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ORIGINAL RESEARCH

VENTRICULAR TACHYCARDIA

The Diagnostic Utility of Holter Monitoring in Catecholaminergic Polymorphic Ventricular Tachycardia

Borna Naderi,[a] Brianna Davies, MSc,[a] Habib Khan, MD,[b] Shubhayan Sanatani, MD,[c] Jason G. Andrade, MD,[a] Matthew T. Bennett, MD,[a] Nathaniel M. Hawkins, MBChB, MD,[a] Santabhanu Chakrabarti, MD,[a] John A. Yeung-Lai-Wah, MD,[a] Marc W. Deyell, MD, MSc,[a] Zachary W.M. Laksman, MD,[a] Thomas M. Roston, MD, PhD,[a] Andrew D. Krahn, MD[a]

ABSTRACT

BACKGROUND Holter monitoring may raise suspicion of an underlying catecholaminergic polymorphic ventricular tachycardia (CPVT) diagnosis. Although not a primary investigation for CPVT, Holter monitoring is ubiquitously used as a diagnostic tool in the heart rhythm clinic.

OBJECTIVES The objective of this study was to explore Holter monitoring in CPVT diagnosis.

METHODS This retrospective cohort study analyzed off-therapy Holter monitoring from 13 ryanodine receptor 2–positive CPVT and 34 healthy patients from the Canadian Hearts in Rhythm Organization national registry. Using the Edwards method, the ratio of ambient-maximum heart rate during Holter monitoring was correlated with exertion level to separate premature ventricular contractions (PVCs) during periods of adrenergic and nonadrenergic stress. A receiver operating characteristic curve analysis determined the optimal threshold for isolating CPVT-induced PVCs during adrenergic states.

RESULTS PVC burden differed between groups ($P = 0.001$) but was within population norm, suggesting ambient PVCs are uncommon in CPVT. CPVT patients had higher PVC counts than healthy controls ($P = 0.002$), with a different distribution based on adrenergic state. The optimal threshold for separating PVCs into periods of adrenergic and nonadrenergic stress in CPVT patients was 76% of the maximum heart rate during the monitoring period. Compared with healthy controls, CPVT patients had a higher PVC count, limited to periods of adrenergic stress, defined by >76% maximum heart rate threshold ($P = 0.002$; area under the receiver operating characteristic curve: 0.84). Below this threshold, there was no significant PVC difference ($P = 0.604$).

CONCLUSIONS Holter monitor PVC counts alone are inadequate for CPVT diagnosis, owing to the adrenergic nature of the disease. Quantifying PVC prevalence at a heart rate threshold >76% identified CPVT with moderate sensitivity (69%) and high specificity (94%). (JACC Clin Electrophysiol. 2024;10:2337–2344) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Centre for Cardiovascular Innovation, St. Paul's and Vancouver General Hospitals, University of British Columbia, Vancouver, British Columbia, Canada; [b]Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, Western University, London, Ontario, Canada; and the [c]British Columbia Children's Hospital, Vancouver, British Columbia, Canada.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver operating characteristic curve

CPVT = catecholaminergic polymorphic ventricular tachycardia

ECG = electrocardiogram

ETT = exercise tolerance test

HiRO = Hearts in Rhythm Organization

PVC = premature ventricular contractions

ROC = receiver operating characteristic

RYR2 = ryanodine receptor 2

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited arrhythmia condition that manifests as polymorphic and bidirectional ventricular tachyarrhythmias during periods of adrenergic stimuli.[1] Clinical symptoms typically begin during childhood and early adulthood, and can include palpitations, presyncope, syncope, and cardiac arrest. The diagnosis requires the presence of reproducible exercised-induced ventricular arrhythmia, typically assessed using exercise treadmill testing (ETT),[1,2] in the setting of a structurally normal heart and normal resting electrocardiogram (ECG).[3] Damaging variants in Ryanodine Receptor 2 (RYR2), which lead to excessive calcium release, are identified in the majority of CPVT cases.[4]

Symptoms of arrhythmia often prompt clinicians to request prolonged ECG monitoring, such as a 24-h Holter monitor during the initial evaluation. Frequent ambient premature ventricular contractions (PVCs) may raise suspicion for an underlying inherited arrhythmia or cardiomyopathy. The utility of this from a diagnostic perspective is unknown for CPVT. Exploring the potential diagnostic utility of Holter monitoring is relevant given the frequency with which Holter monitoring is ordered in the clinic, CPVT's potential lethality, and its tendency to be misdiagnosed or underdiagnosed.[5] Holter monitoring may also be useful in patients with suspected CPVT who cannot undergo exertional testing, often because of young age, intellectual dysfunction, or neurologic injury after cardiac arrest.[5-7] Furthermore, genetically elusive and RYR2-positive CPVT may differ in terms of susceptibility to arrhythmia and heritability of disease.[8] Because Holter monitoring is so ubiquitously used in clinical practice, describing its test characteristics in CPVT is highly relevant. We sought to compare the characteristics of PVCs in CPVT patients to healthy controls during Holter monitoring, and potentially define a Holter monitor phenotype that associates with CPVT.

METHODS

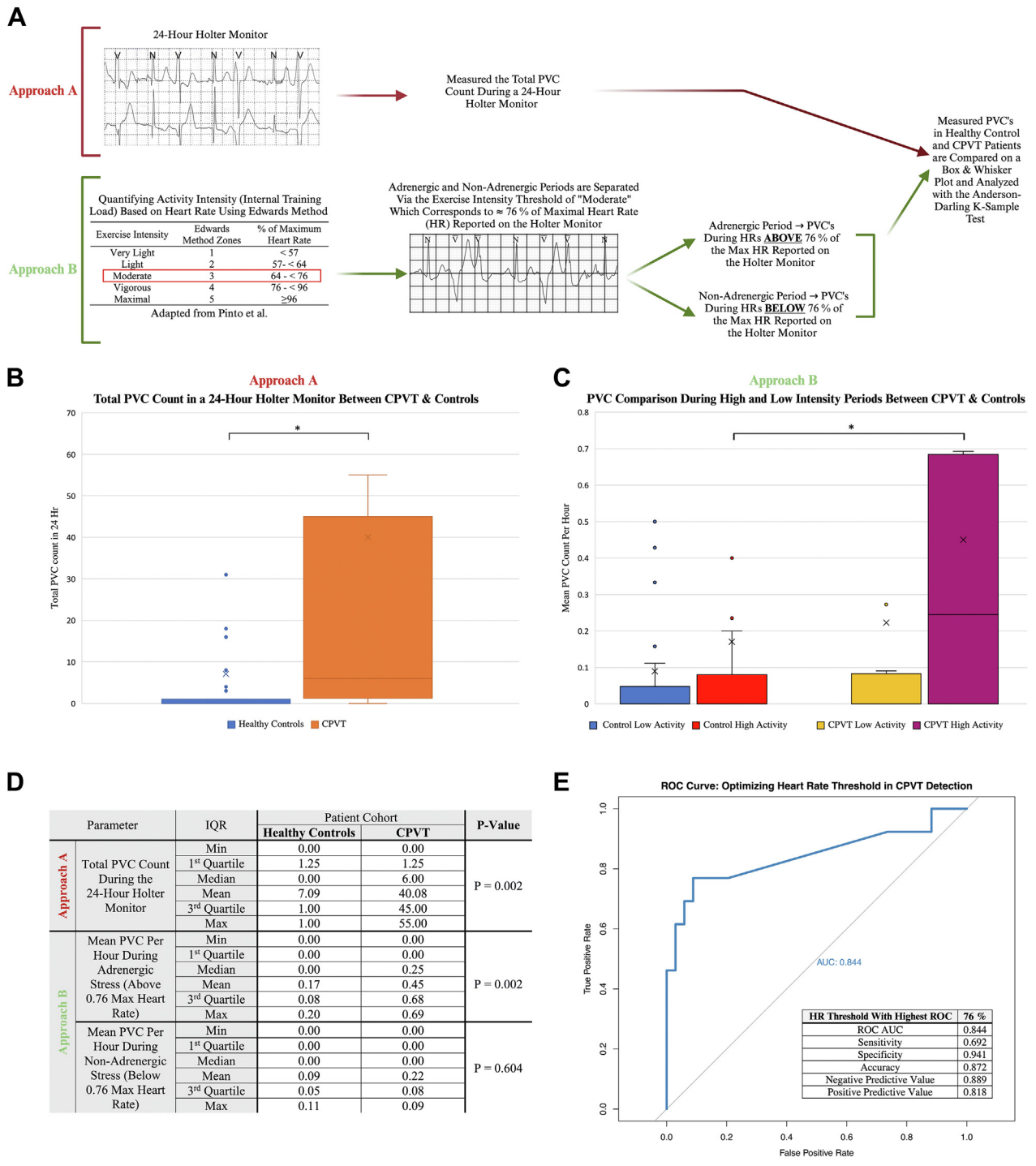
This retrospective cohort study includes CPVT patients from the National Hearts in Rhythm Organization (HiRO) registry enrolled between July 1, 2004-July 11, 2023.[9] Available data was acquired from 3 HiRO tertiary referral centers in Canada where Holter monitoring was conducted in CPVT patients: St. Paul's Hospital (Vancouver), British Columbia Children's Hospital, and London Health Sciences Centre. Research Ethics Board approval was obtained (UBC-H22-00012).

INCLUSION CRITERIA. This study includes HiRO participants with off-therapy 24-h Holter monitors. Two cohorts were included: 1) healthy controls who underwent Holter monitoring due to a family history of an inherited arrhythmia, who were confirmed to not carry the familial variant via genetic testing and screened for cardiomyopathies through echocardiography, ECG, or ETTs; and 2) CPVT patients diagnosed with a pathogenic or likely pathogenic RYR2 variant according to the 2015 American College of Medical Genetics and Genomics-American Association of Molecular Pathology criteria[10] and a clinical diagnosis of CPVT. Participants with a RYR2 variant of uncertain significance were excluded. The CPVT phenotype was defined as the presence of polymorphic and/or bidirectional ventricular ectopy. During the monitoring period, patients were advised to continue with their routine activities without any restrictions on movement.

ANALYTICAL APPROACH. Holter-reported PVCs were assessed via 2 methods (**Figure 1A**). Approach A compared the total PVC count during the 24-h monitoring period between healthy controls and CPVT patients. Approach B compared PVCs when isolated to periods of high and low adrenergic state. This separation was based on the Edwards method where heart-rate zones, defined by the relative ratio of ambient heart rate to maximum heart rate, were used as a reference measurement for internal training load.[11] Using this method, the relationship between hourly heart rate and maximum heart rate recorded during the monitoring period was used to stratify PVCs into periods of nonadrenergic (low activity) and adrenergic (high activity) stress. To determine the optimal maximum heart rate percentage that effectively separated CPVT-induced PVCs during adrenergic states, a receiver operating characteristic (ROC) curve analysis was performed.[12]

Within this analysis, we assessed model performance at various threshold levels using the parameters of mean PVC count above and below the specified cut-off percentage. Age and sex were also integrated into the model as supplementary factors. For each threshold, a ROC curve was constructed, and then the area under the receiver operating characteristic curve (AUC) was computed to quantitatively measure the model's discriminatory power. The heart rate percentage with the highest ROC-AUC value was deemed as the optimal threshold for separating PVCs during noradrenergic and adrenergic periods in CPVT

FIGURE 1 Overview



	Parameter	IQR	Patient Cohort: Healthy Controls	Patient Cohort: CPVT	P-Value
Approach A	Total PVC Count During the 24-Hour Holter Monitor	Min	0.00	0.00	P = 0.002
		1st Quartile	1.25	1.25	
		Median	0.00	6.00	
		Mean	7.09	40.08	
		3rd Quartile	1.00	45.00	
		Max	1.00	55.00	
Approach B	Mean PVC Per Hour During Adrenergic Stress (Above 0.76 Max Heart Rate)	Min	0.00	0.00	P = 0.002
		1st Quartile	0.00	0.00	
		Median	0.00	0.25	
		Mean	0.17	0.45	
		3rd Quartile	0.08	0.68	
		Max	0.20	0.69	
	Mean PVC Per Hour During Non-Adrenergic Stress (Below 0.76 Max Heart Rate)	Min	0.00	0.00	P = 0.604
		1st Quartile	0.00	0.00	
		Median	0.00	0.00	
		Mean	0.09	0.22	
		3rd Quartile	0.05	0.08	
		Max	0.11	0.09	

Overview of PVC analysis in Holter monitoring. (A) Methods of PVC analysis: Approach A compares total 24-h PVC count, and Approach B compares PVCs during adrenergic and nonadrenergic periods. (B) Comparison of total PVC count (24-h) in healthy controls and CPVT patients. Asterisk denotes significance ($P = 0.002$). (C) Comparison of mean PVC count per hour during periods of adrenergic (high activity) and nonadrenergic stress (low activity) in healthy controls and CPVT patients. Asterisk denotes significance ($P = 0.002$). (D) IQR analysis; *P* values derived from Anderson-Darling K-Sample test. (E) Model performance evaluation through ROC curve analysis. (B and C) Both are Box-and-Whisker Plots: the ends of the box plot are the first and third quartiles, the middle horizontal line is the median, and the whiskers represent the minimum and maximum. Outliers are denoted by the individual points and mean by the "X" symbol. AUC = area under the receiver operating characteristic curve; CPVT = catecholaminergic polymorphic ventricular tachycardia; HR = heart rate; PVC = premature ventricular contractions; ROC = receiver operating characteristic.

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TABLE 1 Summary of Patient Characteristics

	Patient Cohort		
	Healthy Controls (n = 34)	CPVT (n = 13)	*P* Value
Median age, y	37.5 ± 14.3	42.0 ± 19.2	0.318
Gender			1.000
Male	41% (14)	46% (6)	
Female	59% (20)	54% (7)	
Maximum HR	139.7 ± 18.5	139.2 ± 46.4	0.234
Mean HR	75.3 ± 8.06	71.3 ± 10.0	0.128
HR threshold of adrenergic state[a]	106.2 ± 14.0	105.8 ± 35.3	0.234
PVC burden, %	0.01 ± 0.04	0.33 ± 1.06	0.001
PVC count	7.09	40.08	0.002
QRS complexes	103,302 ± 12,531	100,764 ± 14,406	0.626

Values are mean ± SD or % (n). All reported HR and PVC are from the 24-h Holter Monitor Summary Report.
[a]Threshold defined by 76% of maximum HR.
HR = heart rate (beats/min); PVC = premature ventricular contraction.

patients. A confusion matrix was also constructed to assess the model's ability to discriminate between healthy controls and CPVT patients based on the calculated optimal heart rate cut-off. Mean PVC per hour during periods of high and low activity as defined by the threshold was then compared between the groups.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD, or median (IQR). Categorical variables are presented as percentages/ratios. To accommodate small sample sizes in patient demographic comparisons, continuous variables were tested using a Mann-Whitney *U* test, and categorical variables were tested using a Fisher exact test. PVCs were compared using the nonparametric Anderson-Darling K-Sample test and plotted on a Box and Whiskers Plot. An AUC-ROC curve was computed for the optimal threshold and model performance metrics including sensitivity, specificity, accuracy, negative predictive value, and positive predictive value were calculated from the confusion matrix. For all statistical testing, a *P* value of <0.05 was considered significant. Data analysis was performed on RStudio version 2023.09.1 (Build 494) using the following packages: kSamples[13] (version 1.2-10), pROC,[14] ROCit[15] (version 2.1.1), and tidymodels.[16]

RESULTS

STUDY SAMPLE DESCRIPTION. There were 54 healthy controls and 40 CPVT patients in the 3 HiRO enrolling sites. Of these, 34 healthy controls and 13 CPVT patients were included in the study (Supplemental Figure 1). The remainder were excluded either due to no off therapy Holter monitor being available and/or the absence of a pathogenic/likely pathogenic RYR2 variant. Patient Holter monitor characteristics are summarized in Table 1. The age and sex of the 2 cohorts were similar. The mean and maximum heart rate reported on the Holter report were also similar between groups.

HOLTER MONITORING. The overall PVC burden was statistically different between groups yet remained generally low, suggesting high ambient PVCs are not typical in CPVT (0.33% and 0.01% of overall beats in CPVT and healthy patients, respectively; $P = 0.001$; Table 1). Holter PVC counts were analyzed via 2 approaches (Figure 1A). In approach A, when comparing total PVC prevalence during the 24-h monitoring, CPVT patients had significantly higher numbers of PVCs compared with healthy controls (40.08 vs 7.09; $P = 0.002$). Both mean and maximum PVC counts were higher in CPVT patients, with a larger range of variability observed in this group (Figure 1D).

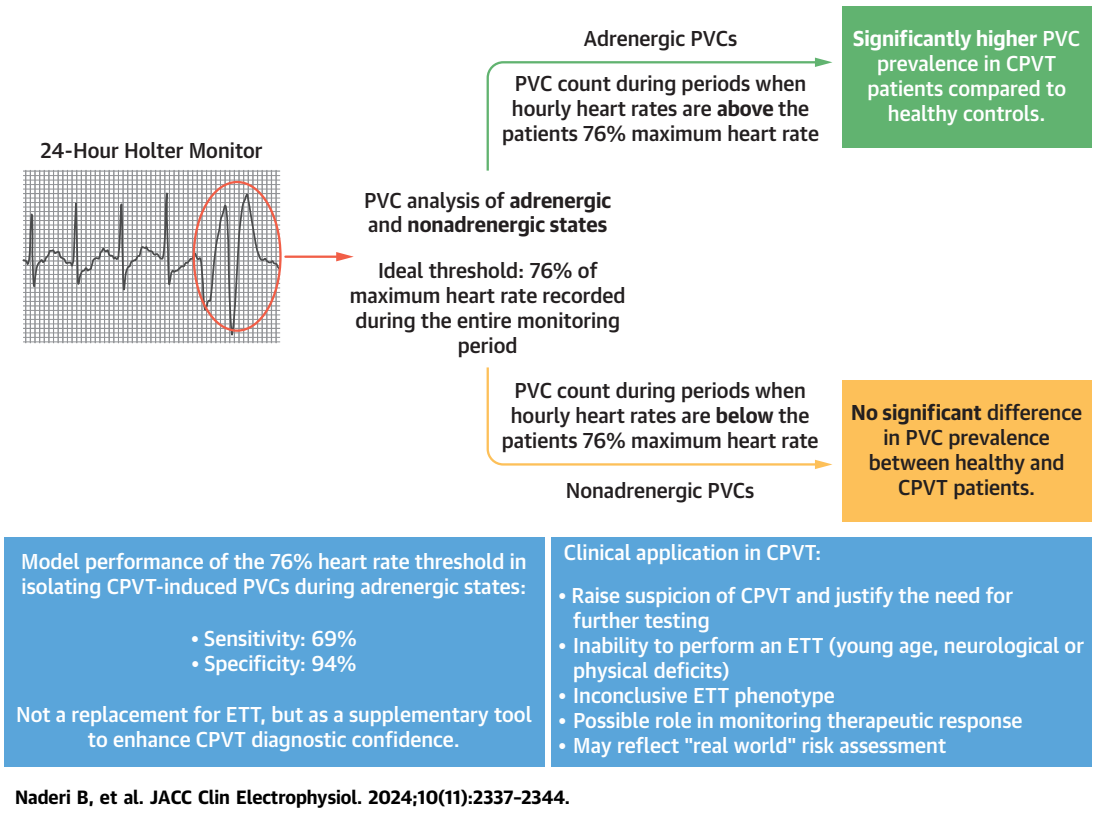
In approach B, PVC count comparison between the 2 groups was limited to periods of nonadrenergic and adrenergic stress as defined by a heart rate threshold. Using the AUC-ROC analysis, the optimal cut-off for detecting CPVT based on the adrenergic categorization of PVC count was determined as 76% of the Holter-recorded maximum heart rate (Figure 1E). Adjusting for age and sex did not substantially alter the analysis performance (AUC: 0.850). A difference in PVC prevalence between CPVT and healthy controls was observed only when isolating the analysis to periods of adrenergic stress defined by the 76% maximum heart rate cut-off ($P = 0.002$) (Figure 1D). Both groups had similar PVC counts during nonadrenergic periods ($P = 0.604$).

Using the 76% maximum heart rate threshold resulted in a sensitivity of 69% and a specificity of 94% in detecting CPVT based on the PVC-heart rate relationship (Figure 1E). The negative predictive value and positive predictive value of this approach were computed as 0.89 and 0.82, respectively.

DISCUSSION

This multicenter, retrospective cohort study from the HiRO Registry[9] assessed the Holter monitor PVC phenotype of RYR2 gene-positive CPVT patients not on therapy. Major findings of Holter monitoring include the following: 1) CPVT patients had relatively low PVC burdens when simply taking into consideration the total PVC count and PVCs occurring during ambient activity; 2) CPVT patients had high PVC counts when examining only periods of adrenergic

CENTRAL ILLUSTRATION Holter Monitor Phenotype in CPVT



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Overview of isolating Holter monitor PVC counts into periods of adrenergic and nonadrenergic stress using HR. CPVT = catecholaminergic polymorphic ventricular tachycardia; ETT = exercise tolerance test; HR = heart rate; PVC = premature ventricular contractions.

stress; and 3) analyzing PVC counts occurring at >76% of the patient's Holter-detected maximum heart rate may be particularly useful in assessing for potential CPVT. Collectively, these data indicate that the yield of CPVT evaluation based on ambient PVC count is low, but clinicians should pay particular attention to PVCs occurring at higher heart rates in individuals fitting the typical features of CPVT. The **Central Illustration** outlines this novel approach to Holter monitor analysis in CPVT.

Although overall PVC burden was statistically different between the groups, it was within population norms for age and sex.[17] Similarly, CPVT patients had a significantly higher total PVC count during the monitoring period when compared with healthy controls, albeit counts were generally low. The number of QRS complexes also remained nonsignificant, indicating that these findings are not attributed to sinus node dysfunction, which is a recognized characteristic of CPVT.[18] This suggests that ambient PVCs are not a distinguishing feature of CPVT, and relying solely on the total number of ventricular ectopy or the PVC burden from a Holter monitor is not specific to diagnose CPVT. Total PVC count during the monitoring period can be influenced by the patient's level of activity and other arrhythmia-inducing conditions unrelated to CPVT.

A novel approach to Holter analysis in CPVT patients involves restricting PVC comparisons to periods of adrenergic and nonadrenergic stress. To isolate PVC counts to periods of high physical stress, Edwards heart rate zones were used as a reference to quantify the internal training load of each patient and correlate each participant's exertion level to their reported heart rate.[11] All heart rate cut-offs were compared using a ROC analysis to determine the threshold above which PVC prevalence was restricted to adrenergic state in CPVT patients. The optimal threshold was determined as 76% of the individual's Holter-detected maximum heart rate, which

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corresponds to above moderate level of activity (Figure 1A). This approach to Holter analysis demonstrated moderate sensitivity (69%) and high specificity (94%) in isolating adrenergic-induced PVCs that are typical in CPVT presentation. The cut-off aligns with current literature, because CPVT-specific ectopic activity is largely observed above the sinus threshold of 110-120 beats/min in an ETT.[19,20] A recent cohort study also showed that, during Holter monitoring, PVCs were first noted at a mean heart rate of 111 ± 19 beats/min with more complex PVCs present at higher sinus rates.[8] In our study, the 76% Holter-detected maximum heart rate threshold corresponded to a heart rate of 105.8 ± 35.3 beats/min, which closely mirrors the ETT phenotype of CPVT. These logical findings support our existing understanding of CPVT, which is a condition generally unmasked by adrenergic stimulation (eg, exercise, stress, emotion), but largely absent at rest.[21,22] Conversely, a high PVC count during low adrenergic states may argue against CPVT and instead point toward other mechanisms of ectopy. Hence, analyzing the maximum heart rate to PVC correlation and comparing PVC count during nonadrenergic and adrenergic periods can uncover the CPVT PVC phenotype. Conveniently, many Holter monitor laboratories are capable of providing raw tabular representations of PVC prevalence during periods of tachycardia, which should be requested and analyzed whenever available.

CPVT is a genetically heterogeneous condition that clinically presents with a wide spectrum of phenotypic manifestations. Only 60% of all clinical CPVT cases are attributed to pathogenic RYR2 variants[4] with many other variants contributing to the etiology. Our exploration of PVC distributions was limited to RYR2 patients to ensure a strong genotype-phenotype correlation in the analysis. The Holter PVC phenotype of other CPVT variants should also be explored to further understand the arrhythmic profiles of different genetic mutations. Sy et al[8] have also identified a form of gene-negative CPVT that manifests later in life, has a lower risk of major cardiac events, and is negative for all known genetic causes of CPVT. Analyzing the distribution of Holter PVCs as a function of adrenergic stress could provide insight into this subtype of CPVT, potentially revealing it as a distinct disease entity. Studying these patients may ultimately help with the veracity of diagnosis, given the spectrum of clinical phenotypes and equivocal genetic results.

Although not adjudicated in our study, the Holter may also have a role in monitoring therapeutic response during routine daily activities, which may not be easily captured on a single ETT. Unlike an ETT, which evaluates cardiac function under structured and short-term physical stress, Holter analysis captures a broader spectrum of heart rhythms that reflects the patient's typical levels of exertion and stress. This enables clinicians to better capture patient's daily activity profile and offer personalized treatment strategies to better manage CPVT. Holter monitoring also offers a more comprehensive view of a patient's cardiac activity during typical daily engagements, potentially providing a more physiologically relevant measure of arrhythmic risk than what might be observed during an ETT. Using the heart rate to PVC correlation for identifying adrenergic PVCs may offer a more realistic approach to risk stratification in CPVT. Patients with minimal adrenergic PVCs during the monitoring period would intuitively have a lower risk profile and be considered for less aggressive management, even when ETT suggests a higher risk. Incorporating Holter monitoring into routine therapeutic evaluations or as an alternative to repeat ETTs during risk assessment could advance patient care and warrants further investigation. Studying the correlation between Holter PVC distributions, symptom severity, and ETT findings will help us further understand the prognostic and monitoring benefit of Holter monitoring.

Our observations have other important implications for clinical care. In some situations, performing an ETT to diagnose CPVT is not feasible. Oftentimes children are too young to safely undertake an ETT and in situations of cardiac arrest, many patients are unable to exercise due to neurologic or physical deficits.[5] Furthermore, CPVT is often missed as a diagnosis, either because the ETT phenotype is subtle or an ETT is not performed after an adrenergic-triggered event.[23] High burden PVC findings should dramatically lessen suspicion of CPVT, and direct attention to other mechanisms. However, because Holter monitoring is often performed as a routine part of heart rhythm care, a higher PVC prevalence during higher heart rates on Holter monitoring may provide a clue and lead to diagnostic exercise testing.

STUDY LIMITATIONS. The study sample size in this study limits the generalizability and may have been underpowered to detect differences between groups. Testing across a broader age range may enable age-specific findings to guide populations like small children who typically do not perform structured exercise testing. Hence, future validation studies are warranted. Further, the heart rate cut-off threshold that separates periods of adrenergic and non-adrenergic stress should be studied in more depth to help differentiate between CPVT and its mimics. We only

included patients with pathogenic or likely pathogenic variants in RYR2 to assure that the CPVT diagnosis was as strong as possible. It remains unclear whether there is a role for Holter monitoring in other forms of the disease, which represent the minority of CPVT cases.

CONCLUSIONS

CPVT patients have a very low overall burden of PVCs on Holter monitoring. The PVC count agnostic to the associated heart rate should not be used to diagnose CPVT. Instead, analyzing the PVC count during Holter monitoring at higher heart rates is a useful approach that may provide an adjunct to exercise testing for diagnostic assessment.

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ADDRESS FOR CORRESPONDENCE: Dr Andrew D. Krahn, Center for Cardiovascular Innovation, Heart Rhythm Services, Division of Cardiology, University of British Columbia, Room 220, 1033 Davie Street, Vancouver, British Columbia V6E 1M7, Canada. E-mail: akrahn@mail.ubc.ca. X handle: @HeartsInRhythm.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The development of PVCs during periods of higher heart rate on Holter monitoring may be a helpful clue in diagnosing CPVT, but those occurring during ambient states are not suggestive of the condition. Given the adrenergic nature of CPVT, ambient PVCs during a 24-h Holter monitoring are not a typical presentation. We found that the 76% Holter-detected maximum heart rate threshold could isolate adrenergic PVCs and distinguish between CPVT and controls.

TRANSLATIONAL OUTLOOK: This novel approach to Holter monitor analysis, which relies on a 76% heart rate cut-off to isolate adrenergic PVCs, can be used in combination with standard treadmill exercise testing to improve the diagnostic accuracy of CPVT. It also offers a valuable diagnostic tool in cases where a standard treadmill exercise test is not feasible.

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KEY WORDS catecholaminergic polymorphic ventricular tachycardia, Holter monitoring, inherited, ventricular arrhythmia

APPENDIX For a supplemental figure, please see the online version of this paper.