Family History and Warning Symptoms Precede Sudden Cardiac Death in Arrhythmogenic Right Ventricular Cardiomyopathy (from a Nationwide Study in Sweden)

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiac disease explaining about 4% of sudden cardiac death (SCD) cases in the young in Sweden. This study aimed to describe the circumstances preceding SCD in all victims <35 years of age who received an autopsy-confirmed diagnosis of ARVC from January 1, 2000, to December 31, 2010, in Sweden (n = 22). Data on demographics, medical and family history, circumstances of death, and anatopathological findings were collected from several compulsory national health registries, clinical records, family interviews, and autopsy reports. Registry-based data were compared with age-matched, gender-matched, and geographically-matched population controls. During the 6 months preceding SCD, 15 cases (68%) had experienced symptoms of cardiac origin, mainly syncope or presyncope (54%) and chest discomfort (27%). A total of 8 cases (36%) had sought medical care because of cardiac symptoms. The occurrence of hospital visits was significantly increased in cases compared with controls (odds ratio 4.62 [1.35 to 15.8]). A total of 10 cases (45%) had a family history of SCD. The most common activity at the time of death was exercise (41%). A complete cardiac investigation was seldom performed; only 1 case was diagnosed with ARVC before death. In conclusion, in this nationwide study, we observed a high prevalence of symptoms of cardiac origin, healthcare use, and family history of SCD preceding SCD in the young caused by ARVC. Increased awareness of these warning signals in younger patients is critical to improving risk stratification and early disease detection. © 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) (Am J Cardiol 2022;178:124–130)

**Introduction**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiac disease affecting 1:1000 to 1:5000 patients.\textsuperscript{1,2} ARVC is characterized by integrity loss of the intercalated disk, followed by apoptosis and fibrofatty replacement of the myocardium, leading to arrhythmia and impaired systolic function.\textsuperscript{1,3} Early disease recognition is a pervasive challenge; patients can present with a spectrum of ventricular arrhythmias, from benign premature extrasystoles (ventricular extrasystoles) to sustained ventricular tachycardias (VTs) and sudden cardiac death (SCD) before detectable structural changes occur.\textsuperscript{1,3} ARVC is indeed one of the leading causes of SCD in the younger population, explaining 5% to 15% of SCD cases in Europe and up to 32% of SCD in competitive athletes.\textsuperscript{1–3,5} In Sweden, the incidence of SCD in patients aged 1 to 35 years between 2000 and 2010 was 1.3 × 100,000 person-year, and ARVC was the cause of death in 22 cases (4%).\textsuperscript{9,10} In the present study, we describe the family history, symptoms, hospital care use, and circumstances of the death of these 22 patients, based on data from national health registries, medical records (MRs), family interviews, and autopsy reports.

**Methods**

All subjects aged 1 to 35 years who died of SCD with autopsy-confirmed ARVC as the probable cause of death from January 1, 2000, to December 31, 2010, in Sweden were included in the study (n = 22). Cases were identified through nationwide registry data from the Swedish National Board of Forensic Medicine and the Swedish Cause of Death Registry. Autopsy reports and death certificates were manually reviewed by a single forensic pathologist to confirm the postmortem ARVC diagnosis. The nationally standardized autopsy protocols followed during the study period, and the criteria by which SCD subjects were
selected have been previously described. For every case, 5 controls matched by gender, birth year, and county were identified from the Swedish Register of the Total Population and Population Changes (n = 110). Parents of the cases were identified from the Swedish Multi-generation Register.

Data from cases, patients, and controls were extracted from the SUDDY (Swedish SUDden Cardiac Death of the Young study database), which integrates multisource data from several mandatory Swedish National Health Registries (Supplementary Table 1). Data from the National Patient Registry (NPR), the Swedish Cause of Death Registry, and the longitudinal integrated database for health insurance and labor market studies LISA were specifically retrieved for this study. The NPR includes all hospital visits (hospitalizations and outpatient visits) from all Swedish private and public caregivers. Primary care visits are not covered. Hospital visits and registered diagnoses related to the cardiovascular system, according to the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10) (R00-R09, R55, R56, I42-I43, I44-I49, I30-41, I50-52), were compared between cases and controls. The time preceding SCD was defined as the 6 months before death occurred. The date when the control was the same age as the matched case at the date of death was taken as the reference date. MRs from all hospital visits were retrieved. MRs from primary care visits were retrieved only when they were included in the autopsy report. Electrocardiograms (ECGs) were collected from MRs and premilitary conscription examination and revised by a cardiologist with expertise in ARVC and arrhythmias, together with the reports from echocardiography, cardiac magnet resonance imaging, and 24 hours ECG recordings when performed. All MRs were pseudonymized by assigning each subject a case number.

In 16 cases (73%), a parent or spouse agreed to answer a standardized interview-based questionnaire over the phone, including a three-generation family history.

In Sweden, autopsies are performed either at the regional centers of the Swedish National Board of Forensic Medicine (forensic autopsy) or the hospital clinical pathology departments (clinical autopsy). Full reports from the forensic and clinical autopsies were available.

Data from the MRs, family interviews, and autopsy reports were systematically extracted and integrated using a standardized protocol, including (1) medical history, (2) symptoms before death, (3) information on intensity and frequency of physical activity, including previous sports participation; (4) family history of SCD, cardiomyopathy, arrhythmogenic syndrome or implantable cardioverter-defibrillator (Only family history before the index case died was included); (5) time and circumstances of death, prodromal symptoms; and (6) autopsy findings. All cardiac investigations performed were retrospectively assessed according to the ARVC 2010 Task Force Criteria (TFC). Exercise-related SCD was defined as an SCD that occurred during or within 1 hour after exercise. Sports-related SCD was defined as exercise-related SCD in competitive athletes. Competitive sports were defined as sports in which the participants trained either regularly or inconsistently without requiring systematic training or pursuing excellence. The study was approved first by the Regional Ethical Review Boards at Umeå and later at Uppsala University (Dnr: 2017/430 and 2017/431). Participating parents signed informed consent.

Descriptive statistics were presented as numbers and percentages for categorical variables, and mean and SDs for continuous variables. Odds ratios (ORs) (95% confidence intervals [CI]) comparing cases and controls were assessed using conditional logistic regression accounting for matching. The p < 0.05 from 2-sided tests were considered statistically significant. The analyses were performed with SPSS Statistical Software Version 26.0 (IBM SPSS Statistics, Armonk, New York) and R Version 4.0, 2020 (http://www.R-project.org) (The R Foundation for Statistical Computing, Vienna, Austria).

### Results

The sociodemographic characteristics of the 22 patients aged <35 years who died of SCD caused by autopsy-confirmed ARVC from 2000 to 2010 and 110 matched controls are listed in Table 1. The age of death ranged from 12 to 35 years, and 64% were male. Cases were evenly distributed during time and across the country (Supplementary Table 2).

During the 6 months preceding death, 15 cases (68%) were reported to have experienced warning symptoms such as palpitations (41%), syncope (27%), presyncope (27%), chest discomfort (27%, defined as either chest pain or dyspnea), and seizures (14%) (Figure 1, Table 2). A total of 8 subjects (36%) sought medical care for cardiac symptoms during this period (Figure 1). They received a diagnosis of myocarditis (n = 1), right ventricular outflow tract (RVOT)
tachycardia (n = 1), ARVC (n = 1), dyspepsia (n = 2), or none (n = 3). A total of 2 additional subjects had healthcare visits for other reasons, a postpartum complication and a preauricular cyst excision, respectively.

Based on national data from the NPR alone, 41% of the cases (9 of 22) had registered at least 1 hospital visit compared with 17% (19 of 110) of the controls (OR 4.63 [95% CI 1.35 to 15.8] p = 0.010). Furthermore, a cardiac-related ICD-10 diagnosis code was registered in 5 case hospital visits compared with none of the controls (p < 0.001) (Table 3).

A history of VT was present in 4 cases (19%). One of these was (the only case) diagnosed with ARVC before death. Another case had a slightly impaired left ventricular ejection fraction (approximately 50%). After extensive investigation with echocardiography, coronary angiography, and signal average ECG, this case was diagnosed with benign RVOT tachycardia and was scheduled for an ablation, but died the day before the procedure. The third case had survived a cardiac arrest at the age of 10 years and was diagnosed with long QT syndrome (LQTS). Genetic testing could not confirm the diagnosis. The fourth case had documented ventricular extrasystoles and a non-sustained VT during a neck surgery at the age of 11 years, but further investigation was not performed. Two years later, this patient experienced seizures and received a diagnosis of epilepsy, despite an inconclusive electroencephalogram. None of the cases had received an implantable cardioverter-defibrillator.

A 12-lead ECG was available for 11 cases, of which 3 were performed within 6 months before death (range 14 days to 17 years). Echocardiography was performed on 4 subjects because of syncope/presyncope (n = 2), seizures (n = 1), or within the framework of family screening (n = 1). Further investigation with 24 hours ECG monitoring was performed in 3 of them. Retrospectively, 4 cases fulfilled at least 1 major or minor criteria according to the later implemented 2010 TFC, including 2 who fulfilled criteria for definitive ARVC diagnosis and 1 for a borderline diagnosis (Supplementary Table 3). One individual had clinical suspicion of myotonic dystrophy type 1; however, no cardiac examination nor genetic testing was documented in the MRs.

A total of 8 cases (36%) were female. Of them, 4 had previously been pregnant, and 3 had a history of spontaneous (not recurrent) abortions. One case had an emergency cesarean section because of fetal stress and significant intrapartum hemorrhage 2 months before death, and another was 8 weeks pregnant at the time of death.

A total of 10 subjects (45%) had a family history of SCD (Figure 1). Of those, only 2 occurred in first-degree relatives and the rest in second-degree relatives. Moreover, 4 cases had lost 2 or more relatives because of SCD, and in 7 relatives, SCD had occurred before the age of 40. In addition, 2 cases had a living relative with an arrhythmogenic syndrome (Table 4). Genetic testing had only been performed in the case diagnosed with LQTS without the identification of any disease-causing variants.

Most subjects were physically active, and 23% were involved in competitive sports, whereas 55% practiced recreational sports activities. Most (68%) participated in high dynamic physical activities such as soccer, ice hockey, basketball, running, floorball, and swimming (Table 5). Death
Cardiomyopathy/SCD due to ARVC among the young in Sweden

Table 2
Clinical characteristics of cases suffering SCD due to ARVC

<table>
<thead>
<tr>
<th>Symptoms six months preceding sudden cardiac death</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All symptoms</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>No symptoms</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy (ARVC)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Channelopathy</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Aborted SCD</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Impaired systolic cardiac function</td>
<td></td>
</tr>
<tr>
<td>- Right ventricle (FAC&lt;40)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>- Left ventricle (LV-EF&lt;55%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>- Sustained</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>- Non-sustained</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>- PVC&gt; 500/24 hours</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (14%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac investigation performed</th>
<th>Minor - major TFC fulfilled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>4 (18%) 1 (4.5) - 0</td>
</tr>
<tr>
<td>ECG</td>
<td>11 (50%) 2 (9) - 2 (9)</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>2 (9%) 1 (4.5) - 1 (4.5)</td>
</tr>
<tr>
<td>Depolarization abnormalities</td>
<td></td>
</tr>
<tr>
<td>24-hours ECG recording</td>
<td>3 (14%) 0 - 2 (9)</td>
</tr>
</tbody>
</table>

The table shows the number of cases with arrhythmogenic right ventricle cardiomyopathy (ARVC) that were reported to have symptoms during the six months preceding SCD (sudden cardiac death), as well as information on previous medical history and cardiac investigations from birth according to the medical records. Available full reports of echocardiograms and electrocardiograms (ECG) where evaluated according to the ARVC 2010 Task Force Criteria (TFC).11

FAC = fractional area change; LV-EF = left ventricle ejection fraction; PVC = Premature ventricular complex.

was exercise-related in 9 cases (41%), occurring either during exercise (n = 5) or ≤1 hour after exercise (n = 4). Two of these subjects were competitive athletes and therefore considered to have a sports-related death. The next most common activities were rest (23%), sleep (23%), and daily routine activities (14%) (Figure 2).

A total of 7 subjects (32%) experienced prodromal symptoms immediately before cardiac arrest, including chest pain, palpitations, seizures, or nausea; 5 (23%) collapsed without any prodromal symptoms, and in 10 cases, death was unobserved (45%).

The autopsy findings are listed in Table 6. All cases received a postmortem diagnosis of ARVC as the probable cause of death after a forensic (12 of 22) or a clinical autopsy (10 of 22) (inclusion criteria). Histopathological examination was performed in all cases. Complementary microbiology and toxicology investigations were performed in 4 and 13 cases, respectively. The myocardial changes (fibrosis, fatty infiltration, or both) were evident only after microscopic histopathological examination in 13 cases (60%), and biventricular involvement was present in 12 (55%). In 2 cases, blood samples were collected at the autopsy and archived in a research biobank for future studies, but no genetic testing was done.

Discussion

The most important finding in this nationwide study is that most young patients who died of SCD because of ARVC had experienced cardiac symptoms during the last 6 months preceding death. The most common symptoms were syncope/pre-syncope followed by chest discomfort, consistent with previous reports.8,14,15 Health care use in cases was significantly higher compared with age-matched, gender-matched, and geographically-matched population controls, and a large proportion of the cases had a family history of sudden premature death. Despite this, only a few of the symptomatic cases were further assessed for malignant arrhythmias. Retrospectively, 4 cases fulfilled at least 1 major ECG criterion for ARVC during a health care visit according to the later implemented 2010 TFC. However, the ECG was considered normal at that time in 3 of the cases. Significant dilatation of either the right ventricle (27%) or both ventricles (32%) was evident on autopsy, suggesting that most subjects could probably have been diagnosed if echocardiography had been performed. These findings emphasize why early recognition of the disease in patients seeking medical care with alarming symptoms and family history is critical, as SCD can be the first disease manifestation, often before detectable structural changes occur.

About half of the cases had a family history of SCD, and some had lost multiple relatives because of early SCD. The affected patients were more often second-degree relatives, probably reflecting the incomplete penetrance of the disease estimated to be up to 50%.16,17 This also indicates a considerable risk of death in first-degree and second-degree relatives of SCD victims and, therefore, the need for comprehensive clinical evaluation of surviving relatives. The importance of careful family history for patients at risk of SCD is well recognized.18 Despite this, it was poorly documented in the MRs, even for the athletes. The 2010 TFC only considers a positive family history of ARVC or SCD <35 years in first-degree relatives as a major criterion.14 However, given the phenotypic overlap of inherited cardiomyopathies and arrhythmogenic syndromes, all cases of cardiac disease and unexplained deaths in first-degree and second-degree relatives should be taken into consideration during family history assessment.

Our results agree with previous nationwide studies in Sweden, Denmark, and the United States, also reporting a high prevalence of symptoms, medical contacts, and family history.8,15,19,20 In Sweden, the same trend, including a low diagnostic rate, was observed in young victims of SCD because of ARVC in a nationwide study from 1992 to 1999,15 indicating that no significant improvement was made in the risk assessment of young patients who sought medical care because of heart-related symptoms during the following 10 years.

In line with previous studies, the prevalence of exercise-related SCD observed in ARVC subjects (41%) was higher...
than in all SCD victims from the SUDDY cohort (12%). Although only 9% of exercise-related deaths occurred in subjects considered competitive athletes, most subjects practiced sports as recreational activities. Independently of the level of training, most victims (68%) were involved in high dynamic sports.

In contrast to our results, a recent study in the United Kingdom on SCD victims because of arrhythmogenic cardiomyopathy reported a much lower frequency of symptoms and a higher percentage of sports-related SCD. However, this cohort consists of an older population with a broader phenotypic spectrum of arrhythmogenic cardiomyopathy.

A total of 8 cases in our cohort were female (36%). Recent complications during delivery and pregnancy at the time of SCD were observed. Pregnancy has been, however, considered to be well-tolerated in ARVC regarding arrhythmias and heart failure. More studies investigating the role of pregnancy in ARVC are needed.

The table shows the number of cases who had a family history of SCD or a living relative with an arrhythmogenic syndrome at the time of death. The causes of SCD in relatives are shown. In five relatives the postmortem diagnosis after SCD was unknown. Family history of ICD and epilepsy were included, as they were considered suggestive of cardiac disease. Family history was investigated among all first- (FDR) and second-degree relatives. ARVC TFC diagnostic criteria were fulfilled only in two cases who had a FDR with ARVC, including one who suffered SCD.

ARVC = arrhythmogenic right ventricular cardiomyopathy, TFC = Task Force Criteria, ICD = implantable cardioverter defibrillator, SCD = sudden cardiac death.

In Table 4, the number of cases who had a family history of SCD or a living relative with an arrhythmogenic syndrome at the time of death is shown. The causes of SCD in relatives are shown. In five relatives the postmortem diagnosis after SCD was unknown. Family history of ICD and epilepsy were included, as they were considered suggestive of cardiac disease. Family history was investigated among all first- (FDR) and second-degree relatives. ARVC TFC diagnostic criteria were fulfilled only in two cases who had a FDR with ARVC, including one who suffered SCD.

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ARVC = arrhythmogenic right ventricular cardiomyopathy, TFC = Task Force Criteria, ICD = implantable cardioverter defibrillator, SCD = sudden cardiac death.
The results of the present study highlight how challenging it is to recognize ARVC early and identify young patients at risk of SCD. Remarkably, most cases who sought medical care before death underwent minimal, if any, investigation, reflecting an unfortunate trend to underestimate symptoms in younger patients. Warning symptoms of possible impaired cardiac function in children and adolescents should not be overlooked, and expedited complete cardiac evaluation should be guaranteed, particularly in the presence of a family history of SCD or other inherited cardiovascular disorders, as the time window to intervene is very narrow.20

The limitations of the study include that it is retrospective and based on autopsies performed at different centers following standardized protocols available at the time of investigation. To overcome this, all autopsy reports in the SUDDY cohort were manually revised to confirm the diagnosis; however, we cannot exclude that some ARVC cases went unrecognized. Cases whose deaths were not sudden and resuscitated victims of SCD are not included; this study is, therefore, a series of cases with the worst outcome. Retrieving retrospective data through phone calls and questionnaires to family members may lead to underreporting or erroneous recall of symptoms, signs, and history of physical activity of the deceased. However, registry-based data regarding medical contacts was consistent with the information provided by the relatives. Finally, postmortem genetic testing was not routinely performed during the study period; therefore, the ARVC diagnosis was not genetically confirmed in any of the cases. Recommendations are in place today to include genetic testing as part of the postmortem investigation of SCD.25,26

In conclusion, in this nationwide, longitudinal study of SCD in the young, we observed that most victims of SCD caused by ARVC had warning symptoms of cardiac origin, with syncope/presyncope being the most prevalent symptom before death. Despite that half of the patients with cardiac symptoms had sought medical care, only 1 was recognized as having a potentially fatal disease. Furthermore, family history of SCD and arrhythmogenic disease was common but in most cases, overlooked and inherited cardiac disease was not suspected.

Disclosures
The authors have no conflicts of interest to declare.

Acknowledgment
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Data availability
Because of Swedish legislation, the data is not freely accessible. However, within a collaboration, aggregated data would be available.
Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajconline.2022.05.015.


