CPVT: Arrhythmogenesis, Therapeutic Management, and Future Perspectives. A Brief Review of the Literature

Baltogiannis, Giannis G; Lysitsas, Dimitrios N; di Giovanni, Giacomo; Ciconte, Giuseppe; Sieira, Juan; Conte, Giulio; Kolettis, Theofilos M; Chierchia, Gian-Battista; de Asmundis, Carlo; Brugada, Pedro

Abstract: Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a primary electrical disease characterized by a normal resting electrocardiogram and induction of malignant arrhythmias during adrenergic stress leading to syncope or sudden cardiac death (SCD). CPVT is caused by mutations in the cardiac ryanodine receptor (RyR2) or in the sarcoplasmic reticulum protein calsequestrin 2 genes. The RyR2 mutations are responsible for the autosomal dominant form of CPVT, while mutations are rare and account for the recessive form. These mutations cause a substantial imbalance in the homeostasis of intracellular calcium resulting in polymorphic ventricular tachycardia through triggered activity. Beta blockers were for years the cornerstone of therapy in these patients. Sodium channel blockers, especially flecainide, have an additive role in those not responding in beta blockade. Implantation of defibrillators needs a meticulous evaluation since inappropriate shocks may lead to electrical storm. Finally, cardiac sympathetic denervation might also be an alternative therapeutic option. Early identification and risk stratification is of major importance in patients with CPVT. The aim of the present review is to present the arrhythmogenic mechanisms of the disease, the current therapies applied and potential future perspectives.

DOI: https://doi.org/10.3389/fcvm.2019.00092

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: https://doi.org/10.5167/uzh-176106

Journal Article
Published Version

The following work is licensed under a Creative Commons: Attribution 4.0 International (CC BY 4.0) License.

Originally published at:
Baltogiannis, Giannis G; Lysitsas, Dimitrios N; di Giovanni, Giacomo; Ciconte, Giuseppe; Sieira, Juan; Conte, Giulio; Kolettis, Theofilos M; Chierchia, Gian-Battista; de Asmundis, Carlo; Brugada, Pedro (2019). CPVT: Arrhythmogenesis, Therapeutic Management, and Future Perspectives. A Brief Review of the Literature. Frontiers in cardiovascular medicine, 6:92.

DOI: https://doi.org/10.3389/fcvm.2019.00092
CPVT: Arrhythmogenesis, Therapeutic Management, and Future Perspectives. A Brief Review of the Literature

Giannis G. Baltogiannis1,∗, Dimitrios N. Lysitsas2, Giacomo di Giovanni1, Giuseppe Ciconte1, Juan Sieira1, Giulio Conte1, Theofilos M. Kolettis3, Gian-Battista Chierchia1, Carlo de Asmundis1 and Pedro Brugada1

1 Heart Rhythm Management Centre, Vrije University, Brussels, Belgium, 2 St. Luke’s Hospital Thessaloniki, Thessaloniki, Greece, 3 Cardiology Department, University of Ioannina, Ioannina, Greece

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a primary electrical disease characterized by a normal resting electrocardiogram and induction of malignant arrhythmias during adrenergic stress leading to syncope or sudden cardiac death (SCD). CPVT is caused by mutations in the cardiac ryanodine receptor (RyR2) or in the sarcoplasmic reticulum protein calsequestrin 2 genes (CASQ2). The RyR2 mutations are responsible for the autosomal dominant form of CPVT, while CASQ2 mutations are rare and account for the recessive form. These mutations cause a substantial imbalance in the homeostasis of intracellular calcium resulting in polymorphic ventricular tachycardia through triggered activity. Beta blockers were for years the cornerstone of therapy in these patients. Sodium channel blockers, especially flecainide, have an additive role in those not responding in beta blockade. Implantation of defibrillators needs a meticulous evaluation since inappropriate shocks may lead to electrical storm. Finally, cardiac sympathetic denervation might also be an alternative therapeutic option. Early identification and risk stratification is of major importance in patients with CPVT. The aim of the present review is to present the arrhythmogenic mechanisms of the disease, the current therapies applied and potential future perspectives.

Keywords: channelopathies, CPVT, arrhythmias, genes, sudden death, risk stratification

INTRODUCTION

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a primary electrical disease characterized by a normal resting electrocardiogram and induction of malignant arrhythmias during adrenergic stress leading to syncope or sudden cardiac death (SCD) (1). CPVT phenotype is a result of mutations of Ryanodine receptor (RyR2) and calsequestrin 2. The RyR2 mutations account for the commonest phenotype and they are inherited through an autosomal dominant manner. CASQ2 mutations represent the recessive form (2, 3).

CPVT is responsible for SCD especially among children and young adults. According to previous reports, the incidence of arrhythmias in CPVT patients was 32% over 8 years (2), but the true frequency of the disease is unknown. This is due to the fact that unlike other inherited
channelopathies such as long QT syndrome, it is present not only with a structurally normal heart, but also without resting ECG abnormalities (2).

Beta blockade is the main therapeutic option. Sodium channel blockers, such as flecainide, have an additive role to those not responding to beta blockers, along with left cardiac stellate sympathectomy. Implantable cardiac defibrillators (ICDs) are life-saving therapy for the majority of patients with cardiac channelopathies; however CPVT patients need to be carefully selected, since inappropriate shocks may lead to adrenergic stimulation and electrical storm, despite optimal programming.

**CPVT AND ARRHYTHMOGENESIS**

Arrhythmogenesis in CPVT patients is attributed to mutations in different proteins resulting in bidirectional ventricular tachycardia through different arrhythmogenic mechanisms. Arrhythmias produced by gain-of-function mutations in RyR2 are postulated to result from destabilization of the channel with increased diastolic SR Ca$^{2+}$ leak in ventricular myocytes, leading to delayed afterdepolarizations and triggered activity via the Na$^+$/Ca$^{2+}$ exchanger current. Yet, new evidence has shown that the cardiac Purkinje network appears to be involved in the initiation of bidirectional VT and polymorphic ventricular tachycardia in this disease (4). It is estimated that over 160 mutations cause CPVT 1. Most of them cause a gain of function of the RyR2 channels (1–3), whereas others, such as CASQ2 gene, regulate RyR receptor through other proteins (junctional and triadin) resulting to a leakage of Ca in diastole.

According to previous published data (5), gene mutations responsible for CPVT lead to ventricular arrhythmia through the alteration of the Ca$^{2+}$ homeostasis. Specifically, mutations in the RyR2 and CASQ2 genes lead to a leakage of Ca$^{2+}$ from the SR in diastole, particularly under adrenergic stress (exercise, emotional stress), resulting in delayed afterdepolarizations and therefore vulnerable to ventricular arrhythmias. Other less prevalent gene mutations like KCNJ2, triadin (TRDN), junctin (JCN), calmodulin (CALM1 and CALM2), and NKYRIN-B (6) may predispose to CPVT as well as in the future, other not yet identified genes might be found responsible for the disease.

**CLINICAL PRESENTATION-DIAGNOSTIC EVALUATION**

Nevertheless, irrespective of the responsible mutation, CPVT is characterized by polymorphic ventricular tachycardia under adrenergic stress. Apart from syncope less specific signs and symptoms, such as dizziness or palpitations might be exerted (7). The first manifestation of the disease occurs during childhood and the majority of patients have experienced syncope episode or cardiac arrest by their adulthood (7). The study of Hayashi et al. (2) depicted that the earliest a CPVT is diagnosed the worse the prognosis is. This can be attributed, at least in part, to the fact that children performing strenuous physical activities are more sensitive to external stimulations (children have more opportunities to engage in strenuous activities), (1) patients with more severe forms of CPVT will be diagnosed earlier, and (2) beta-blockers are frequently underdosed in children if based on weight given increased hepatic clearance. Sudden cardiac death or syncope in first degree family members is detected in one third of CPVT patients (8). Despite its life threatening nature, CPVT remains often unnoticed. This is due to normal baseline electrocardiograms on top of incomplete penetrance (8, 9) and thus variable expressivity. Some authors have reported bradycardia, and others have observed U waves in electrocardiograms (10). CPVT is unmasked by a treadmill stress test (11). When patients start exercising ventricular ectopy develops, increasing in complexity as the heart rate increases. Specifically, dynamic exercise during a BRUCE protocol induces premature ventricular complexes that may degenerate to more complex ventricular tachyarrhythmias or even sustained VT (12, 13).

**THERAPEUTIC MANAGEMENT**

**Beta Blockers**

Therapeutic management for patients with CPVT includes beta blockers without intrinsic sympathomimetic activity. Nadolol is the beta-blocker of choice in a high dosage, 1–2 mg/kg. The incidence of arrhythmic events in CPVT patients on beta-blockers is still high. Other non-selective beta-blockers are equally effective especially propranolol. Clinical follow up with holter monitoring and treadmill stress test should be performed so that the optimal therapy is adjusted (14).

In the study of Priori et al. (14), there is significantly lower incidence of SCD in patients on beta-blockers. Hence, the event rates in the patients on therapy were not negligible. This could be attributed to poor therapy compliance. Priori et al. suggest that taking different beta blockers than nadolol could be associated with higher incidence rates. Furthermore, data from treadmill stress tests reveal that it is not the ultimate tool during follow up, despite the fact that it is widely used as a diagnostic tool, due to low sensitivity and specificity (14).

Chatzidou et al. (15) suggested that patients presenting with electrical storm independently of the underlying mechanism should be treated with oral propranolol as the preferred beta-blocker agent.

**Flecainide**

The study of van de Weerf et al. (16) supports the use of flecainide on top of beta blockers as it reduces ventricular arrhythmias during exercise. This is of major importance, since several studies have demonstrated a significant event rate despite conventional therapy (2, 9, 17–23). Therefore, adding flecainide in combination with β-blocker therapy should be considered.

In CPVT the rise of intracellular Ca$^{2+}$ activates the electrogenic Na$^+$/Ca$^{2+}$ exchanger (NCX), which produces a transient inward current (ITi). ITi generates delayed afterdepolarizations, which can lead to triggered activity, and the initiation of ventricular arrhythmias (24). Flecainide directly targets the molecular defect in CPVT by inhibiting RyR2 channels and preventing arrhythmogenic Ca$^{2+}$ waves. Flecainide’s Na$^+$ channel blockade further reduces the rate of
triggered beats (5, 25, 26). This dual action could explain why flecainide is so effective in severe CPVT and provides a rationale for combination therapy with β-blockers. The rationale for flecainide use for treatment of CPVT is supported by in vitro studies demonstrating that flecainide blocks RyR2 in lipid bilayers (27) suppresses calcium waves in CASQ2-knockout myocytes, abolishes delayed afterdepolarization-mediated triggered activity, and reduces exercise induced ventricular arrhythmias inCASQ2 and RYR2 mouse models. The efficacy of flecainide in human patients with CPVT has been demonstrated in the 3 retrospective cohorts. Kannankeril et al. (25) supported that a median dosage of 300 mg/d was required to achieve target trough drug levels. One could speculate that chronotropic incompetence from combination therapy with β-blocker plus flecainide would result in lower levels of exertion during exercise and thus a lower arrhythmia score. However, maximal workload achieved during each exercise test did not differ significantly, suggesting similar levels of effort across the three exercise tests.

Liu et al. support that the antiarrhythmic effect of flecainide is that it reduces the availability of sodium channels, thus preventing the development of triggered APs (28).

Radwanski et al. suggested that flecainide may exert its antiarrhythmic action by antagonizing catecholamine-dependent augmentation of Na+ influx via sodium channel isoforms, and Nav1.6 in particular (29).

**Left Cardiac Sympathetic Denervation**

In patients who are refractory to maximal pharmacologic treatment, left cardiac sympathetic denervation (LCSD) could be an alternative, with significant reduction in arrhythmic events, as noted by De Ferrari et al. (30). However, the procedure is not widely available and is associated with complications such as pneumothorax and Horner syndrome (30).

**Implantable Cardioverter Defibrillator**

An ICD, usually the ultimate solution for primary or secondary prevention of SCD for other channelopathies should be used in CPVT patients who, despite optimal medical management or/and other therapies such as left cardiac sympathectomy continue to be in danger. Patients who have experienced an aborted cardiac arrest before the initiation of therapy, should be on medical therapy together with an ICD implantation (31). Hence, implantation of an ICD is a technical challenge in a pediatric population and problems such as inappropriate shocks, proarrhythmic effects of the ICD, and the need for a lifetime protection requiring multiple reinterventions should be addressed when the decision is taken (32).

**REFERENCES**

1. Coumel P, Fidelle J, Lutet V, Attuel P, Bouvrais Y. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. Br Heart J. (1978) 40(Suppl):28–37.
2. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buissen NR, Lupoglouzeff JM, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia: A population-based study. Circulation. (2009) 119:2426–34. doi: 10.1161/CIRCULATIONAHA.108.829267
3. Liu N, Rizzi N, Boveri L, Priori SG. Ryanodine receptor and calsequestrin in arhythmogenesis: what have we learnt from genetic diseases and transgenic mice. J Molec Cell Cardiol. (2009) 46:149–59. doi: 10.1016/j.yjmcc.2008.10.012
4. Willis BC, Pandit SV, Ponce-Balbuena D, Zarzoso M, Guerrero-Serna G, Limbu B, et al. Constitutivel Intracellular Na+ excess in purkinje cells promotes arrhythmogenesis at lower levels of stress than ventricular myocytes from mice with catecholaminergic polymorphic ventricular tachycardia. Circulation. (2016) 133:2348–59. doi: 10.1161/CIRCULATIONAHA.116.021936
Baltogiannis et al. CPVT: Arrhythmogenesis and Therapeutic Management

5. Rizzi N, Liu N, Napolitano C, Nori A, Turcato F, Colombi B, et al. Unexpected structural and functional consequences of the R33Q homozygous mutation in cardiac calsequestrin: a complex arrhythmogenic cascade in a knock in mouse model. Circ. Res. (2008) 103:298–306. doi: 10.1161/CIRCRESAHA.108.171660

6. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arhythmol. (2016) 32:344–351. doi: 10.1016/j.joa.2015.09.008

7. Fernández-Falgueras A, Sarquella-Brugada G, Brugada I, Brugada R, Camputazo O. Cardiac channelopathies and sudden death: recent clinical and genetic advances. Biology. (2017) 6:167. doi: 10.3390/biology60601007

8. Priori SG, Napolitano C. Cardiac and skeletal muscle disorders caused by mutations in the intracellular Ca2+ release channels. J Clin Invest. (2005) 115:2033–8. doi: 10.1172/JCI25564

9. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, et al. Catecholaminergic polymorphic ventricular tachycardia: RyR2 mutations, bradyarrhythmia, and follow up of the patients. J Med Genet. (2005) 42:863–70. doi: 10.1136/jmg.2004.026893

10. Aizawa Y, Komura S, Okada S, Chinushi M, Aizawa Y, Morita H, et al. Distinct U wave changes in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). Int Heart J. (2006) 47:381–9. doi: 10.1013/ihj.47.381

11. Refaat MM, Hotait M, Tseng ZH. Utility of the exercise electrocardiogram testing in sudden cardiac death risk stratification. Ann Noninvasive Electrocardiol. (2014) 19:313–8. doi: 10.1111/anec.12191

12. Napolitano C, Priori SG, Bloise R. Catecholaminergic polymorphic ventricular tachycardia. In: Pagon RA, Adam MP, Ardinger HH, Kretzmann R, Williams SM, Chakravarti A, et al. Gene Reviews. Seattle, WA: University of Washington (1993).

13. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. Prog Cardiovasc Dis. (2008) 51:23–30. doi: 10.1016/j.pcad.2007.10.005

14. Priori SG, Wilde AA, Morice A, Toy H, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace. (2013) 15:1389–406. doi: 10.1093/europace/eut071

15. Chattidou S, Kontogiannis C, Tsilimigras DI, Georgiopoulos G, et al. Catecholaminergic polymorphic ventricular tachycardia. In: Pagon RA, Adam MP, Ardinger HH, Kretzmann R, Williams SM, Chakravarti A, et al. Gene Reviews. Seattle, WA: University of Washington (1993).

16. van der Werf C, Kannankeril PJ, Mørkøv M, van der Meer P, Viskin S, Leenhardt A, et al. Autosomal recessive catecholamine- or exercise-induced life-threatening ventricular arrhythmias. J Am Coll Cardiol. (2016) 67:341–5. doi: 10.1016/j.jacc.2015.09.008

17. Bauce B, Rampazzo A, Basso C, Bagattin A, Daliento L, Tiso N, et al. Exercise electrocardiogram testing in sudden cardiac death risk stratification. Ann Noninvasive Electrocardiol. (2014) 19:313–8. doi: 10.1111/anec.12191

18. Chatzidou S, Kontogiannis C, Tsilimigras DI, Georgiopoulos G, et al. Catecholaminergic polymorphic ventricular tachycardia. In: Pagon RA, Adam MP, Ardinger HH, Kretzmann R, Williams SM, Chakravarti A, et al. Gene Reviews. Seattle, WA: University of Washington (1993).

19. Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, et al. Autosomal recessive catecholaminergic or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13–21. Circulation. (2001) 103:2822–7. doi: 10.1161/01.CIR.103.23.2822

20. van der Werf C, Kannankeril PJ, Mørkøv M, van der Meer P, Viskin S, Leenhardt A, et al. Autosomal recessive catecholamine- or exercise-induced life-threatening ventricular arrhythmias. J Am Coll Cardiol. (2016) 67:341–5. doi: 10.1016/j.jacc.2015.09.008

21. Haugaa KH, Leren IS, Berge KE, et al. High prevalence of exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia mutation-positive family members. Europace. (2010) 12:417–23. doi: 10.1093/europace/eup248

22. Maltsev VA, Lakatta EG. Dynamic interactions of an intracellular Ca2+ clock and membrane ion channel clock underlie robust initiation and regulation of cardiac pacemaker function. Circ Cardiovasc. Res. (2008) 77:274–84. doi: 10.1093/cvr/cvm058

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Baltogiannis, Lysisitas, di Giovanni, Ciccone, Sieria, Conte, Kolettis, Chierchia, de Asmundis and Brugada. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.