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ORIGINAL ARTICLE

Heart Rate Recovery After Exercise Is Associated With Arrhythmic Events in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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BACKGROUND: Risk stratification in catecholaminergic polymorphic ventricular tachycardia remains ill defined. Heart rate recovery (HRR) immediately after exercise is regulated by autonomic reflexes, particularly vagal tone, and may be associated with symptoms and ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. Our objective was to evaluate whether HRR after maximal exercise on the exercise stress test (EST) is associated with symptoms and ventricular arrhythmias.

METHODS: In this retrospective observational study, we included patients ≤65 years of age with an EST without antiarrhythmic drugs who attained at least 80% of their age- and sex-predicted maximal HR. HRR in the recovery phase was calculated as the difference in heart rate (HR) at maximal exercise and at 1 minute in the recovery phase (ΔHRR1′).

RESULTS: We included 187 patients (median age, 36 years; 68 [36%] symptomatic before diagnosis). Pre-EST HR and maximal HR were equal among symptomatic and asymptomatic patients. Patients who were symptomatic before diagnosis had a greater ΔHRR1′ after maximal exercise (43 [interquartile range, 25–58] versus 25 [interquartile range, 19–34] beats/min; $P<0.001$). Corrected for age, sex, and relatedness, patients in the upper tertile for ΔHRR1′ had an odds ratio of 3.4 (95% CI, 1.6–7.4) of being symptomatic before diagnosis ($P<0.001$). In addition, ΔHRR1′ was higher in patients with complex ventricular arrhythmias at EST off antiarrhythmic drugs (33 [interquartile range, 22–48] versus 27 [interquartile range, 20–36] beats/min; $P=0.01$). After diagnosis, patients with a ΔHRR1′ in the upper tertile of its distribution had significantly more arrhythmic events as compared with patients in the other tertiles ($P=0.045$).

CONCLUSIONS: Catecholaminergic polymorphic ventricular tachycardia patients with a larger HRR following exercise are more likely to be symptomatic and have complex ventricular arrhythmias during the first EST off antiarrhythmic drug.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: autonomic nervous system ■ death, sudden ■ exercise test ■ heart rate ■ humans

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WHAT IS KNOWN?

- Risk stratification in catecholaminergic polymorphic ventricular tachycardia is ill defined.
- Vagal reflexes, assessed by heart rate recovery following an exercise stress test, are associated with the probability of being symptomatic in congenital long-QT syndrome type 1.

WHAT THE STUDY ADDS?

- Catecholaminergic polymorphic ventricular tachycardia patients with a higher heart rate recovery at the first exercise stress test off antiarrhythmic drugs are more likely to have been symptomatic before diagnosis.
- Heart rate recovery is higher in catecholaminergic polymorphic ventricular tachycardia patients with complex ventricular arrhythmias (couplets and nonsustained ventricular tachycardias) at the first exercise stress test off antiarrhythmic drugs.
- Vagal reflexes assessed through heart rate recovery are associated with symptoms before diagnosis and complex ventricular arrhythmias during exercise in catecholaminergic polymorphic ventricular tachycardia patients.

Nonstandard Abbreviations and Acronyms

ΔHRR1′	absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 minute after termination of exercise
ΔHRR2′	absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 minute after termination of exercise
AAD	antiarrhythmic drug
ACA	aborted cardiac arrest
ANS	autonomic nervous system
CPVT	catecholaminergic polymorphic ventricular tachycardia
EST	exercise stress test
HR	heart rate
HR_{max}	maximum heart rate
$HRR_{@1}'$	heart rate at the first minute of recovery
$HRR_{@2}'$	heart rate at the second minute of recovery
IQR	interquartile range
LQTS	long-QT syndrome
OR	odds ratio
SCD	sudden cardiac death
VA	ventricular arrhythmia
VT	ventricular tachycardia

Inherited arrhythmia disorders such as catecholaminergic polymorphic ventricular tachycardia (CPVT) are an important cause of sudden cardiac death (SCD) among young individuals.[1] Patients with CPVT have a normal 12-lead ECG and a structurally normal heart.[2] However, in the setting of increased sympathetic activity such as exercise or emotions, these patients display progressive ventricular ectopy of escalating complexity that may include bidirectional or polymorphic ventricular arrhythmias (VAs) and may lead to SCD.[2] The exercise stress test (EST) is the gold standard to establish the diagnosis of CPVT.[3] Young age at diagnosis, aborted cardiac arrest (ACA), and the complexity of VAs have been identified as predictors of risk of arrhythmic events in patients with CPVT.[4] However, in many patients, the risk of future arrhythmic events cannot accurately be estimated.

Heart rate behavior during exercise and recovery from exercise is mediated chiefly by the balance between the two components of the extrinsic autonomic nervous system (ANS): the sympathetic and parasympathetic branches.[5] The ANS has long been known to play a role in arrhythmogenesis and cardiac electrical stability.[6] This was first demonstrated in a study associating SCD in postmyocardial infarction patients with reduced heart rate variability and baroreflex sensitivity—both measures of the ANS.[7] A contrary observation was seen in a South African founder population of patients with congenital long-QT syndrome (LQTS) type 1. Here, subjects with strong autonomic reflexes, assessed by baroreflex sensitivity[8] and accentuated heart rate recovery (HRR),[9] had a higher probability of being symptomatic.

Since patients with LQT1 and CPVT both have arrhythmic events under circumstances of increased sympathetic activity, we hypothesized that CPVT patients with strong autonomic reflexes may also be at increased risk for arrhythmic events. Here, we studied the association between HRR and arrhythmic events in patients with CPVT.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design, Setting, and Population

The study population was derived from the International CPVT Registry. This is a retrospective, multicenter cohort study instituted in 2014 by the Academic Medical Center (Amsterdam, the Netherlands), which has included patients with CPVT from 25 international centers to date. The diagnosis of CPVT is based on the clinical phenotype and genetically confirmed by the identification of a pathogenic CPVT-associated mutation, primarily in the *RYR2*-encoded ryanodine receptor/calcium release channel (CPVT1), according to the expert consensus guidelines.[3] All centers received institutional review board approval for this type of study.

Deidentified clinical and genetic data were recorded on specifically designed web-based forms both at baseline evaluation and during follow-up. Detailed information was required regarding the first available EST without antiarrhythmic drugs (AADs), in particular β-blockers, and the first EST performed on the maximal tolerable dose of β-blockers.

For this study, we selected patients from the International CPVT Registry who had an EST performed without AAD and with available information about the maximum heart rate (HR_{max}) reached during exercise and the heart rate during the first minute of recovery (n=267). Of these, we excluded patients who were over the age of 65 years at the time of EST because of the known negative correlation between age and vagal reflexes in this age group. To guarantee an appropriate chronotropic competence and minimize potential confounding factors due to different EST protocols used across the study population, we excluded patients who did not reach 80% of their predicted HR_{max} (calculated by age and sex). The available 12-lead ECG traces of the EST of patients reported to have both complex VAs during the EST and either a maximum HR value in the higher decile or an HRR value in the lower decile were directly inspected. If supraventricular or ventricular arrhythmias were found to affect the maximum HR or the recovery HR (impossible to determine the sinus node activity), the patients were excluded from the analysis (1 patient with complex VAs and 1 patient with atrial arrhythmias were excluded; Figure 1).

Symptomatic patients were defined as patients who had experienced an arrhythmic syncope or ACA before CPVT was diagnosed. Asymptomatic patients had to be at least 15 years old at the time of the EST and off AAD. After the EST without AAD, we followed the patients until their first arrhythmic event after diagnosis or date of last contact. Arrhythmic events during follow-up were defined as arrhythmic syncope, ACA, appropriate ICD shock, or SCD.

EST Evaluation

ESTs of the patients included in the present study were performed between April 1995 and March 2017. A multistage fatigue-limited EST was performed according to local protocols. HR decrease during the recovery phase was calculated as the difference (Δ) in HR between the values recorded at peak exercise (HR_{max}) and those recorded one ($HRR_{@1'}$) and 2 ($HRR_{@2'}$) minutes after termination of exercise and is abbreviated by ΔHRR1′ and ΔHRR2′. HR increase was defined as the difference between the HR at peak exercise and the pretest HR.

Severity of VAs on the EST was scored according to the worst VA noted and was categorized into the following 5 categories: no VAs, single ventricular premature beats only, bigeminal ventricular premature beats, couplets, nonsustained ventricular tachycardia (VT), or sustained VT. Couplets, nonsustained VT, and sustained VT were considered complex VAs.

Statistical Analysis

Data were analyzed using IBM SPSS statistics database (released 2011, IBM SPSS Statistics for Windows, version 24; IBM Corp, Armonk, NY) and with R, version 3.4.3 (The R Project for Statistical Computing).

We performed 3 analyses. The first and second analyses assessed potential correlations between characteristics of the first EST without AAD and the first available EST on the maximal tolerable dose of β-blockers and the presence of symptoms before these ESTs. The third analysis assessed potential correlations between characteristics of the first EST without AAD and the presence of arrhythmic events after this EST.

Clinical parameters are presented for the entire study population, as well as for the study population stratified by symptom status. Continuous variables are presented as median (interquartile range [IQR]), were inspected for normality of the distribution, and compared by the Student *t* test or the Mann-Whitney *U* test where appropriate. Categorical variables are expressed as absolute and relative frequencies and were compared with the χ^2 test.

ΔHRR had a nonlinear relationship with the occurrence of symptoms before diagnosis. Therefore, we dichotomized this variable at the upper tertile of its distribution to assess the association between ΔHRR and the presence of symptoms. Odds ratios (ORs) with 95% CIs were estimated by logistic regression. To compensate for possible correlation of characteristics between relatives within a family, generalized estimating equations with a logit link function and an exchangeable correlation structure were applied. Receiver operating characteristic curves were constructed, and the area under the curve was used to determine the performance of the ΔHRR in discriminating between symptomatic and asymptomatic cases. Sensitivity analyses were performed excluding the *RYR2* p.R420W mutation. We used the Kaplan-Meier method to provide survival estimates, which were assessed with the log-rank test. $P<0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 187 patients with CPVT from 95 families were included in the study (Table 1; Figure 1). The median age at the EST without AAD was 36 years (IQR, 19–47). Sixty-eight patients (36%) were symptomatic before diagnosis: 52 patients (76%) had an arrhythmic syncope and 16 patients (24%) an ACA as their worst symptom before diagnosis (median age at worst symptom, 14 years [IQR, 11–20]). Symptomatic patients were more often the familial proband (49% versus 8%; $P<0.001$) and were younger at the EST (23 [IQR, 12–39] versus 40 [IQR, 27–50] years; $P<0.001$). The vast majority of the patients (94.7%) had a CPVT1-causative variant in *RYR2* (Table I in the Data Supplement).

Heart Rate Recovery During Exercise Testing and Risk of Symptoms

Pretest HR, HR_{max}, and HR at the first ventricular premature beat were equal between symptomatic and asymptomatic patients (Table 1; Figure 2A). However, HRR after the cessation of exercise was different between the groups. Symptomatic patients had a lower $HRR_{@1'}$ (125 [IQR, 110–147] versus 143 [IQR, 129–154] beats/min; $P<0.001$) and $HRR_{@2'}$ (104 [IQR, 88–123] versus 120 [IQR, 107–134] beats/min; $P<0.001$). Significantly

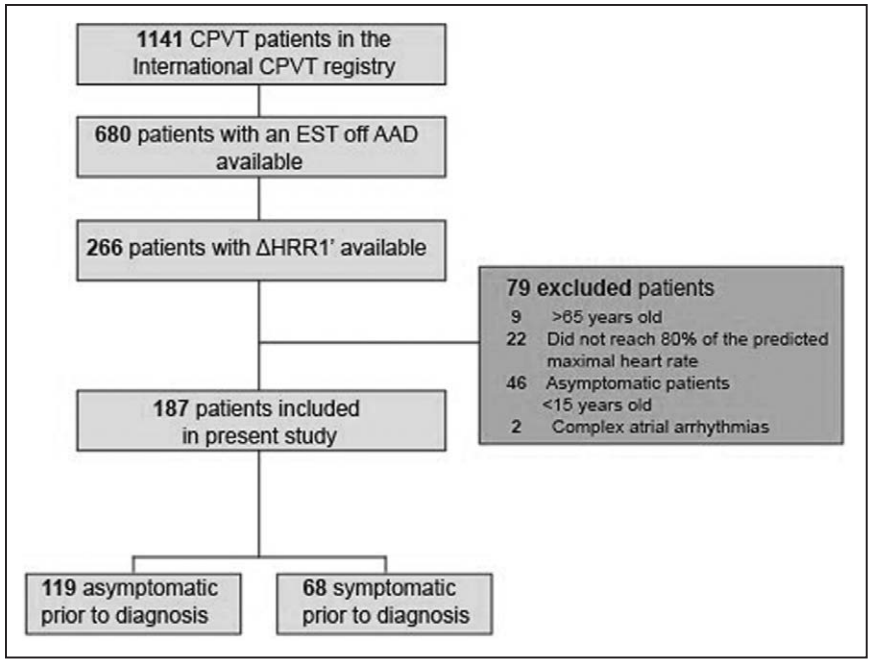

Figure 1. Flowchart of the included patients.
ΔHRR1′ indicates difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; AAD, antiarrhythmic drug; CPVT, catecholaminergic polymorphic ventricular tachycardia; and EST, exercise stress test.

higher values of ΔHRR1′ (43 [IQR, 25–58] versus 25 [IQR, 19–34] beats/min; $P<0.001$) and ΔHRR2′ (66 [IQR, 46–89] versus 49 [IQR, 36–58] beats/min; $P<0.001$) were observed in symptomatic patients (Figure 2B). Expressed as percentages, symptomatic and asymptomatic patients had a ΔHRR1′ decrease of 26% and 15% ($P<0.001$) and a ΔHRR2′ decrease of 40% and 28% ($P<0.001$), respectively.

Within the symptomatic patient group, there were no significant differences in ΔHRR1′ or ΔHRR2′ between patients who had an arrhythmic syncope and patients who had an ACA as their worst symptom before diagnosis (data not shown).

To assess the association between ΔHRR1′ and symptoms, we dichotomized the ΔHRR1′ value at ≥36 beats/min, which represented the upper tertile of its distribution. Indeed, patients in the upper tertile of ΔHRR1′ had an increased risk of being symptomatic (OR, 5.0 [95% CI, 2.6–9.8]; $P<0.001$). We considered age and sex to be potential confounders in the association between ΔHRR1′ and symptoms before diagnosis. In addition, since some patients were related to each other, we also considered relatedness to be a potential confounder. Following adjustment for age, sex, and relatedness, patients with a ΔHRR1′ ≥36 beats/min (representing the upper tertile of its distribution) still had an OR of 3.6 ([95% CI, 1.9–6.9]; $P<0.001$) of being symptomatic before diagnosis compared with patients with a ΔHRR1′ ≤36 beats/min (area under the curve, 0.74; Figure I in the Data Supplement).

Since 39 patients (21%) carried the p.R420W variant in *RYR2*, we performed a sensitivity analysis excluding patients with this mutation to see whether the results are not driven by this mutation. Results did not differ on the univariate analysis (OR, 4.7 [95% CI, 2.3–9.8]; $P<0.001$) or following adjustment for age, sex, and relatedness (OR, 3.4 [95% CI, 1.6–7.4]; $P<0.0014$).

VA Burden and Heart Rate Recovery

Next, we evaluated the relationship between VA burden and HRR. Fifty asymptomatic (42%) and 36 symptomatic (53%) patients had complex VAs (couplets, nonsustained VT, or sustained VT) as the worst VA on the EST ($P=0.19$; Table 1). Patients with complex VAs had a greater ΔHRR1′ (33 [IQR, 22–48] versus 27 [IQR, 20–36] beats/min; $P=0.01$) and ΔHRR2′ (56 [IQR, 40–76] versus 51 [IQR, 38–60] beats/min; $P=0.01$; Figure 3), compared with patients with simple VAs. We then stratified patients with complex VAs by symptom status. Symptomatic patients with complex VAs had a greater ΔHRR1′ (51 [IQR, 33–63] versus 26 [IQR, 19–37] beats/min; $P<0.001$) and ΔHRR2′ (76 [IQR, 57–97] versus 47 [IQR, 34–61] beats/min; $P<0.001$) than asymptomatic patients with complex VAs (Figure 4).

EST on Maximal Tolerable Dose of β-Blockers

An EST on the maximum tolerated dose of β-blockers was performed in a total of 112 patients (59.9%), and in 71 of these patients (63.4%), information about $HRR_{@1}$′ was available. Median interval between the baseline EST without AAD and the first EST on the maximal tolerable dose of β-blockers was 2.3 years (IQR, 0.6–5.5). The most frequently used β-blockers were metoprolol (31.0%) and bisoprolol (29.6%). Table II in the Data Supplement shows the β-blocker dosages.

Symptomatic patients were younger at the EST on β-blockers (33 [IQR, 16–45] versus 43 [IQR, 28–50] years; $P=0.02$; Table III in the Data Supplement). We

Table 1. Baseline Characteristics and Results of First EST Off Antiarrhythmic Drugs

	All (n=187)	Asymptomatic (n=119)	Symptomatic (n=68)	*P* Value
Proband	43 (23)	10 (8)	33 (49)	<0.001
Female sex	110 (59)	62 (52)	48 (71)	0.021
Age at exercise test, y	36 (19–47)	40 (27–50)	23 (12–39)	<0.001
Age at worst symptom, y	14 (11–20)	NA	14 (11–20)	
Syncope	52 (28)	NA	52 (76)	
ACA	16 (9)	NA	16 (24)	
Pretest HR, bpm	76 (66–87), n=181	76 (67–87), n=114	76 (65–86), n=75	0.970
HR at first VPB, bpm (n=135)*	126 (110–140), n=99/135	130 (112–149), n=56/84	120 (108–135), n=43/51	0.113
HR_{max}	169 (160–179)	168 (157–178)	173 (160–183)	0.074
Percentage of max predicted HR	94 (89–100)	95 (90–100)	92 (87–99)	0.030
Heart rate increase, bpm	93 (79–106)	91 (79–104)	98 (79–111)	0.116
$HRR_{@1'}$	137 (121–151)	143 (129–154)	125 (110–147)	<0.001
ΔHRR1′	28 (21–43)	25 (19–34)	43 (25–58)	<0.001
%ΔHRR1′	17 (12–25)	15 (11–20)	26 (15–33)	<0.001
$HRR_{@2'}$	115 (97–131), n=155	120 (107–134), n=96	104 (88–123), n=59	<0.001
ΔHRR2′	53 (39–68), n=155	49 (36–58), n=96	66 (46–89), n=59	<0.001
%ΔHRR2′	32 (24–40), n=155	28 (22–34), n=96	40 (28–49), n=59	<0.001
Worst VA				0.647
No arrhythmia	52 (28)	35 (29)	17 (25)	
VPB	25 (13)	17 (14)	8 (12)	
Bigeminy	24 (13)	17 (14)	7 (10)	
Couplet	34 (18)	21 (18)	13 (19)	
NSVT/VT	52 (28)	29 (24)	23 (34)	

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as median with IQR. All heart rates are expresses as beats per minute. Mann-Whitney *U* test and Student *t* test were used to calculate the *P* value where appropriate. Total numbers are included when they differ from those in the overall study group. ΔHRR1′ indicates absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; %ΔHRR1′, relative difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; %ΔHRR2′, relative difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; ACA, aborted cardiac arrest; bpm, beats per minute; EST, exercise stress test; HR, heart rate; HR_{max}, maximum heart rate; $HRR_{@1'}$, heart rate at the first minute of recovery; $HRR_{@2'}$, heart rate at the second minute of recovery; IQR, interquartile range; max, maximum; max, maximum; NA, not applicable; NSVT, nonsustained ventricular tachycardia; VA, ventricular arrhythmia; VPB, ventricular premature beat; and VT, ventricular tachycardia.

*Fifty-two patients did not have any VA on the EST.

did not observe any differences in heart rate profile during the EST or at 1 minute (ΔHRR1′, 33 [IQR, 24–44] versus 27 [IQR, 21–36] beats/min; *P*=0.16) or 2 minutes (ΔHRR2′, 50 [IQR, 43–63] versus 45 [IQR, 35–52] beats/min; *P*=0.098) in the recovery phase (Table III in the Data Supplement). Thirty-five patients (49.3%) achieved at least 80% of the predicted maximal heart rate, including 12 symptomatic patients (33.3%). In this subset, symptomatic patients had a significantly greater ΔHRR1′ (40 [IQR, 30–44] versus 25 [IQR, 21–35] beats/min; *P*=0.037) and a significantly greater ΔHRR2′ (58 [IQR, 46–68] versus 47 [IQR 36–55] beats/min; *P*=0.023; Table 2; Figure 5).

Arrhythmic Events After Diagnosis

After the first EST off AAD and during a median follow-up of 3.5 years (IQR, 1.1–7.4), 10 patients (5.3%) experienced an arrhythmic event: 6 patients (3.2%) experienced an appropriate implantable cardioverter defibrillator shock and 4 (2.1%) had an arrhythmic syncope. Patients with a ΔHRR1′ in the upper tertile of its distribution had significantly more arrhythmic events (n=7) after diagnosis as compared with patients in the combined lower and middle tertile (n=3; *P*=0.045; Figure 6).

DISCUSSION

Our findings, obtained in a relatively large multicenter cohort of patients with CPVT, indicate that the magnitude of HRR both at 1 and 2 minutes after the cessation of exercise to at least 80% of maximum predicted heart rate identified CPVT patients more likely to have been symptomatic before diagnosis (and thus before the initiation of AADs). Patients with a large ΔHRR1′ were 5× more likely to have been symptomatic before diagnosis. Furthermore, patients with a larger ΔHRR1′ and ΔHRR2′ were also more likely

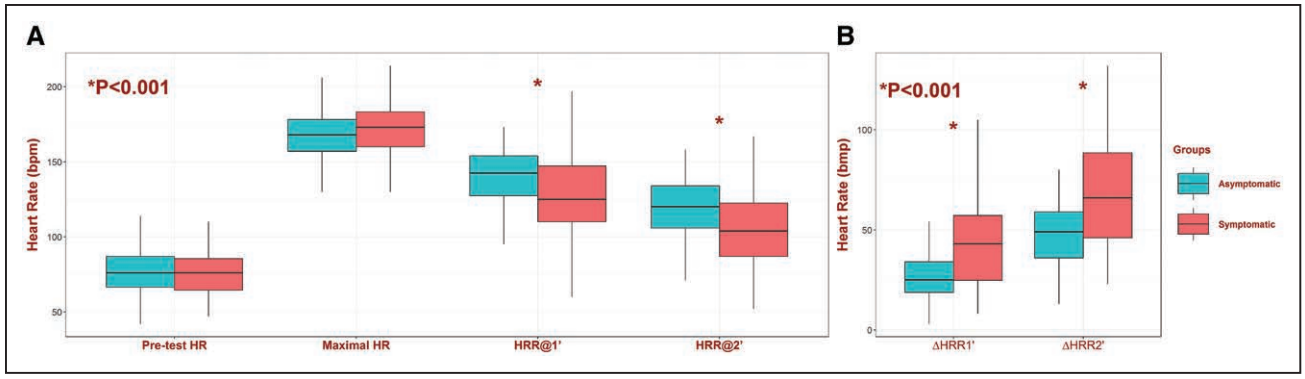

Figure 2. Exercise test parameters without antiarrhythmic drugs.
Comparison of heart rates (HRs) in symptomatic and asymptomatic patients at different points of exercise testing without antiarrhythmic drugs (**A**) and ΔHRR1′ and ΔHRR2′ (**B**). Mann-Whitney *U* test and Student *t* test were used to calculate *P* where appropriate. ΔHRR1′ indicates absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; bpm, beats per minute; $HRR_{@1}$′, heart rate at the first minute of recovery; and $HRR_{@2}$′, heart rate at the second minute of recovery.

to have complex VAs during the first EST off AAD. These results could also be confirmed in the EST on a maximal tolerable dose of β-blockers. Finally, in an analysis that was unadjusted for potential confounders, patients with a ΔHRR1′ in the upper tertile of its distribution (ie, ≥36 beats/min) had significantly more arrhythmic events as compared with patients in the other tertiles after diagnosis.

Autonomic Reflexes in the General Population

The heart rate changes observed during exercise and the recovery from exercise are mediated by the interplay between the sympathetic and the parasympathetic limbs of the ANS. Therefore, the EST can be considered as a simple and economic tool to indirectly assess cardiac autonomic reflexes. Based on studies in animals and healthy humans, the reactivation of the vagal nerve is considered the main force of these heart rate changes during the first 4 minutes of the recovery from exercise.[10]

In stark contrast to the observations in this CPVT cohort in this present study, multiple associations between an increased risk of SCD and reduced vagal activity or increased sympathetic activity have been identified over the years. Clinical studies in different settings consistently showed that a lower ΔHRR1′ was an independent predictor of both cardiovascular and all-cause mortality in middle-aged individuals.[11,12] The Paris Prospective Study was the largest study to assess the relationship between heart rate profile during exercise and recovery from exercise and a risk for lethal arrhythmias.[13] During a 23-year follow-up period, the authors found a 2-fold increase in the risk of sudden death among those with a ΔHRR1′ in the lowest quintile (<25 beats/min) as compared with the highest quintile (>40 beats/min). The underlying mechanism of this association remains largely elusive.

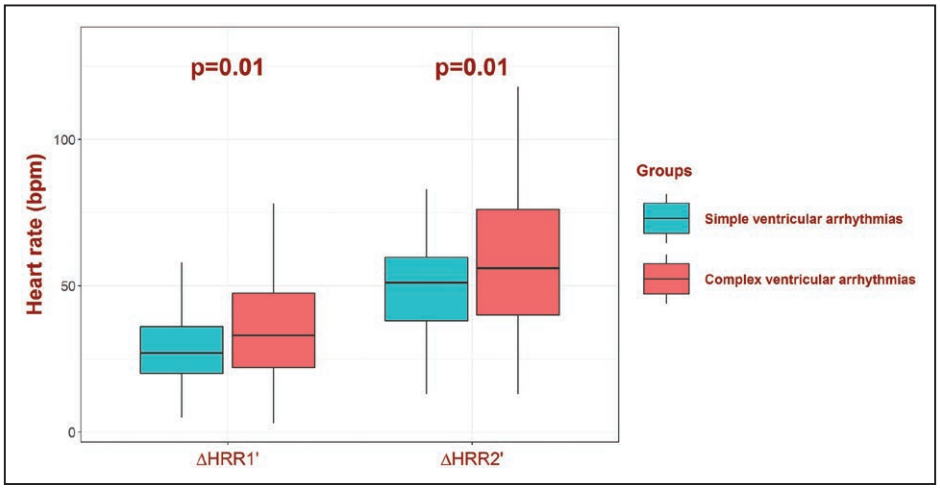

Figure 3. Comparison between ΔHRR1′ and ΔHRR2′ for patients with simple and complex ventricular arrhythmias.
Mann-Whitney *U* test and Student *t* test were used to calculate *P* where appropriate. ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; and bpm, beats per minute.

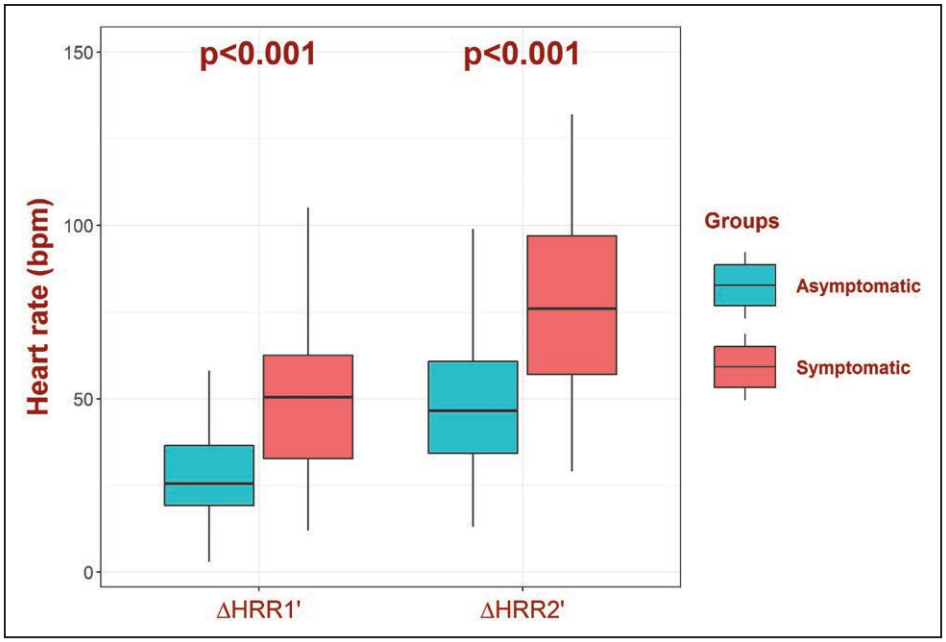

Figure 4. The behavior of the ΔHRR1′ and ΔHRR2′ in patients with complex ventricular arrhythmias stratified by symptom status. Mann-Whitney *U* test and Student *t* test were used to calculate *P* where appropriate. ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; and bpm, beats per minute.

Autonomic Reflexes in Inherited Arrhythmia Disorders

Due to the well-documented influences of the ANS on arrhythmogenesis and cardiac electrical stability, there is a strong rationale to assess autonomic reflexes in inherited arrhythmia disorders such as congenital LQTS and CPVT.

In 2008, Schwartz et al[8] assessed the impact of the ANS in a South African founder population harboring the KCNQ1-A341V mutation causing LQT1. LQT1 is caused by loss-of-function mutations in the *KCNQ1*-encoded Kv7.1 potassium channel, which provides the slowly activating delayed rectifier current (I_{Ks}).[14] The authors suggested that strong autonomic reflexes, assessed through baroreflex sensitivity, may be detrimental in the setting of an intrinsically increased cardiac susceptibility to both catecholamines and abrupt heart rate changes. In a subsequent study, the authors were able to replicate this finding using a simpler clinical tool: HRR.[9] In this study, ΔHRR1′ was also assessed in LQTS patients with preserved I_{Ks} (LQTS types 2 and 3), and no differences between symptomatic and asymptomatic patients were observed. Finally, they found a good correlation between baroreflex sensitivity, determined by the phenylephrine method, and ΔHRR1′ with a similar ability to predict the risk of life-threatening arrhythmias (area under the curve>0.70).[9]

While the suggested proarrhythmogenic mechanism in LQT1 is through the effects of sympathetic activation on I_{Ks},[9] in CPVT, the proarrhythmogenic diastolic calcium leakage from the sarcoplasmic reticulum becomes more pronounced in the setting of high sympathetic tone, ultimately resulting in delayed afterdepolarizations that may lead to triggered arrhythmias. At the end of exercise, there is an instantaneous rebound of vagal reflexes while abundant catecholamines are still in the heart. This increases the heterogeneity of recovery periods, which may confer increased susceptibility for reentrant arrhythmias (VT and fibrillation).[15] In addition, the higher the sympathetic activation during exercise, the higher the heart rate will be at peak exercise. The amount of heart rate increase at peak, combined with the strength of vagal reflexes, will determine the delta and thereby the greatest disparity in the recovery period. Interestingly, and probably related to the concept just expressed, suppression of the vagal activity by atropine had antiarrhythmic effects in Casq2 knockout and *RyR2*$^{R4496C/+}$ mice.[16] Since patients with inherited arrhythmia disorders are often young and otherwise healthy, the variability in HRR mainly reflects a genetic effect,[17] leaving physical training as the most significant nongenetic confounding factor. Indeed, the genetic traits controlling autonomic reflexes are inherited independently from the mutations causing the inherited arrhythmia disorders and, therefore, may act as an independent modifier of arrhythmic risk.

In our study, we focused on those patients who reached at least 80% of their predicted HR_{max} during the EST, because the steepness of HRR is influenced by exercise intensity and HR_{max}.[18] The mean HR_{max} at the EST without AAD in our cohort (169 beats/min) was similar to HR_{max} in previously published CPVT populations[19–21] but higher than reported by Crotti et al[9] in their LQT1 population (145 beats/min). This may reflect the fact that CPVT patients are exercised maximally to try to

Table 2. Results of First EST While on Maximal β-Blocker Dose

	All (n=35)	Asymptomatic (n=23)	Symptomatic (n=12)	*P* Value
Proband	9 (26)	3 (13)	6 (50)	0.049
Women	22 (63)	12 (52)	10 (83)	0.149
Age at EST, y	40 (26–51)	41 (26–51)	39 (24–45)	0.297
Pretest HR	71 (61–83), n=34	71 (60–83), n=22	73 (61–82)	0.896
HR at first VPB (n=30)*	132 (114–137), n=20/30	132 (119–139), n=12/20	132 (106–136), n=8/10	0.956
HR_{max}	153 (148–162)	150 (146–161)	161 (155–164)	0.377
Percentage of max predicted HR	88 (84–93)	87 (84–93)	90 (85–94)	0.322
$HRR_{@1'}$	125 (113–136)	126 (116–140)	119 (106–127)	0.230
ΔHRR1′	30 (23–44)	25 (21–35)	40 (30–44)	0.037
%ΔHRR1′	18 (14–27)	17 (13–20)	25 (19–30)	0.040
$HRR_{@2'}$	108 (93–116), n=33	109 (101–116), n=21	97 (83–109)	0.092
ΔHRR2′	50 (40–59), n=33	47 (36–55), n=21	58 (46–68)	0.023
%ΔHRR2′	30 (26–38), n=33	28 (24–34), n=21	37 (30–47)	0.020

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as median with IQR. All heart rates are expressed as beats per minute. Mann-Whitney *U* test and Student *t* test were used to calculate the *P* value where appropriate. Total numbers are included when they differ from those in the overall study group. ΔHRR1′ indicates absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; %ΔHRR1′, relative difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; %ΔHRR2′, relative difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; EST, exercise stress test; HR, heart rate; HR_{max}, maximum heart rate; $HRR_{@1'}$, heart rate at the first minute of recovery; $HRR_{@2'}$, heart rate at the second minute of recovery; IQR, interquartile range; VA, ventricular arrhythmia; and VPB, ventricular premature beat.

*Five patients did not have any VA on the EST.

elicit repetitive VAs to determine the arrhythmic risk of the patient. This may also explain why the mean values of ΔHRR1′ that we observed in our cohort are higher than those observed in the LQT1 population[9] but in line with ΔHRR1′ in healthy individuals with comparable age and exercise intensity.[22]

We performed a subset analysis in 71 patients in whom data on an EST on β-blocker therapy including information about the $HRR_{@1'}$ was available. When we selected the patients who had achieved at least 80% of the predicted heart rate, we found that symptomatic patients had a significantly larger ΔHRR2′ and a trend toward a larger ΔHRR1′. Kannankeril et al[10] evaluated the parasympathetic effects on HRR in healthy subjects and concluded that the effects are most pronounced in the first 4 minutes of the recovery phase. In addition, Sundaram et al[23] evaluated the contribution of the sympathetic withdrawal to $HRR_{@1'}$. In that study, they found that β-adrenergic withdrawal is not a significant factor in the $HRR_{@1'}$. These results suggest that EST in the presence of β-blockers should have no effect on reinstitution of vagal tone and, therefore, no effect on HRR as compared with HRR in the absence of AAD. In addition, since heart rate declines exponentially after exercise, ΔHRR1′ depends on the HR_{max} achieved and is not an optimal marker to assess HRR during submaximal exercise.

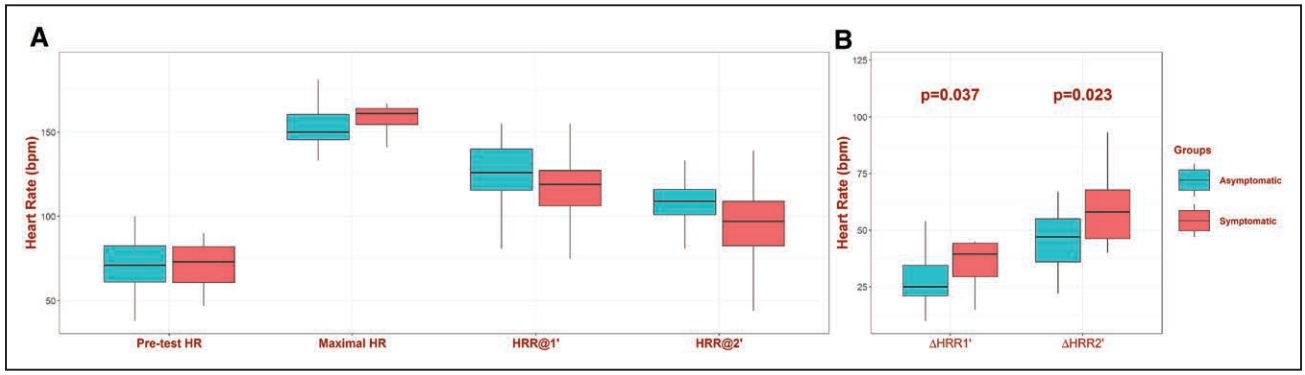

Figure 5. Exercise test parameters on β-blockers.
Comparison of heart rates in symptomatic and asymptomatic patients at different points of exercise testing on the maximum tolerable dose of β-blockers (**A**) and ΔHRR1′ and ΔHRR2′ (**B**). Mann-Whitney *U* test and Student *t* test were used to calculate *P* where appropriate. ΔHRR1′ indicates absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; ΔHRR2′, absolute difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 2 min after termination of exercise; bpm, beats per minute; $HRR_{@1'}$, heart rate at the first minute of recovery; and $HRR_{@2'}$, heart rate at the second minute of recovery.

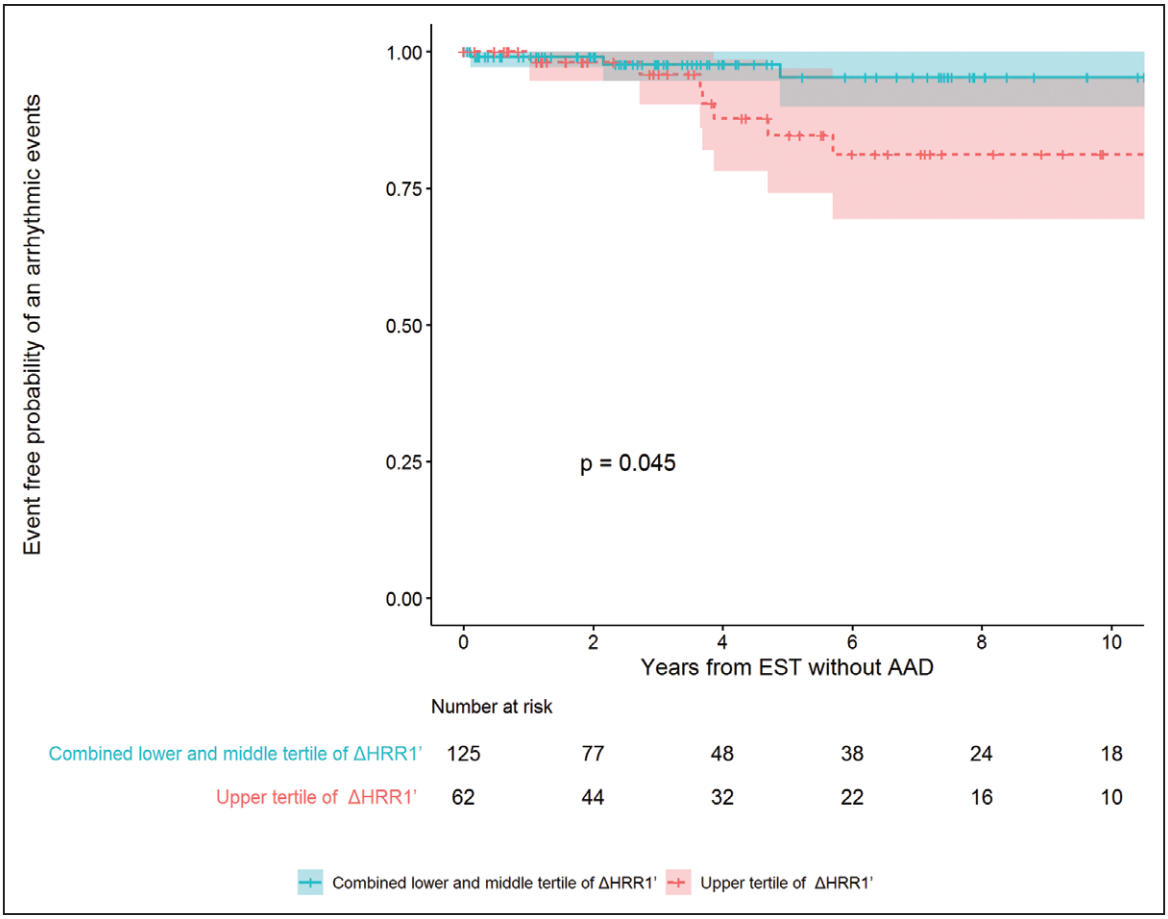

Figure 6. Comparison in arrhythmic events after the exercise stress test without antiarrhythmic drugs of upper tertile ΔHRR1′ vs rest group.

Kaplan-Meier curves displaying arrhythmic events after the exercise stress test without antiarrhythmic. ΔHRR1′ indicates difference (Δ) in heart rate between the values recorded at the peak exercise and those recorded 1 min after termination of exercise; AAD, antiarrhythmic drug; and EST, exercise stress test.

Therefore, it is most likely that the different protocols used in our study play a role in these findings.

Clinical Implications

Our findings have important clinical implications. We were able to demonstrate that HRR in the EST without AAD is associated with the presence of arrhythmic events before the diagnosis (and thus before the initiation of medical therapy) and the severity of EST-induced VAs in a large cohort of CPVT patients. Considering the fact that ≈42% of the asymptomatic patients had an EST with complex VAs despite never having experienced an arrhythmic event, our data may be a useful tool for refined risk stratification. Additionally, at a comparable intensity of exercise, HRR is a reproducible measurement in the same subject.[24] For example, in asymptomatic genotype-positive relatives, the presence of strong vagal tone in the absence of VAs during the first EST could be an argument to be more aggressive with β-blocker therapy than in those without strong vagal activation post-exercise.

Limitations of the Study

Due to the retrospective nature of the study, not all parameters were available for all patients. In a relatively large proportion of patients in the International CPVT Registry, an EST off AAD or HRR parameters at EST off AAD were not available for analysis. Patients with missing HRR parameters at EST off AAD were significantly younger on the EST without AAD and more often symptomatic. Therefore, a selection bias cannot be excluded. Due to the multicenter and retrospective nature of the study, different types of EST and recovery protocols were used. In addition, we cannot fully exclude that in some patients the EST was terminated due to VAs rather than due to fatigue. However, we only included patients who were exercised to at least 80% of their maximal predicted heart rate to account for the different exercise protocols and the possibility of a submaximal EST. A large proportion of the patients (77%) include family members of the familial proband. These patients are typically diagnosed through cascade screening and are, therefore, diagnosed at a relatively old age. This patient group may manifest

with a milder phenotype with less arrhythmic risk compared with the proband who often present at a younger age. However, our population likely represents the general CPVT population because disease severity may have been overestimated in the earlier cohorts.[2] Finally, due to the low number of arrhythmic events during follow-up in the subset of patients analyzed, we were unable to build a multivariable model for predictors of arrhythmic events after diagnosis.

ARTICLE INFORMATION

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