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Predicting Utility of Exercise Tests Based on History/Holter in Patients with Premature Ventricular Contractions

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Abstract

Premature ventricular contractions (PVCs) are considered benign in patients with structurally normal hearts, particularly if they suppress with exercise. Catecholaminergic polymorphic ventricular tachycardia (CPVT) requires exercise testing to unmask the malignant phenotype. We

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Conflict of interest None.

studied risk factors and Holter monitor variables to help predict the necessity of exercise testing in patients with PVCs. We retrospectively reviewed 81 patients with PVCs that suppressed at peak exercise and structurally normal hearts referred to the exercise laboratory in 2011. We reviewed 11 patients from 2003 to 2012 whose PVCs were augmented at peak exercise (mean age 13 ± 4 years; 52 % male, 180 exercise studies). We recorded clinical risk factors and comorbidities (family history of arrhythmia or sudden unexpected death [SUD], presence of syncope) and Holter testing parameters. Family history of VT or SUD ($P = 0.011$) and presence of VT on Holter ($P = 0.011$) were significant in predicting failure of PVCs to suppress at peak heart rate on exercise testing. Syncope was not statistically significant in predicting suppression ($P = 0.18$); however, CPVT was diagnosed in four patients with syncope during exercise. Quantity of PVCs, Lown grade, couplets on Holter, monomorphism, and PVC elimination at peak heart rate on Holter were not predictors of PVC suppression on exercise testing. Patients with syncope during exercise, family history of arrhythmia or SUD, or a Holter monitor showing VT warrant exercise testing to assess for CPVT.

Keywords

Catecholaminergic polymorphic ventricular tachycardia; Exercise testing; Holter monitor; Premature ventricular contractions

Introduction

In patients with a structurally normal heart, premature ventricular contractions (PVCs) are benign if they suppress with exercise [4]. Most pediatric cardiologists assess ventricular function and structure with a chest radiograph or echocardiogram. However, the type of exercise testing that cardiologists order varies from informal exercise (jumping jacks in the office) to formal exercise testing in a cardiopulmonary exercise lab. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, lethal, genetic channelopathy characterized by adrenergically mediated polymorphic ventricular tachycardia induced by exercise or emotional stress in otherwise healthy children. CPVT often requires an exercise test (ETT) to unmask the phenotype [7]. No data exist to determine the criteria for when to order an ETT in children presenting with PVCs. We studied risk factors and Holter monitor variables to help predict the necessity of exercise testing in patients with PVCs.

Methods

After institutional review board permission was obtained, we retrospectively studied 81 patients with PVCs on electrocardiogram (ECG) or Holter monitor, eight patients with CPVT, and three patients whose PVCs augmented at peak exercise (positive condition). These 92 patients had a total of 180 exercise studies (86 on treadmill, 94 on bike ergometer) at our hospital (mean age 13 years [SD, 4]; 52 % male). We obtained the majority of patients by taking all patients referred to the exercise laboratory for testing for PVCs in 2011. We added the eight CPVT patients in our practice to discover how these patients compare and contrast with the patients with PVCs. All these patients had tests from 2003 to 2012. All patients had ECGs with normal QTc intervals, no evidence of Brugada syndrome, no evidence of hypertrophy or strain, and no evidence of coronary artery disease. All patients

had normal ECGs and underwent a 24-h Holter monitor (Spacelab, Issaquah, WA) and maximal ETT. The Holter monitor report printed out peak heart rate (PHR) rhythm for 1 min. We recorded sex; age at first presentation; family history of arrhythmia or sudden unexpected death (SUD); symptoms (syncope); quantity of PVCs; Lown grade; presence of monomorphism; presence of couplets/triplets (VT) on Holter; and whether the PVCs eliminated on Holter monitor at PHR on the basis of the 1-min print out, defined as the patient having PVCs during that 1 min of maximal heart rate. Using augmentation of PVCs (PVCs becoming more frequent with exercise) on exercise testing as the dependent variable (positive condition), we tested whether each of the independent variables could predict elimination of PVCs during exercise testing. CPVT was diagnosed by genetic testing or presence of polymorphic VT on exercise testing. Accelerated idioventricular rhythm or slow VT was diagnosed by ventricular tachycardia at a rate of 120 bpm or more or at a rate only slightly faster than the sinus rate on Holter monitor or ETT [3]. Beta blocker treatment was prescribed in three patients before performing the ETT: one with hypertension and two with CPVT.

Definitions

A true positive Holter monitor test showed lack of PVC suppression at PHR defined as the patient having PVCs during the 1 min of maximal heart rate on ANY Holter. A true negative Holter monitor test was defined as the patient not having any PVCs on this maximal heart rate strip. A true positive Holter monitor test for VT was defined as three or more PVCs in a row. A true positive condition (dependent variable) was defined as the patient having PVCs that did not suppress on ANY ETT—the PVCs increased in frequency with exercise. A true negative condition meant that the patient's PVCs suppressed or attenuated during exercise testing.

Exercise Testing

Patients were exercised on a previously calibrated, electronically braked cycle ergometer (VIA Sprint 150P; Sensormedics, Yorba Linda, CA). The pedaling rate was maintained at 75–85 rpm. During the ETT, continuous 12-lead ECG and blood pressure were monitored. All patients exercised to exhaustion. The patients were monitored for cardiac arrhythmia during the exercise period and for 5 min afterward. The workload was based on the patient's weight and sex. Boys underwent a workload of 0.33 W/kg/min rounded to the nearest 5 W. Girls underwent a workload of 0.30 W/kg/min rounded to the nearest 5 W. The initial workload was zero, which increased at 10, 15, 20, or 25 W/min, depending on the aforementioned formula. Additional data measured were weight, height, resting and PHR, respiratory rate, blood pressure, exercise time, and total work. Patients not able to use the cycle ergometer (usually because of small stature, inability to ride a bike, or symptoms while running) exercised on the treadmill (Series 2000 Treadmill; GE Marquette Medical Systems, Milwaukee, WI) according to a Bruce protocol [2].

Statistics

Two-sample unpaired student *t*-tests with unequal variances and the Fisher's exact test were used to compare the continuous demographic variables and Holter parameters between those whose PVCs suppressed and those whose PVCs did not suppress during ETT. Univariable

logistic regressions were employed to assess the predictive strength of each covariate (family history of arrhythmia/SUD, couplets on ETT, VT on first Holter, diagnosis of CPVT). The receiver operating curves (ROCs) and area under curve (AUC) estimates were reported. The multivariable logistic regression was performed to obtain the best subset of covariates that have the highest synergetic prediction accuracy.

Results

An irregular heart rate or PVCs on ECG was the reason for referral in 59/92 (64 %), syncope in 10/92 (11 %), chest pain in 9/92 (10 %), miscellaneous reasons in 10/92 (10 %, including two with VT and two with premature atrial contractions/chaotic atrial rhythm), and family history of SUD/CPVT in 4/92 (4 %) (demographics in Table 1). More than one ETT was performed in 20/92 (22 %); of these patients, 8/20 had CPVT—six after the first test was positive and two were repeated because of family history of CPVT or syncope. In three, the ETT was repeated for PVCs at peak exercise on the initial ETT. In nine, the test was repeated for gastric banding protocol, large burden of PVCs, test medication efficacy, s/p radiofrequency ablation to see if VT was still inducible, polymorphic VT on first ETT, a triplet at peak exercise, recheck of QTc interval, and for chest pain in two.

Two or more Holters were done in 51/92 (55 %). The PHR on Holter (average 151 ± 26 bpm) was less than the PHR on ETT (173 ± 22 bpm, $P < 2.2e-16$ by two-sample *t* test). Presence of VT on Holter ($P = 0.011$) or family history of either arrhythmia or SUD ($P = 0.011$) were significant in predicting failure of PVCs to suppress at PHR on ETT. Syncope was not statistically significant in predicting suppression ($P = 0.18$). However, in four patients with syncope with exercise, CPVT was present. One patient had syncope with exercise after his first ETT. Low grade, couplets on Holter, polymorphism, PVC elimination at PHR on Holter, and number of PVCs were not predictors of PVC suppression on ETT. Couplets on ETT were predictive ($P = 0.00013$) for a positive condition but were a surrogate of VT so were not helpful (Table 2). The ROCs were constructed. Using family history of arrhythmia or SUD and VT on first Holter, the ROC generated an AUC of 0.77 (Table 3; Fig. 1).

Of the 92 total patients, eight were diagnosed with CPVT after the initial cardiology visit. All eight CPVT patients had a positive ETT. In 6/8 patients with CPVT, the first ETT was positive. A second ETT was performed in the remaining 2/8 patients because of family history of CPVT or history of syncope. In the eight patients with CPVT, VT was present on Holter in 4/8—two on the first Holter ordered. In 3/4 with CPVT and VT on Holter, the ETT was positive for VT before the Holter and 1/4 with CPVT and VT had VT on their Holter before the ETT. Positive family history of SUD or CPVT was present in 5/8 patients with CPVT.

There were three non-CPVT patients with a positive ETT. One patient had idiopathic VT during exercise but did not have polymorphic VT at peak exercise and had VT on Holter monitor before ETT. Of the two patients whose PVCs did not suppress at peak exercise (one on the second ETT and one on the third ETT), neither was felt to have CPVT since their PVCs were unifocal. Neither of these two patients had VT on their Holter monitors.

Of those who did not have CPVT, 7/84 (8 %) had VT on Holter; of those, 6/7 did not have VT during ETT (one had idiopathic VT; see above). One patient had accelerated idioventricular rhythm on Holter but no VT on ETT. Of these seven patients, two were ablated successfully, two were treated with beta blockers, one was studied in the electrophysiology laboratory and was noninducible, one had a follow-up Holter that did not show VT, and one transferred care.

Discussion

We sought to predict which patients with PVCs will need ETT on the basis of history and Holter monitoring. On the basis of our data, patients with PVCs that present with a family history of arrhythmia or SUD warrant an ETT. This is consistent with the literature as there is a family history of SUD before age 40 years in 30 % of patients with CPVT [6]. Although syncope was not a statistically significant predictor of failure to suppress ectopy on ETT, four patients that had syncope with exercise did have CPVT, so this finding is highly specific and predictive. Suppression of PVCs at PHR on Holter monitor and other Holter parameters (besides VT) did not accurately predict whether PVCs would suppress during exercise testing. One explanation may be that the maximal achievable heart rate did not occur while wearing the Holter because the patients might not have been as motivated outside the exercise laboratory as in the laboratory.

Holter monitor tests were helpful in management of our patients. For the non-CPVT population, Holters are still helpful in detecting VT in patients who do not have VT on their ETT, which is helpful in the clinical management of these patients. This differs from the original paper by Jacobsen et al. [4], who did not recommend Holters in these patients. The Bethesda guidelines [1] suggest that a 24-h Holter may be helpful for athletes with PVCs if structural heart disease is present. On the basis of our data, patients with a strong family history of CPVT or exercise-induced syncope may require multiple ETTs or Holters before the test result is positive.

The incidence of PVCs in the adolescent population is as high as 35 % [6]. The Bethesda guidelines recommend exercise testing in athletes with PVCs. If the PVCs increase in frequency with exercise, the patient should be restricted from competitive sports [5]; however, if all adolescent athletes with PVCs undergo an ETT, exercise laboratories would be burdened with a very large number of tests. Our data may help lessen this burden on exercise laboratories as exercise testing provides added clinical information only if VT is present on Holter monitor, a positive family history for arrhythmia or SUD is present, or syncope during exercise has occurred.

Limitations

This was a retrospective chart review, so the true sensitivity and specificity of Holter parameters could not be assessed. A prospective study looking at patients presenting with PVCs is required to determine true sensitivity and specificity. Given of the rarity of the positive condition (PVCs that augment with exercise), this would require a large sample size. Another limitation is that the morphology of the PVCs (right ventricular outflow tract

or other origin) was not always available in the patient's chart. Thus, we could not tell if this may have been a predictor of a positive condition.

Recommendations

In patients with PVCs and a normal structural heart, a Holter monitor is a helpful part of the evaluation to document the burden of PVCs, complexity of the ventricular ectopy, and presence of VT. Patients with exertional syncope or family history of SUD, arrhythmia, or VT on Holter are most likely to have true pathology such as CPVT. For this subgroup, an ETT is indicated. More than one ETT may be needed to make the diagnosis in patients with these risk factors. Similarly, repeat Holter monitoring studies might uncover VT if missed on initial studies. Future larger prospective studies are indicated to predict exactly who needs ETT on the basis of Holter monitor and history.

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Fig. 1.
Multivariable logistic regression model for premature ventricular contraction suppression during exercise testing

Table 1

Demographic summary

Variable	Percentage	
Sex	<i>N</i>	
Female	44	(47.8 %)
Male	48	(52 %)
At time of first ETT		
Age (years)	13 ± 3.93	
Weight (kg)	55.3 ± 26.3	
Height (cm)	155.7 ± 20.7	
BMI (kg/m ²)	21.6 ± 6.43	
ETT mode	<i>N</i>	
Bike	94	(52 %)
Treadmill	86	(48 %)
Reason for referral	<i>N</i>	
Irregular HR/PVCs on ECG	59	(64 %)
Syncope	10	(11 %)
Chest pain	9	(10 %)
Family history of SUD/CPVT	4	(4 %)
Miscellaneous	10 ^a	
All Holter duration (hrs)	22.4 ± 6.12	
Family history arrhythmia/SUD	11 patients	
CPVT	5	
Grandfather had atrial fibrillation	1	
Father/PGM had PVCs	1	
Mother had WPW/SVTs/p RFA	1	
Mother had palpitations	1	
SUD in third cousin	1	
Maternal uncle died SUD	1	

ETT exercise test, *BMI* body mass index, *PVC* premature ventricular contractions, *HR* heart rate, *ECG* electrocardiogram, *CPVT* catecholaminergic polymorphic ventricular tachycardia, *PAC* premature atrial contraction, *SUD* sudden unexpected death, *PGM* paternal grandmother, *WPW* Wolff Parkinson White syndrome, *SVT* supraventricular tachycardia, *RFA* radiofrequency ablation

^aIncluded 2 VT, 2 PACs, 3 symptom related, 1 gastric banding, 1 chest pain/WPW, 1 murmur/dental clearance

Table 2

Predictors of positive condition

Categorical variable	<i>N</i>	<i>P</i> value
Family history of arrhythmia/SUD	<i>N</i>	0.011
No	81 (88 %)	
Yes	11 (12 %)	
Syncope (as reason for referral or symptom)	<i>N</i>	0.18
No	79 (88.8 %)	
Yes	10 (11.2 %)	
No data	3	
VT on Holter (ever)	<i>N</i>	0.011
No	81 (88 %)	
Yes	11 (12 %)	
Couplets on ETT	<i>N</i>	0.00013
No	84 (91.3 %)	
Yes	8 (8.7 %)	
Lown Grade	<i>N</i>	0.322536 *
0	9 (10 %)	
1	18 (20 %)	
2	34 (37.8 %)	
3	2 (2.2 %)	
4a	15 (16.7 %)	
4b	12 (13.3 %)	
No data	2	
Monomorphism	<i>N</i>	0.6335
No	17 (21 %)	
Yes	64 (79 %)	
No data	11	
PVC elimination at PHR on Holter	<i>N</i>	1
No	29 (32.6 %)	
Yes	60 (67.4 %)	
No data	3	
Couplets on Holter	<i>N</i>	0.2385
No	62 (69.7 %)	
Yes	27 (30.3 %)	
No data	3	
Number of PVCs	Absolute #	0.1846
Mean	8633.7	
SD	13354	
No data	2	
% PVCs	Percentage	0.0659
Mean	7 %	

Categorical variable	<i>P</i> value
SD	10.2 %
No data	5

N, total number of patients. Percentages represent % of available data. *P* value is patients whose PVC did not get worse (disappeared/attenuated) versus those whose augmented.

* *P* value determined by logistic regression. All other *P* values from Fisher exact test

ETT exercise test, *PVC* premature ventricular contractions, *VT* ventricular tachycardia, *PAC* premature atrial contraction, *SUD* sudden unexpected death, *PHR* peak heart rate

Table 3

Univariable and multivariable logistic regressions results

Variable	Odds ratio	P value	95 % confidence interval	AUC
Univariable model				
Family history of arrhythmia/SUD	0.12	0.01	0.024, 0.552	0.68
Couplets on ETT	0.03	0.00	0.004, 0.161	0.76
CPVT ^a	0.00	0.00	0.000, 0.030	0.88
VT on first Holter	0.11	0.01	0.020, 0.641	0.66
Final multivariable model				
Family history of arrhythmia/SUD ^b	0.08	0.005	0.013, 0.481	0.77
VT on first Holter	0.12	0.029	0.016, 0.859	

AUC area under the curve, *ETT* exercise test, *CPVT* catecholaminergic polymorphic ventricular tachycardia, *VT* ventricular tachycardia, *SUD* sudden unexpected death

^a CPVT not in final multivariable model

^b Referent group = No family history of arrhythmia or SUD