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EDITORIAL COMMENT

A Different Way to Slow Down in Catecholaminergic Polymorphic Ventricular Tachycardia

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Arrhythmia events in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) can be dramatic. The disease is rare enough that many practices care for only a handful of patients with CPVT (the prevalence is estimated at 1:10,000).[1] It is appropriate that many patients, especially probands who have survived a life-threatening arrhythmia, are the focus of intensive campaigns of medication adjustment and recurrent exercise testing. For many patients, therapy adjustments are a lifelong part of CPVT treatment.

A recent burst exercise testing protocol seems to improve the test characteristics of exercise stress tests.[2] Putatively, burst testing optimizes the adrenergic stimulus in CPVT. Having established a maximal slope and speed for the treadmill in a prior test, patients start exercising immediately at their previous peak level. This protocol has found favor to unmask veiled phenotypes and to reassure families that antiarrhythmic therapy is working. In high-risk patients, therapies include one or more major components: oral therapy with noncardioselective beta adrenergic receptor blockers (beta-blockers), oral flecainide therapy, left cardiac sympathetic denervation, and implantable cardioverter-defibrillators (ICDs).[3] Beta-blockers are the foundation of most treatment regimens.

In summary, patients with CPVT who have recovered from a life-threatening event are often in the forefront of our clinical memories, and the urgent and recurring therapeutic question is, "Is this patient sufficiently protected?"

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

In this issue of *JACC: Clinical Electrophysiology*, Neves et al[4] re-examined part of the CPVT risk model. Rather than continue to underscore the urgent questions of optimal protection in high-risk patients, they asked a slower-paced question: "Is there a population with CPVT for whom less therapy is better?" In particular, they searched for a subgroup who maintained a low burden of arrhythmia after stopping beta-blockers. This question is important because the dramatic stories of CPVT are memorable but can provide anchor bias. Timely, clinically useful research strives to see patients with a new perspective, shedding anchor bias when possible.

A 2018 expert consensus statement defined CPVT to include "patients (index case or family members) who have a pathogenic mutation," without stipulating a minimum clinical phenotype.[3] In the current study, the authors interrogated the International CPVT Registry and found 100 patients who had been treated without beta-blockers for at least 6 months, based on the recommendations from each patient's clinical cardiologist. The retrospective report separated those patients into 2 groups. The first group received no therapy (intentional nontherapy, INT); the second group received therapy with other strategies, but not beta-blockers. These were not randomly selected patients. For example, the same genotype was present in 30 of the patients (*RYR2* p.R420W), and family interactions were not controlled in the analysis.

The first group in this study was nearly exclusively composed of genotype-positive, phenotype-negative relatives of a clinically affected proband. In addition to a pathogenic or likely pathogenic variant (or a variant of uncertain significance with a concerning family history), patients in the INT group had 3 major characteristics in common:

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1. **They were not CPVT probands.** Ninety seven percent of INT patients had been diagnosed using cascade screening and none were symptomatic before diagnosis.
2. **They did not have complex arrhythmia on stress test or Holter.** Ninety-six percent of INT patients had no arrhythmia on exercise stress test or Holter at any time. The remaining 4% had only ventricular bigeminy or couplets.
3. **They were diagnosed younger than 7 years of age or older than 20 years of age.** This caveat is slightly weaker than the others, because 23% of group 1 patients were between 7 and 20 years of age when beta-blockers were stopped.

During a mean follow-up duration of 6 years, 1 of the 73 INT patients had exertional syncope, likely related to CPVT (1.4%). In 2 patients, subsequent testing showed sufficiently complex ventricular arrhythmias (2.7%). These patients returned to a beta-blocker strategy. Although INT was safe in the sense that there were no deaths in this subgroup, a 4% incidence of significant ventricular arrhythmias over 6 years is higher than the population risk.

The second, smaller group of patients were more diverse. Approximately one-third were probands, 30% had an ICD implanted, and nearly half were symptomatic before diagnosis. In the words of the authors, these patients, "Needed to be treated, but did not tolerate or did not want to be on beta-blockers."[4] In this second, higher-risk group, patients continued to receive an antiarrhythmic strategy (flecainide, left cardiac sympathetic denervation, or ICD), but did not receive beta-blockers. In this second group, there was a similarly small, but not negligible, rate of cardiac rhythm events (1 ICD shock among 27 patients; 3.7%).

This study respects a central insight about autonomy: patients with CPVT are continually balancing safety and quality of life. For many patients, beta-blockers have side effects. In a retrospective study of patients with long QT syndrome, at least 1 side effect was noted in 55% of patients on beta-blockers, including marked fatigue and gastrointestinal side effects.[5] In contrast to long QT syndrome, beta-blocker doses in CPVT are maximized by chasing and extinguishing ectopy on stress tests. CPVT is often clinically expressed between age 7 and 20 years. At these ages, some children have been on beta-blockers for a good portion of their lives and can only identify side effects once they stop taking beta-blockers. For all these reasons, the frequency of beta-blocker side effects in CPVT may be even higher than the 55% in long QT syndrome.

Side effects are a frequent cause of nonadherence. In a recent survey of 218 CPVT patients, the prevalence of self-reported nonadherence was 15%. Nonadherent participants rated the statement "How much does CPVT affect you emotionally?" significantly higher than adherent participants, suggesting that nonadherent patients see their quality of life differently than adherent patients. A similar registry study found a 16% prevalence of self-reported nonadherence among patients with genetic heart disease.[6] Self-report has known limitations. A recent Danish study, with high-fidelity independent adherence data, documented that a third of long QT patients had treatment breaks of more than 2 months' duration, suggesting that nonadherence in patients with genetic heart disease may be higher than found in self-reported surveys.[7]

Between side effects and other reasons for nonadherence, some patients are not going to take beta-blockers. The study in this issue of *JACC: Clinical Electrophysiology* is pragmatic. It is part of a long tradition of meeting patients where they actually are, rather than where a set of experts wish that they might be. Therefore, the study should not be judged on whether the either group was arrhythmia free, but rather on whether these data help identify lower-risk patients and whether these data meaningfully inform conversations about risk. This study retrospectively identified 2 groups of lower-risk patients who, in consultation with their physicians, were not prescribed beta-blockers for at least 6 months. In these groups, the rate of significant arrhythmia was approximately 4% during 6 to 7 years of follow-up, albeit with small numbers of patients.

The paradigm of performing an exercise test, adjusting therapy, and repeating the exercise test is critical in patients with CPVT, and was continued even in the patients off beta-blockers in this study. This study does not define a risk-free patient group with CPVT. It does not even relieve the burden of providing emotional and practical support for patients who are best served by adhering to a complex regimen but are struggling to do so. However, this study helps us define a group of patients in whom physicians and other practitioners can slow down, respect autonomy, and communicate quantifiable risks and benefits to patients and families to support family-centered decisions about beta-blockers.

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