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Comparing adolescent- and adult-onset unexplained cardiac arrest: Results from the Dutch Idiopathic VF Registry

Lisa M. Verheul, MD,[1] Wiert F. Hoeksema, MD,[2] Sanne A. Groeneveld, MD, PhD,[1] Bart A. Mulder, MD, PhD,[3] Marianne Bootsma, MD, PhD,[4] Marco Alings, MD, PhD,[5] Reinder Evertz, MD,[6] Andreas C. Blank, MD, PhD,[7] Janneke A.E. Kammeraad, MD, PhD,[8] Sally-Ann B. Clur, MBBCh, MSc(Med), FCP(SA)Paed, PhD,[2,9] Sing-Chien Yap, MD, PhD,[10] Pieter G. Postema, MD, PhD,[2,9] Arthur A.M. Wilde, MD, PhD,[2,9] Paul G.A. Volders, MD, PhD,[9,11] Rutger J. Hassink, MD, PhD[1,9]

ABSTRACT

BACKGROUND Current cohorts of patients with idiopathic ventricular fibrillation (IVF) primarily include adult-onset patients. Underlying causes of sudden cardiac arrest vary with age; therefore, underlying causes and disease course may differ for adolescent-onset vs adult-onset patients.

OBJECTIVE The purpose of this study was to compare adolescent-onset with adult-onset patients having an initially unexplained cause of VF.

METHODS The study included 39 patients with an index event aged ≤19 years (adolescent-onset) and 417 adult-onset patients from the Dutch Idiopathic VF Registry. Data on event circumstances, clinical characteristics, change in diagnosis, and arrhythmia recurrences were collected and compared between the 2 groups.

RESULTS In total, 42 patients received an underlying diagnosis during follow-up (median 7 [2–12] years), with similar yields (15% adolescent-onset vs 9% adult-onset; $P = .16$). Among the remaining unexplained patients, adolescent-onset patients (n = 33) had their index event at a median age of 17 [16–18] years, and 72% were male. The youngest patient was aged 13 years. In comparison with adults (n = 381), adolescent-onset patients more often had their index event during exercise ($P < .01$). Adolescent-onset patients experienced more appropriate implantable cardioverter-defibrillator (ICD) therapy during follow-up compared with adults (44% vs 26%; $P = .03$). Inappropriate ICD therapy (26% vs 17%; $P = .19$), ICD complications (19% vs 14%; $P = .41$), and deaths (3% vs 4%; $P = 1$) did not significantly differ between adolescent-onset and adult-onset patients.

CONCLUSION IVF may occur during adolescence. Adolescent-onset patients more often present during exercise compared with adults. Furthermore, they are more vulnerable to ventricular arrhythmias as reflected by a higher incidence of appropriate ICD therapy.

KEYWORDS Idiopathic ventricular fibrillation; Adolescent; Adult; Sudden cardiac arrest; Ventricular arrhythmia; Electrophysiology

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From the [1]University Medical Center Utrecht, Utrecht, The Netherlands, [2]Amsterdam UMC location University of Amsterdam, Department of Cardiology, Heart Failure and Arrhythmias, Amsterdam, The Netherlands, Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, The Netherlands, [3]University Medical Center Groningen, Groningen, The Netherlands, [4]Leiden University Medical Center, Leiden, The Netherlands, [5]Amphia Hospital, Breda, The Netherlands, [6]Radboud University Medical Center, Nijmegen, The Netherlands, [7]Wilhelmina Children's Hospital, Utrecht, The Netherlands, [8]Erasmus MC–Sophia Children's Hospital, Cardiovascular Institute, Department of Pediatric Cardiology, Rotterdam, The Netherlands, [9]Member of the European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart: ERN GUARD-Heart,", [10]Cardiovascular Institute, Thorax Center, Erasmus MC, Rotterdam, The Netherlands, and [11]Maastricht University Medical Center, Maastricht, The Netherlands.

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Introduction

Underlying causes of sudden cardiac arrest (SCA) or sudden cardiac death (SCD) vary across the age spectrum.[1] Although coronary artery disease is the main cause overall, primary electrical diseases, genetic cardiomyopathies, and myocarditis are more pronounced causes in the young.[1–3] When a complete diagnostic workup does not identify an underlying cause after SCA, idiopathic ventricular fibrillation (IVF) is diagnosed.[4] With approximately 5% of SCA survivors eventually receiving the diagnosis IVF, IVF is rare.[5,6] Currently, pediatric patients are underrepresented in cohort studies focusing on unexplained cardiac arrest (UCA) or IVF. Available studies that focused on pediatric patients with either UCA or IVF (the largest study of 54 patients) indicated a more malignant course of ventricular fibrillation (VF) recurrences.[7,8] When directly compared with adults, pediatric IVF patients with VF onset before age 16 years more often had arrhythmia recurrences during follow-up.[9] A discrepancy is reported regarding discovery of the underlying cause, which is also influenced by the initial diagnosis (UCA or IVF).[7,8] Knowledge regarding possible differences in onset of VF, clinical characteristics, and disease course between adult and pediatric or adolescent IVF patients is still limited. The variety of underlying causes of SCA in general suggests a possible difference between patients with VF onset during a younger age. This might have consequences for clinical management and possibly family screening. Therefore, the purpose of this study was to describe patients with adolescent-onset VF without a definite cause and compare them with patients having adult-onset VF.

Methods

Study population

The study population was derived from the Dutch Idiopathic VF Registry. This registry enrolls patients with an initial diagnosis of IVF according to the latest consensus criteria.[1] IVF was defined as an SCA survivor, preferably with documentation of VF, after exclusion of structural, channelopathic, metabolic, and toxicological etiologies. Patients with an index event aged ≤19 years were considered adolescent-onset patients. This cutoff was comparable to that reported in the study by Cunningham et al,[8] which focused on pediatric UCA patients, and the definition by the World Health Organization.[10] All other patients were considered adult-onset patients. The Medical Ethics Committee from the University Medical Center Utrecht exempted this study from the Medical Research Involving Human Subjects Act. The study adhered to the principles of the Declaration of Helsinki.

Abbreviations

AV: atrioventricular

ICD: implantable cardioverter-defibrillator

IVF: idiopathic ventricular fibrillation

PVC: premature ventricular complex

SCA: sudden cardiac arrest

SCD: sudden cardiac death

SVT: supraventricular tachycardia

UCA: unexplained cardiac arrest

VF: ventricular fibrillation

VT: ventricular tachycardia

Clinical characteristics

Patients underwent detailed clinical investigation as described previously.[11] Data were collected by review of medical records, both retrospectively and prospectively. Diagnostic workup was performed at the discretion of the treating physician. Clinical information and diagnostic results regarding demographics, circumstances during the index event, medical history, laboratory testing, 12-lead electrocardiography, Holter monitoring, exercise treadmill test, coronary imaging (either invasive coronary angiography or computed tomography), cardiac imaging (echocardiography, cardiac magnetic resonance), sodium channel blocker provocation, ergonovine/acetylcholine provocation, endomyocardial biopsy, and genetic testing were collected. A high premature ventricular complex (PVC) burden was defined as >1000 PVCs during Holter monitoring, >20 PVCs during exercise treadmill test, or bigeminy/trigeminy on telemetry/electrocardiography/Holter/exercise treadmill test. To analyze differences between "true" IVF patients with a complete diagnostic workup, we considered a workup complete when, in addition to standard testing by electrocardiography, echocardiography, and coronary imaging, all 3 high-yield tests (cardiac magnetic resonance imaging, exercise treadmill test, and sodium channel blocker provocation) were performed.[11,12]

Follow-up and outcomes

Management of patients during follow-up was performed at the discretion of the treating physician at each participating center of the registry. When deemed appropriate, additional diagnostic tests were performed and those results collected. Determination of an underlying diagnosis during follow-up was based on established diagnostic criteria (Supplemental Table S1). Patients who received an underlying diagnosis during follow-up were excluded from further analysis. Other outcomes included arrhythmia recurrence, defined as nonsustained ventricular tachycardia (VT) (≥3 consecutive complexes for ≤30 seconds); appropriate implantable cardioverter-defibrillator (ICD) therapy; either shock or antitachycardia pacing; and inappropriate ICD therapy. ICD readouts were evaluated to ascertain whether ICD therapy was appropriate. When ventricular arrhythmias were absent during ICD therapy, the therapy was considered inappropriate. Information regarding ICD complications and death was collected. Deaths were differentiated between cardiac and noncardiac causes of death.

Statistical analysis

Data were analyzed using SPSS Version 27.0 (SPSS Inc., Chicago, IL). Continuous variables are given as mean ± SD or median [interquartile range] and were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables are given as number (percentage), and were compared using the χ^2 or Fisher exact test, as

appropriate. Kaplan-Meier method was used to determine cumulative freedom from appropriate ICD therapy. Differences were evaluated with a log-rank test. Univariate and multivariate Cox proportional hazard analyses were used to further explore the influence of sex, age, high PVC burden, nonsustained VT, and the presence of the *DPP6* risk haplotype on appropriate ICD therapy in true IVF patients during follow-up. $P < .05$ was considered significant.

Results

Study population

As of July 2023, 456 patients with a median age at index event of 40 [28–52] years were registered in the Dutch Idiopathic VF Registry. Among these patients, 39 adolescent-onset patients who had their event at age ≤19 years were identified. The majority of the included patients had their index event during adulthood (Figure 1). Forty-two patients received an underlying diagnosis during follow-up. The yield did not differ statistically between adolescent-onset and adult-onset patients (15% vs 9%; $P = .16$). Among 6 adolescent-onset patients with an underlying diagnosis, half were diagnosed with a channelopathy (2 catecholaminergic polymorphic VT, 1 early repolarization syndrome). Two patients were diagnosed with a cardiomyopathy (arrhythmogenic cardiomyopathy and dilated cardiomyopathy). One patient was diagnosed with enhanced atrioventricular (AV) nodal conduction, which was considered the underlying cause of the index event. One of the 2 patients diagnosed with catecholaminergic polymorphic VT did not undergo exercise treadmill testing during initial workup, which prevented the diagnosis of catecholaminergic polymorphic VT. A diagnosis was made in adolescent-onset patients after a median of 12 [3–21] years and in adult-onset patients after a median of 7 [2–12] years ($P = .27$). An overview of each specific diagnosis stratified between adolescent-onset and adult-onset patients is given in Figure 2.

Clinical characteristics of UCA patients

In total, 33 adolescent-onset and 381 adult-onset patients remained undiagnosed during follow-up. Median age at the index event in adolescent-onset patients was 17 [16–18] years. The youngest patient was 13 years old. In total, 11 patients had their index event at age ≤16 years. Circumstances during the index event differed between adolescent-onset patients and adult-onset patients (Figure 3 and Supplemental Table S2). Adolescent-onset patients had their event more often during exercise (42% of adolescent-onset patients vs 16% of adult-onset patients; $P < .01$), whereas adult-onset patients had their event more often during rest (64% of adult-onset patients vs 39% of adolescent-onset patients; $P = .01$). The 13 adolescent-onset patients who had exercise-induced VF were performing a variety of sports. Most patients experienced VF during school gymnastics (n = 3) or team sport activities (eg, soccer, hockey [n = 3]). In 3 patients, VF occurred during regular physical activity (walking the stairs, biking to school), and 1 patient was participating in endurance sports (running). For 3 patients, the specific type of exercise was unknown. Other clinical characteristics are listed in Table 1. Most patients were asymptomatic before the event. No differences were identified between the 2 age-onset groups regarding a complete diagnostic workup or the prevalence of the *DPP6* risk haplotype. The diagnostic workup performed differed statistically for adolescent-onset patients vs adult-onset patients with regard to the diagnostic workup used to assess cardiac ischemia and the initiation of toxicological screening (Supplemental Table S3). The number of pathogenic or likely pathogenic variant carriers identified by genetic testing did not differ between adolescent-onset and adult-onset patients. A complete list of all variants found is given in Supplemental Table S4.

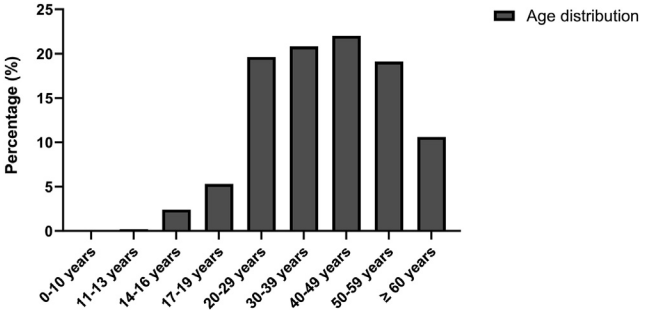

Figure 1
Age distribution of all patients.

Arrhythmia recurrences during follow-up

The follow-up of adolescent-onset and adult-onset patients did not significantly differ (6 [3–14] vs 7 [2-12] years). During follow-up, 109 patients (28%) experienced appropriate ICD therapy (Table 1). Adolescent-onset patients experienced appropriate ICD therapy more often than adult-onset patients (44% vs 26%; $P = .03$). The numbers of patients experiencing multiple episodes of appropriate ICD therapy during follow-up were comparable. Clinical characteristics of adolescent-onset patients with or without appropriate ICD therapy during follow-up are listed in Table 2. Three adolescent-onset patients (21%) with appropriate ICD therapy carried the *DPP6* risk haplotype. The number of patients with syncope before the index event and the family history of SCD were comparable in both groups. Adolescent-onset patients who experienced appropriate ICD therapy more often used antiarrhythmic therapy. This difference was observed only when including patients who started antiarrhythmic drugs after appropriate ICD therapy. Among adolescent-onset patients with antiarrhythmic therapy, 4 were treated with quinidine; 3 of these patients carried the *DPP6* risk haplotype. In all, quinidine was started after arrhythmia recurrences. Survival free from appropriate ICD therapy during follow-up was significantly less for adolescent-onset patients compared with adult-onset patients ($P = .04$) (Figure 4). Median age at first recurrence was 19 [18–20] years. One adolescent-onset patient died of SCD during follow-up at age 21; no ICD was implanted because the index event occurred before 1990.

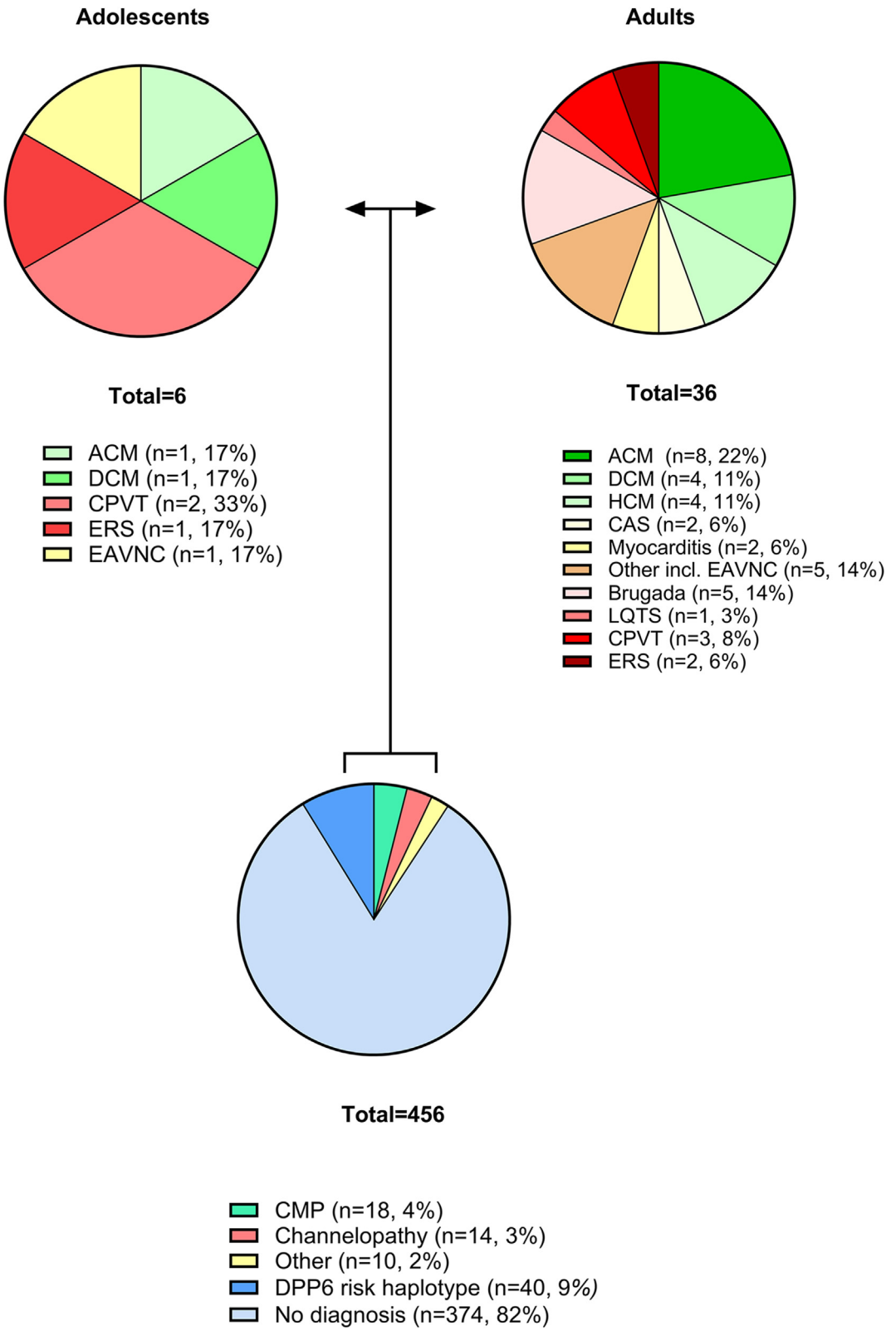

Figure 2
Overview of underlying diagnoses revealed during follow-up, stratified between adolescent-onset and adult-onset patients. ACM = arrhythmogenic cardiomyopathy; CAS = coronary artery spasm; CMP = cardiomyopathy; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; EAVNC = enhanced atrioventricular nodal conduction; ERS = early repolarization syndrome; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome.

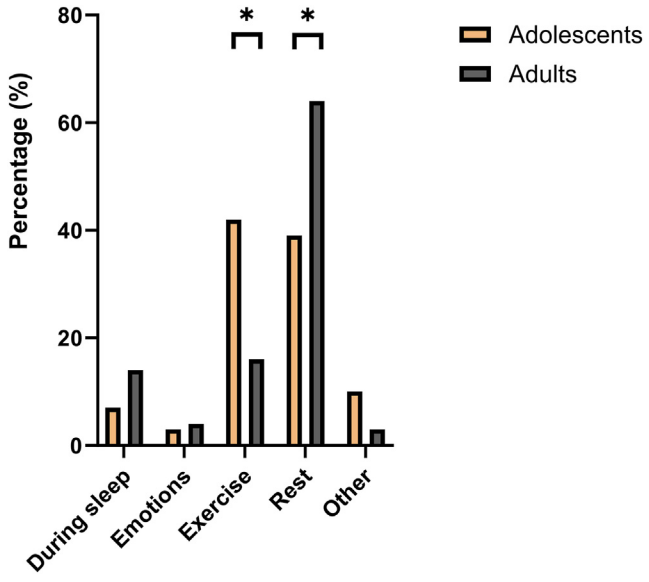

Figure 3
Differences in arrest circumstances between adolescent-onset and adult-onset patients. *Statistically significant.

Device complications

Inappropriate ICD therapy occurred in 68 patients (17%). Among those patients, 8 adolescent-onset patients (26%) experienced inappropriate ICD therapy compared with 60 adults (17%) ($P = .19$). Patients who did not receive inappropriate ICD therapy had their index event during more recent years than patients who received inappropriate ICD therapy (2014 [2009, 2017] vs 2009 [2003, 2014]; $P < .01$). Specific information on device complications, stratified between adolescent-onset and adult-onset patients, is given in Supplemental Table S5. Device complications other than inappropriate therapy occurred at comparable rates in the 2 age-onset groups. In total, 6 adolescent-onset patients experienced other ICD complications, the majority due to lead dysfunction (n = 2 [33%]) or pocket complications (n = 3 [50%]).

"True" IVF patients

Among 414 patients who did not receive an underlying diagnosis during follow-up, 169 underwent cardiac magnetic resonance, exercise treadmill, and sodium channel blocker provocation testing at baseline (16 adolescent-onset and 153 adult-onset patients). Again, the prevalence (50% adolescent-onset patients vs 21% adult-onset patients; $P = .025$) and survival free from appropriate ICD therapy differed between adolescent-onset and adult-onset patients. When exploring the risk for appropriate ICD therapy in this group, age itself was not of influence, but VF onset during adolescence and the presence of the *DPP6* risk haplotype were (Figure 5 and Supplemental Table S6).

Discussion

This study comprehensively compares adolescent-onset and adult-onset patients to expand and corroborate the limited knowledge on pediatric UCA patients. In addition, we focused on a subgroup that underwent in-depth investigation, referred to as "true" IVF patients. To the best of our knowledge, this is the first study to directly compare these groups to this extent. Our main findings are as follows: (1) adolescent-onset patients most often present during adrenergic-driven circumstances; (2) a more severe disease course with regard to ventricular arrhythmia recurrences is present in adolescent-onset patients; and (3) the discovery of an underlying disease during follow-up is comparable between adolescent-onset and adult-onset patients.

Table 1 Clinical characteristics and follow-up stratified between adolescent- and adult-onset patients

	All (N = 414)	Adolescents (n = 33)	Adults (n = 381)	*P* value
Age at first event (y)	40 [28–52]	17 [16–18]	43 [31–52]	<.01
Male	250 (60)	24 (72)	226 (59)	.13
Family member with SCD	65/408 (16)	5 (15)	60/375 (16)	.90
Asymptomatic	238/395 (60)	21/31 (68)	217/364 (60)	.38
Complete diagnostic workup*	169 (41)	16 (49)	153 (40)	.35
Pathogenic or likely pathogenic variant	50/364 (14)	5/32 (16)	45/332 (14)	.79
DPP6 risk haplotype	40 (10)	3 (9)	37 (10)	1
Variant of uncertain significance	108/364 (30)	12/32 (38)	96/332 (29)	.31
Year event	2013 [2007–2017]	2013 [2006–2017]	2013 [2007–2017]	.99
Follow-up				
Follow-up duration (y)	7 [2–12]	6 [3–14]	7 [2–12]	.67
Appropriate ICD therapy (either shock or ATP)	109/396 (28)	14/32 (44)	95/364 (26)	.03
Multiple recurrences of appropriate ICD therapy during follow-up	61/105 (58)	6/14 (43)	55/91 (60)	.22
Death	16 (4)	1 (3)	15 (4)	1

Values are given as median [interquartile range] or n (%) unless otherwise indicated.
ATP = antitachycardia pacing; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.
*Workup was considered complete when cardiac magnetic resonance, exercise treadmill, and sodium channel blocker provocation tests were performed.

Table 2 Clinical characteristics of adolescent-onset patients stratified by appropriate ICD therapy during follow-up

	Appropriate ICD therapy during follow-up (N = 14)	No appropriate ICD therapy during follow-up (N = 18)	*P* value
Age at first recurrence (y)	19 [18 – 20]		
First event ≤16 y	3 (21)	8 (44)	.26
Male	11 (79)	12 (67)	.69
First arrest during exercise	6/13 (46)	7/17 (41)	.79
Syncope before event	1 (7)	1/16 (6)	1
Family history of SCD	3 (21)	1 (6)	.30
DPP6 risk haplotype	3 (21)	0 (0)	.07
High PVC burden	5/9 (56)	4/15 (27)	.21
Nonsustained VT	6/10 (60)	7/15 (47)	.69
Antiarrhythmic therapy	9/10 (90)	6/15 (40)	.02
Antiarrhythmic therapy initiated before first appropriate ICD therapy	4/10 (40)	6/15 (40)	1

Values are given as median [interquartile range] or n (%) unless otherwise indicated.
ICD = implantable cardioverter-defibrillator; PVC = premature ventricular complex; SCD = sudden cardiac death; VT = ventricular tachycardia.

Current literature on pediatric patients

Studies focusing on pediatric SCA have shown that IVF can present during adolescence or even before.[13–18] Interestingly, patients included in an ICD study focusing on infants and toddlers had already received the diagnosis of apparent IVF.[19] The diagnostic workup and inclusion criteria influenced the number of underlying diagnoses determined at baseline or during follow-up in these studies, which are limited by their small sample sizes. A proportion of unexplained SCA/IVF cases up to 46% in a pediatric population presenting with an arrest or VF is high.[15] Adult studies focusing on determining the underlying causes of SCA reported lower proportions (between 1.2% and 6.8%) for IVF.[5,6] Because it was not the focus of most of the studies reporting on the epidemiology of SCA, the details of the diagnostic workup performed was not consistently reported. Current studies have focused on the diagnostic workup being performed in adults.[20] Recently, a post-SCA diagnostic workup for pediatric SCA patients, adapted from Stiles et al,[20] was proposed.[17] Performance of a complete diagnostic workup is important for both adults and pediatric SCA patients. As shown in our study, only a small proportion of UCA patients received a complete diagnostic workup. With these newly available diagnostic protocols for both pediatric and adult patients, the performance of diagnostic workups should increase, ultimately leading to a reduction in the percentage of unexplained cases. Awareness of this diagnostic protocol and its importance is needed outside the field of cardiology, especially with regard to pediatric patients, who are also treated by noncardiologists after SCA.

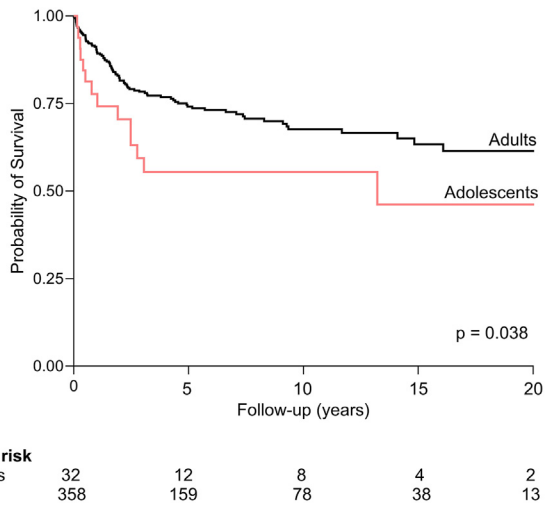

Figure 4
Clinical course with regard to appropriate implantable cardioverter-defibrillator (ICD) therapy stratified by age at ventricular fibrillation onset. Kaplan-Meier curves show a significant difference in survival free from appropriate ICD therapy between adolescent and adult presenting cases.

Malignant disease course for adolescent-onset patients

Consistent with previous literature, our study found that adolescent-onset IVF patients experienced more appropriate ICD therapy during follow-up compared with adult-onset IVF patients. Conte et al[9] showed similar results when comparing IVF patients having VF onset at age <16 years with adult-onset patients. In their study, age was the only predictor for arrhythmic events during follow-up. We did not find this risk previously[21]; however, at that time we focused only on age in a continuous matter. In this study, we looked at both and found results similar to those of Conte et al and others.[7–9] Frontera et al[7] showed that enhanced arrhythmic recurrences in pediatric IVF patients occurred over a prolonged period of time. In our study, median age at the second event was 19 [18–21] years, and multiple recurrences of appropriate ICD therapy during follow-up occurred at comparable rates with adult-onset patients. The survival curve indicates that adolescent-onset patients also have a more malignant course during early follow-up. In addition to appropriate ICD therapy, even though there were no statistical differences between adolescent-onset and adult-onset patients with regard to device complications, younger implant age might expose adolescent-onset patients to a higher overall lifetime burden. However, given our small sample size, future research should further clarify these findings. Given the differences in presentation compared with adult-onset patients, more insights into the role of adrenergic tone and hormonal influences during adolescent age could help explain the substrate and disease course in adolescent-onset patients.

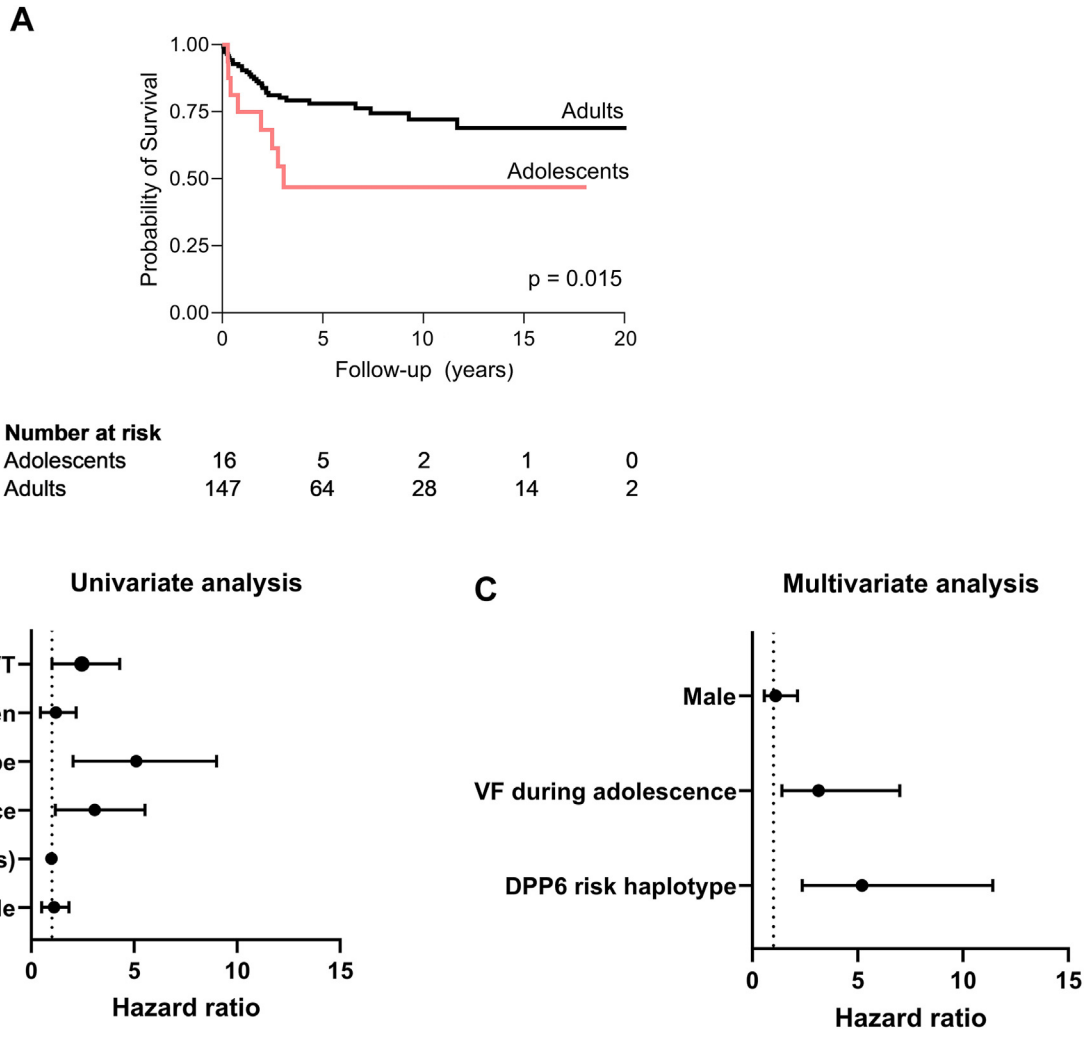

Figure 5
Clinical course of idiopathic ventricular fibrillation (VF) patients with a complete diagnostic workup. **A**: Kaplan-Meier curve indicating a significant difference in survival free from appropriate implantable cardioverter-defibrillator therapy during follow-up between adolescent-onset and adult-onset patients. **B, C:** VF during adolescence and carrying the *DPP6* risk haplotype did not overlap 1.0 for both univariate (**B**) and multivariate (**C**) analysis. NSVT = nonsustained ventricular tachycardia, PVC = premature ventricular complex.

Underlying explainable diagnoses

In our study, an underlying diagnosis was found in comparable rates between adolescent-onset and adult-onset patients. Our yield for adolescent-onset patients was higher than that found by Frontera et al[7] (diagnostic yield 15% vs 4%, respectively). The mean age of patients included in the study by Frontera et al[7] was lower compared with our study (12.7 ± 3.7 years), which might explain the difference in yield. In addition, the performed diagnostic workup could have been of influence. Some explainable diagnoses might be specifically applicable to pediatric or adolescent-onset IVF patients. As shown by Marsman et al,[22] a specific genetic (CALM) pathogenic variant might underlie childhood and adolescence IVF in some cases. In addition, supraventricular tachycardias (SVTs) without pre-excitation could be a more prevalent cause of ventricular arrhythmias in the pediatric population. The role of SVTs as a cause of SCA is described in adults and recently in pediatric patients as well.[23,24] Choi et al[24] described 3 cases in which an SVT was the cause of an initially unexplained arrest among 7 pediatric SCA patients. When the AV node is still capable of rapid conduction (eg, during pediatric age), SVTs as a cause of the arrest might be of more relevance. We previously reported 2 cases in which atrial fibrillation in combination with most likely enhanced AV nodal conduction was considered to be the cause of VF in 2 young IVF patients.[25] These findings, and as previously emphasized by Belhassen and Shauer,[26] indicate that an electrophysiological study could be of importance in adolescent-onset IVF patients.

Study limitations

The Dutch Idiopathic VF registry is one of the largest registries including IVF patients; however, our sample size of adolescent-onset patients was small. This limits our ability to identify differences having a clinical impact between adolescent-onset and adult-onset patients and to generalize our results. The retrospective aspects might have further influenced our results. To distinguish adolescent-onset and adult-onset patients, we used a cutoff of ≤19 years. Even though

this cutoff is frequently used in other studies also focusing on pediatric patients with SCA, it is arbitrary. Lastly, primarily cardiologists who see adult patients contribute to the Dutch Idiopathic VF Registry, so pediatric patients who did not reach adult care could be missed. For participating centers Amsterdam UMC and Erasmus MC Sophia Children's Hospital, these children most likely were included in the recent study by Bakker er al.[17]

Conclusion

IVF patients with onset during adolescence differ with regard to underlying triggers during the index event and have higher vulnerability to ventricular arrhythmias during follow-up.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.03.031.

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Address reprint requests and correspondence: Dr Lisa M. Verheul, University Medical Center Utrecht, Heidelberglaan 100, 3584CX, Utrecht, The Netherlands. E-mail address: l.m.verheul-5@umcutrecht.nl

References

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Developed by the task force for the management of patients with death of the European Society of Cardiology. Eur Heart J 2022;43:3997–4126.
2. 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;7:205–211.
3. 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;7:1383–1389.
4. Visser M, van der Heijden JF, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic ventricular fibrillation. Circ Arrhythm Electrophysiol 2016;9:1–11.
5. Waldmann V, Bougouin W, Karam N, 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.
6. Conte G, Luce Caputo M, Regoli F, et al. True idiopathic ventricular fibrillation in out-of-hospital cardiac arrest survivors in the Swiss Canton Ticino: prevalence, clinical features, and long-term follow-up. Europace 2017;19:259–266.
7. Frontera A, Vlachos K, Kitamura T, et al. Long-term follow-up of idiopathic ventricular fibrillation in a pediatric population: clinical characteristics, management, and complications. J Am Heart Assoc 2019;8:e011172.
8. Cunningham T, Roston TM, Franciosi S, et al. Initially unexplained cardiac arrest in children and adolescents: a national experience from the Canadian Pediatric Heart Rhythm Network. Heart Rhythm 2020;17:975–981.
9. Conte G, Belhassen B, Lambiase P, 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;21:1670–1677.
10. World Health Organization. Adolescent Health, https://www.who.int/health-topics/adolescent-health#tab=tab_1. Accessed January 23, 2024.
11. Groeneveld SA, Verheul LM, van der Ree MH, et al. The importance of systematic diagnostic testing in idiopathic ventricular fibrillation. JACC Clin Electrophysiol 2022;9:345–355.
12. Alqarawi W, Dewidar O, Tadros R, et al. Defining idiopathic ventricular fibrillation: a systematic review of diagnostic testing yield in apparently unexplained cardiac arrest. Heart Rhythm 2021;18:1178–1185.
13. Alapati S, Strobel N, Hashmi S, Bricker JT, Gupta-Malhotra M. Sudden unexplained cardiac arrest in apparently healthy children: a single-center experience. Pediatr Cardiol 2013;34:639–645.
14. Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. Int J Cardiol 2018;270:214–220.
15. Hylind RJ, Chandler SF, Ladouceur VB, et al. Clinical and genetic findings in children presenting with ventricular fibrillation as the first manifestation of cardiovascular disease. J Am Heart Assoc 2020;9:9–11.
16. Robinson JA, Lapage MJ, Atallah J, et al. Outcomes of pediatric patients with defibrillators following initial presentation with sudden cardiac arrest. Circ Arrhythm Electrophysiol 2021;14:e008517.
17. Bakker AM, Albrecht M, Verkaik BJ, et al. Sudden cardiac arrest in infants and children: proposal for a diagnostic workup to identify the etiology. An 18-year multicenter evaluation in the Netherlands. Eur J Pediatr 2024;183:335–344.
18. Heersche JHM, Blom NA, Van De Heuvel F, et al. Implantable cardioverter defibrillator therapy for prevention of sudden cardiac death in children in the Netherlands. Pacing Clin Electrophysiol 2010;33:179–185.
19. Zahedivash A, Hanisch D, Dubin AM, et al. Implantable cardioverter defibrillators in infants and toddlers: indications, placement, programming, and outcomes. Circ Arrhythm Electrophysiol 2022;15:E010557.
20. Stiles MK, Wilde AAM, Abrams DJ, 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–e50.
21. Blom LJ, Visser M, Christiaans I, et al. Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. Europace 2019;21:1519–1526.
22. Marsman RF, Barc J, Beekman L, et al. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. J Am Coll Cardiol 2014;63:259–266.
23. 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;18:1711–1719.
24. Choi NH, Silver ES, Liberman L. Supraventricular tachycardia without preexcitation as a cause of sudden cardiac arrest in pediatric patients. Pediatr Cardiol 2022;43:218–224.
25. Verheul LM, Groeneveld SA, Tuinenburg AE, Hassink RJ. Atrial fibrillation begets ventricular fibrillation when the AV node fails. J Electrocardiol 2023;76:66–70.
26. Belhassen B, Shauer A. Nine reasons for performing an electrophysiology study in patients with apparently idiopathic ventricular fibrillation. Heart Rhythm 2022;19:1212–1213.