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CLINICAL RESEARCH
Arrhythmias

Short-coupled ventricular fibrillation represents a distinct phenotype among latent causes of unexplained cardiac arrest: a report from the CASPER registry

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Aims The term idiopathic ventricular fibrillation (IVF) describes survivors of unexplained cardiac arrest (UCA) without a specific diagnosis after clinical and genetic testing. Previous reports have described a subset of IVF individuals with ventricular arrhythmia initiated by short-coupled trigger premature ventricular contractions (PVCs) for which the term short-coupled ventricular fibrillation (SCVF) has been proposed. The aim of this article is to establish the phenotype and frequency of SCVF in a large cohort of UCA survivors.

Methods and results We performed a multicentre study including consecutive UCA survivors from the CASPER registry. Short-coupled ventricular fibrillation was defined as otherwise unexplained ventricular fibrillation initiated by a trigger PVC with a coupling interval of <350 ms. Among 364 UCA survivors, 24/364 (6.6%) met diagnostic criteria for SCVF. The diagnosis of SCVF was obtained in 19/24 (79%) individuals by documented ventricular fibrillation during follow-up. Ventricular arrhythmia was initiated by a mean PVC coupling interval of 274 ± 32 ms. Electrical storm occurred in 21% of SCVF probands but not in any UCA proband ($P < 0.001$). The median time to recurrent ventricular arrhythmia in SCVF was 31 months. Recurrent ventricular fibrillation resulted in quinidine administration in 12/24 SCVF (50%) with excellent arrhythmia control.

Conclusion Short-coupled ventricular fibrillation is a distinct primary arrhythmia syndrome accounting for at least 6.6% of UCA. As documentation of ventricular fibrillation onset is necessary for the diagnosis, most cases are diagnosed at the time of recurrent arrhythmia, thus the true prevalence of SCVF remains still unknown. Quinidine is effective in SCVF and should be considered as first-line treatment for patients with recurrent episodes.

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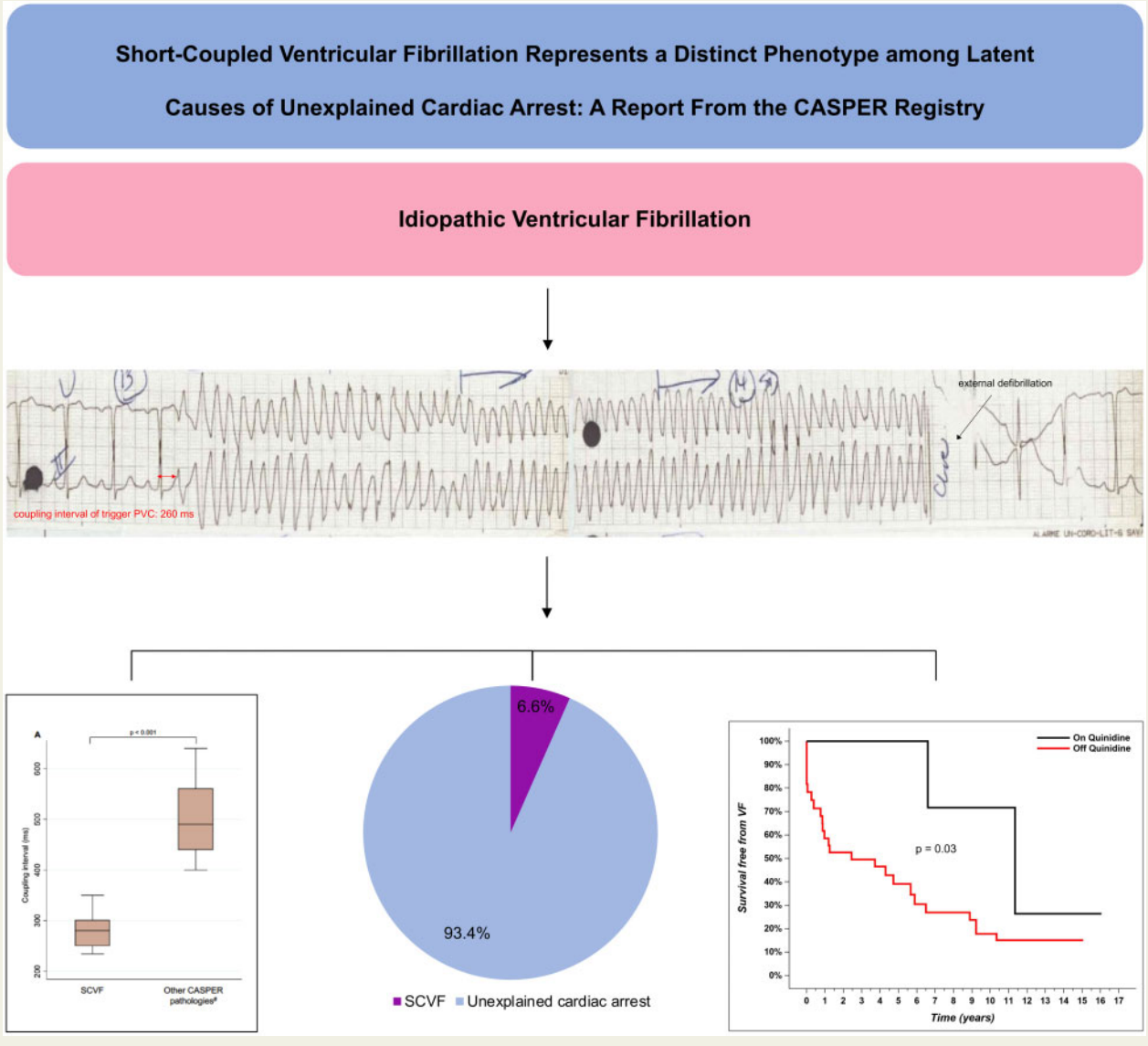
Graphical Abstract



Short-coupled ventricular fibrillation (SCVF) is a distinct primary electrical disorder accounting for at least 6.6% of otherwise idiopathic VF. Quinidine is highly effective for SCVF.

Keywords CASPER • Short-coupled ventricular fibrillation • Unexplained cardiac arrest • Idiopathic ventricular fibrillation • Premature ventricular contraction • Quinidine

Background

Sudden unexplained death (SUD) and aborted unexplained cardiac arrest (UCA) are devastating events that account for up to 30–45% of life-threatening conditions in younger (<45 years) individuals with cardiac arrest.[1] Previous studies have demonstrated that a significant proportion of UCA/SUD events are related to previously undiagnosed inherited arrhythmia conditions.[1,2] Use of a comprehensive stepwise approach of clinical and genetic testing reveals a specific diagnosis in up to 56% of individuals with arrhythmic cardiac arrest in the absence of overt structural heart disease or other reversible causes.[3] The remaining UCA individuals are typically labelled with a diagnosis of idiopathic ventricular fibrillation (IVF). This diagnosis has been used historically as a purely descriptive term for unexplained ventricular fibrillation (VF) in the absence of structural heart disease and included specific primary electrical diseases such as Brugada

syndrome or short-QT syndrome prior to their characterization.[4] Current guidelines define IVF as 'a resuscitated cardiac arrest victim, preferably with documentation of VF, in whom known cardiac, respiratory, metabolic and toxicological etiologies have been excluded through clinical evaluation'.[5]

However, over the past 30–35 years, a specific subtype of IVF has been described that is typically initiated by short-coupled trigger premature ventricular contractions (PVCs).[6–9] There is now growing evidence that this particular phenotype is actually a distinct electrical entity for which we propose the term 'short-coupled ventricular fibrillation' (SCVF).[6–12] Due to the lack of stringent terminology, the terms IVF and SCVF are still often confounded and erroneously used as synonyms in the literature. The first suspicion that SCVF may actually represent a distinct primary electrical disorder has been evoked in the early 1990s when the concept of VF with short-coupled trigger PVCs was first reported.[7–9] However, there is still no standardized definition of SCVF distinguishing this particular arrhythmia from other primary arrhythmia syndromes with similar findings such as early repolarization syndrome or short-QT syndrome that have subsequently emerged and may have contaminated historical cohorts of patients with unexplained VF.

We hypothesized that SCVF represents a distinct primary electrical disease. Data about the proportion, in-depth characterization, and optimal treatment of SCVF in contemporary cohorts of UCA are limited.

The aim of this study was to assess the overall prevalence of SCVF in a large cohort of UCA survivors and to provide in-depth standardized clinical and genetic characterization of affected patients. We also propose standardized criteria to facilitate the diagnostic approach to this particular condition.

Methods

Study population

The present study is a substudy from the CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry) registry, which is a national, multicentre registry enrolling since January 2004 UCA survivors and their 1st-degree family members as well as 1st-degree relatives of SUD victims with negative autopsy and toxicology screening.[3,13] A detailed description of the protocol and eligibility criteria has been published previously (see also Supplementary material online, *Table S1*).[3] Standardized, guideline-derived diagnostic criteria for known inherited arrhythmia syndromes and genetic cardiomyopathies were applied as previously published by our group (Supplementary material online, *Table S2*).[14]

For the present study, we included probands with a history of resuscitated cardiac arrest and working diagnosis IVF/UCA after comprehensive stepwise clinical assessment and negative or inconclusive genetic testing (*Figure 1*). Eligible individuals were enrolled from January 2004 until September 2019. All individuals with recurrent VF/polymorphic ventricular tachycardia (VT) at any point during follow-up were eligible. For UCA patients without recurrent ventricular arrhythmia, a minimal follow-up of 12 months was recommended to increase the sensitivity for late arrhythmic events. Written informed consent was obtained from all study subjects, and the study protocol was approved by the local research ethics board of each participating centre.

Definition of short-coupled ventricular fibrillation

We propose the term SCVF for this distinct phenotype. To distinguish this particular condition from other primary electrical disorders and reversible conditions associated with spontaneous polymorphic VT/VF, we sought to determine clinical and electrophysiological features unique for this particular condition. The coupling interval of trigger PVCs in confounding conditions such as hereditary long-QT syndrome, (post)-ischaemia-related VF, or pause-dependent torsade de pointes is typically at least at 490–514 ms.[15,16] We defined the coupling interval of the trigger PVCs as the interval between the QRS onset of the preceding conducted sinus beat and the QRS onset of the PVC initiating VF/polymorphic VT. Assuming a normal distribution of the spontaneous variation in coupling intervals for these conditions, we analysed the upper coupling limit of SCVF trigger PVCs to define a cut-off value that (i) would be separated by ≥ 2 standard deviations (excluding 95% of potentially confounding differential conditions), and (ii) represent the 95% percentile of all SCVF cases. Based on these requirements and the results of our observations (see Results section), we propose a definition of SCVF requiring all of the following:

(1) documentation of VF or polymorphic VT initiated by a PVC with a coupling interval of < 350 ms;
(2) absence of QTc prolongation according to current definitions[5];
(3) absence of pause-dependent torsade de pointes [preceding R–R interval prior to the trigger PVC >1500 ms in individuals without pacemaker/implantable cardioverter-defibrillator (ICD) or >1300 ms in individuals with pacemaker/ICD] following a stable baseline rhythm.[15] However, initiation of ventricular arrhythmia by short-long-short cycles (R–R cycles <1300 ms) with short-coupled trigger PVCs was eligible as described previously for Brugada syndrome and early repolarization syndrome[17];
(4) absence of type 1 Brugada pattern (spontaneous or inducible), early repolarization pattern or short-QT according to current definitions and guidelines at the index cardiac arrest or during follow-up[5,18,19];
(5) absence of catecholaminergic polymorphic ventricular tachycardia (CPVT) according to current definitions[14];
(6) absence of structural heart disease (no active ischaemia or coronary artery disease with >50% stenosis, no left ventricular ejection fraction <50%) or other primary electrical disorder or arrhythmogenic cardiomyopathy as previously defined[3];
(7) absence of reversible metabolic or pharmacological/toxicological conditions that may cause similar electrophysiological findings.

Implantable cardioverter-defibrillator interrogations

Appropriate and inappropriate ICD therapies were independently assessed and ICD-recorded episodes of SCVF were only accepted if complete interrogation data including tracings of the event-related intracardiac electrogram were available. In addition, diagnostic electrocardiogram (ECG) or telemetry tracings of corresponding arrhythmic events were also included where available. All ICD tracings and available ECG/telemetry tracings were reviewed and reclassified by an experienced electrophysiologist (C.S.). There was no VF/VT undersensing in any of the analysed ICD tracings.

Cardiac investigations

All study subjects underwent extensive comprehensive cardiac testing to screen for structural heart disease or inherited arrhythmia syndromes using a stepwise systematic approach as previously reported (Supplementary material online, *Figure S1*).[3] After elimination of coronary artery

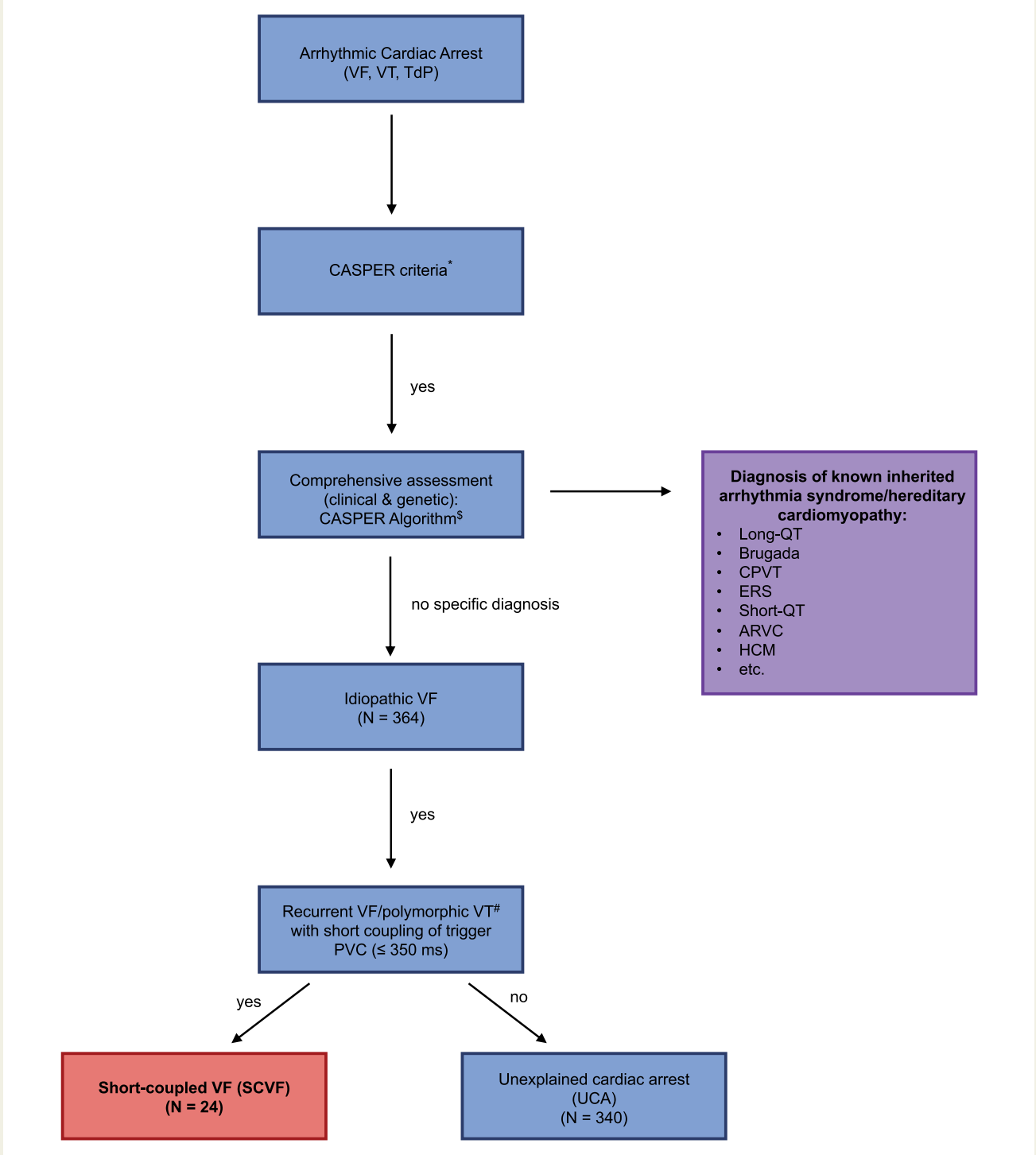


Figure 1 Study flow chart. Shown is the diagnostic approach for CASPER probands with an initial working diagnosis of idiopathic ventricular fibrillation. Key criteria for short-coupled ventricular fibrillation include the documentation of recurrent ventricular fibrillation/polymorphic ventricular tachycardia initiated by a trigger premature ventricular contraction with a coupling interval of ≤ 350 ms and absence of diagnostic criteria for other distinct inherited arrhythmia syndromes. *Refer to the CASPER inclusion criteria in the Supplementary material online, *Methods* section. $Please refer to the recommended diagnostic CASPER inclusion criteria (Supplementary material online, *Table S1*). #Recurrent ventricular fibrillation/polymorphic ventricular tachycardia episodes included episodes during follow-up or documented episodes of spontaneous ventricular fibrillation/polymorphic ventricular tachycardia recurrence during the index hospitalization (including those individuals with electrical storm upon initial presentation). ARVC, arrhythmogenic right ventricular cardiomyopathy; CASPER, Cardiac Arrest Survivors With Preserved Ejection Fraction Registry; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; PVC, premature ventricular contraction; SCVF, short-coupled ventricular fibrillation; TdP, torsade de pointes; VF, ventricular fibrillation; VT ventricular tachycardia.

disease by coronary angiography or cardiac computed tomography, basic cardiac workup included a detailed personal history and family history with a three-generation pedigree, repeat resting ECGs with standard and high precordial leads, symptom-limited exercise treadmill testing, ambulatory Holter monitoring, signal-averaged ECG, and transthoracic echocardiogram. Interpretation of electrocardiographic exams was performed according to guideline-derived criteria as previously described.[20] Cardiac magnetic resonance imaging was performed in most individuals, and pharmacological provocation with procainamide or epinephrine was performed in selected patients based on clinical suspicion and physician preference.

Genetic testing

All SCVF patients underwent whole exome sequencing (WES) that was performed by a commercial laboratory (Blueprint Genetics, Espoo, Finland) or a research laboratory (Montreal Heart Institute, Montreal, Canada), targeting a mean coverage of 100×. Sequencing platforms used for this study included the Illumina HiSeq2000 (Illumina, San Diego, CA, USA) and the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Analysis was performed using a virtual panel of genes previously implicated in cardiac arrhythmias and/or cardiomyopathies. With regard to the DPP6 gene, complete sequencing of all exons and exon-intron boundaries was performed by no haplotype analysis. Exon capture was performed using the Roche NimbleGen SeqCap EZ kit (Roche, Madison, WI, USA) (along with the HiSeq200) and SeqCap EZ MedExome kit (Roche, Madison, WI, USA) (along with the NovaSeq 6000).

Variant analysis was performed using the genome analysis toolkit (GATK) (Broad Institute, Cambridge, MA, USA) and in-house scripts as reported previously.[21] Variant analysis was subsequently limited to 196 pre-specified genes (Supplementary material online, *Table S3*). Unlimited WES analysis was performed by a commercial laboratory in 4/24 SCVF individuals (17%). As this approach was previously not available for clinical diagnostic purposes, it was only performed in the four most recently diagnosed SCVF patients.

Genetic variants were classified according to current guidelines.[22] Additional tools used for variant interpretation included freely available online tools such as VarSome and ClinVar.[22–25] *In silico* prediction was performed using the SIFT, PolyPhen-2, and MUTTASTER-2 software.[26–29]

Diagnostic strength

All clinical diagnoses were re-evaluated at the time of study follow-up and revised on the basis of clinical events during follow-up, or new evidence from repeated clinical or genetic testing. Based on the weight of clinical and genetic evidence, the working diagnosis was further classified using a qualitative descriptor of a previously described categorization of strength of the diagnosis as definite, probable, and possible (Supplementary material online, *Table S2*).[3,14,20]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, or as median and interquartile range (IQR) where appropriate. Categorical variables are expressed as absolute number and percentage and analysed using χ^2 test and Fisher's exact test. Student's *t*-test or Mann–Whitney *U* test was performed for continuous variables with independent measures where appropriate. Time-to-event analysis comparing survival free from recurrent VF between SCVF and UCA patients was performed using Kaplan–Meier function and log-rank test. To assess the effect of quinidine on VF recurrence in SCVF, a modified Kaplan–Meier method was used estimating the cumulative hazard rates of events according to the presence or absence of quinidine (conditional Poisson distribution) as previously described.[30] The duration of follow-up on quinidine was defined as the observation on-therapy and the period before starting quinidine as the observation time off-therapy with patients serving as their own controls. All *P*-values were two-sided and statistical significance was considered for *P*-values <0.05. All statistical analyses were conducted using STATA 14.1 software (StataCorp LP, College Station, TX, USA) and SAS v9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Study population

A total of 364 adult CASPER probands remained with a working diagnosis of IVF after extensive clinical assessment. Of these, 24 (6.6%) individuals met the proposed diagnostic criteria for SCVF. Only in 5/24 (21%) individuals, the diagnosis of SCVF could be made at the time of the index cardiac arrest because VF onset could be documented in the context of electrical storm or frequent non-sustained polymorphic VT. In the remaining 19/24 (79%) patients, the diagnosis of SCVF was made at the time of VF recurrence during follow-up. For the remaining 340 individuals, we retained a working diagnosis of non-specific UCA. *Table 1* shows baseline characteristics of SCVF and UCA patients. Recurrent VF in UCA patients over time did not meet SCVF criteria. Ethnic distribution and age at index cardiac event were similar. There were slightly more females in the SCVF group, but this did not reach statistical significance (54% vs. 36%; $P = 0.06$). A family history of SUD was rare in SCVF and was documented in only 2/24 (8.3%) individuals. Representative examples of SCVF are shown in *Figures 2 and 3*.

Clinical findings

All individuals underwent extensive clinical assessment in accordance with the stepwise systematic CASPER algorithm (Supplementary material online, *Figure S1*). Acute ischaemia and significant coronary artery disease as the cause of the index cardiac arrest were excluded in all patients. None of the SCVF and UCA patients had evidence of structural heart disease or showed features of another distinct inherited arrhythmia syndrome. Exercise treadmill testing did not show any abnormal QTc dynamics and there were no signs of CPVT or other exercise-inducible ventricular arrhythmia. The extent of clinical testing is summarized in Supplementary material online, *Table S4* and was similar in individuals with SCVF and UCA. Comparison of the resting ECG did not reveal a distinct electrocardiographic phenotype in SCVF compared with UCA. The median resting QTc interval was unremarkable [400 ms (IQR 42) vs 396 ms (IQR 41); $P = 0.54$] (*Table 2*). Recordings of signal-averaged ECGs showed no significant differences between groups and only 20% of SCVF patients had an abnormal (≥2 out of 3 abnormal parameters) signal-averaged ECG ($P = 0.66$).

Table 1 Baseline characteristics

	SCVF N = 24	UCA N = 340	P-value
Age, years	45 ± 13	42 ± 14	0.30
Female sex, *n* (%)	13 (54)	123 (36)	0.06
Ethnicity,[a] *n* (%)			
Caucasian	21 (88)	263 (77)	0.48
Asian	2 (8)	25(7)	
African	1 (4)	7 (2)	
Arab	0	6 (2)	
Latin American	0	7 (2)	
First Nations	0	1 (0.3)	
Unreported	1 (4)	28 (8)	
Family history of unexplained SUD, *n* (%)	2 (8)	54 (17)	0.39
LVEF (%)	60 ± 8	56 ± 8	0.15
Symptoms prior to cardiac arrest, *n* (%)			
Syncope	0	37 (20)	
Pre-syncope	0	12 (7)	
Unexplained palpitations[b]	0	25 (14)	
ICD implantation post cardiac arrest, *n* (%)	24 (100)	328 (96)	0.44

Data are expressed as mean ± standard deviation, or as median (interquartile range) where appropriate.
ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; SCVF, short-coupled ventricular fibrillation; SUD, sudden unexplained death; UCA, unexplained cardiac arrest.
[a]Self-reported.
[b]Unexplained palpitations were defined as unprovoked palpitations not related to physical activity/exercise, strong emotions, or heart rate increasing medication.

Coupling threshold of premature ventricular contraction triggers in short-coupled ventricular fibrillation

All episodes of ventricular arrhythmia occurred either at rest/sleep or in a non-adrenergic state. The preceding rhythm was sinus rhythm in all individuals, and the median ambient heart rate preceding the ventricular arrhythmia was 78 b.p.m. in SCVF (IQR 11 b.p.m.). None of the SCVF-related episodes was pause-dependent, i.e. initiated after a prolonged R–R interval >1500 ms following a stable baseline rhythm. However, in a few patients, SCVF was initiated after short–long–short R–R sequences (*Figure 2B*) that occurred during periods of frequent ventricular ectopy. The coupling intervals of PVC triggers in SCVF probands were compared with the trigger PVCs of patients with known long-QT syndrome, arrhythmogenic cardiomyopathy and UCA probands from the CASPER registry. Recurrent VF in the latter was typically initiated by long-coupled trigger PVCs (501 ± 74 ms) ($P < 0.001$), which is consistent with previous reports.[15,16] According to our pre-specified cut-off criteria, the upper coupling limit for SCVF trigger PVCs was expected to be at 352 ms.

Table 3 shows electrophysiological characteristics of the documented ventricular arrhythmia in SCVF. The mean cycle length of SCVF was 217 ± 65 ms, and the mean coupling interval of the trigger PVC was 274 ± 31 ms (range 234–350 ms) (*Figure 4A*). Histogram distribution of the coupling interval of the trigger PVCs and the corresponding z-score are shown in *Figure 4B* and Supplementary material online, *Figure S2*. The 90%, 93%, and 95% percentile of the coupling interval in our SCVF cohort were 319 ms [95% CI 290–350 ms], 328 ms [95% CI 300–350], and 343 ms [95% CI 300–350], respectively. Only 4/24 individuals (16.6%) had a documented trigger PVC with a coupling interval ≥300 ms (*Figure 4B*). There was little variability of the coupling interval of the trigger PVCs. In 91.7% of all SCVF patients, the coupling interval was within a z-score of -1 to 1.5 (*Figure 4B* and Supplementary material online, *Figure S2*).

Follow-up and recurrent ventricular arrhythmia

The median follow-up duration was 51 (25, 100) months and was similar between individuals with SCVF and UCA ($P = 0.86$) corresponding to 768 patient-months of follow-up for SCVF patients and 17 862 patient-months for UCA probands. Frequent resting ECGs during follow-up (average ECG number 12 ± 8 per individual) did not show evidence of intermittent spontaneous type 1 Brugada pattern or intermittent early repolarization pattern in any of the SCVF patients.

In addition to the index cardiac arrest, recurrent sustained ventricular arrhythmia occurred in 22/24 (92%) individuals with SCVF but only in 8/340 (2.4%) individuals with UCA ($P < 0.001$). This also included five individuals with SCVF who experienced electrical storm the day of their index cardiac arrest (21%) after initial resuscitation and admission to the hospital ($P < 0.001$). Two individuals with SCVF presented with frequent, recurrent non-sustained SCVF during the first 24 h after hospital admission.

Given the fact that VF recurrence was necessary to establish the diagnosis of SCVF in 79% of all SCVF patients, it is likely that the true incidence of VF recurrence is lower than observed in this study. Considering this limitation, the incidence rate of recurrent VF per

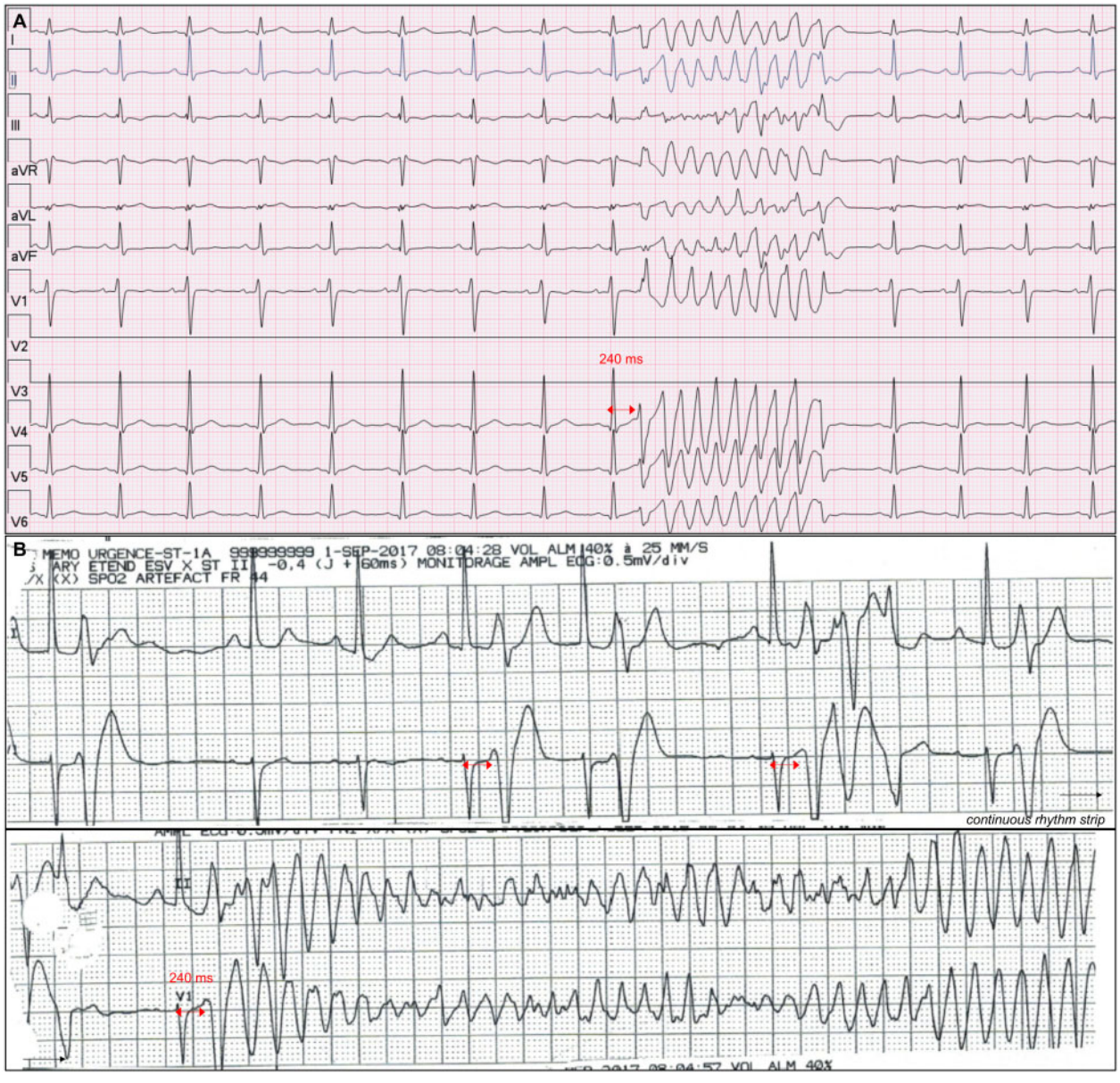


Figure 2 Examples of short-coupled ventricular fibrillation (SCVF) recorded on ECG and telemetry. (*A*) Resting ECG of a 16-year-old male patient with short-coupled ventricular fibrillation. There is no evidence of J-wave abnormalities and no evidence of early repolarization. Note the relatively short, corrected QT interval of 375 ms. Repeat episodes of non-sustained polymorphic ventricular tachycardia initiated with a short coupling interval of only 240 ms. (*B*) Telemetry tracings of continuous rhythm strips of a 48-year-old female patient with short-coupled ventricular fibrillation who experienced unexplained cardiac arrest at home (ventricular fibrillation). After successful resuscitation, the patient was transferred to the hospital and experienced electrical storm shortly after admission. Underlying sinus rhythm at 75 b.p.m. with normal QTc intervals and no evidence of J-point abnormalities. There is frequent ventricular ectopy with short-coupled, monomorphic premature ventricular contractions. The QRS width of the premature ventricular contractions is 130 ms. Eventually, initiation of another run of ventricular fibrillation triggered by the same premature ventricular contraction with a coupling interval of 240 ms after a short–long–short sequence.

100 patient-months was 2.21 [95% CI 1.30–3.46] in SCVF compared with 0.05 [95% CI 0.02–0.09] in UCA ($P < 0.001$) (*Figure 5*). Excluding SCVF patients with electrical storm the day of their index cardiac arrest, the median time to recurrent ventricular arrhythmia was 30.6 months (8.6, 70.7; range 0.3–124) in SCVF patients compared with 51.2 months (25.4, 96.3; range 0.9–559) in UCA probands.

During follow-up, 12/24 individuals with SCVF (50%) were placed on quinidine (average daily dose 667 ± 400 mg) for recurrent VF. Patients receiving quinidine were typically individuals with multiple appropriate ICD shocks or those who had experienced electrical storm. Quinidine therapy significantly reduced the risk of recurrent VF in SCVF patients (*Figure 6*). Over a median follow-up duration of

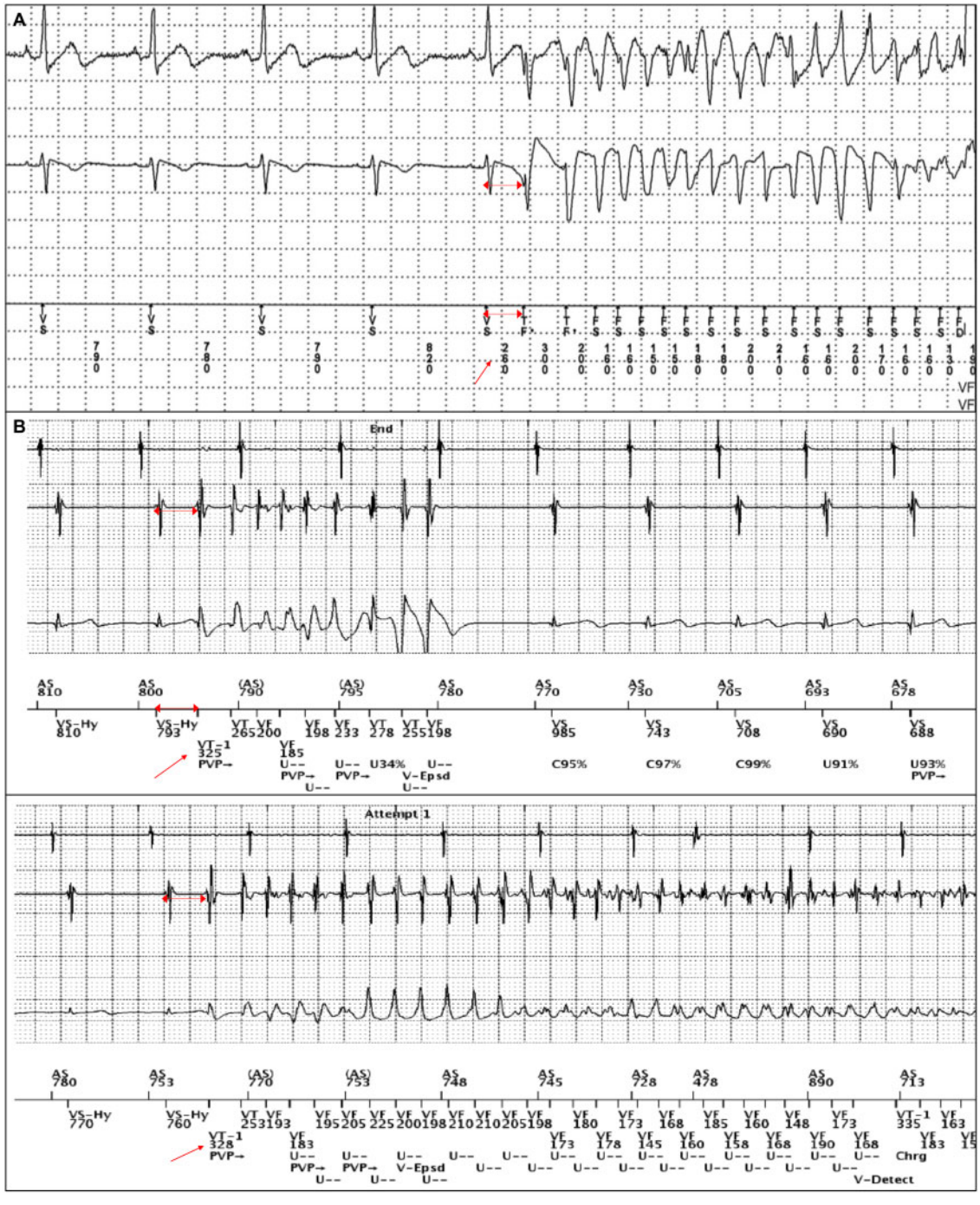


Figure 3 Examples implantable cardioverter-defibrillator-recorded short-coupled ventricular fibrillation episodes. (*A*) Implantable cardioverter-defibrillator tracing of a 42-year-old male patient with a history of unexplained cardiac arrest. The tracing displays an episode of recurrent ventricular fibrillation that occurred at rest and was initiated by a trigger premature ventricular contraction with an extremely short coupling interval of 260 ms (red arrow). The ambient heart rate was 76 b.p.m. (*B*) A 53-year-old female patient with unexplained cardiac arrest and no evidence of structural heart disease. The patient experienced recurrent ventricular fibrillation only 48 h after implantable cardioverter-defibrillator implantation. Ventricular fibrillation was initiated by a short-coupled premature ventricular contraction [coupling interval of 253 ms (red arrow)] and successfully terminated by an implantable cardioverter-defibrillator shock. The upper tracing shows a run of non-sustained polymorphic ventricular tachycardia that occurred several minutes before the sustained ventricular fibrillation episode (lower tracing). Similar runs of polymorphic non-sustained polymorphic ventricular tachycardia were recorded since hospital admission and prior to implantable cardioverter-defibrillator implantation. Coupling intervals of trigger premature ventricular contractions were typically between 250 and 265 ms. The patient was put on quinidine and had no further ventricular fibrillation recurrence.

Table 2 Comparison of resting ECGs between short-coupled ventricular fibrillation and unexplained cardiac arrest probands

	SCVF *N* = 24	UCA *N* = 340	*P*-value
HR, b.p.m.	66 (58, 74)	69 (57, 80)	0.44
PR, ms	157 ± 19	159 ± 26	0.63
QRS, ms	86 ± 6	97 ± 11	<0.001
QT, ms	374 ± 38	371 ± 37	0.81
QTc, ms	395 ± 40	398 ± 33	0.54
Tpe, ms	64 ± 19	67 ± 20	0.24

Data are presented as mean ± standard deviation, or median (interquartile range).
HR, heart rate; QT, absolute QT interval; QTc, corrected QT interval; SCVF, short-coupled ventricular fibrillation; Tpe, Tpeak—Tend; UCA, unexplained cardiac arrest.

65.5 months (19.5, 138) on quinidine, VF recurrence with appropriate ICD therapy occurred in 2/12 (16.6%) SCVF patients. The mean time to recurrent VF on quinidine therapy was 43.8 ± 18.5 months. Interestingly, the two SCVF patients with recurrent VF on quinidine had daily doses of <300 mg.

Genetic findings

All individuals underwent WES and subsequent analyses were restricted to 196 pre-specified genes (Supplementary material online, *Table S4*). Results of genetic testing are shown in *Table 4*. Whole exome sequencing did not reveal a pathogenic or likely pathogenic variant in any SCVF proband that could explain the phenotype. A total of 10 variants of unknown significance were found in 7/24 SCVF probands but not in individuals with UCA (*Table 4*).

Based on our genetic analyses, we did not detect a robust genetic substrate to explain the SCVF phenotype, and there was no evidence of familial forms.

Discussion

The findings of the present study suggest that SCVF is a distinct primary electrical disease and an important cause of UCA/SUD (6.6% of all CASPER apparently UCA survivors) (*Graphical abstract*).

Unlike other primary electrical diseases such as Brugada syndrome or long-QT syndrome, SCVF does not exhibit distinct electrocardiographic findings, rendering the clinical diagnosis particularly challenging. A Japanese study reported an increased association of complete right bundle branch block—after exclusion of Brugada syndrome—in a cohort of patients with IVF, but this finding was completely absent in the CASPER SCVF cohort.[31] At present, the sole diagnostic criteria for SCVF are the electrophysiological finding of VF initiation by a trigger PVC with a short coupling interval (<350 ms) in the absence of type 1 Brugada or early repolarization pattern, prolonged QTc intervals, and preceding pause. A cut-off value of 350 ms included the 95% percentile providing the most distinct upper limit inclusion criteria. A similar cut-off value was used as inclusion criteria by Haïssaguerre *et al.*[32] in a recent study of SCVF patients referred for ablation of VF drivers. The fact that 84% of trigger PVCs of all arrhythmic episodes had a coupling interval of <300 ms and 100% of ≤350 ms, demonstrates that short-coupled PVCs are the dominant trigger events within a narrow window of coupling intervals. Considering the mean coupling interval of trigger PVCs related to other inherited arrhythmia syndromes or VF episodes in undifferentiated UCA patients, our observations and previous reports suggest that our proposed cut-off value for SCVF would be separated by two standard deviations from those conditions minimizing the chance of diagnostic overlap. In this context, it should be mentioned that polymorphic VT/VF initiated by relatively short-coupled trigger PVCs may also occur in individuals with established coronary artery disease or myocardial inflammation.[33–35] Two recent studies demonstrated short-coupled ventricular arrhythmia in patients with acute and chronic coronary artery disease.[34,35] Interestingly, the mean coupling interval of trigger PVCs in both studies on coronary artery disease patients by Viskin *et al.* was still much longer (376 ± 49 and 364 ± 36 ms, respectively) than the mean coupling interval in our SCVF cohort (274 ± 31).

Table 3 Electrophysiological characteristics of short-coupled ventricular fibrillation

Total, *n*	24
VF CL, ms	217 ± 65
Coupling interval of trigger PVC, ms	274 ± 32
Preceding heart rate, b.p.m.	78 (75, 87)
Preceding sinus rhythm, *n* (%)	24 (100)
Cumulative number of appropriate ICD shocks since implantation, *n*	1.5 [range 1–18]
Electrical storm, *n* (%)	5 (21)

Data are expressed as mean ± standard deviation, or median (interquartile range).
The VF CL was estimated from the averaged VF rate as indicated on the recorded ICD tracings. In short-coupled ventricular fibrillation patients with recurrent VF episodes/electrical storm during the initial presentation, the VF CL was estimated from the telemetry recordings of the VF rate.
CL, cycle length; ICD, implantable cardioverter-defibrillator; PVC, premature ventricular contraction; VF, ventricular fibrillation.

Case series of IVF initiated by short-coupled PVCs were first reported in the 1990s, but most likely described heterogeneous study populations including early repolarization syndrome, short-QT syndrome, and undiagnosed Brugada syndrome in addition to true SCVF.[8,9,12] The two largest of those previous studies reported coupling intervals of 245–300 ms, and the seminal study by Leenhardt *et al.* introduced the term 'short-coupled torsade de pointes' to describe the electrophysiological hallmark of their findings, which we believe is identical to SCVF.[7,9] Given significant differences in pathophysiology, and to avoid future confusion with true long-QT syndrome or pause-dependent torsade de pointes, we propose to prioritize the term SCVF.

Incidence and prevalence of SCVF are difficult to determine and are most likely underestimated. As documentation of ventricular arrhythmia onset is essential for the diagnosis of SCVF, the true incidence may even be higher, and it is possible that more SCVF cases will be identified among our UCA patients over time. The risk of recurrent VF seems to be elevated in SCVF. In our study, 92% of all SCVF patients experienced recurrent VF; however, this may

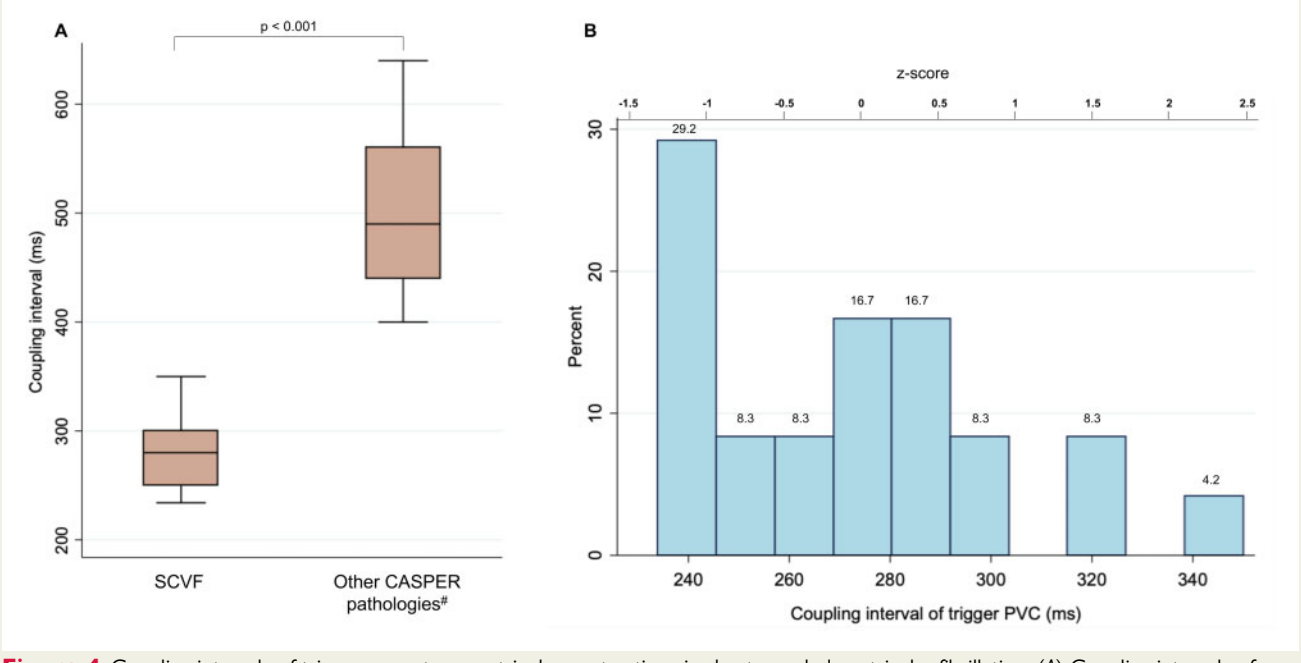


Figure 4 Coupling intervals of trigger premature ventricular contractions in short-coupled ventricular fibrillation. (*A*) Coupling intervals of ventricular fibrillation trigger premature ventricular contractions between short-coupled ventricular fibrillation patients and other CASPER probands with different pathologies. #Excluding Brugada syndrome, early repolarization syndrome or short-QT syndrome as these three conditions are also known to initiate ventricular arrhythmia by trigger premature ventricular contractions with short coupling intervals. (*B*) Histogram distribution of the coupling intervals in the CASPER short-coupled ventricular fibrillation cohort (*N* = 24). The majority of short-coupled ventricular fibrillation probands presented with coupling intervals of 240–300 ms. The coupling interval of the trigger premature ventricular contractions was <330 ms in 93% and <343 ms in 95% of short-coupled ventricular fibrillation probands. The corresponding z-score shows that the coupling intervals are in a z-score of -1 to 1.5 in 92% of short-coupled ventricular fibrillation probands.

represent an overestimation as VF recurrence is required for the majority of cases to establish the diagnosis of SCVF. Previous studies of IVF have reported recurrence rates of 18–39% over similar follow-up periods.[36–39] In addition, 21% of our SCVF cohort experienced electrical storm (≥3 VF episodes in 24 h) documenting a particular severe phenotype. Compared with similar inherited arrhythmia syndromes such as early repolarization syndrome,[11] our data suggest that the risk of electrical storm seems to be even more pronounced in pure SCVF.

The pathophysiology and molecular mechanisms of SCVF still remain largely elusive. Functional data and electroanatomic mapping studies suggest a crucial role of the His-Purkinje system for the initiation of trigger PVCs.[10,11,40] The proarrhythmogenic role of Purkinje fibres seems to be linked to an (increased) activity of the Purkinje fibre-I_{to} channel resulting in short-coupled trigger PVCs.[40] Further support for the role of abnormal I_{to} function comes from the observation that quinidine, a strong I_{to} inhibitor, is highly effective in SCVF.[41] Although abnormal Purkinje fibre firing is implicated in the pathogenesis, this mechanism is not exclusive for SCVF but has also been observed in Brugada syndrome and early repolarization syndrome.[32,42]

The lack of a conclusive genetic substrate in our SCVF cohort is consistent with previous reports suggesting that the vast majority of SCVF cases do not follow a classic Mendelian inheritance pattern.[43] One female patient was found to be heterozygous for a likely pathogenic CASQ2 mutation (c.1185delC; p.D395Ef22) affecting exon 11 of CASQ2. The mutation is rare and has not been observed in gnomAD. However, we do not believe that this CASQ2 variant is related to the patient's SCVF phenotype. Exercise treadmill testing did not reveal any signs of a CPVT phenotype, and there are no segregation or functional data available. Transmission of CASQ2-related CPVT is usually autosomal recessive, but isolated cases of autosomal dominant forms of CPVT have been described for certain CASQ2 variants.[44,45] Another female SCVF patient was found to be heterozygous for a TRPM4 missense variant (c.3170A>G; pY1057C). The variant is rare, and there is only one heterozygous individual with the same variant in gnomAD. Three different *in silico* tools suggested a disease-causing effect. Genetic variants of TRPM4 have been typically linked to familial forms of cardiac conduction disease, but an isolated case of IVF has also been reported.[46] The patient in question did not show any signs of cardiac conduction disease, and in the absence of functional data or familial segregation of the TRPM4 variant has to be classified as a variant of unknown significance at this point.

A monogenic subset of hereditary SCVF has been described in the Netherlands and is related to a risk haplotype affecting the noncoding region of the dipeptidyl-aminopeptidase-like protein 6 (DPP6) gene (c.1-340C>T).[47] This DPP6 risk haplotype represents a Dutch founder mutation and has not been described outside the Netherlands to date.[38,48] The Dutch DPP6 haplotype is characterized by a very aggressive phenotype with increased risk of recurrent SCVF, and high

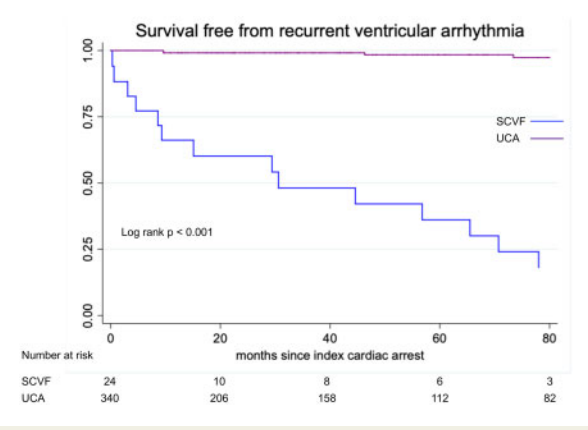


Figure 5 Survival free from recurrent ventricular arrhythmia. Kaplan–Meier curves for recurrent ventricular arrhythmia in short-coupled ventricular fibrillation and unexplained cardiac arrest probands after their index cardiac events. The Kaplan–Meier curves were voluntarily truncated at 100 months of follow-up after the index cardiac arrest. Recurrent ventricular fibrillation occurred significantly more often and earlier in short-coupled ventricular fibrillation probands (92%) compared with unexplained cardiac arrest probands (2.4%).

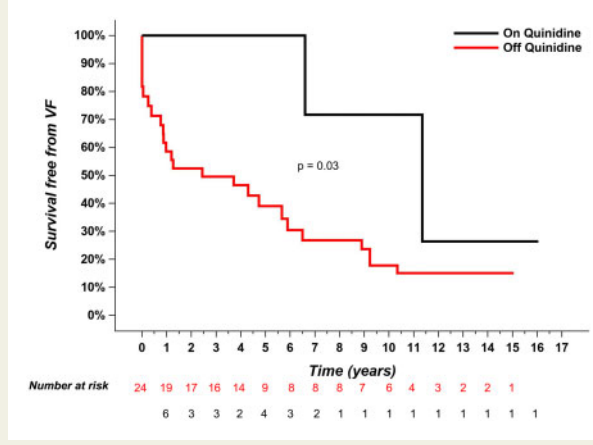


Figure 6 Cumulative risk of recurrent ventricular fibrillation stratified by presence or absence of quinidine therapy. To assess the effect of quinidine on ventricular fibrillation recurrence in short-coupled ventricular fibrillation, a modified Kaplan–Meier method was used estimating the cumulative hazard rates of events according to the presence or absence of quinidine (conditional Poisson distribution). The duration of follow-up on quinidine was defined as the observation on-therapy and the period before starting quinidine as the observation time off-therapy with patients serving as their own controls. Administration of quinidine significantly reduced the risk of recurrent ventricular fibrillation.

penetrance including late onset even after the age of 70.[38,48,49] Functional studies showed that the Dutch risk haplotype results in DPP6 overexpression that subsequently increases the activity of the Purkinje fibre-I_{to} channel.[40,47] Other reports of rare, monogenetic forms of IVF are limited to isolated families or case reports and have described variants in RyR2, CALM1, IRX3, or coding mutations of DPP6.[50–53] No pathogenic or likely pathogenic DPP6 variant was detected in our SCVF cohort, but we did not perform a DPP6 haplotype analysis. Of note, site investigators are aware of the DPP6 entity and typically inquire regarding country of origin in northern European Caucasian patients with SCVF. Unfortunately, this data point was not captured in the registry. At this point, the genetic mechanisms underlying the majority of SCVF cases are largely speculative. Alternative genetic substrates may include mutations of deep intronic regions or SCVF may be linked to oligo- or polygenic causes.

From a pathophysiological perspective, SCVF shows remarkable overlapping features with Brugada syndrome, early repolarization syndrome, and to some extent with short-QT syndrome.[6] Common features include arrhythmia onset during phases of increased vagal tone (sleep, rest), the aforementioned role of Purkinje fibres for arrhythmogenesis, trigger PVCs with short coupling interval and the response to quinidine.[41] All SCVF patients in our study experienced cardiac arrest or recurrent VF at rest or during sleep.

Like in Brugada syndrome, early repolarization syndrome or short-QT syndrome,[30,54,55] quinidine—a potent I_{to} inhibitor—represents the only effective pharmacological therapy in SCVF.[54] In our study, 83% of SCVF patients had no further VF recurrence on quinidine, while 17% had recurrent ventricular arrhythmia over time with a mean delay of 43.8 ± 18.5 months after quinidine introduction. Despite this recurrence, rate hazards for recurrent VF remained significantly lower on quinidine compared with SCVF patients without. At present, the optimal quinidine dose is unknown, and we cannot exclude a dose-dependent efficacy. Recurrent VF on quinidine only occurred in SCVF patients on extremely low quinidine doses (<300 mg daily). Previous studies on other quinidine-sensitive primary electrical disorders have reported mean effective daily doses ranging from 600 to 2000 mg daily.[30,41,54,55]

The balance of effective antiarrhythmic protection and increasing risk of limiting side effects at higher doses remains an ongoing challenge for this medication.[55] Another major problem with quinidine therapy is the currently worldwide limited accessibility.[56]

Additional treatment options for patients with very high arrhythmia burden or drug-resistant forms of SCVF include catheter ablation of VF drivers or predominant trigger PVCs, which was successfully performed for one of our SCVF patients.[32,37,57,58] The trigger PVC of the SCVF patient referred for ablation was of Purkinje origin arising from the moderator band.

Limitations

The major limitation of this study is the somewhat circular diagnosis for SCVF. At present, its phenomenology is solely based on the coupling interval of the initiating trigger PVC.

Given the absence of a genetic or histologic substrate, the phenotype requires documented VF onset, which affects the diagnostic sensitivity. Given the limited number of documented VF events, it remains unclear if the coupling interval of trigger PVCs in SCVF patients could not prolong under certain circumstances. The number of SCVF cases in our study was small, but comparable to previous

Table 4 Results of genetic testing in short-coupled ventricular fibrillation probands

Sex	Gene	Variant	Consequence	ACMG classification	ACMG criteria applied
F	FHOD3	c.646G>A	p.V216I	VUS	PP3
M	TPM1	c.24G>C	p.E8D	VUS	PM2, PM5
	SOS1	c.829C>A	p.P277T	VUS	PM2, PP3
M	TNNI3K	c.1450A>T	p.N484Y	Likely benign	PP3, BS1, BP1
F	ANK2	c.4879G>A	p.V1627I	VUS	PP3
	FLNC	c.6509G>A	p.R2170H	VUS	No criteria met
M	FLNC	c.2891T>C	p.L964P	VUS	PM2, PP3
F	CASQ2	c.1185delC	p.D395Ef*22	Likely pathogenic	PVS1, PM2, BP6 (AR inherited)
F	FLNC	c.1186A>G	p.T396A	VUS	PM2
	TRPM4	c.3170A>G	p.Y1057C	VUS	PM2, PP3

ACMG, American College of Medical Genetics and Genomics; AR, autosomal recessive; F, female; M, male; VUS, variant of unknown significance.

studies describing this distinct arrhythmia syndrome.[7,9,12,37] Also, the small number of ascertained SCVF cases may not reflect the complete clinical spectrum of this novel arrhythmia syndrome. Compared with all previous studies, we suggest standardized diagnostic criteria to provide an increased degree of diagnostic certainty. Using these robust criteria, it is unlikely that our SCVF cohort may have been contaminated by undiagnosed forms of Brugada syndrome or early repolarization syndrome. The necessity of documented VF onset for the diagnosis of SCVF inevitably introduces bias and may overestimate the true incidence of VF recurrence as SCVF patients without recurrent VF, electrical storm or frequent non-sustained VT/VF remain likely undiagnosed. The potential concern of single-observer bias during the blinded analysis of ICD tracings was counterbalanced by the use of the automated measures of the coupling intervals as indicated by the device.

Despite broad genetic testing, we did not identify a genetic substrate related to SCVF. Additional genetic methods including haplotype analysis or unrestricted gene-searching WES or whole-genome sequencing analysis may be useful to reveal the genetic basis of SCVF but were not performed in the present study.

Conclusions

Short-coupled ventricular fibrillation likely represents a distinct arrhythmia syndrome accounting for at least 6.6% of UCA in otherwise healthy individuals. The clinical diagnosis is challenging, given the absence of a distinct electrocardiographic signature and lack of a genetic substrate. Quinidine is highly effective in SCVF and should be considered as first-line therapy in patients with recurrent VF episodes or frequent appropriate ICD therapies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Data availability

Data will be availabe upon request and IRB approval.

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