JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 3, NO. 11, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2017.08.010

EDITORIAL COMMENT

Clockwork and Arrhythmias in Catecholaminergic Polymorphic Ventricular Tachycardia*

Steven A. Lubitz, MD, MPH[a,b]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic arrhythmia syndrome characterized by the risk of sudden death from ventricular arrhythmia. Excessive cytosolic calcium is implicated as the principal mechanism, leading to delayed afterdepolarizations and, ultimately, arrhythmogenesis in patients with CPVT. The calcium overload paradigm is supported by discoveries which have identified mutations in genes related calcium handling in the sarcoplasmic reticulum including *RYR2* (1,2) and *CASQ2* (3,4).

The calcium overload state in CPVT is exacerbated by adrenergic tone and exercise. As such, a cornerstone for treatment of patients with CPVT is management with beta-adrenergic- blocking medications and activity restriction (5). Increasingly, data support the role of adjunctive flecainide therapy to suppress ectopy (6). However, a substantial proportion of patients with CPVT have recurrent events despite treatment (7). Implantable cardioverter-defibrillators (ICD) can be life saving, but morbidity from inappropriate and appropriate defibrillator shocks, both of which can lead to a perpetual cycle of adrenergic stimulation and further arrhythmia, is considerable (8).

It has long been recognized that there are circadian variations in some cardiovascular disease events and sudden cardiac arrest (9–12). Whether such patterns are related to CPVT-associated arrhythmogenesis has not been clear. In this issue of *JACC: Clinical Electrophysiology*, the study by Miyake et al. (13) examined the relationship between the time of day and arrhythmia burden in patients with CPVT. The authors retrospectively aggregated clinical data from patients <21 years of age at diagnosis from 7 institutions throughout the United States and Canada. Continuously monitored data from Holter devices, implantable loop recorders, and ICDs were aggregated, and the timing of ventricular arrhythmia events was noted. The authors used generalized linear models to assess the associations between time of day and arrhythmia occurrence.

SEE PAGE 1308

The series included 80 patients whose arrhythmias were diagnosed at a median of 11 years of age. Almost all were probands, which means that they were likely the most severely affected individuals in their families. Approximately 36% had a history of cardiac arrest, and 61% underwent insertion of a defibrillator. Five patients had implantable loop recorders. The study encompassed a total of 190 Holter monitors, 172 exercise stress tests, and a substantial repository of cardiac rhythm data through various continuous monitoring devices.

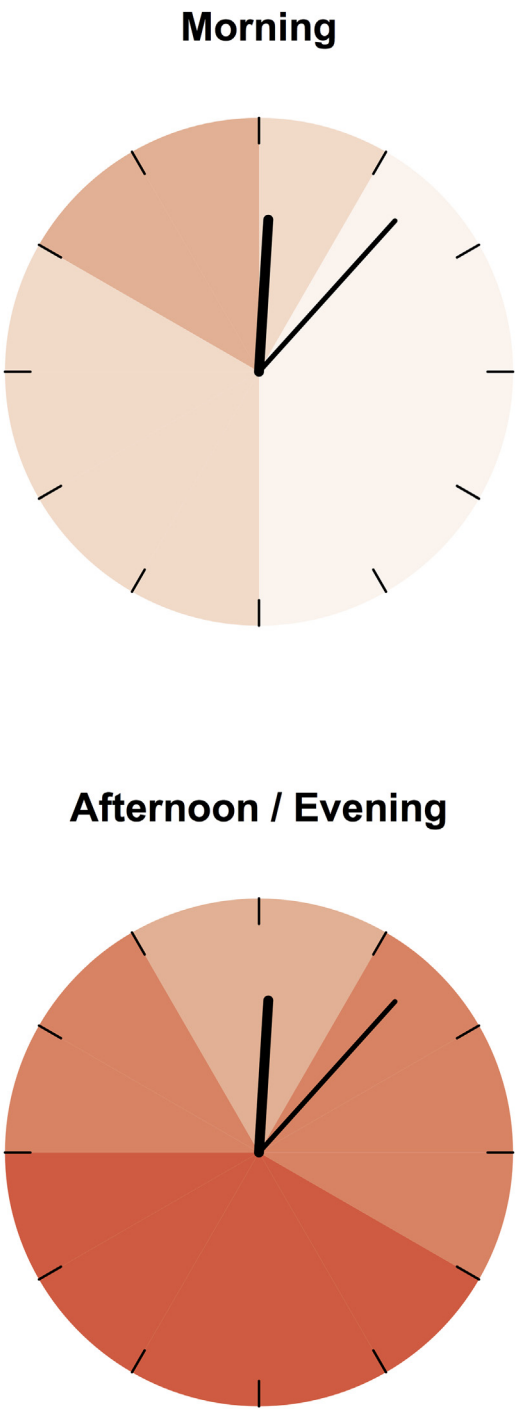
In total, 423 ventricular arrhythmia events occurred, 299 of which were recorded by a defibrillator or loop recorder, 45 by Holter, and 72 by stress

*Editorials published in *JACC: Clinical Electrophysiology* reflect the views of the authors and do not necessarily represent the views of *JACC: Clinical Electrophysiology* or the American College of Cardiology.

From the [a]Cardiovascular Research Center, Cardiac Arrhythmia Service and Cardiovascular Genetics Program, Massachusetts General Hospital, Boston, Massachusetts; and the [b]Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts. Dr. Lubitz is supported by U.S. National Institutes of Health grant K23HL114724, Doris Duke Charitable Foundation clinical scientist development award 2014105, sponsored research support from Bayer HealthCare, Biotronik, and Boehringer Ingelheim; and is a consultant for St. Jude Medical and Quest Diagnostics.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

FIGURE 1 Time of Day and Ventricular Arrhythmia Risk in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia



The risk of ventricular arrhythmia according to time of day is displayed with higher risk indicated by a **darker orange color**. Risk values are projected onto clocks for illustrative purposes and are conceptually informed from the results of the current study.

testing, and 7 were inferred by cardiac arrests. Arrhythmias were more common during waking hours than sleeping hours (Figure 1). Among waking hours, there was a 2.5-fold increased odds of ventricular arrhythmias occurring in the afternoon compared to the morning and nearly 3-fold increased odds in the evening. Exercise test results were more likely to be positive if performed in the afternoon than in the morning. Interestingly, no significant differences in risk of arrhythmias were observed during weekdays versus weekends or season.

What are the implications of the current results? Should patients suspected of having CPVT undergo exercise testing in the afternoon to maximize diagnostic yield? Should medication therapy be augmented to minimize arrhythmias in the afternoon and evening? Should activity restriction be emphasized with particular importance during certain times of day?

Each of these clinical questions is predicated on a causal relation between time of day and arrhythmia. Although the current study provides a greater understanding of the epidemiology of CPVT-related ventricular arrhythmia, the observational and retrospective design limits causal inferences related to the pathogenesis of arrhythmias in patients with CPVT. For example, it is possible that the findings observed in this study could be confounded by the kinetics of pharmacologic therapy (i.e., medications may wear off in the afternoon and evening), the type of physical activity performed in the afternoon and evening, the high-risk sample of patients included, the nonrandom missingness of data given the retrospective nature or other factors that are either difficult to account for or which were not measured. Nevertheless, the current study shines a spotlight on areas in need of future examination in either randomized controlled experiments or in prospective protocols with uniform physical activity counseling, ascertainment of exposures, and endpoints. The current study also highlights, once again, the value of multicenter collaborations in the field of inherited arrhythmia research, a cornerstone of investigation that has successfully yielded important clinical insights into these conditions for decades.

Counseling patients with CPVT presents substantive clinical challenges, particularly because the condition usually presents during childhood, adolescence, or young adulthood, the years of life during which patients are typically very active. Such discussions entail hard conversations about avoidance of competitive athletics and parameters around which physical activity can reasonably be pursued (14), the importance of medication adherence, and the potential tradeoffs of a long-term

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 3, NO. 11, 2017
NOVEMBER 2017:1318–20

sedentary lifestyle that can occur with activity restriction. Given the substantial risks that patients with CPVT may encounter, optimizing our ability to predict the probability of arrhythmia is well warranted and will enhance our ability to both counsel and manage patients.

ADDRESS FOR CORRESPONDENCE: Dr. Steven A. Lubitz, Cardiac Arrhythmia Service and Cardiovascular Research Center, Massachusetts General Hospital, 55 Fruit Street, GRB 109, Boston, Massachusetts 02114. E-mail: slubitz@mgh.harvard.edu.

REFERENCES

1. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 2001;103:196–200.

2. Laitinen PJ, Brown KM, Piippo K, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 2001;103:485–90.

3. Lahat H, Eldar M, Levy-Nissenbaum E, et al. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. Circulation 2001; 103:2822–7.

4. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. Am J Hum Genet 2001;69:1378–84.

5. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–63.

6. Kannankeril PJ, Moore JP, Cerrone M, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. JAMA Cardiol 2017;2:759–66.

7. Sy RW, Gollob MH, Klein GJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2011;8:864–71.

8. Miyake CY, Webster G, Czosek RJ, et al. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. Circ Arrhythm Electrophysiol 2013;6: 579–87.

9. Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313: 1315–22.

10. Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987;75:131–8.

11. Behrens S, Galecka M, Bruggemann T, et al. Circadian variation of sustained ventricular tachyarrhythmias terminated by appropriate shocks in patients with an implantable cardioverter defibrillator. Am Heart J 1995;130:79–84.

12. Arntz HR, Willich SN, Schreiber C, Bruggemann T, Stern R, Schultheiss HP. Diurnal, weekly and seasonal variation of sudden death. Population-based analysis of 24,061 consecutive cases. Eur Heart J 2000;21:315–20.

13. Miyake CY, Asaki SY, Webster G, et al. Circadian variation of ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol EP 2017;3:1308–17.

14. Ackerman MJ, Zipes DP, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 10: the cardiac channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132:e326–9.

KEY WORDS arrhythmia, catecholaminergic polymorphic ventricular tachycardia, circadian, ICD