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REVIEW ARTICLE

Role of Exercise Treadmill Testing in the Diagnosis & Risk Stratification of Cardiac Channelopathies: Considerations for General Cardiology Practice

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Abstract

Channelopathies are the leading causes of sudden cardiac death in patients without structural heart disease. Missing the diagnosis of high-risk but concealed channelopathies could have lethal clinical consequences. However, the diagnosis of channelopathies is often challenging due to the dynamic clinical presentations and elusive electrocardiographic manifestations of these diseases. An integrated approach including clinical assessment, repeated electrocardiography, drug provocation tests, exercise stress test and genetic studies is often required for establishing the diagnosis. Pharmacological provocation testing may have limited sensitivity and may be associated with false positive results. Injudicious use of genetic testing is not recommended due to its relatively low yield, limited cost-effectiveness and availability. Variants of unknown significance could complicate interpretation of genetic findings. This review article focuses on the role of exercise stress testing in the diagnosis and risk stratification of patients with Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia.

Keywords: Exercise stress test, Channelopathies, Risk stratification, Brugada syndrome, Long QT syndrome, Catecholaminergic polymorphic ventricular tachycardia

Key points

- Brugada syndrome (BrS), long QT syndrome (LQTS) and catecholaminergic ventricular tachycardia (CPVT) are channelopathies that are among the commonest causes of primary arrhythmic diseases and sudden cardiac death, particularly in patients without apparent structural heart disease. However, the variable clinical manifestation and concealed ECG features often impose diagnostic challenges.
- Exercise treadmill test (ETT) is a useful investigation for the diagnosis and risk stratification of patients suspected of BrS, LQTS and CPVT.
- In BrS patients, augmentation of ST elevation (rather than J-point elevation) and frequent ventricular premature complexes in the early recovery stage predict high risk of future ventricular arrhythmia and cardiac events.
- In prolonged QTc patients undergoing ETT, paradoxical QTc prolongation at 1 min or 4 min in the recovery stage, a systematic 3-step algorithim and QTc hysteresis can be useful for assisting diagnosis and guiding genotyping of LQTS carriers. Heart rate recovery at 1 min in recovery phase may predict future arrhythmic risk in LQT1 patients.
- CPVT has variable disease penetrance and wide phenotypic diversity. ETT for assessment of CPVT may have variable test results, depending on the definition of a positive test. Burst exercise stress test or adrenaline provocation may increase the diagnostic yield of CPVT.

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Introduction

Sudden cardiac death (SCD) is a leading cause of death and accounts for half of all cardiovascular deaths [1]. While coronary artery disease (CAD) is the commonest cause of SCD in adults over 35 years of age, one-third to 40% of the younger SCD victims have unremarkable autopsy findings, among whom primary arrhythmic diseases are the prevailing suspect [2,3]. In patients with unexplained SCD with negative autopsy findings, about one-third to two-thirds are associated with primary arrhythmic diseases [4–6], accounting for 1–2% of all SCD in Western countries [1,7]. Brugada syndrome (BrS), long QT syndrome (LQTS) and catecholaminergic ventricular tachycardia (CPVT) are the commonest causes of primary arrhythmic diseases. BrS accounts for 4–12% of all SCD and up to 20% of SCD in patients without structural heart disease [8–10]. The reported annual incidence of ventricular arrhythmia or SCD in patients with BrS was 13.5% in patients with history of SCD, 3.2% in those with syncope and 1% in asymptomatic patients [11,12]. In patients with LQTS, the mortality rate could be up to 21% in 1 year after the development of first syncope. The mortality rate could be reduced to ~1% at 15-year follow-up after appropriate treatment [13]. In patients with CPVT, the mortality rate could be up to 30–50% by 35 years of age [14–16]. About a quarter of CPVT patients still experienced at least 1 treatment failure cardiac event despite beta-blocker therapy [17]. The 8-year arrhythmic, near-fatal and fatal cardiac event rates in CPVT patients were still up to 37.2%, 15.3% and 6.4%, respectively, despite beta-blocker therapy [18,19].

Early and accurate diagnosis of high-risk but concealed channelopathies have significant prognostic and therapeutic implications. However, the dynamic ECG manifestations of these diseases often pose diagnostic challenges. Resting ECG could appear normal in up to 25–50% of patients with genetically confirmed LQTS patients [20,21]. Spontaneous type 1 Brugada ECG pattern is only present in 45–71% of patients with Brugada syndrome in major registries [22]. Patients with CPVT usually have normal resting ECG.

Electrophysiology study has a limited role in guiding the diagnosis and management of LQTS and CPVT. Its role in BrS also remains controversial [22–24]. Genetic studies and provocation testing (pharmacological stress test or treadmill exercise test (ETT)) are often required to unmask concealed channelopathies in patients with unexplained SCD. Although genetic testing could assist in diagnosing channelopathies, up to 25% and 65–70% of LQTS and BrS patients are genotype negative or elusive [25,26]. The sensitivity of genetic tests was reported to be only 18% and 59% among patients with suspected and confirmed CPVT, respectively [27].

Pharmacological provocation tests also have intrinsic limitations. Among BrS patients with *SCN5A* mutation, sensitivity of provocation test by sodium channel blockers was 71–80% [28,29]. However, in cohort studies that included survivors of SCD, patients with suspected BrS and family members of SCD victims, the sensitivity of ajmaline and procainamide challenge were only 26% and 4%, respectively. [30] Apart from the suboptimal sensitivity, false positive rate of sodium channel blockers provocation test in the normal population ranged from 4% to 27%.[29, 31,32]. In genotypically confirmed LQTS patients, the sensitivity, specificity, positive and negative predictive values of epinephrine stress test in diagnosing congenital LQT1 were reported to be 92.5%, 86%, 76% and 96%, respectively [21]. However, among survivors of unexplained SCD, the sensitivity, specificity, positive and negative predictive values of epinephrine stress test in diagnosing LQTS were only 38%, 83%, 46% and 78%, respectively (using ETT as gold standard) [33]. Moreover, studies have shown that up to 79% of normal subjects may demonstrate abnormal QTc prolongation during epinephrine infusion [34,35]. Among CPVT patients and their family members, the sensitivity of epinephrine infusion test was only 28% (compared with ETT) [36].

In face of the limitations of resting ECG, drug provocation tests and genetic studies, ETT has been proven to be a simple and cost-effective test in assisting the diagnosis and prognostication of channelopathies.

Role of ETT in the diagnosis, prognostication, and management of channelopathies

Exercise treadmill test (ETT) is traditionally used in the diagnosis and risk stratification of patients with CAD. The diagnostic and prognostic roles of ETT have been under-explored. The roles of ETT in the diagnosis and prognostication of channelopathies are reviewed below.

A. Brugada syndrome

Role of ETT in diagnosis and risk stratification of BrS

Amin et al. [37] studied 50 BrS patients (25 *SCN5A* mutation-positive and 25 genotype-negative men) and 35 male controls. Exercise caused J-point elevation in all 3 groups but caused cove-type ST

segment elevation (STE) only in the BrS patients. The peak J-point elevation in V1-V2 increased further during recovery stage in the BrS patients.

Makimoto et al. [38] studied 93 BrS patients who underwent ETT, including 22 with a history of ventricular fibrillation (VF), 35 patients with history of syncope alone, and 36 asymptomatic patients. Augmentation of STE of 0.05 mV in V1 to V3 was observed at 1−4 min in recovery stage in 37% of patients (N = 34). Augmentation of STE at early recovery stage of ETT was a significant independent predictor of cardiac events (SCD, VF or sustained ventricular tachyarrhythmia (VTA)), particularly among those with history of syncope alone and among the asymptomatic patients. VF occurred more frequently among patients with augmentation of STE (44% vs. 17% p = 0.004) at mean follow-up of 76 ± 38 months.

Morita et al. [39] studied 307 BrS patients among whom 71% had spontaneous type I ECG at baseline. Approximately 1 in 5 of the patients (21.5%) had augmentation of STE during ETT. Presence of ventricular premature complex (VPC) in early recovery phase was found to be independently associated with risk of future VF. A systematic review by Masrur et al. [40] identified 166 BrS patients (98% male, 24 (14.4%) had history of VF, 52 (31.3%) with syncope, 86 (52%) asymptomatic) who had undergone ETT. Augmentation of STE during ETT was observed in 57% of patients. Among them, 93 had STE augmentation during early recovery stage. In 5 patients without baseline type I Brugada ECG features, ETT unmasked cove-type STE in V1 to V3. Three patients developed VTA during recovery phase of exercise. Follow-up data was available in 111 patients. Sudden cardiac death and VF or sustained VTA occurred in 13% of BrS during mean follow-up of 75 ± 38 months. Eighty-three patients received implantable cardioverter defibrillator (ICD) implantation. History of VF and exercise-induced STE augmentation were independent predictors of SCD, cardiac arrest and VTA.

Figure 1 demonstrated an example of exercise-induced ST segment augmentation and non-sustained ventricular tachycardia in a patient with Brugada syndrome.

Mechanisms of ETT-induced augmentation of ST elevation in BrS

Several mechanisms have been proposed to explain STE augmentation during exercise and recovery phase in patients with BrS. Firstly, a specific *SNC5A* mutation 1795insD, augments slow inactivation and delays the recovery of sodium channels. The mutated sodium channels have inadequate time to completely recover from the slow-

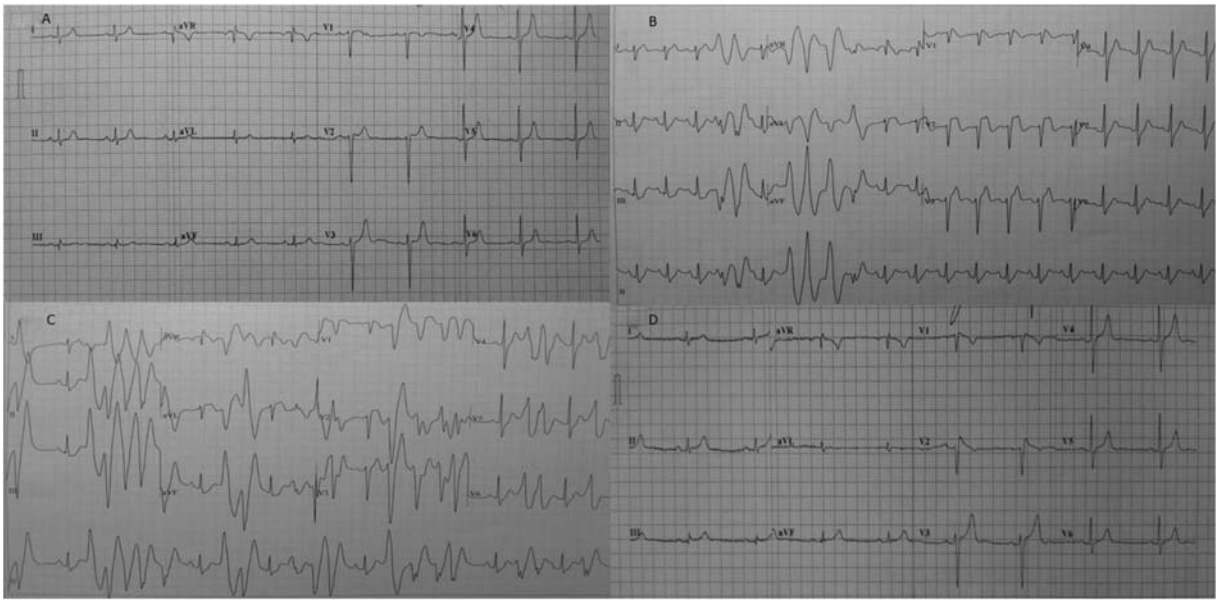

Figure 1. (A) A 55-year-old male developed recurrent exertional syncope while playing soccer. He denied any chest pain. He had no family history of sudden cardiac death. The baseline 12-lead ECG was unremarkable apart from mild anterior early repolarization change. (B) Exercise treadmill showed augmentation of ST segment elevation and non-sustained ventricular tachycardia (NSVT) at 1 min 50 s in recovery stage. The patient reached target heart rate at 17 metabolic equivalents (METs). (C) The patient developed more frequent polymorphic NSVT at 3 min 50 s in recovery stage. He had no chest pain. Blood pressure was stable. Treadmill was stopped. Echocardiogram and coronary angiogram were normal. (D) Repeated resting 12-lead ECG at high-precordial position (with V1 V2 positioned at second intercostal space) showed typical type 1 Brugada Syndrome feature with cove-type ST elevation in V1 and V2. The patient received ICD implant which later salvaged him from arrhythmic death due to spontaneous ventricular fibrillation.

inactivated state during tachycardia due to shortening of the diastolic interval. The accumulation of sodium current in the slow-inactivated state causes augmentation of STE during exercise [41−43]. Second, a temperature-sensitive *SCN5A* missense mutation T1620M causes rapid decay of sodium channel and slows recovery from its inactivated state at high temperature, resulting in ST elevation augmentation at higher temperate during exercise [38,44]. Third, vagal tone reactivation during the early recovery phase of exercise is associated with STE augmentation in BrS patients. Experimental studies have demonstrated that acetylcholine (Ach) administration in the setting of sodium channel blockade could cause augmentation of $I_{K\text{-}ACh}$ and reduction of inward sodium (I_{Na}) and calcium (I_{Ca}) currents, resulting in loss of RV epicardial action potential dome. This could account for the STE augmentation and higher risk of arrhythmia associated with higher vagal tone during recovery phase of exercise [45−47].

Guideline recommendations

In the 2013 HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, it was stated that in asymptomatic patients with BrS features on ECG, attenuation of STE at peak of exercise stress test followed by its appearance during recovery phase is supportive of a diagnosis of BrS. In selected BrS patients (usually, *SCN5A* mutation-positive), STE might become more evident during exercise [48].

B. Long QT syndrome (LQTS)

Role of ETT in diagnosis and risk stratification of LQTS

Sy et al. [19] analyzed 69 first-degree relatives of LQTS patients who underwent ETT. Among the relatives, abnormal resting QTc (defined as ≥480 ms (ms) in female and ≥470 ms in male) was found in only 48% of patients. Four-minute recovery QTc of ≥445 ms reclassified 22 of 25 patients as having LQTS and 19 of 21 patient as being non-carriers. Combined assessment using resting ECG QTc interval and 4-minute recovery QTc was 94% sensitive and 90% specific in detecting LQTS carriers. The sensitivity and specificity were 92% and 82% respectively when the diagnostic algorithm was applied to the validation cohort of 152 patients.

Horner et al. [49] studied 243 patients (82 LQT1, 55 LQT2, 18 LQT3 and 88 genotype-negative subjects with no LQTS) who underwent ETT. It was found that QT and ΔQTc (QTc at 3 min in recovery phase − QTc at baseline in supine position) during peak exercise lengthened in concealed LQT1 patients, but shortened in concealed LQT2, LQT3 patients and the control group. An absolute QTc ≥460 ms during recovery phase or paradoxical increase in ΔQTc ≥30 ms was suggestive of LQT1. Paradoxical QTc prolongation during treadmill exercise stress was not seen in patients with LQT2 and LQT3.

In a study by Chattha et al. [50], 75 patients (25 LQT1, 25 LQT2 and 25 control) underwent upright burst and gradual bicycle exercise stress test. A QTc cut-off value of 445 ms at the end of recovery phase (approximately 4 min in recovery phase) distinguished 92% of LQTS patients from the control, with a sensitivity of 92% and a specificity of 88%. At start of recovery (when RR interval increased by 50 ms from peak exercise) QTc of 460 ms was associated with the correct genotype in 80% of LQT1 (>460 ms) and 92% of LQT2 patients, with a sensitivity of 79% and a specificity of 92%.

Yee et al. [51] studied 208 LQTS patients with *KCNQ1* or *KCNH2* mutation and 215 controls who underwent ETT (across the 5 stages of Bruce protocol). In the cohort, normal to borderline resting QTc values were present in 78% and 74% of male and female carriers, respectively. Authors of the study evaluated the accuracy of a 3-step algorithm [52] in diagnosing genotypically confirmed LQTS using receiver−operator curve analysis. Step 1) Assess the QTc in resting ECG. Resting QTc >470 ms in men or >480 ms in women is suggestive of probable LQTS. Step 2) Assess the 4 min recovery QTc. For patients with normal or borderline QTc, 4-minute recovery QTc of ≥440 ms in men or ≥450 ms in women was suggestive of probable LQTS (with area under curve of 0.82 and 0.9 in men and women respectively. Step 3) Assess the 1-minute recovery QTc. For patients who are regarded as probable LQTS carriers in Step 1 and Step 2, the 1-minute recovery QTc ≥435 ms in men or >455 ms in women was suggestive of LQT1 (Area under curve of 0.7 and 0.82 in men and women respectively). The 1-minute recovery QTc <435 ms in men or <455 ms in women was suggestive of LQT2 [51].

Wong et al. [52] studied 159 patients with suspected LQTS who underwent ETT. Fifty patients had LQT1, and 45 patients had LQT2. Patients with LQT1 had more pronounced QT prolongation (60 ms) compared with those with LQT2 (3 ms) and LQTS-negative patients (5 ms).Patients with LQT2 had more pronounced QT hysteresis (>25 ms) - QT interval difference between exercise and 2-minute into recovery phase at similar heart rate. The use of

beta-blocker caused normalization of these changes. The author concluded that ETT could help predict genotype of LQTS.

In a meta-analysis and systematic review by Yang et al. [53], a total of 22 studies including 1137 LQTS patients were studied to assess the effects of provocative testing on QTc interval. Among 22 studies, 9, 5, 4 and 4 studies evaluated the effects of ETT, bicycle test, epinephrine QT stress test and abrupt standing test on QTc interval, respectively. In the 9 studies evaluating the effect of ETT, 3 also included concomitant abrupt standing test. Among the recruited LQTS patients, 42% and 18% were symptomatic and asymptomatic, respectively. Patients' symptoms were not documented in 40% of the cases. Half, 30% and 7% of the patients had LQT1, LQT2, and LQT3, respectively. One-fifth of the patients had history of cardiac events, among whom about 21% were on beta-blocker therapy. LQTS patients had longer ΔQTc upon abrupt standing test (mean difference +29 ms, $p < 0.001$) compared with the control group, and demonstrated QTc prolongation both at peak stress (+27 ms, $p < 0.001$) and 4–5 min in recovery stage (+29.85 ms, $p < 0.001$). In contrast, in patients who underwent epinephrine infusion stress test, QTc interval were prolonged both in LQTS patients and the control group, but more prominently in LQT1 (+68 ms, $p < 0.001$) and in LQT2 (+60 ms, $p < 0.001$) patients. LQTS patients had increased ΔQTc that was 70 ms greater ($p < 0.001$) compared with the control.

The study summarized 3 different types of QTc changes in response to standing and exercise. LQT1 patients demonstrated a type I response, characterized by QTc prolongation upon standing and peak exercise, persisting in late recovery stage. LQT2 patients demonstrated type II response, characterized by QTc prolongation upon abrupt standing that returned to baseline or was mildly shortened during peak exercise, and gradually increased in late recovery. LQT3 patients demonstrated type III response, characterized by QTc shortening during abrupt standing, peak exercise, and recovery stage.

Crotti et al. [54] studied 169 LQTS patients who underwent ETT. Symptomatic LQTS patients with impaired I_{Ks} had greater heart rate reduction versus their asymptomatic counterpart (19 ± 7 vs 13 ± 5 and 27 ± 10 vs 20 ± 8 bpm, both $p = 0.009$). One-minute heart rate recovery of greater than 21 beats per minute (maximum heart rate minus heart rate at 1 min in recovery phase) identifies LQT1 patients with high arrhythmic risk, independent of beta-blocker therapy. Such difference was not observed among LQT2 and LQT3 patients.

Figure 2 demonstrated the paradoxical QT prolongation and atrioventricular block during recovery phase of exercise treadmill test in a patient with genetically confirmed LQT3.

Mechanisms of paradoxical QT response during ETT in LQTS

LQTS is typically associated with mutation of the slow delayed rectifier channel (I_{Ks}) in LQT1 and rapid delayed rectifier channel (I_{Kr}) in LQT2. LQT1 is associated with the greatest degree of QTc prolongation during exercise compared with LQT2, LQT3 or non-LQTS control. The I_{Ks} is normally enhanced during exercise and sympathetic stimulation. However, LQT1 is associated with loss-of-function mutation of I_{Ks}, resulting in reduction of net potassium efflux during the initial repolarization

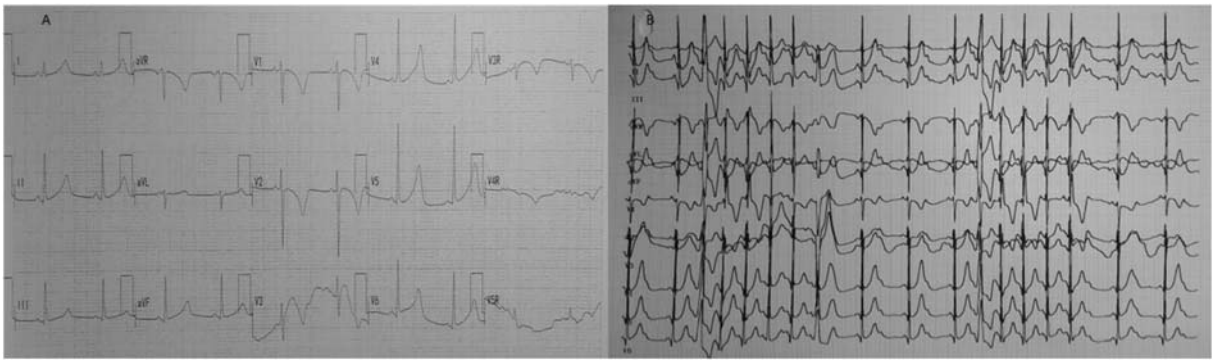

Figure 2. (A) A 12-year-old girl was admitted for recurrent exertional syncope. She enjoyed good past health and was not taking any QT-prolonging medication. She had no family history of sudden cardiac death. Baseline 12-lead ECG showed sinus rhythm with prolonged QTc interval of 511 ms and late peaking of T waves. Serum electrolytes and echocardiogram were unremarkable. (B) Exercise treadmill test (ETT) showed 1 to 1 atrioventricular (AV) conduction up to 116 beats per minute, followed by intermittent 2 to 1 AV block at peak stress. The QTc interval shortened from about 500 ms at baseline to 450 ms at peak stress, followed by paradoxical lengthening to 516 ms at 4 min in recovery stage. The patient's Schwartz score was 6, suggestive of high probability of long QT syndrome. Genetic test detected mutation in SCN5A, confirming diagnosis of congenital LQT3 with co-existing infra-nodal AV block.

phase (phase 2), which in turn leads to impairment of QTc shortening during exercise. In contrast, patients with LQT2 have impaired I_{Kr}, which reduces potassium efflux in the rapid terminal phase of repolarization (phase 3). The I_{Kr} channel mainly functions at the intermediate heart rate range. During peak exercise and early recovery when the heart rate is fast, LQT2 patients still have intact I_{Ks} function, which allows physiological QTc shortening [55]. The above mechanism could explain the difference in QTc response to exercise among LQT1 and LQT2/LQT3 patients.

Guideline recommendations

The 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death [56] suggests that for patients with suspected LQTS, exercise stress test can be useful for establishing a diagnosis and monitoring the response to drug therapy (Class IIa recommendation. Level of evidence: B). The ESC 2022 Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death [57] recommends exercise stress test for the diagnosis of LQTS in probands and the screening of LQTS in relatives of LQTS probands (Class I recommendation). A QTc $\geq$480 ms during 4th minute of recovery phase in exercise stress test could contribute to the diagnosis of congenital LQTS.

C. Catecholaminergic ventricular tachycardia

Role of ETT in the diagnosis and risk stratification of CPVT

Although exercise stress test could provoke ventricular arrhythmia in over 80% of symptomatic CPVT probands [15,58–60]. Up to 72% of *RyR2* p.G357S pathogenic mutation carriers had normal or near-normal exercise stress test [61]. Hayashi et al. [62]studied 67 asymptomatic relatives (of 17 genotype-positive CPVT probands) who had undergone ETT and found 17 (25%) ETT-positive cases. Positive ETT was defined as induction of ventricular tachycardia or VPC consisting of ventricular bigeminies or ventricular couplets. CPVT-related mutation was identified in 94% and 32% of the relatives with positive and negative exercise stress test, respectively. In 32 CPVT mutation carriers, cardiac events occurred in 7 of 16 (44%) ETT-positive and 2 of 16 (13%) ETT-negative relatives at a mean follow-up of 9.6 years. Among the 16 CPVT relatives with positive ETT, the cardiac event rate was lower among those on betablocker therapy.

Studies have shown that ETT has a high specificity of 97% in diagnosing CPVT [62,63] There is a significant association between a positive ETT result and CPVT genetic mutation. However, the sensitivity was only about 50%, indicating that ETT is not sensitive enough for diagnosis of CPVT [62,63]. It is postulated that the arrhythmic events are often triggered by sudden sympathetic surge and abrupt increase in heart rate. A burst exercise stress test might better mimic the physiological trigger in CPVT by triggering sudden and more pronounced cytosolic calcium overload [64]. Oston et al. [64] reported on 6 CPVT patients with disease-associated *RyR2* genotype undergoing non-diagnostic standard ETT, among whom 4 had a history of cardiac arrest, and 2 were family members of a CPVT cohort. Fifty percent of patients were on antiarrhythmic drug therapy at the time of stress test. Patients underwent burst exercise stress testing until occurrence of fatigue, cardiac symptoms or non-sustained VT. The burst exercise stress test was defined by abrupt high-intensity exercise at the immediate onset of testing (equivalent to the maximum stage on previous standard exercise stress test). The occurrence of cardiac symptoms or $\geq$3 beats of non-sustained VT, which occurred in 5 out of the 6 patients, was diagnostic of CPVT. Among the

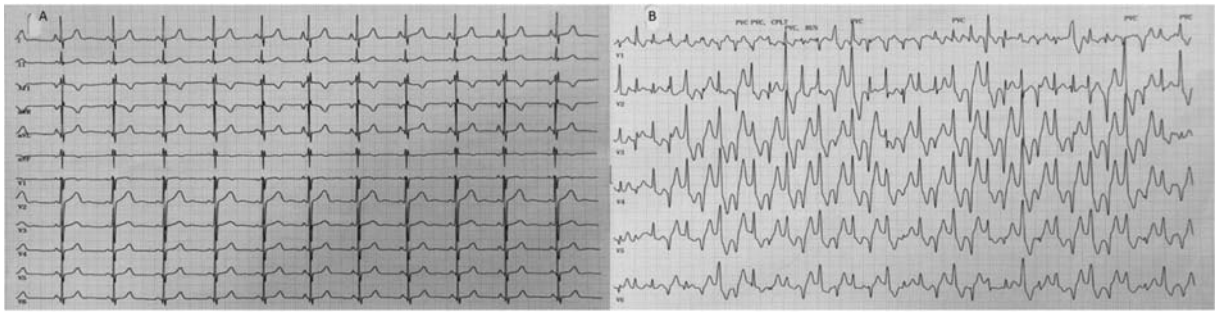

Figure 3. (A) A 13-year-old female developed recurrent exercise-induced syncope. Baseline 12-lead ECG, serum electrolytes and echocardiogram were unremarkable. She was not taking any pro-arrhythmic drug. She had no family history of sudden cardiac death. (B) Exercise treadmill test (ETT) induced bi-directional ventricular tachycardia with beat-to-beat alternation of QRS axis during exercise, supporting the clinical diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT).

Table 1. Role of ETT in diagnosis and risk stratification in channelopathies.

	BrS	LQTS	CPVT
Diagnosis	In patients with suspected BrS, augmentation of ST segment elevation during exercise or in early recovery phase of ETT is supportive of the diagnosis [37−39,48]	In patients with suspected LQTS, paradoxical QTc prolongation during 1 minute & 4min in recovery phase of ETT or a 3-step algorithm may help identify patients with LQT1 Patients with LQT2 may have more pronounced QTc hysteresis during ETT [19, 49−53].	In patients with exercise-induced syncope/SCD or ventricular arrhythmia, a positive ETT may help diagnose CPVT [15,58−63,65]. The sensitivity of ETT could be improved by burst ETT [64].
Prognosis	In patients with confirmed BrS, augmentation of ST segment elevation or ventricular ectopics in recovery phase of ETT are predictive of ventricular arrhythmic event [38,39]	In patients with LQTs, 1-minute heart rate recovery >21 beats per minute identifies LQT1 patients at risk of cardiac arrhythmia [54]	Positive ETT predicts cardiac events in patients with CPVT [62]

Abbreviations: BrS = Brugada Syndrome. LQTS = Long QT syndrome. CVPT = Catecholaminergic polymorphic ventricular tachycardia. ETT = Exercise treadmill test.

5 patients, 60% had previously normal or near-normal standard exercise stress test.

The sensitivity of exercise stress test in CPVT relies on the test definition. When NSVT was used as a criterion of a positive exercise stress test, the sensitivity was 22%. It improved to 50% when ventricular bigeminies and couplets were included in the definition of a positive test [65]. It has been suggested that adrenaline (epinephrine) provocation stress testing may be more sensitive than the exercise stress test in unmasking ventricular arrhythmia in symptomatic CPVT patients, but the specificity was found to be lower than that of exercise stress test [4].

Figure 3 demonstrated an example of exercise-induced bi-directional ventricular tachycardia in a patient with CPVT.

Guideline recommendations

The ESC 2022 guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [57] recommends that ETT should be considered for the diagnosis of CPVT in probands and screening of relatives of CPVT probands (Class I recommendation). Adrenaline or isoproterenol challenge may be considered for the diagnosis of CVPT when exercise stress test is not possible (Class IIb recommendation). The presence of complex arrhythmia during exercise stress test on a full dose of beta-blocker are independent predictor for cardiac arrhythmia.

Table 1 summarizes the role of ETT in diagnosis of risk stratification of channelopathies.

Summary

Channelopathies are the leading causes of SCD in patients without structural heart disease. Accurate diagnosis and risk stratification of these diseases are of paramount importance. However, the diagnosis of channelopathies is sometimes complicated by the elusive clinical and ECG manifestations. An integrated approach, including clinical assessment, repeat ECG, drug provocation, exercise stress test and genetic testing, is often required for diagnosis confirmation. ETT is easily accessible and cost-effective in establishing a diagnosis and for determining the prognosis of patients with BrS, LQTS and CPVT.

Conflict of interest

The author has no conflict of interest to report.

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