Europace (2016) **18**, 1587–1592
doi:10.1093/europace/euv357

Early repolarization pattern: a marker of increased risk in patients with catecholaminergic polymorphic ventricular tachycardia

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Received 6 September 2015; accepted after revision 28 September 2015; online publish-ahead-of-print 23 December 2015

Aims The early repolarization pattern (ERP) has been shown to be associated with arrhythmias in patients with short QT syndrome, Brugada syndrome, and ischaemic heart disease. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome and related to malignant ventricular tachyarrhythmias in a structurally normal heart. The aim of this study was to evaluate the prevalence of ERP and clinical events in patients with CPVT.

Methods and results Digitalized resting 12-lead ECGs of patients were analysed for ERP and for repolarization markers (QT and T_{peak}–T_{end} interval). The ERP was diagnosed as 'notching' or 'slurring' at the terminal portion of QRS with $\geq$0.1 mV elevation in at least two consecutive inferior (II, III, aVF) and/or lateral leads (V4–V6, I, aVL). Among 51 CPVT patients (mean age 36 $\pm$ 15 years, 11 males), the ERP was present in 23 (45%): strictly in the inferior leads in 9 (18%) patients, in the lateral leads in 9 (18%) patients, and in infero-lateral leads in 5 (10%) patients. All patients with ERP were symptomatic at presentation (23 of 23 patients with ERP vs. 19 of 28 patients without ERP, $P = 0.003$). Syncope was also more frequent in patients with ERP (18 of 23 patients with ERP vs. 11 of 28 patients without ERP, $P = 0.005$).

Conclusion A pathologic ERP is present in an unexpected large proportion (45%) of patients and is associated with an increased frequency of syncope. In patients with unexplained syncope and ERP at baseline, exercise testing should be performed to detect CPVT.

Keywords CPVT • Early repolarization pattern • ECG • Syncope

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a cardiac ion channel disorder that is characterized by stress- or emotion-triggered syncope or sudden cardiac death (SCD) in young individuals with structurally normal hearts.[1] Patients typically have a normal baseline ECG, but bidirectional and/or polymorphic ventricular premature ventricular contractions (PVCs) and tachycardia during increased heart rate.

Catecholaminergic polymorphic ventricular tachycardia was first described in 1978, and its genetic basis was discovered later in 2001.[2] Overall, CPVT is quite rare. So far, five causative genes, all related to intracellular calcium handling and, in particular, calcium uptake and release of the sarcoplasmic reticulum (SR), have been

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What's new?

- The present study shows that the early repolarization pattern (ERP) was present in a large proportion (45%) of catecholaminergic polymorphic ventricular tachycardia (CPVT) patients.
- ERP is a significant modifier of arrhythmic events in patients with CPVT. All patients with ERP were symptomatic at presentation, and the presence of ERP was related to increased frequency of syncope.
- Available genetic screening data of 12 of 23 patients with ERP showed that all screened patients with ERP were positive for known mutations.

identified: the *RYR2* gene, encoding the large cardiac SR calcium release channel, is the major gene (around 50–60% of patients have *RYR2* gene mutation; CPVT1), whereas mutations in the *CASQ2* gene, encoding the cardiac calsequestrin, triadin (*TRDN*), and calmodulin (CALM1), are rare.[3] These mutations lead to increased and diastolic spontaneous calcium release from sarcoplasmic reticulum, either due to a gain of function (*RYR2*) or a loss of function (*CASQ2, TRDN*) and finally to delayed afterdepolarization (DAD) that trigger arrhythmias like multifocal PVCs or polymorphic ventricular tachycardia (VT). Initially, DAD-mediated triggered arrhythmias generate an augmentation in transmural dispersion of repolarization, and consequently, slow polymorphic VT becomes re-entrant fast VT degenerating into ventricular fibrillation (VF).

An early repolarization pattern (ERP) was first described in 1936 in healthy individuals, and it has been considered for many decades as a benign ECG finding of a normal variant that typically and frequently occurs in the antero-lateral ECG leads (i.e. V2–V5).[4] In 2000, Gussak *et al.*[5] demonstrated that in arterially perfused canine wedge preparations, ER is a potentially harmful marker that is sufficient to create an electrical re-entry and initiate malignant arrhythmias. In 2008, Haissaguerre *et al.*[6] and Rosso *et al.*[7] revealed in case–control studies that the ERP in infero-lateral leads is significantly more common in survivors of aborted SCD due to idiopathic ventricular VF. In the following years, in several large population-based studies, an association between the presence of ERP and increased risk for arrhythmic death, cardiac death, or all-cause death was shown, including channelopathies such as short QT, long QT, and Brugada syndrome[8–13] and in patients with ischaemic heart disease.[10] Recently, several case reports on patients with survived cardiac arrest and ERPs suggest that a distinct variant in the ATP-sensitive potassium channel gene *KCNJ8* might underlie some forms of ERPs.[14]

The aim of the present study was to evaluate the prevalence of pathologic ERPs in patients with CPVT and to analyse the relationship between ERP, ECG features, and the clinical outcome, respectively.

Methods

Study population and data collection

This multicentre study included 51 patients diagnosed with CPVT from five German arrhythmia clinics. The diagnosis of CPVT was made after an aborted cardiac death, syncope/presyncope, palpitations, or during family screening. We collected the demographical, clinical, and available genetic data and outcome data.

In all patients, 12-lead ECGs at baseline (in the absence of antiarrhythmic drugs including β-blockers) were analysed.

ECG analysis

All resting 12-lead ECGs (paper speed 50 mm/s, gain 10 mm/mV) were scanned in pdf format and analysed for ERP and for QT intervals in lead II and V5. All measurements were performed with electronic caliper after four-fold magnification of the ECGs (using Adobe Acrobat 8 Professional; Adobe Systems Incorporated, San Jose, CA, USA).

For QT- and T_{peak}–T_{end}-interval measurements, the end of T-wave was defined by a standard tangential method. T_{peak} was defined as the highest point on the inclination of ascending and descending limb of the T-wave. The QT- and T_{peak}–T_{end} intervals were corrected for heart rate of preceding RR interval according to Bazett's formula.

Early repolarization pattern was defined by ≥0.1 mV elevation at the terminal portion of the QRS complex, either as 'notching' or 'slurring', in at least two consecutive leads [inferior (II, III, VF) and/or lateral leads (I, VL, V4, V5, V6)] with or without an elevation of the J point indicating the QRS–ST junction. As described by others, 'notching' was defined as a positive deflection of the terminal portion of a positive QRS complex. 'Slurring' was defined as a smooth transition from the terminal QRS complex to the ST-segment with upright concavity (*Figure 1*).[6,7,9] The maximum amplitude of ERP was measured at the QRS–ST junction (or at peak point of 'notching') relative to the QRS onset to minimize a baseline wandering effect. Right precordial leads (V1–V3) were excluded from analysis to avoid potential confounding effects and because these are not part of the pathologic ERP.

The ECGs of each patient were examined for ERP by at least three investigators (E.T., B.R., R.S.) blinded to any clinical information. In case of disagreement, decision was made by majority vote.

The study was approved by the Medical Ethics Committee of University Medical Centre Mannheim.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and when the distributions were skewed, as the median and interquartile range; categorical variables are presented as absolute numbers and percentages. The differences in mean values between groups were analysed with Student's *t*-test for independent samples. When distribution of variable is skewed, the Mann–Whitney *U* test is used for comparison of two groups and the Kruskal–Wallis test is used for comparison of three groups. The categorical variables were analysed with Pearson's χ^2 test. *P*-values <0.05 were considered significant. Statistical analyses were performed using the program 'Statistical Package for Social Science' for Windows (SPSS, Chicago, IL, USA, version 16.0).

Results

Fifty-one index patients with CPVT from five centres were included. Of these, 11 (22%) patients were males. The mean age was 36 ± 15 years (range 9–68 years). The mean follow-up period was 38 months. Patients' demographics, clinical, genetic, and basal ECG data are summarized in *Table 1*. Forty-three patients (83%) had symptoms including 26 patients (51%) with sudden cardiac arrest (3 patients deceased), 31 patients (61%) with syncope, and 12 patients (23%) with presyncope. At initial presentation, 11 patients (22%) had sudden cardiac arrest, 29 patients (57%) had syncope, and 8 patients (15%) had palpitations

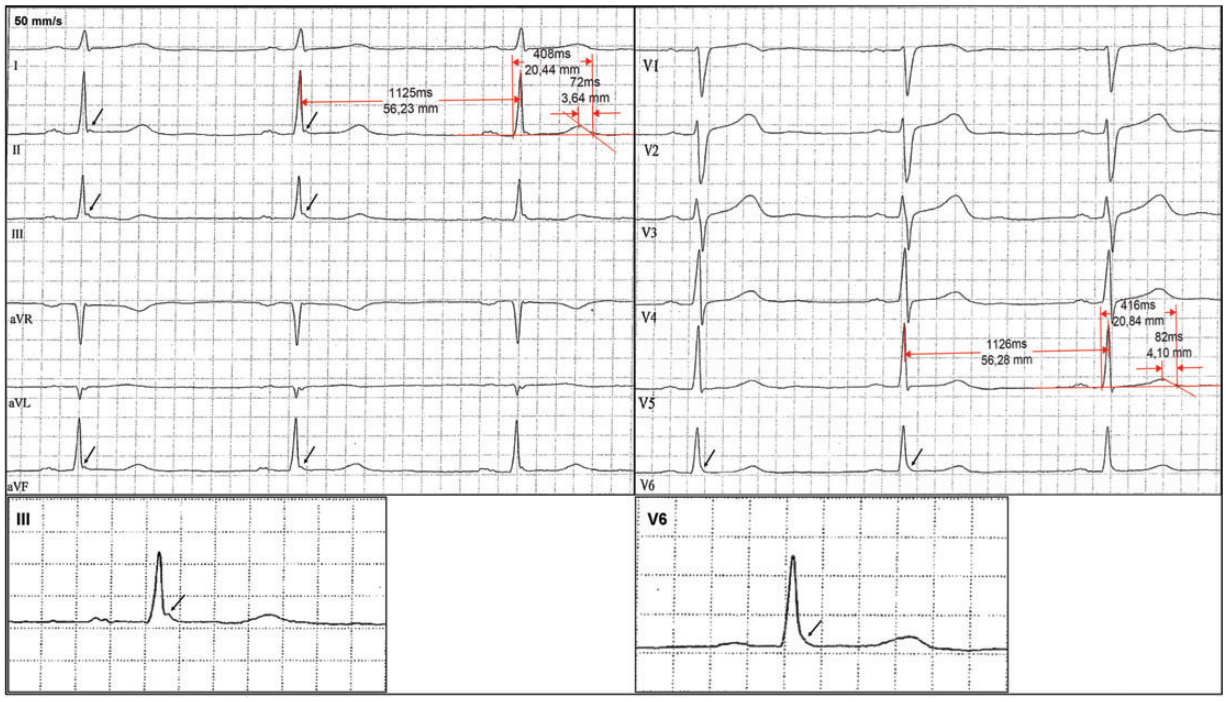

Figure 1 Twelve-lead electrocardiogram showing a 'notching' type ERP in inferior leads (II, III, aVF) and 'slurring' type ERP in lead V6.

(based on detailed clinical history, only the syncopes/presyncopes considered to be of an arrhythmic origin were included in analysis).

The ERP was present in 23 CPVT patients (45%): in the inferior leads in 9 patients (17.6%), in the lateral leads in 9 patients (17.6%), and in the infero-lateral leads in 5 patients (9.8%). 'Slurring' subtype ERP ($n = 13$, 56%) was more common than 'notching' subtype ($n = 8$, 35%). Two patients (9%) had both 'slurring' and 'notching' in different leads. We also analysed the morphology of the ERP: when ERP was present in patients with CPVT, horizontal/descending ST segment morphology was present in all.

All patients with ERP ($n = 23$, 100%) and 19 of 28 patients without the ERP (68%) were symptomatic at presentation ($P = 0.003$). Moreover, significantly more patients with ERP had syncope compared with patients without ERP at initial presentation (18 of 23 patients with ERP vs. 11 of 28 patients without ERP, $P = 0.005$). The positive predictive value of ERP for syncope was 78.3%, with a specificity of 77.3%, sensitivity of 62%, and negative predictive value of 60.7%. Patients with ERP had shorter corrected T_{peak}–T_{end} intervals (69.0 $\pm$ 15.8 ms vs. 61.2 $\pm$ 9.3 ms, $P = 0.04$) and slower heart rates (11 bpm) compared with patients without ERP (*Table 2*).

QT intervals, age, gender, sudden cardiac arrest, and polymorphic VT were not different between patients with and without ERP (*Table 2*).

There was also no difference in QT intervals, T_{peak}–T_{end} intervals, and heart rate with regards to syncope or SCD. However, patients who presented with aborted SCD were younger compared with those who had not SCD (31 vs. 41 years, $P = 0.01$).

Genetic screening data were available in 29 patients: 25 (86%) patients were identified with *RYR2* gene mutation, 1 (3%) patient with *CASQ2* mutation; and 3 patients (10%) were negative for any of known mutations (*Figure 2*). There was no statistical difference in terms of ERP presence in patients with RYR′ gene mutation [ERP positive, $n = 11$ (44%) vs. ERP negative, $n = 14$ (56%), $P = 0.14$]. Twelve of 23 patients with ERP were screened for mutation and all of them had *RYR2* ($n = 11$) and CASQ2 ($n = 1$) mutation. Considering only patients with available genetic screening data, the positive predictive value of ERP for genetic test positivity was 100%, with a specificity of 100%, sensitivity of 46.1%, and negative predictive value of 17.6% (22 patients without genetic screening data were excluded from analysis). However, the remarkable positive predictive value of ERP for genetic test positivity was flawed by the unavailability of genetic screening data of 11 patients with ERP.

Discussion

Catecholaminergic polymorphic ventricular tachycardia is a primary electrical disease associated with 'malignant' polymorphic ventricular tachyarrhythmias, syncope, and/or SCD in otherwise healthy young individuals. Early repolarization was considered as benign electrocardiographic variant for decades, in particular when occurring in the antero-lateral leads. However, during the last few years, there was a rapidly growing evidence of an association between the infero-lateral ERP and idiopathic VF or sudden arrhythmic death in different diseases, including primary electrical diseases like Brugada, short QT or long QT syndrome,[8,9,11,13] and ischaemic heart disease.[10] Thus, ERP may constitute a substantial modifier of the arrhythmogenic risk in primary electrical diseases and/or structural heart disease. Data on patients with CPVT are lacking so far. Therefore, we conducted an analysis in a larger set of CPVT patients and revealed an unexpectedly high prevalence of the ERP (45%).

Table 1 Patients' demographical, clinical, genetic, and basal ECG data ($n = 51$)

Age in years (mean)	36 ± 15
Male sex, *n* (%)	11 (22)
Baseline heart rate (mean ± SD)	64 ± 12
Cardiac arrest, *n* (%)	26 (51)
Syncope, *n* (%)	31 (61)
ECG intervals, ms	
QTc (II) (mean ± SD)	381.7 ± 35.6
QTc (V5) (mean ± SD)	384.8 ± 29.4
T_{peak}–T_{end} (II) (mean ± SD)	65.1 ± 14.1
T_{peak}–T_{end} (V5) (mean ± SD)	68.7 ± 14.5
Early repolarization, *n* (%)	23 (45)
Genetic screening, *n* (%)	29 (56)
RyR2	25 (86)
CASQ2	1 (3)
Negative	3 (10)
Follow-up (in months)	37.7 ± 57.0
Treatment	
ICD implantation, *n* (%)	22 (43)
β-Blocker, *n* (%)	33 (64.7)
β-Blocker and flecainide, *n* (%)	5 (10)
β-Blocker and propafenone, *n* (%)	1 (2)
Flecainide, *n* (%)	3 (6)
Propafenone, *n* (%)	1 (2)

Values are *n* (%) or mean ± SD; β-blockers were metoprolol succinate in 23 patients (45%), bisoprolol in 9 patients (18%), propronolol in 3 patients (6%), atenolol in 1 patient (2%), and nebivolol in 1 patient (2%). One pt (2%) was on verapamil. ICD, implantable cardioverter defibrillator

The prevalence of an ERP is reported to be as high as 13% in the general population and may decrease with age.[15] However, the prevalence is higher among young athletes (up to 46%),[16] in patients with short QT syndrome (65%)[12] and in patients with Brugada syndrome (63%).[8] The overall prevalence of 45% in patients with CPVT appears to be in accordance with other primary electrical disorders but is significantly higher than the prevalence in middle-aged healthy population.

Until 2000, few small reports have been published, suggesting an association between early repolarization and SCD.[17] Likewise, some experimental studies found that ERP is a marker of a substrate that is sufficient to create an electrical re-entry.[18,19] Moreover, in 2008, Haissaguerre *et al.*[6] and Rosso *et al.*[7] revealed in their clinical case–control studies in survivors of aborted SCD due to idiopathic ventricular VF that the ERP is significantly more common in comparison to an age- and sex-matched control group. During the following years, there was rapidly increasing evidence suggesting that ERP is associated with idiopathic VF and SCD based on several large population-based studies and in different clinical situations.[8–10] Furthermore, Watanabe *et al.*[11] showed that ERP has a high prevalence in short QT syndrome. In the presence of short QT syndrome, ERP is also associated with arrhythmic events. Similarly, ERP was shown to be prevalent and also associated with more arrhythmic events and arrhythmic death in Brugada.[8] In the present study, we found that the patients with ERP were more symptomatic at presentation and also the presence of ERP was associated with syncope in patients with CPVT (18 of 23 patients with ERP vs. 11 of 28 patients without ERP, $P = 0.005$). In young, otherwise healthy patients, recognition of syncope of cardiac origin is of paramount importance. Priori *et al.*[20] showed in their study that the mean delay to diagnosis of CPVT after syncope was 2 ± 0.8 years, due to initial attribution of

Table 2 QT intervals and clinical events in patients with and without ERP

Variable	Without ER ($n = 28$)	With ER ($n = 23$)	*P*-value
Male/female gender	6 (21%)/22 (79%)	5(22%)/18 (78%)	0.9
Age, years	33 ± 14	40 ± 15	0.06
Heart rate, bpm	69 ± 11	58 ± 12	**0.001**
QTc (II), ms	391.0 ± 36.2	375.7 ± 25.5	0.09
QTc (V5), ms	391.0 ± 32.0	378.7 ± 24.4	0.1
cT_{peak}–T_{end} (II), ms	69.0 ± 15.8	61.2 ± 9.3	**0.04**
At presentation, *n* (%)			
SCA	7 (25)	4 (17)	0.5
Syncope	11 (40)	18 (78)	**0.005**
VES/VT	2 (13)	0	0.5
Asymptomatic	9 (32)	0	**0.003**
During follow-up, *n* (%)			
SCA	7 (25)	9 (39)	0.2
Syncope	7 (25)	14 (61)	**0.02**
VES/VT	4 (13)	5 (22)	0.4
Asymptomatic	13 (46)	7 (30)	0.2

Values are *n* (%) or mean ± SD. cT_{peak}–T_{end}: T_{peak}–T_{end} interval, corrected according to Bazett's formula. VES, ventricular extrasystole.

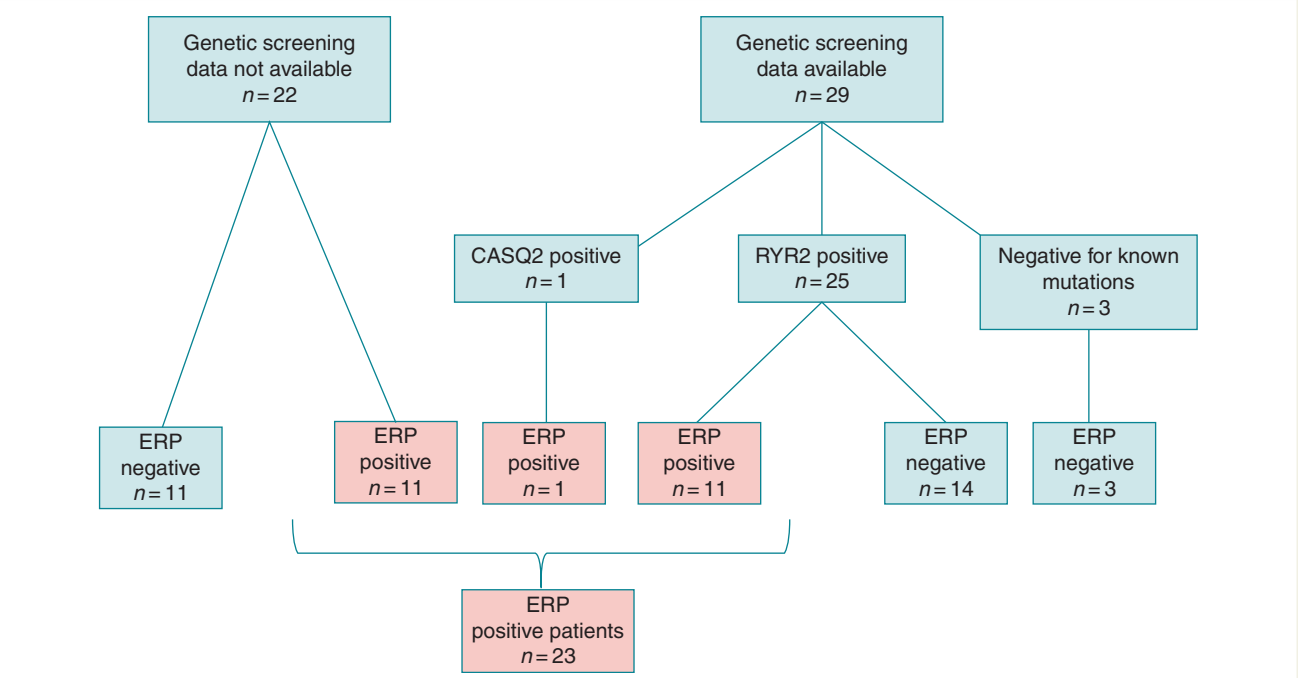

Figure 2 The presence of ERP in patients with and without genetic screening data (ERP positivity was presented in pink shadowed boxes).

vasovagal origin or neurologic factors. As CPVT is a rare disease and often not properly recognized, it is reasonable in patients with ERP and syncope to perform an easily accessible, non-invasive exercise test to diagnose/exclude CPVT as a cause of syncope.

Although patients with ERP appear to be at higher risk for idiopathic VF, ERP is a common ECG pattern in the healthy population, and the relative risk of idiopathic VF or arrhythmic death is low.[7] The morphology and the distribution of ERP improve the prognostic implication of this ECG pattern. Tikkanen *et al.*[21] showed that a horizontal/descending ST segment following ERP is associated with increased risk for arrhythmic death. Among Brugada syndrome patients, Kawata *et al.*[8] demonstrate that patients with a J-wave in both inferior and lateral leads or with horizontal ST-segment morphology had a worse prognosis. In the present study, we noticed that ERP was present in inferior ($n = 9$), lateral ($n = 9$), or infero-lateral leads ($n = 5$), mostly with 'slurring' pattern of ERP ($n = 13$, 56%) followed by a horizontal ST-segment morphology. However, we did not demonstrate an association between ERP and SCD. This result may be due to the unstable existence of ERP in infero-lateral leads or may be simply due to highly malignant character of CPVT that may diminish or obscure the rates of events facilitated by ERP.

In concordance with previous studies, the heart rate of patients presenting with ERP is slower by a mean of 11 bpm. Sinus bradycardia was also previously described in patients with CPVT.[22] Postma *et al.*[22] found that patients with CPVT and proven mutations had slower heart rates compared with an age- and gender-matched control group and also slower heart rate compared with non-affected family members. They hypothesized that the defective calcium handling in sinus node or increased vagal tonus might be the possible mechanisms. The augmented vagal tonus might lower heart rate and thereby increase the ERP. One can speculate that specifically in those patients with CPVT and ERP, increased vagal tone might also diminish the risk of arrhythmic events or death by lowering the heart rate and DAD-mediated triggered arrhythmias. On the contrary to this assumption, patients with ERP had higher rate of syncope and similar rate of sudden cardiac arrest. Our findings may support the impaired calcium handling in sinus node as an operating mechanism in sinus bradycardia. Therefore, the presence of ER is most probably independent from vagal effect and therefore is associated with increased risk of syncope in patients with CPVT.

Limitations

There are several limitations in our study. A major limitation was the retrospective nature of the present study. Thus, some data relevant to arrhythmias or syncopes might have not been collected, and some possible confounders cannot be eliminated.

The intermittent appearance of ERP might be another confounder. We did not prospectively examine the patients for daily or circadian fluctuations of ERP. Previous studies have shown that existence of ERP is not stable and several factors may influence the amplitude and presence. Therefore, we cannot exclude the possibility of temporary presence or absence of ERP as a confounding factor to our analysis.

Antiarrhythmic drugs, such as β-blockers, might have an influence on the occurrence of ERP. As pharmacological therapy was heterogenous in this study group, the potential impact of drug therapy on arrhythmias and arrhythmic events during follow-up cannot be ruled out.

Genetic screening data were available only in 29 of 51 patients (due to patients'/parents' refusal of genetic screening), which limits any conclusive association between ERP and mutations.

Conclusion

The infero-lateral ERP has a high prevalence by 45% in patients with CPVT. Early repolarization pattern was present in inferior ($n = 9$), lateral ($n = 9$), or infero-lateral leads ($n = 5$) in 23 patients (45%) with horizontal ST-segment morphology. All patients with ERP were symptomatic at presentation, and patients with ERP had an increased risk of syncope indicative of a more malignant phenotype of these patients. These findings might have further implications for diagnosis, treatment, and life-style modification. Vice versa, in patients with unexplained syncope and an electrocardiographic ERP at baseline ECG, exercise testing should be performed even in asymptomatic patients to detect CPVT.

Conflict of interest: none declared.

Funding

Grant funding to E.S.-B. and B.S. by the IMF (Münster), to E.S.-B. by the Fondation Leducq (Paris), the SFB656 (subproject C1), and the IZKF.

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