taken. In addition, we created a website (www.umcutrecht.nl/acuutoverlijden) where all necessary forms and contact addresses can be found. Although we think that our roadmap can help guide physicians, we believe that political steps have to be made to ensure higher autopsy rates in the Netherlands. A recent report of the Dutch Taskforce for autopsy concluded that autopsy should always be performed in young SCD victims.[66] This may only be achieved when autopsy is mandatory in all young SCD victims without an evident cause for the arrest. After the autopsy, family screening should be offered to all first-degree family members when an inherited disease is suspected or cannot be excluded. A similar procedure is currently already in place in case of SCD in children. First results of this procedure have been positive, as it seems to be effective in determining the cause of death and encourage family screening when appropriate.[67]

Future directions

The exact mechanisms behind IVF partly remain to be elucidated, but are likely multifactorial. Over the years, several attempts have been made to standardize the diagnostic work-up of IVF patients. Although the importance of systematic diagnostic assessment is increasingly recognized, the adherence remains low. This is problematic, as this creates overuse of the IVF diagnosis which makes the absence of disease less certain. Future guidelines should focus on promoting systematic diagnostic assessment and agree on a minimum of diagnostic tests that

need to be performed before diagnosing IVF.[8,18] In addition, follow-up should be performed regularly and must include systematic documentation of arrhythmia recurrences as it might allow for targeted drug therapy.[19,21,23,31] Ultimately, the goal will be to standardize the diagnostic work-up and follow-up for all patients, regardless of their hospital or country of origin.

Over the years, both clinical and experimental research have enhanced our insights into possible arrhythmogenic substrates in IVF.[23,31,35,45,58,68] In chapter 3, we showed that in the majority of IVF patients, the arrhythmia was triggered by a short-coupled PVC. The detection of SCVF in IVF patients might allow for targeted drug therapy in a subset of patients. The definition for SCVF, however, is rather arbitrary and requires further scrutiny. Larger studies are needed to determine the appropriate cut-off value for SCVF and the effect of heart rate on the coupling interval. Moreover, a randomized prospective study is needed to assess the effectivity of quinidine in patients with SCVF. In chapter 5, we observed that IVF patients had a higher prevalence of inferolateral MAD and MVP. Yet, the clinical implications and underlying mechanisms of these abnormalities remain largely unknown. An international prospective study is needed to study the underlying mechanisms and prognosis of MAD. Invasive and non-invasive mapping of the mitral valve region could be of added value to provide insight into the arrhythmogenic substrate in patients with MAD, which might allow for targeted treatment in the future. Exploring the clinical implications of newly found abnormalities in IVF patients must be one of the main goals for the future. However, considering the rarity and heterogeneity of the disease this might be a challenging task.[31,45] Collaboration between different hospitals and countries is needed to increase the size and reduce diversity of IVF cohorts. This will strengthen the power to determine the clinical impact of newly-found abnormalities.

Discovering new clues for an arrhythmogenic substrate in IVF continues to be a priority. Future research into IVF should be driven by the advancement in resolution and accuracy of invasive and non-invasive imaging techniques, progress in genetic testing and new possibilities of artificial intelligence in the medical field. Over the last years, non-invasive electrocardiographic imaging (ECGi) has increasingly been used to noninvasively map electrical activation and repolarization. Although recent research indicates that ECGi can detect steep repolarization gradients in IVF patients, there are concerns about its accuracy, reproducibility and practicality.[34,69] Future research should focus on the robustness and applicability of ECGi in the detection of repolarization abnormalities. In addition, these results should be confirmed by endo and epicardial invasive mapping. The utility of genetic testing in comprehensively investigated IVF patients is still a matter of debate. The method and extend of genetic testing is heterogeneous and depends on local guidelines and advancing insights into pathogenic genes and variants. Genome-wide association studies showed their ability to identify new genetic variants and their application could provide new insights into disease causing variants in IVF. A better understanding of the genetic predisposition to IVF allows for targeted treatment and better risk assessment in family members. At last, the rapid advancement of artificial intelligence in the medical field is promising. Recently, artificial intelligence showed

to facilitate the detection of novel features on the 12-lead ECG.[70] Application of artificial intelligence algorithms in IVF might enable the detection of previously unknown electrocardiographic abnormalities. These improvements can accelerate further subclassification of IVF patients, which may enable personalized risk stratification and treatment in the future.

Concluding remarks

IVF is a complex and heterogeneous disease in which a clear arrhythmogenic substrate is lacking. Diagnostic testing is the cornerstone of management to exclude known possible causes for the arrest. Both new and old diagnostic tools can provide improved knowledge of the arrhythmogenic substrate. Further subclassification of patients with IVF is of utter importance to provide targeted treatment strategies in the future.

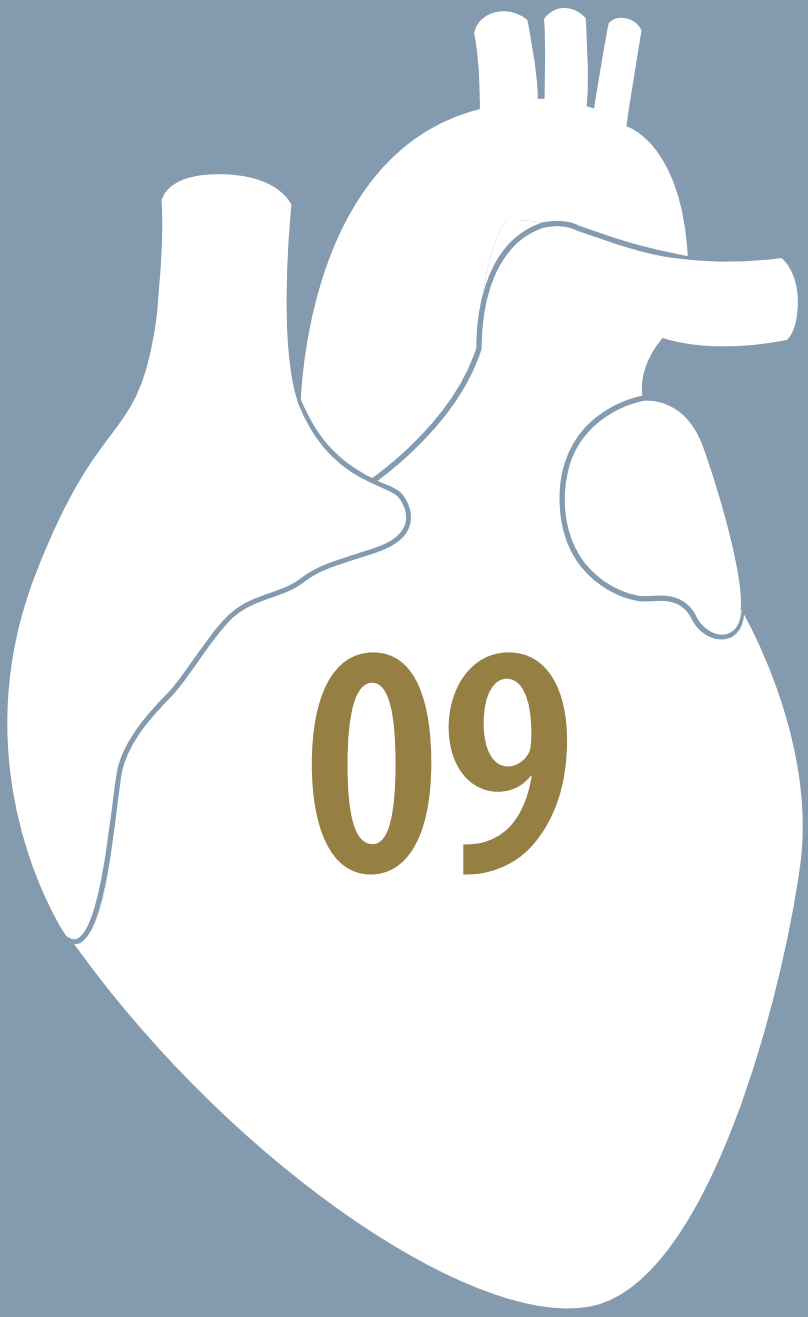
References

1. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* 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(12):1932–63.
2. Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. Survivors of Out-of-Hospital Cardiac Arrest With Apparently Normal Heart. *Circulation*. 1997;95(1):265–72.
3. Visser M, Heijden JF Van Der, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic Ventricular Fibrillation: The Struggle for Definition, Diagnosis, and Follow-Up. *Circ Arrhythmia Electrophysiol*. 2016;9(5):1–11.
4. Ree MH Van Der, Postema PG. What's in a name? further classification of patients with apparent idiopathic ventricular fibrillation. *Eur Heart J*. 2021;1–3.
5. Cheung CC, Krahn AD. The importance of a comprehensive evaluation of survivors of cardiac arrest. *Eur Heart J*. 2018;39(21):1988–91.
6. Jiménez-Jáimez J, Peinado R, Grima EZ, Segura F, Moriña P, Sánchez Muñoz JJ, *et al.* Diagnostic Approach to Unexplained Cardiac Arrest (from the FIVI-Gen Study). *Am J Cardiol*. 2015;116(6):894–9.
7. Conte G, Giudicessi JR, Ackerman MJ. Idiopathic ventricular fibrillation: The ongoing quest for diagnostic refinement. *Europace*. 2021;23(1):4–10.
8. Alqarawi W, Dewidar O, Tadros R, Roberts JD, Steinberg C, MacIntyre CJ, *et al.* Defining idiopathic ventricular fibrillation: A systematic review of diagnostic testing yield in apparently unexplained cardiac arrest. *Heart Rhythm*. 2021;18(7):1178–85.
9. Herman ARM, Cheung C, Gerull B, Simpson CS, Birnie DH, Klein GJ, *et al.* Outcome of Apparently Unexplained Cardiac Arrest: Results From Investigation and Follow-Up of the Prospective Cardiac Arrest Survivors With Preserved Ejection Fraction Registry. *Circ Arrhythmia Electrophysiol*. 2016;9(1):e003619.
10. Stępień-Wojno M, Ponińska J, Rydzanicz M, Bilińska M, Truszkowska G, Baranowski R, *et al.* Sudden cardiac arrest in patients without overt heart disease: A limited value of next generation sequencing. *Polish Arch Intern Med*. 2018;128(12):721–30.
11. Tadros R, Nannenberg EA, Lieve K V., Škorić-Milosavljević D, Lahrouchi N, Lekanne Deprez RH, *et al.* Yield and Pitfalls of Ajmaline Testing in the Evaluation of Unexplained Cardiac Arrest and Sudden Unexplained Death: Single-Center Experience With 482 Families. *JACC Clin Electrophysiol*. 2017;3(12):1400–8.
12. Visser M, Dooijes D, Smagt JJ van der, Heijden JF van der, Doevendans PA, Loh P, *et al.* Next-generation sequencing of a large gene panel in patients initially diagnosed with idiopathic ventricular fibrillation. *Heart Rhythm*. 2017;14(7):1035–40.
13. Grondin S, Davies B, Cadrin-Tourigny J, Steinberg C, Cheung CC, Jorda P, *et al.* Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J*. 2022;1–11.
14. Waldmann V, Bougouin W, Karam N, Dumas F, Sharifzadehgan A, Gandjbakhch E, *et al.* Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: Focus on idiopathic ventricular fibrillation. *Eur Heart J*. 2018;39(21):1981–7.
15. Conte G, Belhassen B, Lambiase P, Ciconte G, Asmundis C De, Arbelo E, *et al.* Out-of-hospital cardiac arrest due to idiopathic ventricular fibrillation in patients with normal electrocardiograms: Results from a multicentre long-term registry. *Europace*. 2019;21(11):1670–7.
16. Siebermair J, Sinner MF, Beckmann B-M, Laubender RP, Martens E, Sattler S, *et al.* Early repolarization pattern is the strongest predictor of arrhythmia recurrence in patients with idiopathic ventricular fibrillation: results from a single centre long-term follow-up over 20 years. *Europace*. 2016;18(5):718–25.
17. Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, Berg MP Van Den, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace*. 2019;21(10):1519–26.

18. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, *et al.* 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm*. 2021;18(1):e1–50.
19. Merghani A, Monkhouse C, Kirkby C, Savvatis K, Mohiddin SA, Elliott P, *et al.* Diagnostic impact of repeated expert review & long-term follow-up in determining etiology of idiopathic cardiac arrest. *J Am Heart Assoc*. 2021;10(12):1–10.
20. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2017;136(21):2068–82.
21. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of Electrophysiologic-Guided Therapy with Class IA Antiarrhythmic Drugs on the Long-Term Outcome of Patients with Idiopathic Ventricular Fibrillation with or without the Brugada Syndrome. *J Cardiovasc Electrophysiol*. 1999;10(10):1301–12.
22. Haïssaguerre M, Shoda M, Jaïs P, Nogami A, Shah DC, Kautzner J, *et al.* Mapping and ablation of idiopathic ventricular fibrillation. *Circulation*. 2002;106(8):962–7.
23. Steinberg C, Davies B, Mellor G, Tadros R, Laksman ZW, Roberts JD, *et al.* Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report from the CASPER registry. *Eur Heart J*. 2021;42(29):2827–38.
24. Viskin S, Belhassen B. Idiopathic ventricular fibrillation. *Am Heart J*. 1990;120(3):661–71.
25. Leenhardt A, Glaser E, Burguera M, Nürnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. *Circulation*. 1994;89(1):206–15.
26. Viskin S, Lesh MD, Eldar M, Fish R, Setbon I, Laniado S, *et al.* Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. *J Cardiovasc Electrophysiol*. 1997;8(10):1115–20.
27. Belhassen B, Pelleg A, Miller HI, Laniado S. Serial Electrophysiological Studies in a Young Patient with Recurrent Ventricular Fibrillation. *Pacing Clin Electrophysiol*. 1981;4(1):92–8.
28. Belhassen B, Tovia-Brodie O. Short-Coupled Idiopathic Ventricular Fibrillation - A Literature Review with Extended Follow-up. *JACC Clin Electrophysiol*. 2022;100310.
29. Sande JNT, Postema PG, Boekholdt SM, Tan HL, Heijden JF Van Der, Groot NMS De, *et al.* Detailed characterization of familial idiopathic ventricular fibrillation linked to the DPP6 locus. *Heart Rhythm*. 2016;13(4):905–12.
30. Postema PG, Christiaans I, Hofman N, Alders M, Koopmann TT, Bezzina CR, *et al.* Founder mutations in the Netherlands: Familial idiopathic ventricular fibrillation and DPP6. Netherlands Hear. J. 2011. p. 290–6.
31. Groeneveld SA, Ree MH van der, Mulder BA, Balt J, Wilde AAM, Postema PG, *et al.* Prevalence of Short-Coupled Ventricular Fibrillation in a Large Cohort of Dutch Patients With Idiopathic Ventricular Fibrillation. *Circulation*. 2022;145(18):1437–9.
32. Belhassen B. Quinidine vs. ICD in patients with short-coupled idiopathic ventricular fibrillation: A call for a multicenter randomized trial. *Eur Heart J*. 2021;42(38):3992.
33. Haïssaguerre M, Nademanee W, Hocini M, Duchateau J, André C, Lavergne T, *et al.* The Spectrum of Idiopathic Ventricular Fibrillation and J-Wave Syndromes: Novel Mapping Insights. *Card Electrophysiol Clin*. 2019;11(4):699–709.
34. Cluitmans MJM, Bear LR, Nguyên UC, Rees B Van, Bekke RMA, Mihl C, *et al.* Noninvasive detection of spatiotemporal activation-repolarization interactions that prime idiopathic ventricular fibrillation. *Sci Transl Med*. 2021;9317(In press):1–11.
35. Haïssaguerre M, Hocini M, Cheniti G, Duchateau J, Sacher F, Puyo S, *et al.* Localized Structural Alterations Underlying a Subset of Unexplained Sudden Cardiac Death. *Circ Arrhythmia Electrophysiol*. 2018;11(7):e006120.
36. Janse MJ, Kléber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. *Circ Res*. 1981;49(5):1069–81.
37. Kubota I, Lux RL, Burgess MJ, Abildskov JA. Activation sequence at the onset of arrhythmias induced by localized myocardial warming and programmed premature stimulation in dogs. *J Electrocardiol*. 1988;21(4):345–54.

38. Holtackers RJ, Gommers S, Heckman LIB, Heyning CM Van De, Chiribiri A, Prinzen FW. Histopathological Validation of Dark-Blood Late Gadolinium Enhancement Without Additional Magnetization Preparation. *J Magn Reson Imaging*. 2022;55(1):190–7.
39. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, *et al.* Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(1):1–11.
40. Mast TP, Taha K, Cramer MJ, Lumens J, Heijden JF van der, Bouma BJ, *et al.* The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy. *JACC Cardiovasc Imaging*. 2019;12(3):446–55.
41. Mast TP, Teske AJ, Walmsley J, Heijden JF van der, Es R van, Prinzen FW, *et al.* Right Ventricular Imaging and Computer Simulation for Electromechanical Substrate Characterization in Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Coll Cardiol*. 2016;68(20):2185–97.
42. Blom LJ, Riele ASJM Te, Vink A, Hauer RNW, Hassink RJ. Late evolution of arrhythmogenic cardiomyopathy in patients with initial presentation as idiopathic ventricular fibrillation. *Hear Case Reports*. 2019;5(1):25–30.
43. Haugaa KH, Edvardsen T, Leren TP, Gran JM, Smiseth OA, Amlie JP. Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high-risk individuals with long QT syndrome. *Eur Heart J*. 2008;30(3):330–7.
44. Scheirlynck E, Malderen S Van, Motoc A, Lie ØH, Asmundis C de, Sieira J, *et al.* Contraction alterations in Brugada syndrome; association with life-threatening ventricular arrhythmias. *Int J Cardiol*. 2020;299:147–52.
45. Groeneveld SA, Ree MH van der, Taha K, Bruin-Bon RHA de, Cramer MJ, Teske AJ, *et al.* Echocardiographic deformation imaging unmasks global and regional mechanical dysfunction in patients with idiopathic ventricular fibrillation: A multicenter case-control study. *Heart Rhythm*. 2021;18(10):1666–72.
46. Dollar AL, Roberts WC. Morphologic comparison of patients with mitral valve prolapse who died suddenly with patients who died from severe valvular dysfunction or other conditions. *J Am Coll Cardiol*. 1991;17(4):921–31.
47. Pocock WA, Bosman CK, Chesler E, Barlow JB, Edwards JE. Sudden death in primary mitral valve prolapse. *Am Heart J*. 1984;107(2):378–82.
48. Kleid JJ. Sudden Death and the Floppy Mitral Valve Syndrome. *Angiology*. 1976;27(12):734–7.
49. Dejgaard LA, Skjølsvik ET, Lie ØH, Ribe M, Stokke MK, Hegbom F, *et al.* The Mitral Annulus Disjunction Arrhythmic Syndrome. *J Am Coll Cardiol*. 2018;72(14):1600–9.
50. Sriram CS, Syed FF, Ferguson ME, Johnson JN, Enriquez-Sarano M, Cetta F, *et al.* Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2013;62(3):222–30.
51. Essayagh B, Sabbag A, Antoine C, Benfari G, Yang LT, Maalouf J, *et al.* Presentation and Outcome of Arrhythmic Mitral Valve Prolapse. *J Am Coll Cardiol*. 2020;76(6):637–49.
52. Hutchins GM, Moore GW, Skoog DK. The association of floppy mitral valve with disjunction of the mitral annulus fibrosus. *N Engl J Med*. 1986;314(9):535–40.
53. Angelini A, Ho SY, Anderson RH, Becker AE, Davies MJ. Disjunction of the mitral annulus in floppy mitral valve. *N Engl J Med*. 1988;318(3):188–9.
54. Perazzolo Marra M, Basso C, Lazzari M De, Rizzo S, Cipriani A, Giorgi B, *et al.* Morphofunctional Abnormalities of Mitral Annulus and Arrhythmic Mitral Valve Prolapse. *Circ Cardiovasc Imaging*. 2016;9(8).
55. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, *et al.* Sudden arrhythmic death syndrome: Familial evaluation identifies inheritable heart disease in the majority of families. *Eur Heart J*. 2008;29(13):1670–80.
56. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, *et al.* Familial cardiological and targeted genetic evaluation: Low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. *Heart Rhythm*. 2013;10(11):1653–60.
57. Lahrouchi N, Raju H, Lodder EM, Papatheodorou E, Ware JS, Papadakis M, *et al.* Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. *J Am Coll Cardiol*. 2017;69(17):2134–45.

58. Mellor GJ, Blom LJ, Groeneveld SA, Winkel BG, Ensam B, Bargehr J, *et al.* Familial Evaluation in Idiopathic Ventricular Fibrillation: Diagnostic Yield and Significance of J Wave Syndromes. *Circ Arrhythmia Electrophysiol*. 2021;(March):296–305.
59. Steinberg C, Padfield GJ, Champagne J, Sanatani S, Angaran P, Andrade JG, *et al.* Cardiac Abnormalities in First-Degree Relatives of Unexplained Cardiac Arrest Victims. *Circ Arrhythmia Electrophysiol*. 2016;9(9):1–9.
60. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AAM. Everybody has Brugada syndrome until proven otherwise? *Heart Rhythm*. 2015;12(7):1595–8.
61. Probst V, Wilde AAM, Barc J, Sacher F, Babuty D, Mabo P, *et al.* SCN5A Mutations and the role of genetic background in the pathophysiology of brugada syndrome. *Circ Cardiovasc Genet*. 2009;2(6):552–7.
62. Mizusawa Y, Wilde AAM. Brugada syndrome. *Circ Arrhythmia Electrophysiol*. 2012;5(3):606–16.
63. Werf C Van Der, Hofman N, Tan HL, Dessel PF Van, Alders M, Wal AC Van Der, *et al.* Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: The experience of a tertiary referral center in the Netherlands. *Heart Rhythm*. 2010;7(10):1383–9.
64. Werf C van der, Hendrix A, Birnie E, Bots ML, Vink A, Bardai A, *et al.* Improving usual care after sudden death in the young with focus on inherited cardiac diseases (the CAREFUL study): a community-based intervention study. *Europace*. 2016;18(4):592–601.
65. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, *et al.* Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur Heart J*. 2011;32(8):983–90.
66. Taskforce lijkschouw en gerechtelijke sectie. De dood als startpunt. 2018;
67. Universitair Medisch Centrum Utrecht; Ministerie van Volksgezondheid Welzijn en Sport. Evaluatierapport NODOK-procedure ten behoeve van het Ministerie van Volksgezondheid , Welzijn en Sport. 2018;Versie aug.
68. Bear LR, Cluitmans M, Abell E, Rogier J, Labrousse L, Cheng LK, *et al.* Electrocardiographic Imaging of Repolarization Abnormalities. *J Am Heart Assoc*. 2021;10:e020153.
69. Duchateau J, Sacher F, Pambrun T, Derval N, Chamorro-Servent J, Denis A, *et al.* Performance and limitations of noninvasive cardiac activation mapping. *Heart Rhythm*. 2019;16(3):435–42.
70. Leur RR van de, Taha K, Bos MN, Heijden JF van der, Gupta D, Cramer MJ, *et al.* Discovering and Visualizing Disease-Specific Electrocardiogram Features Using Deep Learning. *Circ Arrhythmia Electrophysiol*. 2021;14(2):138–47.


09

Nederlandse samenvatting

Plotse hartdood is een belangrijk probleem in de Westerse wereld. Bij jonge mensen wordt een plotselinge hartstilstand vaak veroorzaakt door ventrikelfibrilleren. Dit is een ernstige hartritmestoornis waarbij de ventrikels snel en ongeorganiseerd bewegen waardoor het hart geen bloed meer kan rondpompen. De meest voorkomende oorzaak voor ventrikelfibrilleren is coronarialijden. Echter, moeten daarnaast ook andere oorzaken zoals een cardiomyopathie of een elektrische hartziekte worden uitgesloten. In de meeste gevallen van ventrikelfibrilleren (VF) wordt een oorzaak gevonden voor de plotse hartstilstand. Echter, in een klein deel van de patiënten wordt geen oorzaak gevonden. Deze patiënten krijgen de diagnose "idiopathisch ventrikelfibrilleren" (IVF).

Idiopathisch ventrikelfibrilleren is een diagnose "per exclusionem". Dat betekent dat alle andere mogelijke oorzaken voor ventrikelfibrilleren eerst uitgesloten moeten worden. Uitgebreide diagnostiek is dus noodzakelijk om eventuele onderliggende ziektes uit te sluiten. Door een toename van kennis en mogelijkheden is de prevalentie van IVF gedaald in de afgelopen jaren. Maar helaas zijn er nog steeds patiënten waarbij we geen oorzaak kunnen vinden voor de ritmestoornis. Voor deze patiënten is het noodzakelijk dat we op zoek gaan naar nieuwe diagnostische mogelijkheden om subtiele afwijkingen op te sporen. Afwezigheid van bewijs is namelijk geen bewijs van afwezigheid.

Deel I *Karakteristieken van IVF patiënten*

In de afgelopen jaren is er veel aandacht geweest voor het standaardiseren van diagnostiek bij IVF. Een systematische review liet zien dat met name cardiale magnetische resonantie beeldvorming (CMR), de fietstest en de provocatietest voor Brugada syndroom een hoge diagnostische waarde hebben. Helaas blijkt uit recente literatuur dat IVF patiënten lang niet altijd alle aanbevolen diagnostiek ondergaan. Dit is problematisch omdat sommige patiënten hierdoor onterecht de diagnose IVF krijgen. In **hoofdstuk 2** kijken we naar het belang van diagnostiek in IVF patiënten. Resultaten uit deze studie laten zien dat de hoeveelheid diagnostiek die per IVF patiënt wordt verricht over de jaren is toegenomen, maar nog steeds heterogeen is. In totaal werd in 38 van de 423 IVF patiënten een alternatieve diagnose vastgesteld tijdens follow-up. Onze data liet zien dat IVF patiënten die weinig diagnostiek hebben gehad na het VF, een grotere kans hebben om een alternatieve diagnose te krijgen. Patiënten die een alternatieve diagnose kregen tijdens follow-up hadden een slechtere overlevingskans. Onze resultaten onderstrepen het belang van systematische en complete diagnostiek.

Zonder een evident substraat voor VF zijn de behandelmogelijkheden beperkt. Antiaritmische medicijnen en cardiale ablatie zijn effectief gebleven in enkele subgroepen van IVF patiënten. Echter, voor de meeste patiënten is er momenteel geen behandeling behoudens implantatie van een implanteerbare cardioverter-defibrillator (ICD). Ondanks dat een ICD effectief is in het behandelen van ritmestoornissen, is hij ook geassocieerd met onterechte schokken en andere complicaties. Een interessante subgroep binnen IVF zijn patiënten met short-coupled ventrikelfibrilleren (SCVF). Bij deze patiënten begint de ritmestoornissen met een kort gekoppelde extrasystole. In **hoofdstuk 3** bestuderen we het voorkomen van SCVF in een groot

Nederlands cohort van IVF patiënten. In dit cohort blijkt 14% van alle patiënten SCVF te hebben. SCVF kan alleen vastgesteld worden wanneer er documentatie is van de ritmestoornis. In 91% van de gedocumenteerde ritmestoornissen bleek er sprake te zijn van SCVF. Dit suggereert dat SCVF niet een subtype van IVF is, maar juist het gebruikelijke fenotype. Aangezien klasse I antiaritmische medicijnen effectief zijn gebleken in het voorkomen van recidieven bij SCVF patiënten kan dit een behandelmogelijkheid bieden voor sommige patiënten.

Deel II *Vooruitgang in diagnostiek*

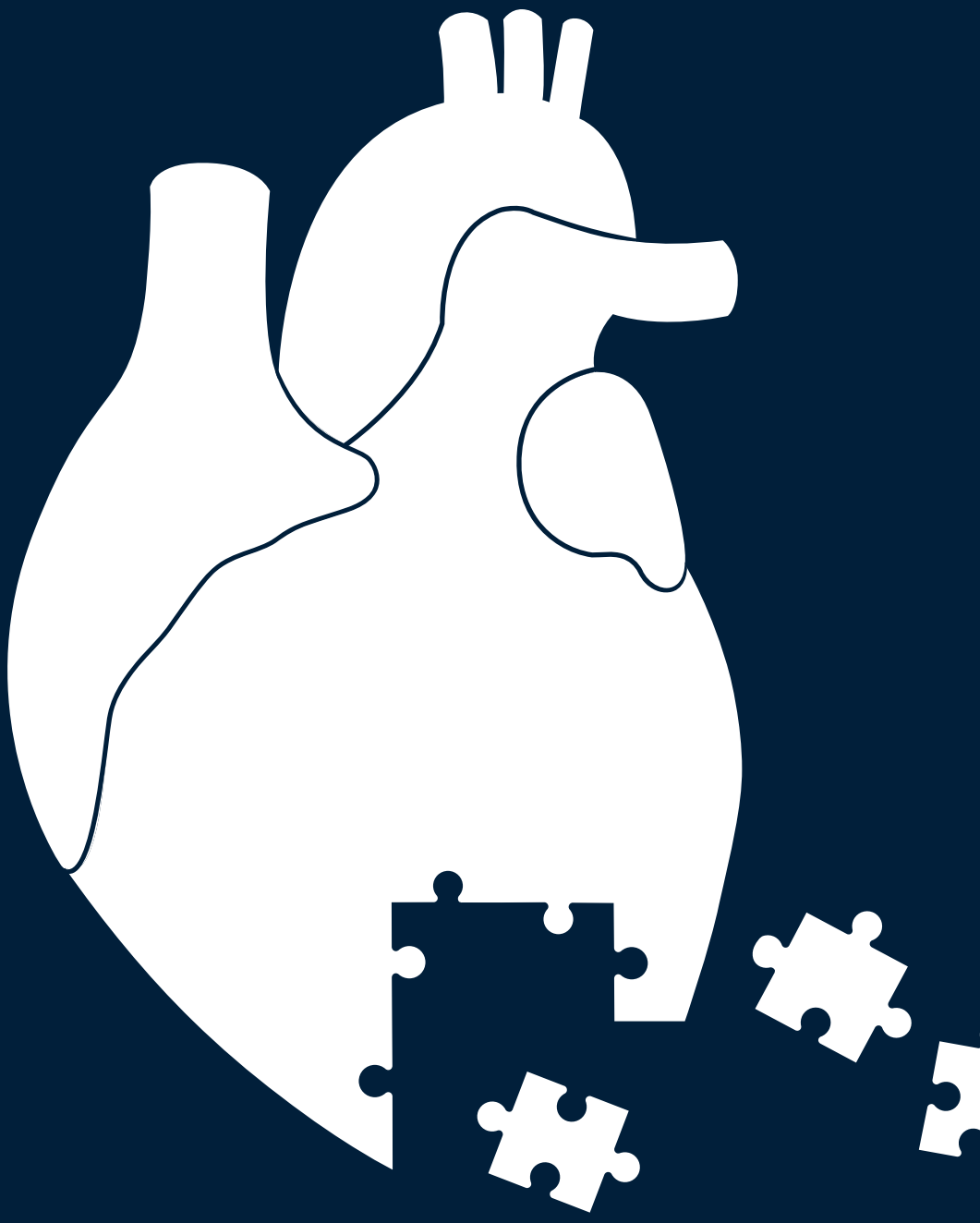
Om vooruitgang te kunnen boeken in diagnostische mogelijkheden bij IVF patiënten, is het belangrijk om na te denken over mogelijke onderliggende mechanismen voor VF. Eerdere endocardiale en epicardiale mapping resultaten lieten zien dat de meerderheid van de IVF patiënten kleine lokale elektrische afwijkingen laten zien. Het is bewezen dat kleine elektrische afwijkingen ook kunnen leiden tot ernstige ritmestoornissen. Beeldvorming zoals echocardiografie en cardiale magnetische resonantie (CMR) spelen een belangrijke rol in de standaard diagnostiek bij IVF. Echter, wordt IVF gekarakteriseerd door de afwezigheid van afwijkingen op conventionele beeldvorming. Het is dus belangrijk dat we op zoek gaan naar nieuwe diagnostische mogelijkheden om subtiele afwijkingen op te sporen. **In hoofdstuk 4** hebben we gekeken naar echocardiografische deformatie beeldvorming bij IVF patiënten. Deze techniek maakt het mogelijk om de mechanische vervorming (deformatie) van de hartspier te kwantificeren en is in staat gebleken om subtiele preklinische afwijkingen bij sommige patiënten te kunnen opsporen. We hebben deformatie beeldvorming van 47 IVF patiënten vergeleken met 47 gezonde controles. Onze studie laat zien dat IVF patiënten zowel regionale als lokale echocardiografische deformatie afwijkingen hebben. Deze resultaten demonstreren dat er in een belangrijk deel van de patiënten sprake is van lokale myocardiale ziekte, welke met de huidige diagnostiek niet opgespoord kunnen worden. Dit onderstreept het belang van nieuwe diagnostische mogelijkheden.

In **hoofdstuk 5** beschrijven we de prevalentie van mitralisklep afwijkingen bij IVF patiënten. Mitralisklepprolaps is geassocieerd met ernstige ritmestoornissen en plotse dood. Echter, recente studies suggereren dat er ook een associatie is tussen mitralisklep annulus disjunctie (MAD) en ernstige ritmestoornissen. MAD is een afwijking van de mitralis annulus waarbij er sprake is van een separatie tussen de aanhechting van de mitralisklep en het ventrikel myocard. In totaal werden 72 IVF patiënten vergeleken met 72 gezonde controles. We vonden een significant hogere prevalentie van mitralisklepprolaps en MAD in IVF patiënten. Dit is een interessante bevinding, welke suggereert dat mitralisklep afwijkingen een rol spelen in de aritmogenese bij sommige IVF patiënten. De exacte mechanismen achter MAD en het klinisch beloop zijn tot dusver onbekend. Het is dus belangrijk om extra aandacht te hebben voor de mitralisklep op beeldvorming bij IVF patiënten.

Deel III *Voorkomen van plotse dood*

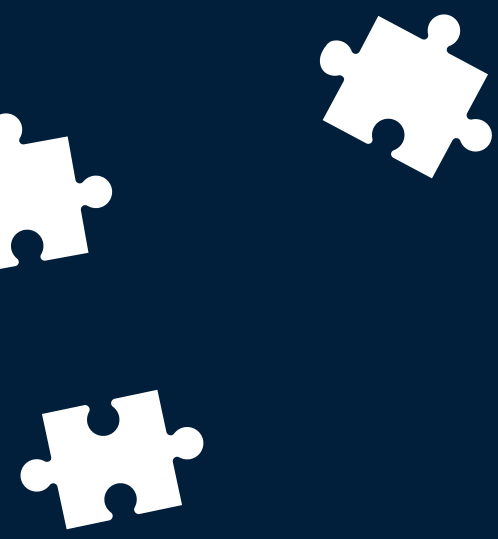
Erfelijkheid speelt een belangrijke rol bij plotse dood. In een-derde van de gevallen van plotse dood bij jonge mensen is er sprake van een erfelijke aandoening. De waarde van familiescreening bij patiënten met IVF was echter onbekend. In **hoofdstuk 6** hebben we onderzoek gedaan naar de opbrengst van familiescreening bij IVF. In totaal werden 201 familieleden van IVF patiënten geïncludeerd in de studie. Een erfelijke hartziekte werd vastgesteld bij 5 (3%) familieleden. Twee familieleden bleken het DPP6 haplotype te hebben, een genetische afwijking met een zeer hoog risico op levensbedreigende hartritmestoornissen. Het DPP6 haplotype was reeds bekend bij de index patiënt. In drie familieleden uit verschillende families was sprake van een positieve provocatie test voor het Brugada syndroom. De betekenis van een positieve provocatie test bij asymptomatische familieleden is dubieus. De opbrengst van familiescreening bij IVF patiënten die systematische diagnostiek hebben gehad is laag en moet heroverwogen worden.

De opbrengst van familiescreening na het optreden van plotse dood bij een jong persoon is hoog. Zeker wanneer de doodsoorzaak onbekend blijft na obductie is er een hoge kans op een erfelijke hartziekte. Het wordt dus sterk aangeraden om obductie en familiescreening uit te voeren in het geval van het plotseling overlijden van een jong persoon. Helaas blijkt uit een groot Nederlands onderzoek dat obductie maar in 43% van de gevallen wordt uitgevoerd na plotseling overlijden. Het percentage familieleden dat zich meldt voor familiescreening ligt nog een stuk lager, namelijk maar op 8%. In **hoofdstuk 7** beschrijven we de huidige problemen rondom obductie en familiescreening in het kader van plotse dood bij een jong persoon. Meerdere problemen spelen een rol, waaronder logistieke problemen rondom het aanvragen van obductie en een gebrek aan kennis over erfelijke hartziekten bij zorgverleners. Om zorgverleners te ondersteunen bij dit lastige proces hebben we een zorgpad ontwikkeld en een website opgezet (www.umcutrecht.nl/acuutoverlijden). Door erfelijke hartziekten vroegtijdig op te sporen kan plotseling overlijden van familieleden namelijk voorkomen worden.



PART V

Appendices



Appendices

List of publications
Dankwoord
About the author

List of publications

Peer-reviewed publications:

1. Groeneveld SA, Verheul LM, van der Ree MH, Mulder BA, Scholten MF, Alings M, van der Voort P, Bootsma M, Evertz R, Balt J, Yap SC, Doevendans PAFM, Postema PG, Wilde AAM, Volders PGA, Hassink RJ. The importance of systematic diagnostic testing in idiopathic ventricular fibrillation: results from the Dutch IVF registry. JACC: Clinical Electrophysiology. In press.
2. Verheul LM, Groeneveld SA, Kirkels FP, Volders PGA, Teske AJ, Cramer MJ, Guglielmo M, Hassink RJ. State-of-the-Art Multimodality Imaging in SUdden Cardiac Arrest with Focus on Idiopathic Ventricular Fibrillation: A Review. Journal of Clinical Medicine. 2022 August;11:4680.
3. Groeneveld SA, Kirkels, FP, Cramer MJ, Evertz R, Haugaa KH, Postema PG, Prakken NHJ, Teske AJ, Wilde AAM, Velthuis BK, Nijveldt R, Hassink RJ. Prevalence of mitral annulus disjunction and mitral valve prolapse in idiopathic ventricular fibrillation patients. Journal of the American Heart Association. 2022 August;11:e025364.
4. Groeneveld SA, van der Ree MH, Mulder BA, Balt J, Wilde AAM, Postema PG, Hassink RJ. Prevalence of Short-Coupled Ventricular Fibrillation in a Large Cohort of Dutch Patients With Idiopathic Ventricular Fibrillation. Circulation. 2022 May 3;145(18):1437-1439.
5. De Wit LE, van Stiphout F, Groeneveld SA, Hassink RJ, Dekker D. Psychofarmaca en het QTc-interval [Psychotropic drugs and QTc prolongation]. Ned Tijdschr Geneeskd. 2021 Jul 22;165:D5725.
6. Groeneveld SA, van der Ree MH, Taha K, de Bruin-Bon RHA, Cramer MJ, Teske AJ, Bouma BJ, Amin AS, Wilde AAM, Postema PG, Hassink RJ. Echocardiographic deformation imaging unmasks global and regional mechanical dysfunction in patients with idiopathic ventricular fibrillation: A multicenter case-control study. Heart Rhythm. 2021 Oct;18(10):1666-1672.
7. Mellor GJ, Blom LJ, Groeneveld SA, Winkel BG, Ensam B, Bargehr J, van Rees B, Scrocco C, Krapels IPC, Volders PGA, Tfelt-Hansen J, Krahn AD, Hassink RJ, Behr ER. Familial Evaluation in Idiopathic Ventricular Fibrillation: Diagnostic Yield and Significance of J Wave Syndromes. Circ Arrhythm Electrophysiol. 2021 Mar;14(3):e009089.
8. Groeneveld SA, Blom LJ, van der Heijden JF, Loh P, Hassink RJ. Follow-up after hemodynamically not tolerated ventricular tachycardia in patients with midrange reduced to normal ejection fraction: A retrospective single-centre case series. Eur J Clin Invest. 2021 Jan;51(1):e13359.
9. Stoks J, Van Rees B, Groeneveld SA, Schipaanboord D, Blom L, Hassink R, Cluitmans M, Peeters R, Volders P. Variability of Electrocardiographic Imaging Within and Between Leadsets. Computing in Cardiology. 2020 Dec;47:1-4.
10. Groeneveld SA, Blom LJ, Hassink RJ. Plotse dood bij jonge mensen [Sudden death in the young: the importance of autopsy and DNA testing]. Ned Tijdschr Geneeskd. 2020 May 20;164:D4342.
11. Blom LJ, Groeneveld SA, Wulterkens BM, van Rees B, Nguyen UC, Roudijk RW, Cluitmans M, Volders PGA, Hassink RJ. Novel use of repolarization parameters in electrocardiographic imaging to uncover arrhythmogenic substrate. J Electrocardiol. 2020 Mar-Apr;59:116-121.
12. Groeneveld SA, Jongejan N, de Winter BJSAAF, Fiolet ATL. Inbreken in een pacemaker [Hacking into a pacemaker; risks of smart healthcare devices]. Ned Tijdschr Geneeskd. 2019 Mar 8;163:D3690.

In preparation

13. Groeneveld SA, Verheul LM, Tuinenburg AE, Hassink RJ. Atrial fibrillation begets ventricular fibrillation when the AV node fails. Submitted.

Dankwoord

Dit proefschrift is tot stand gekomen door ondersteuning van de Nederlandse Hartstichting en de betrokkenheid van ontzettend veel mensen. Alhoewel het onmogelijk is om iedereen die mij de afgelopen jaren geholpen heeft te bedanken, wil ik graag een aantal mensen in het speciaal noemen.

Geachte copromotor dr. **R.J. Hassink**, beste **Rutger**, we hebben elkaar vroeg in mijn carrière ontmoet tijdens mijn semi-arts stage op de afdeling elektrofysiologie. Jou enthousiasme over hartritmestoornissen was aanstekelijk en ik raakte geïntrigeerd door de elektrofysiologie. Jou kennis, recht-door-zee mentaliteit, praktische insteek en droge humor hebben mijn PhD periode tot een succes gemaakt. Je blokte consistent een uurtje "research tijd" en sloot ons overleg altijd af met de woorden *"je mag altijd tussendoor bellen hé, als er wat is".* Jou rustige persoonlijkheid en praktische instelling zorgden altijd voor een snelle oplossing voor ieder mogelijk probleem. Ook onze gezamenlijke passie voor sporten, reizen en skiën werd regelmatig onder het genot van een cappuccino besproken. Helaas kon de "ski stunt les" die we bekokstoofd hadden voor de cardio ski reis niet doorgaan door COVID, maar ik kijk er naar uit om hem later in te halen (en vast te leggen uiteraard!). Rutger, bedankt voor fijne samenwerking, jou betrokkenheid en vooral de mooie jaren. Ik hoop dat ik nog veel met je mag samenwerken in de toekomst!

Geachte promotor Prof. Dr. **P.A.F.M. Doevendans**, beste **Pieter**, bedankt voor de mogelijkheden die ik heb gekregen de afgelopen jaren. Onze gesprekken over onderzoek waren kort maar krachtig, en leverden stimulans om een stap verder te denken. Bedankt voor de begeleiding.

Geachte promotor Prof. Dr. **P.G.A. Volders**, beste **Paul**, bedankt voor de begeleiding en alle levendige discussies over de electrofysiologie. Jou creatieve en kritische blik zorgden altijd voor een nieuwe invalshoek in ons onderzoekswerk. Ook wil ik je bedanken voor de mogelijkheid om te promoveren binnen het VIGILANCE project.

Geachte leden van de leescommissie, Prof. Dr. **Velthuis**, Prof. Dr. **Den Ruijter**, Prof Dr. **Van den Berg**, Prof. Dr. **De Groot** en Prof. **Van Tintelen**, hartelijke dank voor uw bereidheid om zitting te nemen in de beoordelingscommissie van dit proefschrift.

Beste Dr. **Cramer**, beste **Maarten Jan**, bedankt voor je oneindige enthousiasme en interesse. Jij weet altijd de juiste mensen met elkaar te verbinden voor een succesvolle wetenschappelijke samenwerking. We hebben samen een "Imaging Clubje" gevormd, met o.a. Feddo en Karim, waar mooie wetenschappelijke publicaties uit voort zijn gekomen. Ik wil je bedanken voor je begeleiding, visie en niet te vergeten je altijd vrolijke aanwezigheid tijdens mijn promotietraject!

Alle collega's uit de deelnemende centra van de iVF registry, bedankt voor de vruchtbare samenwerking. Het was soms een tijdrovende exercitie om door alle METC vragen heen te komen en om de juiste patiënten op te sporen, maar jullie bereidheid om te helpen was altijd groot. Door jullie hulp heeft de iVF registry kunnen groeien tot zijn huidige formaat. In het speciaal wil ik graag mijn waardering uitspreken naar de Prof. Dr. **Wilde** en Dr. **Pieter Postema** voor de intensieve, vruchtbare en prettige samenwerking. Bedankt voor jullie creatieve input, kritische blik en suggesties voor verbetering van onze papers.

Graag wil ik iedereen uit het **VIGILANCE team** (o.a. Job Stoks, Bianca van Rees, Martijn van der Ree, Lisa Verheul, Wiert Hoeksema, Dr. Lennart Blom, Dr. Matthijs Cluijtmans, Dr. Rachel ter Bekke, Dr. Pieter Postema, Prof. Wilde en Prof. Volders) bedanken voor de fijne samenwerking, uitdagende discussies alsmede de gezelligheid. In het speciaal **Bianca** en **Job**, die de belangrijke taak hadden om de nieuwe VIGILANCE PhDs alle fijne kneepjes van het ECG Imaging vak te leren. Naast jullie uitstekende mentorschap was er ook engelengeduld voor nodig om ons wijs te maken in de wonderen wereld van electrodes, segmentaties en matlab. Gelukkig was er ook nog regelmatig tijd over voor een borrel, en weet ik door jullie nu eindelijk hoe Limburgs Zoervleisj smaakt (maar nog steeds niet hoe je het uitspreekt). **Martijn**, bedankt voor de vruchtbare samenwerking! We hebben niet alleen veel mooie artikelen geschreven samen, maar vooral veel gelachen en niet te vergeten veel koffie en biertjes genuttigd. Door alle uren die we samen hebben gespendeerd aan het plakken van electrodes, het verwijderen van lipjes en het aanbrengen van klontjes gel weet ik nu bijna alles over jou (van je levende gistmengsel tot je Italiaanse vlees kast). Ik zal de Tequila bar in Kopenhagen trouwens ook niet snel vergeten (met name de dag erna). **Lennart**, mijn IVF-voorganger, wat ben ik blij dat jij mij wegwijs hebt gemaakt in het promoveren. Jou kalmte, statische kennis en ongelooflijke droge humor hebben mijn eerste jaar een stuk zonniger gemaakt. **Lisa**, mijn IVF-opvolger, ik heb er alle vertrouwen in dat jij ons mooie onderzoek weer een stuk verder gaat brengen. Bedankt voor de fijne tijd en ik kijk uit naar veel mooie projecten in de toekomst.

Wil en **Rolf**, ontzettend bedankt voor jullie hulp bij al mijn onmogelijke EFO verzoeken. Ik ben jullie eeuwig dankbaar voor alle uren die we samen hebben doorgebracht op de HCK op zoek naar dat ene signaaltje *("hakkeltje")* in een registratie van 3 uur lang. Gelukkig viel er ook genoeg te lachen, ik zal bijvoorbeeld de prachtige avond in "De Treinen-Bar" in Kopenhagen niet snel vergeten.

Alle collega's van de EFO, bedankt voor de prettige samenwerking. Dr. **Mathias Meine**, Dr. **Peter Loh**, Dr. **Anton Tuinenburg**, Dr. **Jeroen van der Heijden**, Dr. **Irene Hof** en Drs. **Nick Clappers** bedankt voor alle leerzame (en gezellige) momenten tijdens de grote visite en daarbuiten. Ook wil ik graag alle dames van het secretariaat bedanken voor de fijne koffie momentjes en jullie hulp bij onder andere weigerende faxmachines, ingewikkelde HIX problemen en andere logistieke uitdagingen.

Essentieel voor mijn welzijn waren natuurlijk mijn mede onderzoekers van de Cardiologie, o.a. **Marijn, Feddo, Karim, Philippe, Arjan, Machteld, Evan, Max, Timion, Aernoud, Lieke, Mimount, Rosanne, Mark, Hugo, Diantha, Rutger, Anne Mar, Fahima, Nicole, Sayonara, Steven, Thomas, Markella en Marijke**. Ik zal alle PhDrinking borrels, weekenden, congressen, dinertjes en stapavonden niet snel vergeten. **Feddo**, het is ongelooflijk hoeveel tijd wij in een donker MRI-hok hebben doorgebracht om een mitralisklep te meten. Gelukkig wisselden we dit ook wel eens af voor een donker cafe met een biertje, waarna ik mij de dag erna altijd verbaasde dat jij weer vrolijk opstond 's ochtends. Ga je ooit nog je geheim met ons delen? **Karim**, de baas van de strain en de ultieme believer van post-systolic shortening, bedankt voor je kalme aanwezigheid en grote glimlach! **Marijn**, jij was mijn partner-in-crime en mede PhDrinking organisator. Samen organiseerden we uitjes van de Utrechtse gevangenis tot in de Belgische Ardennen. Het bubbelvoetbal was toch wel een van de hoogtepunten. Ik zie je nog steeds door de lucht vliegen! **Arjan**, jou brede kennis in combinatie met je vlotte babbel zijn indrukwekkend. Je inschattingsvermogen over een telefoontje van de politie dan weer wat minder. **Machteld**, wat ben ik jou dankbaar voor al je hulp tijdens de metingen. Jou oneindige positiviteit, gezelligheid en indrukwekkende technische kennis hebben mij er meer dan eens doorheen gesleept. **Diantha**, jij was de eerste student die ik heb mogen begeleiden tijdens het afstuderen. Ik wil je bedanken voor je inzet en je doorzettingsvermogen. Je hebt een mooi eindproduct neergezet en ons project weer een eind verder geholpen!

In het speciaal mijn (oud-)villa genoten **Marijn, Philippe, Rutger, Rene, Karim, Feddo, Odette en Bas**, bedankt voor de gezellige chaos in de mooiste kamer van het UMCU. Ik heb niet alleen relevante statische kennis vergaard, maar ook de nodige schaakzetten en dart technieken leren kennen. Na mijn verhuizing van het bureau met de koffiemachine naar het bureau aan het raam werd het in ieder geval een stuk zonniger! Bedankt voor alle gezelligheid, weekend besprekingen op maandag ochtend en de vele koffietjes (vers gemalen aan mijn eerste bureau).

Mijn studie vriendinnetjes **Noor**, **Tessa**, **Fenne**, **Livia** en **Esmee** wat was het fijn om alle mooie (en soms bizarre) momenten van de Geneeskunde opleiding te delen. Onze velen dinertjes en borrel avondjes hebben mij vaak opgevrolijkt na een dagje data invoeren achter mijn bureau.

Mijn tennisteam, **Daan**, **Anne Lieke**, **Julia**, **Thijs**, **Arjen** en **Laurens**, ik wil jullie bedanken voor alle nodige afleiding in de vorm van tennis maar vooral ook in de vorm van dinertjes, feestjes in de Tivoli en spontane La Chouffe avondjes na het tennissen (alhoewel ik er door jullie achter ben gekomen dat dat laatste misschien niet zo'n briljant idee is).

Alle **vrienden** (o.a. **Febe, Max, Bob, Marije, Coen, Vincent, Timo, Noa, Joost, Jasper, Milda**) bedankt voor de ontspanning, ontlading en gezelligheid. In het bijzonder noem ik **Joelle** en **Anouk**, zonder jullie was ik niet geworden wie ik nu was. We zijn samen opgegroeid en onze vriendschap heeft mij gevormd tot wie ik nu ben. Bedankt voor alle gezellig weekendjes weg, goeie gesprekken en late stapavondjes. Ik hoop dat er nog velen mogen komen!

Mijn **paranimfen**, **Marijn** en **Lisa** Bedankt voor jullie hulp en steun tijdens de laatste fase van mijn promotietraject. Ik ben ontzettend blij dat ik jullie aan mijn zijde heb.

Lieve familie en schoonfamilie, bedankt voor alle interesse, vragen en vertrouwen in mijn promotie. **Fenna**, mijn grote zus, bedankt voor je vertrouwen in mij. Ik heb genoten van alle fijne avonden samen, nu ook samen met **Joeri** en mijn nichtje **Lune**. Lieve **Mirjam**, **Leo**, **Manon** en **Jens**. Bedankt voor het warme bad waarin ik beland ben toen ik met Erwin een relatie kreeg. Jullie heerlijke Indonesische rijsttafel en onze goede gesprekken weten mij altijd op te vrolijken. Lieve **San**, **Bert**, **Luc en Ray**, bedankt voor jullie steun, interesse en alle gezellige borrel avondjes.

In het bijzonder mijn **ouders**. Lieve mama en papa, zonder jullie was ik hier nooit gekomen. Door jullie liefde en stabiele basis heb ik al mijn dromen kunnen najagen. Jullie zijn er altijd voor mij, door dik en door dun. Of het nou gaat om een goed gesprek, stoom afblazen op wintersportvakantie, een sommeliers cursus of een bakje met zelfgemaakte gehaktballen, niks is bij jullie te gek. Ook nu we ouder zijn staat jullie deur nog altijd wagenwijd voor ons open. Bedankt voor jullie altijd aanwezige steun en onvoorwaardelijke liefde.

Lieve **Erwin**, als laatste wil ik jou bedanken. Mijn stabiele basis en partner-in-crime. We zijn verschillend maar toch hetzelfde, dat verveelt nooit. Jou rationale kijk op de wereld heeft mij meer dan eens geholpen om lastige zaken in een ander licht te zien. We hebben lief en leed gedeeld, en herinneringen gemaakt die ik nooit meer zal vergeten. Jou liefde, warmte, steun en gezelligheid waren essentieel tijdens mijn promotietraject. Maar ook jou kennis van Microsoft Word, slimme technieken in powerpoint en opmaak-skills kwamen goed van pas. Ik ben je dankbaar voor je onvoorwaardelijke steun en liefde, en ik kijk uit naar de toekomst met jou.

About the author

Sanne Groeneveld was born on 9 september 1994 in Voorburg to Ilona Làven and Harm Groeneveld. She grew up in Leidschendam together with her older sister Fenna Groeneveld. In 2012, she graduated from the Dalton College Voorburg. In that same year, she started medical school at the University of Utrecht. During her study, Sanne obtained an interest for emergency medicine, and especially for the heart. During her masters, she chose to do internships at the intensive care unit, pulmonology ward and cardiology ward. This led to a senior internship at the department of Cardiology at the University Medical Center Utrecht (UMCU). During her senior internship, she met Dr. Rutger Hassink, who offered her to participate in a research internship on ventricular arrhythmias. Here she discovered her fascination for cardiac arrhythmias. Beside her medical training, Sanne was during medical school also an active committee member at TC de Uithof, the largest student tennis club in the Netherlands. After obtaining her medical degree in 2019, she started her PhD on idiopathic ventricular fibrillation, which was also supervised by Dr. Rutger Hassink, Prof. Doevendans and Prof. Volders. During her PhD, she focused on different areas of research such as short-coupled ventricular fibrillation, new imaging techniques for the detection of an arrhythmogenic substrate and the prevention of sudden cardiac death. During her time as a PhD student, she engaged in several board positions to represent the interests of other PhD students. From 2020 until 2022 she was chair of the MD PhD Committee at the UMCU and representative of the UMCU at the Dutch national working group of MD PhD students. In 2022, she finished her PhD, the results of which are presented in this thesis.

Sanne will continue to pursue her career in the field of Cardiology, starting as a Cardiology resident at the Meander Medical Center in Amersfoort.