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CASE REPORT: CLINICAL CASE

Exercise Testing Using Sprint Protocol vs Bruce Protocol in Catecholaminergic Polymorphic Ventricular Tachycardia

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ABSTRACT

We present the case of a relative of a patient with catecholaminergic polymorphic ventricular tachycardia. This relative underwent a standard (Bruce) exercise stress test (EST), which had normal results. He then underwent our modified "sprint" EST, with positive results. This report underlines how the sprint EST may provoke arrhythmias better than the standard Bruce EST. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:996–1000) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

PATIENT 1. A 12-year-old boy was admitted after a witnessed out-of-hospital cardiac arrest while doing exercise. On hospital arrival, the patient was unconscious despite successful resuscitation. No premature ventricular contraction (PVC) or ventricular tachycardia (VT) was observed or recorded after resuscitation. Active care was withdrawn as a result of persisting coma with a poor prognosis of awakening, and the patient died of cerebral incarceration after a few days of hospitalization. An autopsy was not performed because the parents registered the patient as an organ and tissue donor.

Given that an autopsy was not performed, blood was not drawn for genetic analysis initially. Thus, later parental-consented genetic investigations were performed from the patient's Guthrie card, which holds dried blood spots (DBS). DBS have been collected routinely in Denmark since 1981 in all infants at day 5 of life and stored at −25 °C to be used for a variety of metabolic tests.[1]

Genome-based sequencing was performed (**Table 1**). One rare genetic variant was identified: a heterozygous variant in *RYR2* (Thr3921Ser [c.1176A>T]). The variant is not described in the Genome Aggregation Database v.2.1.1 or in the Exome Variant Server database. It is located in an evolutionarily conserved region, and the amino acid exchange in Thr3921Ser is predicted to be harmful in silico. The variant is classified as likely pathogenic, according to the American College of Medical Genetics and Genomics classification.

LEARNING OBJECTIVES

- To be able to diagnose CPVT earlier by using a better triggering protocol (sprint vs Bruce).
- To be able to risk stratify and medically optimize patients with genopositive CPVT.

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The 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 Author Center.

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TABLE 1 Genetic Investigation

Panel	Genes
Arrhythmogenic right ventricular cardiomyopathy	*PKP2, DSC2, DSG2, DSP, JUP, TMEM43,* and *TGFB3*
Long QT syndrome	*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2,* and *KCNJ2*
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*

PATIENT 2

The father of patient 1, a 35-year-old healthy Caucasian man, was referred to our inherited cardiac disease outpatient clinic for clinical evaluation after his son's death.

In the outpatient clinic, echocardiography, electrocardiography (ECG), 24-hour Holter monitoring, complete blood count, magnetic resonance imaging, and an exercise stress test (EST) with the standard Bruce protocol were performed, and all results were normal.

The patient was also offered genetic testing, and it revealed the same likely pathogenic variant in *RYR2* as his son. The mother and siblings of patient #1 also received clinical screening and genetic testing, all with normal results.

All tests were repeated 2 years later, with unremarkable results. The patient received lifestyle advice and was recommended antiarrhythmic medical treatment with β-blockers but refused because he was asymptomatic.

With implementation of a modified "sprint" EST a year later, the patient was tested again. This time the results revealed an increasing number of polymorphic PVCs, both single and in couplets, during exercise. The patient then started medical treatment with a β-blocker.

PAST MEDICAL HISTORY

Patient 1 had had 1 exercise-induced syncope episode 2 months before admission. ECG, electroencephalography, and echocardiography were also performed, all with normal results, and the patient was discharged after 1 day of observation.

Patient 2 (the father) had never experienced syncope or other cardiopulmonary symptoms.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnoses in patient #1 were cardiac channelopathy and cardiomyopathy.

INVESTIGATIONS

The first 2 ESTs in patient 2 were performed using the standard Bruce protocol (Table 2). This protocol is a graded continuous test to a maximal effort on a cycle ergometer or a treadmill. The workload at the beginning of the test is 25 W, and it increases with 25 W every 2 minutes up to the maximal voluntary capacity or until the occurrence of a ventricular arrythmia such as VT or ventricular fibrillation (VF). Continuous ECG and blood pressure measurements are obtained during the test.[2]

The third time patient 2 performed an EST (Table 3), we used a modified protocol called "sprint," where the workload is high from the beginning. The patient works with high intensity on a cycle ergometer with maximum effort from the beginning of the test, usually lasting for 3 to 6 minutes, and then going straight to the recovery phase. ECG and blood pressure measurements are monitored throughout the test. The patient continues in the work phase until fatigue or occurrence of criteria for a positive test

ABBREVIATIONS AND ACRONYMS

CPVT = catecholaminergic polymorphic ventricular tachycardia

ECG = electrocardiography

EST = exercise stress test

PVC = premature ventricular contraction

VF = ventricular fibrillation

VT = ventricular tachycardia

TABLE 2 EST With Bruce Protocol

EST	Stage	Time, min	Work, W	Heart Rate, beats/min	Blood Pressure, mm Hg	PVCs
1						
	1	02:00	25	100	128/80	0
	2	02:00	50	104	130/77	0
	3	02:00	75	114	149/75	0
	4	02:00	100	126	151/76	0
	5	02:00	125	142	172/76	0
	6	02:00	150	157	199/89	0
	7	02:00	175	165	190/85	0
	Total test time	14				
	Results: No increasing polymorphic PVCs, nonsustained VT, bidirectional VT, or sustained VT or VF induced.					
2						
	1	02:00	25	81	141/76	0
	2	02:00	50	88	135/74	0
	3	02:00	75	103	143/72	0
	4	02:00	100	117	169/73	0
	5	02:00	125	134	182/77	0
	6	02:00	150	151	174/76	0
	7	02:00	175	173	201/74	0
	Total test time	14				
	Results: A few single PVCs at rest; no increasing polymorphic PVCs, nonsustained VT, bidirectional VT, or sustained VT or VF induced					

EST = exercise stress test; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE 3 EST With Sprint Protocol

EST	Stage	Time, min	Work, W	Heart Rate, beats/min	Blood Pressure, mm Hg	PVCs
3						
	Resting	01:00	0	75	119/84	0
	Work	03:00	200	162	129/66	2 × single PVCs 2 × couplet PVCs
	Recovery	02:00	0	81	100/85	0
	Total test time	4				
	Results: Increasing number of polymorphic PVCs during exercise both single and in couplets; no nonsustained VT, bidirectional VT, or sustained VT or VF induced					
4						
	Resting	01:00	0	57	121/86	0
	Work	03:00	175	180	163/82	2 × single PVCs
	Recovery	03:00	0	84	191/75	0
	Total test time	4 min				
	Results: A few single PVCs during exercise; no nonsustained VT, bidirectional VT, or sustained VT or VF induced					
5						
	Resting	02:00	0	59	110/70	0
	Work	03:00	200	142	198/76	2 × polymorphic PVCs 2 × couplet PVCs
	Recovery	02:00	0	64	115/80	0
	Total test time	4				
	Results: A few polymorph PVCs and in bigeminy during exercise; no nonsustained VT, bidirectional VT, or sustained VT or VF induced					

Abbreviations as in Table 2.

result (ie, increasing number of polymorphic PVCs, nonsustained VT, bidirectional VT, or sustained VT or VF). Although the first test revealed an increasing number of polymorphic PVCs, both single and in couplets, during exercise (Figure 1), repeated tests while the patient was receiving β-blocker therapy showed a good effect of treatment (Table 3) (EST 4 and EST 5).

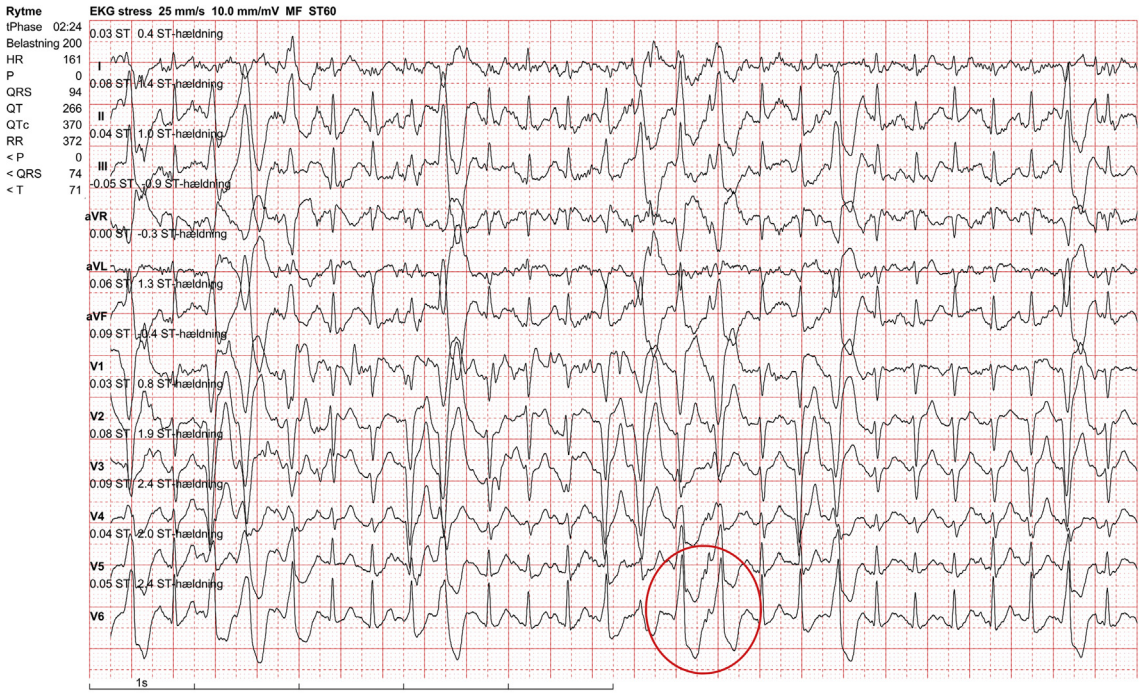
MANAGEMENT (MEDICAL OR INTERVENTIONS)

The positive stress test result led to the initiation of treatment with propranolol extended-release capsules at an initial dose 80 mg once a day.

DISCUSSION: ASSOCIATION WITH CURRENT GUIDELINES, POSITION PAPERS, AND CURRENT PRACTICE

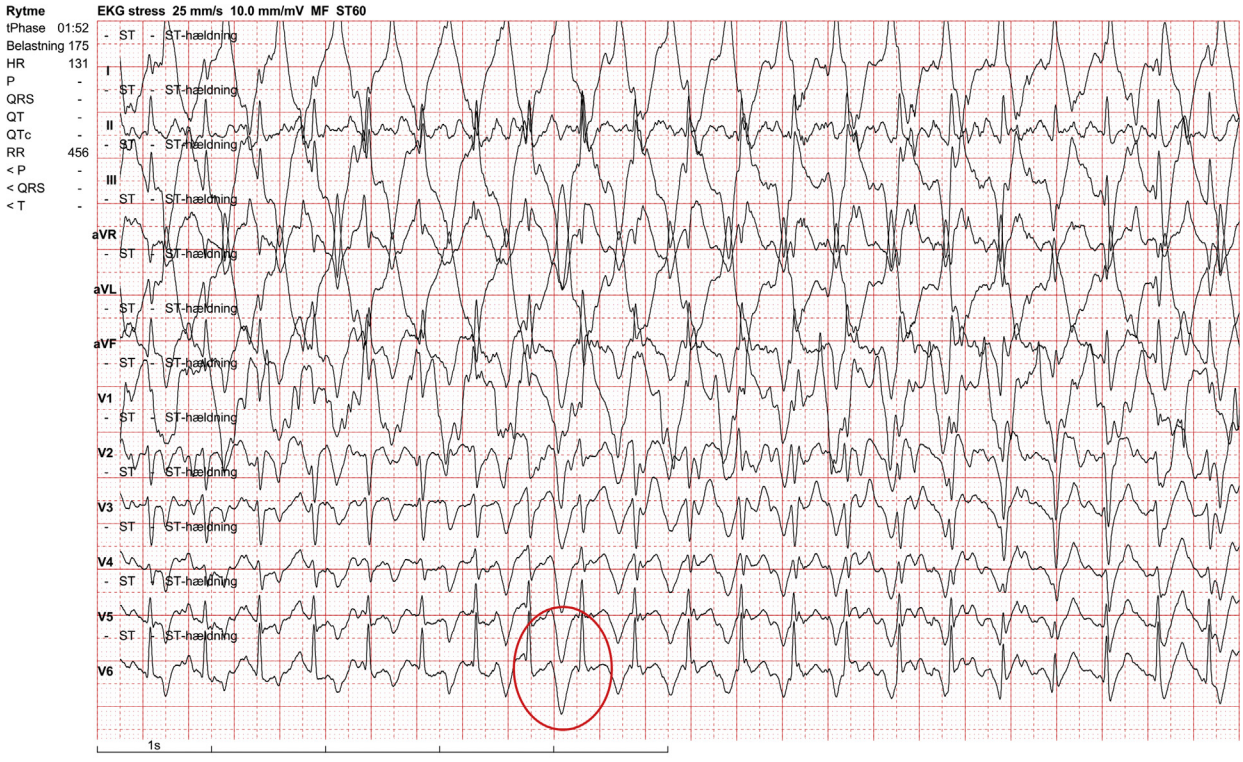
The standard EST using the Bruce or equivalent protocol is currently used as a diagnostic and risk-stratifying tool in patients with suspected or diagnosed catecholaminergic polymorphic VT CPVT, but sudden cardiac death is still seen in individuals with a normal test result without inducible arrhythmias.[3] Studies have shown that the test has a specificity of

FIGURE 1 Abnormal Electrocardiogram From the First Sprint Exercise Stress Test



Electrocardiography during an exercise stress test using the Sprint protocol for the first time in the exercise phase of patient 2 at maximum workload shows premature ventricular contractions and a couplet **(circle).**

FIGURE 2 **Normal Electrocardiogram From the Second Sprint Exercise Stress Test**



Electrocardiography during an exercise stress test using the Sprint protocol in the exercise phase of patient 2 at maximum workload, 7 months after β-blocker treatment, shows a few single premature ventricular contractions **(circle).**

97% and that there is a significant association between a positive EST result and a genetic mutation. However, the sensitivity has been found to be only 50%, thus indicating that the protocol is not sensitive enough for dismissing a diagnosis of CPVT if the test result is negative.[2,4]

The case presented in patient 2 demonstrates how the initial standard EST showed negative results, and later, a modified sprint protocol EST showed positive results. This finding is consistent with results presented by Roston et al,[5] who tested 6 genopositive patients with CPVT who underwent both a standard EST (Bruce or equivalent protocol) and a modified EST protocol. The modified protocol was defined by high-intensity exercise from the beginning of the test until fatigue, symptoms, or more than 2 beats of nonsustained VT. These investigators found that the burst EST induced new arrhythmias in 5 of 6 patients.

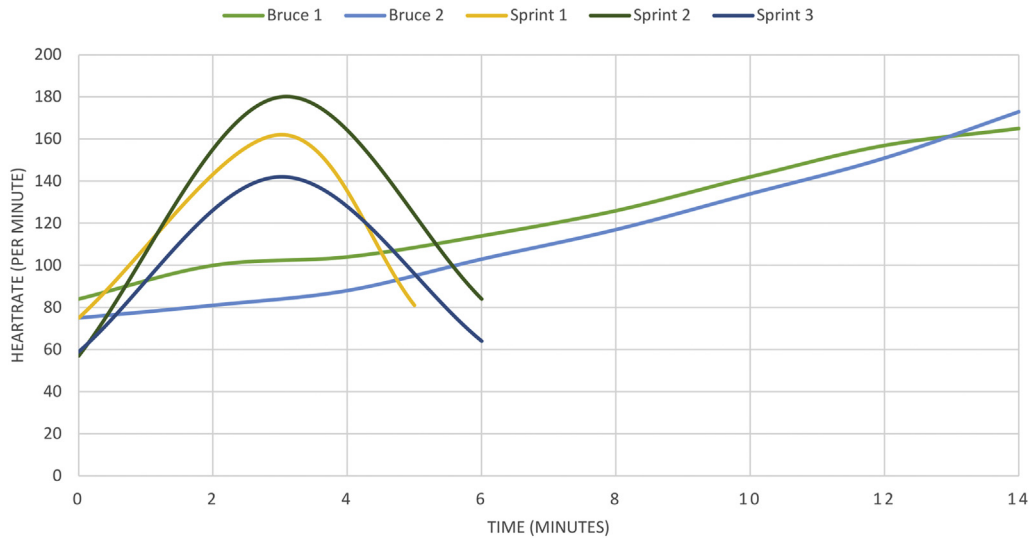
Similarly, we find this protocol to be better in patients with CPVT. The stress-induced autonomic nervous system activity causes abnormal calcium-induced calcium release in patients with CPVT. When using the sprint protocol, the sudden catecholamine surge leads to a reduction in the vagal input compared with the Bruce protocol, with a maintained level of vagal activation during the test.[6,7]

A correct diagnosis is crucial, and early diagnosis is fundamental. Studies have shown that timely diagnosis is delayed by 2 years from the first syncope episode, on average, because the cardiac events are initially considered vasovagal or caused by neurologic factors. This finding shows how challenging it is to diagnose this condition and why more CPVT-specific protocols should be assessed.[8]

FOLLOW-UP

A few months after initiating β-blocker treatment, a follow-up modified EST was performed, showing only a few PVCs and thus indicating a good effect of medical treatment (**Figure 2**). One year later, the patient again performed a modified EST, which induced PVCs progressing into bigeminy. The dose of β-blocker

FIGURE 3 Visual Difference of the 2 Protocols



The 3 Sprint tests show an immediate heart rate response to high-intensity work. The 2 Bruce tests show a slow increase in the heart rate resulting from a graduated work increment.

was increased to 160 mg once a day. Follow-up is planned. Both protocols are illustrated in Figure 3.

CONCLUSIONS

A modified sprint EST protocol in individuals suspected of having CPVT with an initial negative standard EST result can provide better triggering of typical CPVT and thereby prevent future cardiac events by correct diagnostics and early initiation of treatment.

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KEY WORDS **catecholaminergic polymorphic ventricular tachycardia, exercise stress test, *RYR2*, sudden cardiac death**