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INNOVATIONS IN CLINICAL ELECTROPHYSIOLOGY: NEUROCONTROL

Burst Exercise Testing Can Unmask Arrhythmias in Patients With Incompletely Penetrant Catecholaminergic Polymorphic Ventricular Tachycardia

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ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by cardiac arrest during sudden exertion. However, standard exercise stress testing (EST) lacks sensitivity, leading to misdiagnosis and undertreatment. After a nondiagnostic standard gradual EST, we report 6 patients who underwent a novel burst exercise test characterized by sudden high workload at the outset of testing. In 5 of 6 patients, the burst EST induced new and more complex arrhythmias versus standard EST, which compelled medication initiation in 3 patients. We postulate that this simple EST modification better mimics a typical CPVT triggering event and could improve diagnostic sensitivity and therapeutic decision making. (J Am Coll Cardiol EP 2021;7:437–41) © 2021 by the American College of Cardiology Foundation.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) often presents with adrenergically triggered cardiac arrest. A missed or delayed diagnosis is a tragic feature of the condition (1,2). This is partially due to the poor sensitivity of the exercise stress test (EST), which fails to induce complex ventricular arrhythmias in most patients, especially genetically affected family members (3). In fact, an alarming 72% of RyR2-p.G357S pathogenic variant carriers had an initially normal or near-normal standard EST (4). Additionally, despite atrial arrhythmias being an established phenotype of CPVT, they are identified in <25% of patients using standard testing (1). Unfortunately, some patients die suddenly from CPVT despite previously having no documentation of complex ventricular arrhythmias (1), suggesting that the standard EST cannot reliably reproduce the circumstances that lead to polymorphic or bidirectional ventricular tachycardia (VT). Therefore, a more sensitive test for CPVT is urgently needed to improve diagnosis, risk stratification, and titration of medical therapy. In our experience, CPVT arrhythmic events typically occur during sudden catecholamine surges that may induce an abrupt heart rate increase (e.g., sprinting, rollercoaster ride, or major physiologic stressor) (1,5), rather than during gradual exertion. We leveraged this observation by developing a "burst" EST protocol aimed at unmask-

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ing incompletely penetrant CPVT phenotypes. We hypothesized that our new protocol would be more effective at inducing CPVT arrhythmias compared with a standard gradual protocol.

METHODS

A novel provocative EST, termed the burst protocol, was evaluated in prospectively enrolled CPVT patients from November 2018 to October 2020. All patients meeting consensus diagnostic criteria for RyR2-related CPVT (6) who had undergone a standard EST (Bruce or equivalent) protocol followed by a burst EST during the study period were included. The burst EST was defined by abrupt high-intensity exercise at the immediate onset of testing (equivalent to the maximum stage reached on previous standard EST), which was continued until volitional fatigue, cardiac symptoms, or ≥3 beats of nonsustained VT occurred. Arrhythmias documented on burst EST were compared with the most recent standard EST. All ESTs were retrospectively reviewed by at least 2 cardiologists experienced in inherited arrhythmia (T.M.R., Z.W.L., S.S., and/or A.D.K.). Any complication related to either protocol was recorded. Median with interquartile range or mean ± SD were reported for continuous variables as appropriate. The 2 types of EST were compared using Student's *t*-test, with statistical significance defined as a 2-sided p value of <0.05. Ethical approval was obtained (UBC-H20-03085).

RESULTS

In this pilot study, 6 patients underwent a burst EST, 5 of whom made a running start on the treadmill at a high stage of exercise (equivalent to prior maximal stage on standard EST) and 1 who exercised on the recumbent bicycle due to a lower extremity soft tissue injury, with rapidly escalating resistance (**Table 1**). The median age of the cohort was 18.5 years (interquartile range: 14.5 to 39.0 years) and 3 (50%) were female. Four (67%) patients had prior cardiac events and 2 (33%) were screened family members. There were 3 (50%) patients on antiarrhythmic therapy during the burst EST. No patients had undergone cardiac sympathectomy. All prior arrhythmic events documented in the cohort were triggered by typical adrenergic stimuli, and included dancing, rock climbing, running, and extreme emotion.

Mean resting and peak heart rates and heart rates at first ventricular ectopic beat were similar between tests (**Table 1**). Mean heart rate was numerically greater at 1 min into exercise and 1 min into recovery during burst EST, though this did not reach statistical significance (139 vs. 108 beats/min; $p = 0.11$; and 132 vs. 104 beats/min; $p = 0.16$, respectively). Compared with the previous standard EST, the burst EST induced new atrial or ventricular arrhythmias in 5 of 6 (83%) patients, and thus provided incremental data on their phenotypes. Of these 5 patients, 3 (60%) had normal or near-normal standard ESTs previously and were thought to have minimally penetrant CPVT. In 1 of these patients (case 1), the new arrhythmia observed was not ventricular in origin, but rather the development of rapidly conducting symptomatic atrial fibrillation (AF). Case 3 also experienced new AF, in addition to sustained VT that had not been previously recorded. After the burst EST, antiarrhythmic treatment was started for the first time in 3 patients. This included dual therapy with nadolol and flecainide in 2 of these patients due to the severity of the arrhythmia induced by burst testing. A median of 3 (interquartile range: 2 to 5) standard ESTs were performed before the burst EST. No complications related to the new protocol occurred.

DISCUSSION

We describe the initial 6 CPVT patients who underwent a prospectively devised burst EST protocol, defined by an initial burst of exercise, which was designed to better mimic the circumstances that precede CPVT events, as compared with the standard gradual Bruce protocol used mainly for detecting ischemia. This simple modification induced a more severe and diagnostic arrhythmic phenotype in patients with incompletely penetrant standard ESTs. The novel protocol and observations of the study are illustrated in the **Central Illustration**, using EST data recorded in case 3.

These pilot data support the hypothesis that provoking a sudden catecholamine surge with burst, rather than gradual exercise, may better target the mechanism of CPVT arrhythmogenesis, possibly by inducing marked vagal inhibition leading to increased cytosolic calcium overload. This hypothesis is supported by recent data showing that cardiac vagal activity is maintained throughout submaximal exercise (7), as would occur during the early stages of a standard EST. This type of exercise with initially preserved or increased vagal activity may paradoxically protect against arrhythmia. However, with sudden onset of maximal exercise, especially in untrained individuals, it is possible that a more pronounced and sustained reduction in vagal output causes more cytosolic calcium overload (8), which is the established mechanism of CPVT arrhythmias. While our pilot data show a numerically higher heart rate at 1 min into exercise, this was a nonsignificant finding.

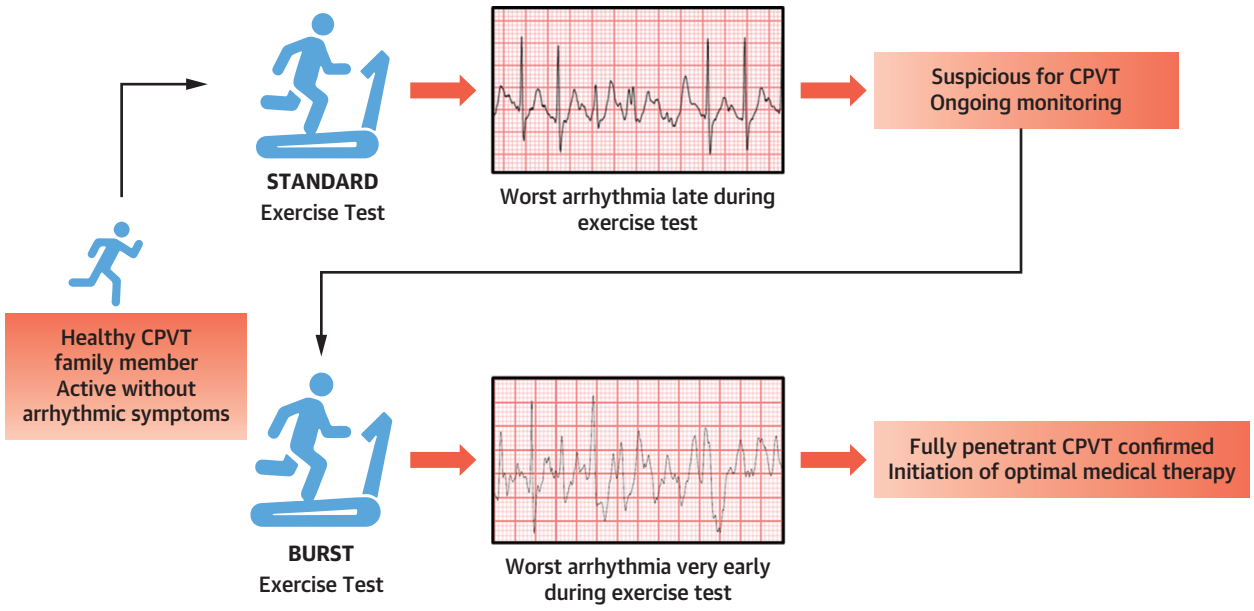
TABLE 1 Patient Characteristics and Burst Exercise Test Results

	Age at Burst EST (yrs), Sex	RyR2 Variant*	Cardiac History	Therapy Change After Burst Test	Worst Arrhythmia During Last Standard EST	Worst Arrhythmia During Burst EST	Peak Heart Rate During Last Standard EST (beats/min)	Peak Heart Rate During Burst EST (beats/min)	Heart Rate Recovery at 1 min During Last Standard EST (beats/min)	Heart Rate Recovery at 1 min Recovery During Burst EST (beats/min)	METS During Last Standard EST	Peak METS During Burst EST
Case 1	19, M	p.V4771I	Proband; Exercise- and emotion-induced syncope	Continued nadolol 40 mg daily (0.7 mg/kg/day) and flecainide 50 mg BID (1.8 mg/kg/day)	Ventricular couplets and triplet at peak exercise	AF with ventricular rate of 126 beats/min at 3 min lasting 30 s	134	131	30	30	5.6	9.4
Case 2	15, M	p.R420W	Proband; Exercise-induced SCA	New initiation of nadolol 40 mg daily (0.6 mg/kg/day) and flecainide 50 mg BID (0.8 mg/kg/day)	Rare isolated PVCs at peak heart rate, 3 in a bigeminal pattern	Rare isolated PVCs at 160 beats/min, progressing to bigeminal runs and couplet at peak heart rate†	160	179	46	31	4.4	13.9
Case 3†	13, M	p.F4192C	Asymptomatic relative; Family screening	New initiation of nadolol 40 mg daily (0.6 mg/kg/day) and flecainide 50 mg BID (1.4 mg/kg/day)	Rare isolated PVCs at 162 beats/min, progressing to single triplet at peak exercise	Isolated PVCs at 162 beats/min progressing to sustained polymorphic VT at 190 beats/min; subsequent AF with ventricular rate of 214 beats/min	179	214	91	54	4.5	7.1
Case 4	18, F	p.I4855M	Proband; Exercise-induced SCA	Continued carvedilol 12.5 mg BID (0.5 mg/kg/day)	Single PVC at 143 beats/min	Rare isolated PVCs at 136 beats/min, progressing to couplets at peak exercise	150	141	41	20	4.4	9.1
Case 5†	39, F	p.F4192C	Asymptomatic relative; Family screening	New initiation of nadolol 40 mg daily (0.67 mg/kg/day)	Two PVCs at peak exercise	Frequent PVCs at 200 beats/min, progressing to run of sustained VT at peak exercise lasting 35 s	166	222	27	38	9.0	11.8
Case 6	39, F	p.T3866A	Proband; Exercise-induced syncope and SCA	Continued nadolol 40 mg BID (1.5 mg/kg/day) and flecainide 50 mg BID (1.9 mg/kg/day)	None	None	130	122	40	21	18.5	20.3
Mean Values	–	–	–	–	–	–	154.0 ± 17.0	168.0 ± 40.0	46.0 ± 21.0	32.0 ± 11.0	7.7 ± 5.1	11.9 ± 4.3

Values are mean ± SD, unless otherwise indicated. *Variant positioning refers to NM_001035.2(RYR2). †First-degree relatives. ‡Bicycle test.

AF = atrial fibrillation; BID = twice daily; EST = exercise stress test; METS = metabolic equivalents; PVC = premature ventricular complex; SCA = sudden cardiac arrest; VT = ventricular tachycardia.

CENTRAL ILLUSTRATION **Typical Approach to the Burst Exercise Test in CPVT**



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Flow diagram of testing in the cohort and the typical findings observed on standard and burst exercise testing. Data presented are from case 3.
CPVT = catecholaminergic polymorphic ventricular tachycardia.

Likewise, limited heart rate recovery post-exercise is a risk predictor in CPVT (9). Our data showed a numerically blunted heart rate recovery after burst EST compared with standard exercise. Determining if these markers of autonomic tone are significantly different for burst versus gradual exercise in a larger cohort may substantiate the putative physiologic mechanism of the burst EST protocol. Physical conditioning may play a role in arrhythmia susceptibility as well, with individuals of greater fitness level experiencing fewer CPVT arrhythmias (10). Therefore, our observations may indirectly suggest that CPVT patients are better suited to participating in moderate intensity exercise with a gradual warm-up period than sports that involve sudden exertion without any warm-up opportunity. The present study did not address this postulate but does show that the specific type of the exercise may influence arrhythmic risk.

STUDY LIMITATIONS. The limitations of this study include its retrospective and pilot design. There is the possibility of type II error, whereby nonsignificant differences between groups occurred due to an inadequate population size. We were not blinded to the type of test performed, and there was a period between last standard EST and burst EST (median 14 months) during which time the phenotype may have changed. However, all patients were post-puberty, and so an altered phenotype was deemed unlikely. Finally, by only selecting patients who did not have fully penetrant CPVT on standard protocol to undergo the novel protocol, the analyses may overestimate the diagnostic yield of the burst protocol. Future validation studies in larger cohorts are needed to compare the sensitivity and reproducibility of each protocol.

CONCLUSIONS

Based on these pilot data, we propose that the burst EST represents a safe modification to existing exercise protocols and may improve diagnosis and therapeutic decision making in CPVT. Further data are needed to reproduce these findings in a larger CPVT cohort and to elucidate the mechanism by which burst exercise may better provoke arrhythmias.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CPVT causes cardiac arrest during sudden exertion, but the standard gradual EST lacks sensitivity for the condition. We propose a novel "burst" EST defined by a sudden high workload at the outset of exercise to unmask latent arrhythmias.

TRANSLATIONAL OUTLOOK: "Burst" EST is a simple modification to existing exercise protocols that can unmask incompletely penetrant CPVT, thus improving our ability to diagnose and treat the condition. Larger cohorts are needed to define the sensitivity of this test compared with standard gradual exercise protocols.

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