HHS Public Access

Author manuscript

J Cardiovasc Electrophysiol. Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

J Cardiovasc Electrophysiol. 2019 October ; 30(10): 1923–1929. doi:10.1111/jce.14043.

Chronotropic Incompetence as a Risk Predictor in Children and Young Adults with Catecholaminergic Polymorphic Ventricular Tachycardia

Sonia Franciosi, PhD[a,1], **Thomas M. Roston, MD**[a,b,c,1], **Frances K.G. Perry**[a], **Bjorn C. Knollmann, MD, PhD**[d], **Prince J. Kannankeril, MD, MSCI**[d,e], **Shubhayan Sanatani, MD**[a,*]

[a]Children's Heart Centre, BC Children's Hospital & Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada

[b]Department of Medicine, University of British Columbia, Vancouver, BC, Canada

[c]Department of Medicine, University of Alberta, Edmonton, AB, Canada

[d]Vanderbilt Center for Arrhythmia Research and Therapeutics (VanCART), Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, TN

[e]Department of Pediatrics, Vanderbilt University Medical Center and the Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN

Abstract

Introduction: Risk stratification tools for catecholaminergic polymorphic ventricular tachycardia (CPVT) are limited. The exercise stress test (EST) is the most important diagnostic and prognostic test. We aimed to determine whether heart rate (HR) and blood pressure (BP) response during EST were associated with risk of arrhythmias.

Methods: We studied the association between HR and BP response and ventricular arrhythmia burden on EST in 20 CPVT patients. HR reserve values < 80% and ≤62% were used to define chronotropic incompetence (CI) off and on therapy respectively. Symptoms and ventricular arrhythmia score (VAS) in all patients with respect to chronotropic incompetence (CI) and BP during index EST off therapy and on maximal therapy were compared.

Results: CI in CPVT patients off therapy was associated with a worse VAS during EST ($p = 0.046$). Patients with CI also more frequently presented with syncope and/or cardiac arrest compared to patients with a normal chronotropic response ($p = 0.008$). Once on therapy, patients with CI had similar VAS compared to patients without CI ($p = 0.50$), suggesting that treatment

[*]**Corresponding Author:** Shubhayan Sanatani, MD, FRCPC, CCDS, FHRS, Head, Division of Cardiology, Department of Pediatrics, Children's Heart Centre, 1F9, British Columbia's Children's Hospital, 4480 Oak Street, Vancouver, BC V6H 3V4, Tel: (604) 875-3619 / Fax: (604) 875-3463, ssanatani@cw.bc.ca.

Author contributions

Drs. Franciosi and Roston: Concept/design, data collection, data analysis and interpretation, drafting article, statistics

Frances Perry: critical revisions of article

Dr. Bjorn Knollman: critical revisions of article

Dr. Prince Kannankeril: provided de-identified patient data, critical revisions of article

Dr. Shubhayan Sanatani:provided de-identified patient data, provided funding, critical revisions of article, approval of article

[1]Contributed equally to this study as shared first authors

Disclosures: Drs. Roston, Kannankeril and Sanatani are consultants for Audentes Therapeutics

attenuates risk related to CI. Patients with CI also had a lower peak systolic BP (p =0.041) which persisted on maximal therapy (p =0.033).

Conclusion: Untreated CPVT patients with CI have more ventricular arrhythmias than those without CI. This may serve as a simple disease prognosticator that can be modified by anti-arrhythmic therapy. A mechanistic link between CI and arrhythmia susceptibility remains unknown. Larger studies are needed to confirm and establish the mechanism of these findings.

Keywords

CPVT; heart rate; exercise stress test; chronotropic incompetence; ventricular arrhythmia

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal heritable channelopathy defined by increasing ventricular ectopy (VE) during exercise stress testing (EST) in the absence of structural heart disease.[1] Early data suggested that CPVT had an unfavorable natural history with nearly 80% of affected patients suffering a life-threatening cardiac event by 40 years of age, and treatment failures and device complications remain common.[2–4] In the current era of cascade genetic screening, there is a growing population of phenotypically silent CPVT patients.[5–7] This observation creates additional dilemmas as optimal management of these patients is unknown, and risk stratification tools are dangerously lacking. The EST provides data on VE burden which is a predictor of subsequent cardiac events.[8] Chronotropic incompetence (CI), or an attenuated heart rate (HR) response during exercise, is an established prognosticator of arrhythmias[9, 10] and cardiac death[11–13] in other conditions. Sinus node dysfunction, which is frequently present in CPVT,[14] is a common cause of CI. We therefore hypothesized that CI during exercise may predict a greater arrhythmic burden in CPVT patients.

Methods

Study population

This is a retrospective study of young patients (≤ 21 years old at first EST) with a diagnosis of CPVT made by expert consensus criteria.[15] The proband was defined as the first identified case of CPVT in a family. Eligible patients were those entered in the Pediatric and Congenital Electrophysiology Society (PACES) CPVT Registry from either British Columbia Children's Hospital or the Monroe Carell Jr. Children's Hospital at Vanderbilt. Only patients from one of these two tertiary centers were eligible because an additional, more in-depth collection of EST-specific data were needed for this study, as these details were not fully captured in the general Pediatric CPVT Registry population. All centers obtained ethical approval from their respective institutional review boards.

Exercise Stress Testing

CPVT patients underwent ESTs using standard exercise protocols with continuous electrocardiographic monitoring. HR and BP were obtained at rest and at the end of each stage of exercise. Two ESTs were analyzed for each patient whenever possible (total n=14

ESTs off therapy and n=17 ESTs on maximal therapy included in analyses); the index EST which was the first EST performed in a subject off therapy and the EST at maximal therapy (defined as the maximum tolerated dose of therapy (beta blocker and/or adjunctive therapy) that was administered to suppress arrhythmia). HR and BP were recorded at regular intervals throughout the EST. We recorded maximal workload achieved (in metabolic equivalents (METS) and total exercise time (in seconds)). Ventricular arrhythmia score (VAS) was determined from ESTs using an established grading scale in CPVT as previously described (no VE=0, isolated ventricular premature beats (VPBs)=1, bigeminy=2, couplets=3 and nonsustained ventricular tachycardia (NSVT)=4).[16]

Calculation of Heart Rate Reserve

CI was defined as a %HR reserve of <80%.[13] HR reserve is the difference between maximal age-predicted HR (MA-PHR) which is calculated as 220- age (in years) and HR at rest. The following equation was used: %HR reserve = ([peak HR – rest HR]/[MA-PHR – rest HR]) x 100. For patients on β blockers, CI was defined as %HR reserve of ≤62% as previously reported in a large cohort of patients taking β-blockers with normal electrocardiograms at rest referred for symptom-limited exercise testing.[17]

Statistical Analysis

For descriptive purposes, patients were initially divided into two groups according to the presence or absence of CI. Results of quantitative variables are presented as mean ± standard error of the mean (SEM). Qualitative variables are presented as absolute values and percentages. Comparison of qualitative characteristics was performed using the Chi square or Fisher's exact test. Quantitative variables were compared using the student's t-test for independent samples and one-way ANOVA with Tukey post hoc comparisons. A two-tailed $p<0.05$ was considered significant. Statistical analysis was performed using Graph Pad 7.0 (Graph Pad Software, San Diego, CA, USA).

Results

The baseline demographic and EST characteristics of the 20 eligible CPVT patients are summarized in Table 1. The median age at first EST was 12 years (range 6–21). Nine of 20 subjects (45%) were male and 14 (70%) were probands. The most severe symptoms reported were syncope in 6 patients (30%) and sudden cardiac arrest (SCA) in 8 patients (40%), while the remaining 6 (30%) were asymptomatic and ascertained through cascade family screening. Genetic testing was performed in 19 of 20 patients. A mutation in *RYR2* was found in 18 of 19 subjects (95%), including one treatment-refractory patient who was also found to be homozygous for a *CASQ2* mutation (Subject 1). All but three asymptomatic patients (Subject 5, 8 and 12) were prescribed beta blockers. There were 12 patients (60%) who required ancillary treatments which included flecainide in 8 (40%), implantable cardioverter defibrillator in 9 (45%) and left cardiac sympathectomy in 3 patients (15%; mean 6.7 ± 4 years after initial cardiac evaluation). Demographic and treatment characteristics of the study population are summarized in Table 1.

Baseline and exercise characteristics of patients off therapy (Subjects 2–12, 17, 19–20) according to the presence or absence of CI are listed in Table 2. Off therapy, the most common reasons for stopping the EST in the CI group was fatigue (40%), cardiac (arrhythmia, bidirectional VT) in 40% and target heart rate met (20%). Those with normal chronotropy stopped the EST due to fatigue (67%), cardiac (ventricular tachycardia, dizziness) in 22% and target heart rate met (11%). Five out of 14 patients (36%) had CI (HR Reserve <80%) off therapy (Subjects 3, 9, 10, 17 and 19). Patients with CI had a worse VAS as compared to those with normal chronotropy (3.4 ± 0.6 vs 1.4 ± 0.6; p = 0.046). Those with CI had lower resting diastolic BP (65 ± 3 vs 74 ± 2; p =0.045, lower peak systolic BP (133 ± 10 vs 168 ± 10; p =0.041) and lower delta systolic BP (peak systolic BP minus resting systolic BP; 24 ± 8 vs 59 ± 11; p =0.047). There was no association between CI and age, HR at rest and systolic BP at rest off therapy (p > 0.05).

Baseline and exercise characteristics of patients on maximal therapy according to the presence or absence of CI are listed in Table 3. Ten out of 17 patients (59%) had CI (HR Reserve ≤62%) on maximal therapy (Subjects 1, 2, 3, 10, 14–19). On maximal therapy, the most common reasons for stopping the EST in the CI group was due to fatigue (80%), shortness of breath (10%) and anxiety (10%). Similarly, those with normal chronotropy generally stopped the EST due to fatigue (86%) followed by chest pain and shortness of breath (14%). Importantly, once CPVT was recognized and treated, the follow-up EST was always symptom/arrhythmia limited, and not stopped due to target HR being met, which was a rare cause for discontinuation on initial diagnostic EST off-therapy. There was no difference in ventricular arrhythmia score between those with CI and those with normal chronotropy on maximal therapy (p =0.50). After maximal therapy, the chronotropic status of 64% remained unchanged, 18% developed CI and 18% of patients developed normal chronotropy. CPVT patients with CI on maximal therapy continued to have lower peak systolic BP (126 ± 6.2 vs 151.4 ± 9.5; p =0.033) compared to patients without CI. There was no association between age, exercise duration, METS achieved, resting HR, resting systolic BP resting diastolic BP and delta systolic BP, and CI in CPVT patients on maximal therapy. All 10 patients on maximal therapy with CI (100%) were probands and symptomatic at presentation (syncope or sudden cardiac arrest) as compared to 43% of CPVT patients with a normal chronotropic response (p =0.008). This difference is less likely a medication effect since no difference in dosage of beta blocker therapy was observed between those with CI versus normal chronotropy (CI: 69.8 ± 13.3 mg nadolol vs normal chronotropy: 40 ± 8.2 mg nadolol; p = 0.2) nor was beta blocker dosage different between those with normal chronotropy who were symptomatic versus asymptomatic at presentation (symptomatic: 73.3 ± 43.7 mg nadolol vs asymptomatic: 50 ± 10 mg nadolol; p = 0.71). Beta blocker therapy had a general depressive effect on heart rate at peak exercise in both the CI (off therapy: 161.2 ± 5.4 vs maximal therapy: 128.5 ± 6.4; p = 0.0058) and normal chronotropy group (off therapy: 197.8 ± 3.3 vs maximal therapy: 157.1 ± 3.4; p < 0.0001) as expected. Nine out of 10 CPVT patients (90%) with CI on maximal therapy required an adjunctive therapy in addition to beta blockers compared to 43% with a normal chronotropic response (p =0.042). No significant difference was found in number of CPVT patients undergoing defibrillator implantation between those with CI versus patients with a normal chronotropic response on maximal therapy (60% vs 43%; p =0.49).

As shown in Table 4, we compared both %HR reserve and VAS on EST off therapy and on maximal therapy in patients with worst symptom of syncope, SCA and asymptomatic patients. Off therapy, %HR reserve was significantly different in patients with a worst symptom of SCA (%HR reserve <80% = CI) as compared to asymptomatic patients ($p<0.01$). VAS distinguished asymptomatic patients from patients with syncope ($p<0.001$) and patients with SCA as worst symptom ($p>0.05$). On maximal therapy, %HR reserve significantly distinguished asymptomatic patients from patients with syncope (%HR reserve ≤62% = CI; $p<0.01$) and patients with SCA (%HR reserve ≤62% = CI) as worst presenting symptom ($p <0.05$) whereas VAS did not distinguish between groups ($p>0.05$). Results would indicate that CI is able to distinguish patients with SCA as worst symptom both off and on maximal therapy whereas VAS is able to distinguish patients with SCA as worst symptom only off therapy.

Discussion

In this retrospective study of young CPVT patients, we found that CI off therapy is associated with ventricular arrhythmia and symptom burden. Untreated patients with CI had a worse VAS on EST (Table 2) and were more likely to have presented with life-threatening symptoms compared to those without CI. Maximal anti-arrhythmic therapy reduced the VAS in those with CI to a score which was not significantly different from that in patients with normal chronotropy (Table 3). Collectively, these data suggest that the EST off therapy (i.e. the initial diagnostic EST) can risk stratify CPVT patients based on CI, which may inform the initial therapy, closeness of follow-up and effectiveness of therapy for CPVT.

Although the EST is the most important test for suspected CPVT, it lacks sensitivity,[18] and sudden death can occur despite a normal, or near normal result.[8, 19] Thus, we sought other simple metrics that can be acquired on a standard EST to predict risk. CI has previously been associated with prognosis in other cardiac disorders, such as atrial fibrillation,[10] hypertrophic cardiomyopathy[20] and coronary artery disease.[11] CI might be particularly useful beyond the VAS since it detected worst symptom (SCA) in the maximally treated patient. CI may be used as a screening tool for those patients who present for family screening, those who are asymptomatic or who have a low VAS on EST for e.g. bigeminy. Further work is needed to compare the sensitivity and specificity of these predictors in a larger cohort. Several previous studies support the findings related to CPVT presented here. Firstly, atrial manifestations, like sinus node dysfunction, are common in CPVT, and may occur in the setting of more damaging mutations.[21, 22] Secondly, pharmacologically increasing sinus rate may protect against CPVT in mice.[23] And thirdly, ventricular arrhythmias actually subsided late in exercise in a subset of CPVT patients who reached >85% of their maximum-predicted HR.[23] While the mechanism of exercise-induced CI and arrhythmic risk in CPVT is unknown, one possible explanation is that some CPVT patients have an inappropriate autonomic response that favors parasympathetic dominance. Faggioni et al hypothesized that a higher HR shortens the diastolic interval, which exceeds the frequency of spontaneous Ca^{2+} release and delayed after depolarizations, ultimately leading to VE suppression.[23] Our study provides clinical data to support these concepts.

Risk related to CI appears to be attenuated by CPVT therapy. Once treated, the occurrence of ventricular arrhythmias was lower in all patients, regardless of CI on initial testing. While it may seem counter-intuitive that ß-blockers, which induce CI, would be protective, several factors may account for this apparent paradox. CPVT arrhythmias are most likely to manifest during an "arrhythmic window" of risk defined by HR.[24] Thus, the benefit of ß-blockers may be derived from narrowing the range of HR during which CPVT is most likely to manifest, rather than by simply decreasing maximal HR. Additionally, the molecular mechanism of CI may be different than the pharmacologic mechanism of ß-blocker protectiveness.

BP response to exercise may also be a CPVT risk predictor. In the present study, lower resting diastolic BP, peak systolic BP and delta systolic BP in those with CI off therapy were associated with a higher VAS. This finding persisted despite maximal therapy in patients with CI. The significance of this remains speculative at present. Since BP is influenced by HR, it may be that CI itself leads to relative hypotension, which would mean that BP response provides no incremental prognostic utility over CI.

Some limitations warrant discussion. The population was small, and we limited our analyses to the index EST and EST on maximal therapy. All patients were on ß-blockers at a minimum, but we did not adjust for ß-blocker type or dosage equivalency on maximal therapy. While it is possible that CI was associated with a higher VAS due to early discontinuation of the EST due to severe CPVT, the practice at both participating centers is to continue the test unless hemodynamically unstable arrhythmias develop, prohibitive symptoms occur, like pre-syncope or exhaustion or no further diagnostic information would be obtained. Further prospective studies of CI comparing maximal HR with METS achieved, exercise duration and symptoms are warranted. Also, in the CI group, ancillary anti-arrhythmic treatments were more often prescribed (p=0.042), suggesting that these patients were indeed more severely affected.

Conclusions

The lack of prognostic tools in CPVT is a major clinical problem. These data suggest that the EST provides valuable clinical information beyond making a CPVT diagnosis. Namely, CI is a marker of increased CPVT risk, which appears to be attenuated by anti-arrhythmic therapy. A relative hypotensive response to exercise may be a novel prognosticator, although this observation may be confounded by the concurrent presence of CI. Our findings imply that the autonomic nervous system plays a role in disease modulation.

Funding information

Dr. Roston was funded by the Queen Elizabeth II Graduate Scholarship at the University of Alberta. Drs. Roston and Sanatani are funded by the Rare Disease Foundation and BC Children's Hospital Foundation. Dr. Sanatani is supported by the Heart and Stroke Foundation of Canada (G-15–0008870). Dr. Knollmann and Dr. Kannankeril are U.S. National Institutes of Health grant recipients (R35-HL144980 to B.K., HL131911 and HD084461 to P.K.).

References

1. Leenhardt A, Lucet V, Denjoy I, et al., Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation, 1995; 91: 1512–1519. [PubMed: 7867192]
2. Celiker A, Erdogan I, Karagoz T, and Ozer S, Clinical experiences of patients with catecholaminergic polymorphic ventricular tachycardia. Cardiol Young, 2009; 19: 45–52.
3. Roston TM, Vinocur JM, Maginot KR, et al., Catecholaminergic polymorphic ventricular tachycardia in children: analysis of therapeutic strategies and outcomes from an international multicenter registry. Circ Arrhythm Electrophysiol, 2015; 8: 633–642. [PubMed: 25713214]
4. Mohamed U, Napolitano C, and Priori SG, Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. J Cardiovasc Electrophysiol, 2007; 18: 791–797. [PubMed: 17578347]
5. van der Werf C, Nederend I, Hofman N, et al., Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. Circ Arrhythm Electrophysiol, 2012; 5: 748–756. [PubMed: 22787013]
6. Sy RW, Gollob MH, Klein GJ, et al., Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm, 2011; 8: 864–871. [PubMed: 21315846]
7. Roston TM, Yuchi Z, Kannankeril PJ, et al., The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. Europace, 2018; 20: 541–547. [PubMed: 28158428]
8. Hayashi M, Denjoy I, Extramiana F, et al., Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation, 2009; 119: 2426–2434. [PubMed: 19398665]
9. Rib Y, Zhussupova G, Igimbayeva G, Abdrakhmanov A, and Jalali SF, Can chronotropic incompetence predict life-threatening ventricular arrhythmias in patients with stable ischemic heart disease? Caspian J Intern Med, 2018; 9: 164–170. [PubMed: 29732035]
10. O'Neal WT, Qureshi WT, Blaha MJ, et al., Chronotropic Incompetence and Risk of Atrial Fibrillation: The Henry Ford ExercIse Testing (FIT) Project. JACC Clin Electrophysiol, 2016; 2: 645–652. [PubMed: 28451646]
11. Lauer MS, Okin PM, Larson MG, Evans JC, and Levy D, Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation, 1996; 93: 1520–1526. [PubMed: 8608620]
12. Lauer MS, Francis GS, Okin PM, et al., Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA, 1999; 281: 524–529. [PubMed: 10022108]
13. Azarbal B, Hayes SW, Lewin HC, et al., The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol, 2004; 44: 423–430. [PubMed: 15261942]
14. Faggioni M, van der Werf C, and Knollmann BC, Sinus node dysfunction in catecholaminergic polymorphic ventricular tachycardia: risk factor and potential therapeutic target? Trends Cardiovasc Med, 2014; 24: 273–278. [PubMed: 25112803]
15. Priori SG, 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: 1932–1963. [PubMed: 24011539]
16. van der Werf C, Kannankeril PJ, Sacher F, et al., Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol, 2011; 57: 2244–2254. [PubMed: 21616285]
17. Khan MN, Pothier CE, and Lauer MS, Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). Am J Cardiol, 2005; 96: 1328–1333. [PubMed: 16253608]

18. Hayashi M, Denjoy I, Hayashi M, et al., The role of stress test for predicting genetic mutations and future cardiac events in asymptomatic relatives of catecholaminergic polymorphic ventricular tachycardia probands. Europace, 2012; 14: 1344–1351. [PubMed: 22383456]

19. Nof E, Belhassen B, Arad M, et al., Postpacing abnormal repolarization in catecholaminergic polymorphic ventricular tachycardia associated with a mutation in the cardiac ryanodine receptor gene. Heart Rhythm, 2011; 8: 1546–1552. [PubMed: 21699856]

20. Magri D, Agostoni P, Sinagra G, et al., Clinical and prognostic impact of chronotropic incompetence in patients with hypertrophic cardiomyopathy. International Journal of Cardiology, 2018; 271: 125–131. [PubMed: 30087038]

21. Faggioni M, van der Werf C, and Knollmann B, Sinus node dysfunction in catecholaminergic polymorphic ventricular tachycardia – risk factor and potential therapeutic target? Trends in cardiovascular medicine, 2014; 24: 273–278. [PubMed: 25112803]

22. Sumitomo N, Sakurada H, Taniguchi K, et al., Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. Circ J, 2007; 71: 1606–1609. [PubMed: 17895559]

23. Faggioni M, Hwang HS, van der Werf C, et al., Accelerated sinus rhythm prevents catecholaminergic polymorphic ventricular tachycardia in mice and in patients. Circ Res, 2013; 112: 689–697. [PubMed: 23295832]

24. Leren IS, Saberniak J, Majid E, et al., Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with beta1-selective beta-blockers in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm, 2016; 13: 433–440. [PubMed: 26432584]

Table 1.

Characteristics of CPVT patients included in the pilot study.

Subject	Sex	Case Status	Age at first EST	Presenting symptoms	Worst VE on EST	Worst symptom	Genetic Mutation	Therapies
1	M	Proband	7	Syncope	PMVT	SCA	RYR2 M1107T (heterozygous) & CASQ2 IVS5+1G>C (homozygous)	Nadolol, flecainide, ganglionectomy, defibrillator
2	F	Proband	12	Syncope	PMVT	Syncope	RYR2 E4183Q	Nadolol
3	F	Proband	8	Syncope	PMVT	Syncope	RYR2 L2200F	Nadolol, verapamil, flecainide, defibrillator
4	M	Relative	12	Asymptomatic, referred for family screening	Ventricular bigeminy	Asymptomatic	RYR2 R122H	Nadolol
5	F	Relative	12	Asymptomatic, referred for family screening	None	Asymptomatic	RYR2 R420W	None
6	M	Relative	10	Asymptomatic, referred for family screening	Frequent VPBs	Asymptomatic	RYR2 R420W	Nadolol switched to Bisoprolol (intolerance)
7	F	Relative	8	Asymptomatic, referred for family screening	Frequent VPBs	Asymptomatic	RYR2 R420W	Nadolol
8	M	Relative	6	Asymptomatic, referred for family screening	Frequent VPBs	Asymptomatic	RYR2 R420W	None
9	F	Proband	11	Asymptomatic, screening prior to psychiatric medications	Frequent VPBs	SCA	RYR2 I4855M	Carvedilol, defibrillator
10	M	Proband	11	Syncope	PMVT	Syncope	RYR2 V4771I	Nadolol switched to bisoprolol (intolerance), flecainide
11	M	Proband	17	Syncope	PMVT	Syncope	RYR2 R15P	Nadolol
12	M	Relative	21	Asymptomatic, referred for family screening	Frequent VPBs	Asymptomatic	RYR2 R15P	None
13	M	Proband	11	SCA	Ventricular couplets	SCA	No genetic testing performed	Nadolol, flecainide, defibrillator
14	F	Proband	15	SCA	Ventricular bigeminy	SCA	RYR2 V4125F	Nadolol, flecainide, sympathectomy, defibrillator
15	F	Proband	15	SCA	Ventricular couplets	SCA	RYR2 L1894F	Nadolol, defibrillator
16	F	Proband	14	Syncope	PMVT	Syncope	RYR2 K4751Q	Nadolol, flecainide
17	F	Proband	6	Syncope	PMVT	SCA	RYR2 A4091T	Nadolol, flecainide, sympathectomy, defibrillator
18	F	Proband	6	Syncope	Ventricular bigeminy	Syncope	RYR2 R4201H	Nadolol, flecainide
19	M	Proband	14	SCA	PMVT	SCA	No RYR2 variants identified	Nadolol, defibrillator
20	F	Proband	15	SCA	PMVT	SCA	RYR2 E2314K	Nadolol, flecainide, defibrillator

J Cardiovasc Electrophysiol. Author manuscript; available in PMC 2020 October 01.

Abbreviations: CASQ2, calsequestrin 2; EST, exercise stress test; PMVT, polymorphic ventricular tachycardia; RYR2, ryanodine receptor 2; SCA, sudden cardiac arrest; VE, ventricular ectopy; VPB, ventricular premature beat.

Table 2.

Baseline and Exercise Characteristics of Subjects Off Medication Based on Percent Heart Rate Reserve (Index ETT).

Variable	HR Reserve <80% (n=5)	HR Reserve ≥ 80% (n=9)	p Value
age	9.8 ± 1.4	13.2 ± 1.2	0.10
Exercise duration (sec)	361.8 ± 98.3	754.9 ± 62.6	0.0041
METS achieved	4.9 ± 1.3	13.4 ± 1.4	0.0018
HR at rest (beats/min)	69.4 ± 3.9	73.6 ± 5.1	0.59
HR at peak exercise (beats/min)	161.2 ± 5.4	197.8 ± 3.3	<0.0001
Blood Pressure (mm Hg)			
Systolic Blood Pressure at rest	109.0 ± 3.3	110.2 ± 4.3	0.85
Diastolic Blood Pressure at rest	65.0 ± 2.9	73.2 ± 2.2	0.045
Peak Systolic Blood Pressure	133.4 ± 9.7	169.4 ± 10.3	0.041
Delta Systolic Blood Pressure (peak-rest)	24.4 ± 7.9	59.2 ± 10.7	0.047
Ventricular Arrhythmia Score	3.4 ± 0.6	1.6 ± 0.5	0.046

Abbreviations: HR, heart rate; METS, metabolic equivalents; min, minute; mm Hg, millimetre of mercury; sec, second.

Table 3.

Baseline and Exercise Characteristics of Subjects On Medication Based on Percent Heart Rate Reserve (ETT on maximum therapy).

Variable	HR Reserve ≤62% (n=10)	HR Reserve >62% (n=7)	p Value
age	14.7 ± 0.5	15.6 ± 1.1	0.41
Exercise duration (sec)	557.6 ± 44.1	685.1 ± 63.1	0.11
METS achieved	8.0 ± 1.1	9.8 ± 1.5	0.33
HR at rest (beats/min)	59.3 ± 2.7	54.9 ± 6.1	0.47
HR at peak exercise (beats/min)	126.7 ± 5.6	159.7 ± 2.3	0.0003
Blood Pressure (mm Hg)			
Systolic Blood Pressure at rest	101.4 ± 3.3	107.9 ± 4.7	0.26
Diastolic Blood Pressure at rest	61.9 ± 2.5	67.7 ± 1.9	0.11
Peak Systolic Blood Pressure	126.0 ± 6.2	151.4 ± 9.5	0.033
Delta Systolic Blood Pressure (peak-rest)	24.6 ± 6.0	43.6 ± 10.2	0.11
Ventricular Arrhythmia Score	1.8 ± 0.5	2.3 ± 0.5	0.50

Abbreviations: HR, heart rate; METS, metabolic equivalents; min, minute; mm Hg, millimetre of mercury; sec, second.

Table 4.

CI and VAS on and off therapy according to worst symptom.

	Worst Symptom			
	Asymptomatic (n=6)	**Syncope (n=4)**	**SCA (n=4)**	**p Value**
EST Off Therapy				
%HR Reserve	93.2 ± 1.5	85.9 ± 8.5	64.7 ± 3.5	0.0032
Ventricular Arrhythmia Score	0.7 ± 0.3	4 ± 0	2.75 ± 1.2	<0.0001
	Asymptomatic (n=3)	**Syncope (n=6)**	**SCA (n=8)**	**p Value**
EST On Maximal Therapy				
%HR Reserve	73.6 ± 1.5	51.7 ± 3.8	52.9 ± 4.1	0.0078
Ventricular Arrhythmia Score	1.3 ± 0.3	2.5 ± 0.6	1.9 ± 1.3	0.69

Abbreviations: HR= heart rate; SCA= sudden cardiac arrest.