Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia

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BACKGROUND Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by adrenergically induced ventricular tachycardia (VT) associated with syncope and sudden death.

OBJECTIVE This study sought to characterize arrhythmias associated with CPVT with respect to provocation by exercise and drugs, electrocardiographic characteristics, and association with long-term outcomes; and to explore the relation between age and clinical presentation.

METHODS Seventy patients from 16 families were evaluated with exercise and selective adrenaline challenge, and screened for RyR2 mutations. CPVT was diagnosed in probands with symptoms and stress- or adrenaline-provoked VT, or in asymptomatic relatives with provoked VT or RyR2 mutations. Patients were followed up for recurrent syncope, VT, and sudden death.

RESULTS Twenty-seven patients including 16 probands were identified (median age 35 years, 67% female). Presentation was cardiac arrest in 33% and syncope in 56%, and 11% were asymptomatic. Polymorphic or bidirectional VT was provoked with exercise in 63% and adrenaline in 82%. The initiating beat of VT was late-coupled and wide (coupling interval 418 ± 42 ms; QRSd 131 ± 17 ms), and QRS morphology suggested an outflow tract origin in 59%. During follow-up of 6.2 ± 5.7 years, 2 patients died despite an implantable cardioverter-defibrillator (ICD), 4 patients received ICD therapy for VT, and 5 patients had inappropriate therapy for supraventricular tachycardia. Patients presenting with late-onset CPVT (age > 21; n = 10) were often female (80%) and less likely to have RyR2 (Ryanodine receptor type 2) mutations (33%), and fatal events were not observed during follow-up (4.1 ± 3.6 years).

CONCLUSION Ventricular arrhythmia in CPVT is often initiated from the outflow tract region. Despite β-blocker therapy and selective ICD implantation, breakthrough arrhythmias occur and may be associated with adverse outcomes.

KEYWORDS Ventricular tachycardia; Genetics; Sudden death; Catecholamines; Electrocardiogram

ABBREVIATIONS **CPVT** = catecholaminergic polymorphic ventricular tachycardia; **ECG** = electrocardiographic; **ICD** = implantable cardioverter-defibrillator; **LBBB** = left bundle branch block; **RBBB** = right bundle branch block; **RyR2** = ryanodine receptor type 2; **VT** = ventricular tachycardia

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial condition characterized by adrenergically induced ventricular arrhythmias associated with syncope and sudden death.[1,2] Although it is rare (prevalence approximately 1:10,000) and frequently lethal when untreated, an understanding of the underlying genetic basis, arrhythmia substrate, diagnosis, and prognosis have come from cohort studies.[3-6]

The diagnosis is currently based on exercise-induced polymorphic or bidirectional ventricular tachycardia (VT) in the absence of structural heart disease or a prolonged QT interval.[7] Mutations in the gene encoding the cardiac ryanodine receptor type 2 (RyR2) can be found in 50% to 55% of patients with clinical CPVT. A further 1% to 2% of patients will be homozygous for mutations in the gene encoding calsequestrin (CASQ2).[4,5,8,9] The relation between genetic mutations, calcium handling, and adrenergically induced ventricular arrhythmias has recently been characterized.[10] The cornerstone of management remains β-blocker therapy with selective implantation of defibrillators in high-risk patients.

The primary aim of the study was to explore the means of provocation of ventricular arrhythmia, determine the electrocardiographic (ECG) characteristics of the initiating beats, and describe the long-term outcome of patients during follow-up. The secondary aim of the study was to investigate the potential relation between age, clinical presentation, and outcomes.

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Methods

Patients and setting

Patients were referred to the Inherited Arrhythmia Clinics at the University of Western Ontario and the University of Ottawa after an unexplained cardiac arrest, syncope, or palpitations or were first-degree relatives of patients with a known inherited arrhythmia syndrome. The University of Western Ontario Institutional Ethics Review Board approved the study.

Clinical evaluation, provocation testing, and ECG characterization

All patients were assessed clinically and underwent investigations including baseline 12-lead ECG, echocardiography, and 48-hour Holter monitoring. Patients with a history of cardiac arrest also underwent coronary angiography and cardiac MRI.

Patients underwent provocation testing in the form of exercise testing and/or adrenaline infusion. Symptom-limited treadmill exercise testing was performed in all patients using a modified or standard Bruce protocol. Adrenaline infusion was performed in all patients after unexplained cardiac arrest and was performed at the discretion of the treating physician in other patients. The protocol for the adrenaline infusion has been previously described.[11] In brief, adrenaline infusion was initiated at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated at 5-minute intervals to a maximum dose of 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Continuous ECG monitoring was performed during both exercise testing and adrenaline infusion. Episodes of VT were analyzed digitally, with emphasis on the initiating beat (morphology, QRS duration, coupling interval).

Genetic testing

Molecular genetic testing was offered to all patients with a clinical diagnosis of CPVT and to first-degree relatives where a disease-causing mutation had been previously identified in the family. RyR2 (reference sequence NM_001035) selected exons 2-4, 6-15, 17-20, 26, 37, 39-49, 83, 84, 87-97, 99-105 were assessed.[12] In index cases, genomic DNA isolated from blood lymphocytes was screened using temperature-gradient capillary electrophoresis (SpectruMedix, State College, Pennsylvania). Polymerase chain reaction–amplified DNA samples were separated by capillary electrophoresis under 2 temperature gradient conditions (50° to 58° and 55° to 63°). Samples containing mutations were identified on the basis of altered electrophoretic patterns of heteroduplexes caused by their different melting equilibriums and electrophoretic mobilities. Samples containing heteroduplexes then underwent direct DNA sequencing. If a mutation was identified, first-degree relatives were screened by direct DNA sequencing. Testing was not performed for genes associated with long QT syndrome because QT intervals were normal during all testing in all patients. Testing for calsequestrin was not performed because it was considered a very rare cause of CPVT.[9]

Diagnostic criteria

CPVT was diagnosed in probands with a history of sudden cardiac arrest or symptoms occurring in the context of physical activity or acute emotion in conjunction with exercise or adrenaline-induced polymorphic or bidirectional VT of ≥4 beats.[2] First-degree relatives of affected individuals were also evaluated, and CPVT was diagnosed if polymorphic or bidirectional VT was observed during exercise or adrenaline challenge, on Holter monitoring, or if genetic testing was positive for the disease-causing mutation in the family.[13] Structural heart disease was excluded at the time of initial assessment by echocardiography and/or cardiac MRI. Coronary artery stenosis of >50% was excluded by angiography in patients with a prior cardiac arrest. Patients with structural abnormalities on cardiac imaging or persistent prolongation of the resting QTc (>460 ms for male patients and >480 ms for female patients) were excluded.

Treatment and follow-up

β -Blockers were recommended to all patients with a diagnosis of CPVT, with atenolol 25 to 100 mg once daily, nadolol 20 to 80 mg once daily, or bisoprolol 2.5 to 10 mg once daily.[14] Exercise restriction was also recommended. Implantable cardioverter-defibrillators (ICD) were implanted in patients with previous cardiac arrest, or with recurrent syncope or documented VT despite β-blockers. The dose of β-blocker was titrated on the basis of repeat exercise testing and ICD interrogation.[15] Adjunctive strategies such as flecainide, calcium channel blockade, and cardiac sympathectomy were offered to patients who remained symptomatic despite adequate β -blockade.[2,16-18]

Patients were followed up for clinical events and were offered annual clinical reassessment and repeat exercise testing. In addition, patients with ICDs were followed up in the arrhythmia device clinic every 6 months. Patients were encouraged to contact the clinic in the event of new symptoms.

Subgroup analysis

We sought to explore the potential relation between the age of patients at presentation and the clinical/genetic profile of CPVT by subgroup analysis. The cohort was divided into 2 groups (juvenile-onset CPVT vs. late-onset CPVT) based on the age of presentation of the proband, with an empirical cut-off of 21 years. Characteristics and outcomes were compared between the 2 groups.

Statistical analyses

Comparisons between groups were performed using 1-way ANOVA, χ^2 test, or Kruskal-Wallis test as appropriate. Two-sided P values of <.05 were considered significant for all analyses. All analyses were performed using SPSS 16.0 for Mac (SPSS Inc, Chicago, Illinois). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the article as written.

Results

Patient characteristics

Seventy individuals from 16 families were assessed for possible CPVT (Table 1). The overall median age was 28 years (range 3 to 72), and 63% of patients were female. Twenty-seven patients were diagnosed with CPVT, including 16 pro-