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Spectrum and Prognostic Significance of Arrhythmias on Ambulatory Holter Electrocardiogram in Hypertrophic Cardiomyopathy

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OBJECTIVES The goal of this study was to assemble a profile and assess the significance of arrhythmias in a nontertiary-based hypertrophic cardiomyopathy (HCM) cohort.

BACKGROUND Hypertrophic cardiomyopathy is associated with arrhythmia-related consequences, particularly sudden death. Ventricular tachyarrhythmias on Holter electrocardiograms (ECG) have been reported as markers for sudden death in highly selected HCM populations.

METHODS We assessed the profile of ventricular and supraventricular ectopy and bradyarrhythmia on ambulatory 24-h Holter ECG and also related these findings to clinical outcome in 178 HCM patients.

RESULTS Of the 178 study patients, 157 (88%) had premature ventricular complexes (PVCs), including 21 (12%) with ≥500 PVCs, 74 (42%) had couplets, 67 (37%) had supraventricular tachycardia (SVT), and 56 (31%) had nonsustained ventricular tachycardia (NSVT). Mean number of PVCs was 330 ± 763 (range 1 to 5,435) and increased with age ($p < 0.01$); NSVT was associated with greater left ventricular hypertrophy ($p = 0.01$) and severe symptoms (New York Heart Association functional classes III and IV) ($p = 0.04$); SVT occurred more commonly in patients with outflow obstruction ($p = 0.02$). Over a follow-up of 5.5 ± 3.4 years, 11 (6%) patients died suddenly (annual mortality rate, 1.1%) including 5 patients with NSVT. For sudden death, NSVT on Holter ECG had negative and positive predictive values of 95% and 9%, and sensitivity and specificity of 45% and 69%, respectively.

CONCLUSIONS In this nontertiary-based HCM cohort, ventricular and supraventricular tachyarrhythmias were particularly frequent and demonstrated a broad spectrum on ambulatory (Holter) ECG. Paradoxically, despite such a highly arrhythmogenic substrate, sudden death events proved to be relatively uncommon. Ventricular tachyarrhythmias had a low positive and relatively high negative predictive value for sudden death in this HCM population. (J Am Coll Cardiol 2005;45:697–704) © 2005 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease associated with a risk for sudden death as a direct consequence of ventricular tachyarrhythmias (1–9). Indeed, HCM is the most common cause of sudden cardiac death in young people, including trained athletes (2,10–18).

Ambulatory Holter electrocardiography (ECG) has been used extensively in the evaluation and risk stratification of HCM patients (19–24). Previously, in HCM cohorts from tertiary care centers with a disproportionate representation of high-risk patients, nonsustained ventricular tachycardia (NSVT) on 24- to 48-h ambulatory ECG proved to be predictive of future events (20,21,24). However, arrhythmia profile (and its prognostic significance) in less selected HCM cohorts that are closest to the true disease state in the community remains unresolved and is the focus of this investigation.

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METHODS

Selection and demographics of study patients. Between 1975 and 2001, 535 patients with HCM were evaluated at the Minneapolis Heart Institute, a large community-based clinic and hospital service primarily supporting the Minneapolis and St. Paul metropolitan area (population, 3 million) and the state of Minnesota (population, 5 million) (2–4). Of these, 296 patients from the five-state Upper Midwest region (Minnesota and the contiguous states of Wisconsin, Iowa, North Dakota, and South Dakota), not subject to tertiary center referral, were initially included in the study group. None of these patients had been selectively referred to our institution for specialized care of HCM. The other 239 HCM patients evaluated at our institution since 1994, who were preferentially referred to the senior author (B.J.M.) for specialized care related to HCM (in the context of tertiary referral) were excluded from the present cohort. Patients in this study were initially referred for cardiac symptoms (e.g., dyspnea or chest pain), findings on physical examination (e.g., heart murmur), abnormal ECG, evaluation of other cardiac diseases (e.g., coronary artery disease), or acute cardiovascular events (e.g., syncope, atrial fibrillation).

Abbreviations and Acronyms

AV = atrioventricular
HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
NSVT = nonsustained ventricular tachycardia
NYHA = New York Heart Association
PVC = premature ventricular complex
SVT = supraventricular tachycardia

Of the 296 HCM patients, 178 were identified as having at least one 24-h ambulatory (Holter) ECG recording (Fig. 1). These studies were obtained on a routine clinical basis by the participating cardiologists at our institution, and constitute the present study group. Although Holter ECGs are part of our standard outpatient evaluation for the risk stratification of HCM patients, it was not our general practice to routinely obtain these recordings in children and the older patients (i.e., ages <20 years and >50 years). Consequently, 82% (n = 97) of the 118 patients without a Holter ECG were in these age groups.

At study entry, the 178 HCM study patients ranged in age from 5 to 89 years (mean 50 ± 18 years) and 101 (57%) were male. Of the 178 patients, 84 (48%) were in New York Heart Association (NYHA) functional class I, 61 (34%) were class II, and 32 (18%) were severely symptomatic in classes III/IV. Thirty-nine (22%) patients had a left ventricular (LV) outflow gradient of ≥30 mm Hg under basal conditions. Follow-up period extended from the time of the Holter ECG recording to June 2001, or when death occurred, and ranged from 1 to 22 years (mean 5.5 ± 3.4 years) (Table 1). At the time of the Holter recording, 119 (66%) patients were taking one or more of a variety of cardioactive medications: beta-adrenergic receptor blockers (n = 79), verapamil (n = 52), disopyramide (n = 7), and amiodarone (n = 4). Twenty-two patients (12%) had cardioverter defibrillator implanted prophylactically.

Definitions. Diagnosis of HCM was based on the echocardiographic demonstration of a hypertrophied (defined as a wall thickness ≥13 mm in adult patients or the equivalent wall thickness relative to body surface area in children) nondilated LV in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident in that patient (25,26); NSVT and supraventricular tachycardia (SVT) were defined as three or more consecutive premature complexes with a heart rate >100 beats/min. Couplets were two consecutive premature ventricular complexes (PVCs). Sinus bradycardia was defined as an average heart rate <60 beats/min during the 24-h monitoring period.

Sudden cardiac death was defined as unexpected sudden collapse occurring <1 h from the onset of symptoms in a patient who had previously experienced a relatively stable or uneventful clinical course. Unwitnessed death was also classified as sudden if it occurred unexpectedly (e.g., at night, in a patient without prior severe symptoms). In addition, potentially lethal cardiovascular events in which 3 patients either were successfully resuscitated from cardiac arrest (n = 1) or received appropriate shocks from an implanted cardioverter-defibrillator (n = 2) were regarded as equivalents of sudden cardiac death in the present data analysis (3).

Ambulatory Holter ECGs. Ambulatory Holter ECG recordings were obtained in a standard fashion with a portable tape recorder and modified V_1 and V_5 leads. Holter ECG recordings were scanned on a DelMar Reynolds AccuPlus (model 363) Holter Analysis System (Del Mar Reynolds Medical, Irvine, California), which utilizes technician interaction in arrhythmia analysis aided by visual superimposition to correct for artifact and any erroneous analysis. In each case the arrhythmias were verified by an experienced cardiologist who was blinded to the clinical, echocardiographic, and follow-up data. Arrhythmia frequency was normalized to 24 h for recordings, which did not include a full 24-h of interpretable rhythm due to noise or loss of

Table 1. Demographics and the Clinical Profile of 178 HCM Patients With 24-h Ambulatory ECG

Age (yrs)	50 ± 18
Male gender	101 (57%)
NYHA functional class	
I	84 (48%)
II	61 (34%)
III/IV	32 (18%)
LV outflow obstruction at rest ≥30 mm Hg	39 (22%)
Maximal LV wall thickness (mm)	
≤15	11 (6%)
16–19	46 (26%)
20–24	81 (45%)
25–29	19 (11%)
≥30	21 (12%)
Left atrial size (mm)	43 ± 9
LV end-diastolic diameter (mm)	44 ± 7
Drugs	
Beta-blocker	80 (45%)
Calcium channel blocker	52 (29%)
Disopyramide	7 (4%)
Amiodarone	4 (2%)
Follow-up from Holter recording (yrs)	5.5 ± 3.4

ECG = electrocardiography; HCM = hypertropic cardiomyopathy; LV = left ventricular; NYHA = New York Heart Association.

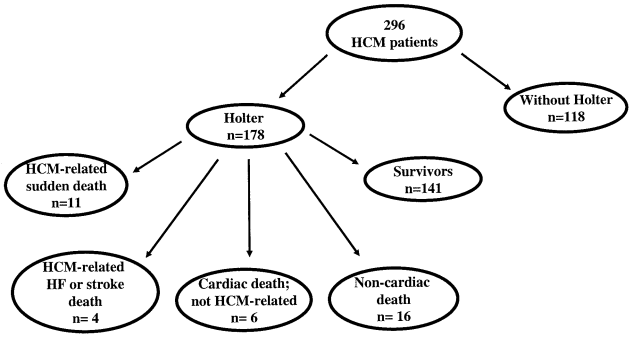

Figure 1. Flow diagram showing the clinical outcome of 178 patients with hypertrophic cardiomyopathy (HCM) who underwent 24-h ambulatory (Holter) electrocardiogram monitoring. HF = heart failure.

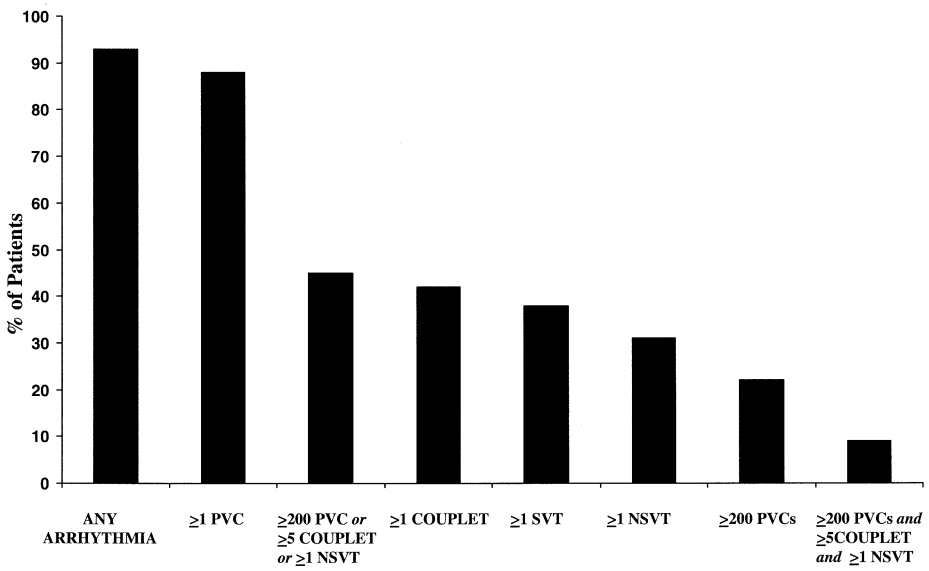

Figure 2. Prevalence of ventricular and supraventricular arrhythmias on 24-h ambulatory (Holter) electrocardiogram recording in 178 patients with hypertrophic cardiomyopathy. NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex; SVT = supraventricular tachycardia.

signal. In those patients with >1 ambulatory Holter ECG, the recording with the most substantial ectopy (i.e., the highest frequency of either NSVT, couplets, or PVCs) was included in the data analysis.

Echocardiography. Echocardiographic studies were performed with commercially available Hewlett-Packard instruments. Greatest thickness measured at any site in the LV wall was considered as the maximal thickness (27). Peak instantaneous LV outflow gradient was estimated with continuous-wave Doppler (28).

Statistical methods. Data are presented as mean values ± SD. Categorical data were analyzed using chi-square test. Outcome variables were compared between groups using *t* tests (or Mann-Whitney *U* tests when not normally distributed). Relationships between arrhythmia occurrence and frequency and demographic variables were assessed with Pearson correlation coefficients (or Spearman correlation coefficients when not normally distributed). Distributional normality was assessed using the Lilliefors test. Odds ratios for predicting sudden death were obtained by logistic regression. A p value of ≤0.05 was taken as statistically significant.

For each individual study patient and the overall study group, the number of PVCs, couplets, and NSVT runs that occurred in *each hour of the day* was tabulated separately. The presence of a diurnal pattern was assessed using a Poisson regression model with logarithmic link function. The GENMOD procedure in SAS software (version 8.1, SAS Institute Inc., Cary, North Carolina) was applied. The repeated occurrence of arrhythmias within a given patient was taken into account in the analysis. The expected number of episodes was modeled as a linear combination of sine and cosine functions with 1, 2, 3, or 4 cycles in 24 h. The cycles that did not contribute to the model were sequentially eliminated (29).

RESULTS

Ventricular tachyarrhythmias. PVCS. Of the 178 study patients, 157 (88%) had ≥1 PVC (range 1 to 5,435; mean 330 ± 763) including 40 (22%) with ≥200 PVCs and 21 (12%) with ≥500 PVCs (Fig. 2); PVCs were multifocal in 110 patients and unifocal in 47 patients. The number of PVCs increased with age (Spearman rho = 0.32, $p < 0.01$) (Fig. 3).

COUPLETS. Seventy-four (42%) patients had couplets (range 1 to 549; mean 24 ± 78). Occurrence of couplets correlated with

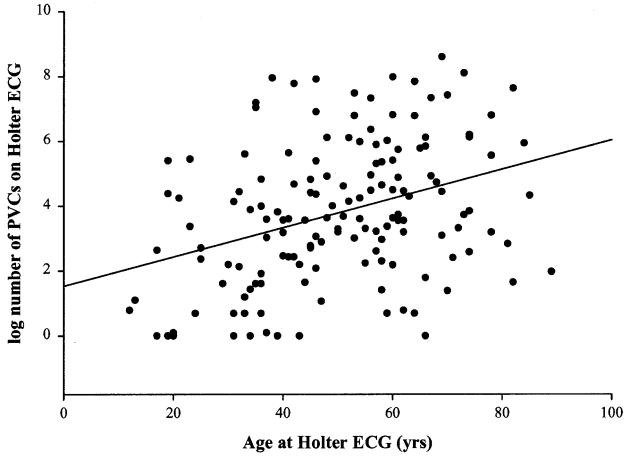

Figure 3. Relation between age at 24-h ambulatory (Holter) electrocardiogram (ECG) monitoring and the number of premature ventricular complexes (PVCs) in the 157 hypertrophic cardiomyopathy patients with PVCs.

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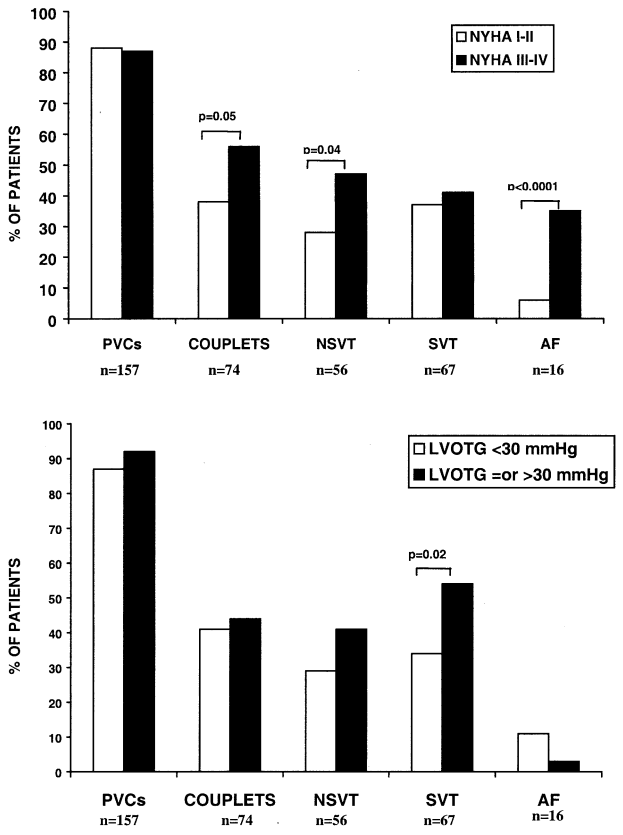

Figure 4. Relation of symptom severity **(top panel)** and left ventricular outflow obstruction **(bottom panel)** with the occurrence of arrhythmias on 24-h ambulatory (Holter) electrocardiogram monitoring in 178 hypertrophic cardiomyopathy patients. AF = atrial fibrillation; LVOTG = left ventricular outflow tract gradient; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular complex; SVT = supraventricular tachycardia.

older age ($p = 0.002$) and advanced symptoms (NYHA functional classes III or IV) ($p = 0.05$) (Fig. 4).

NSVT. Fifty-six (31%) patients had runs of NSVT (range 1 to 115; mean 6 ± 17) including 18 (10%) with ≥3 runs, and 12 (7%) with ≥5 runs. Bursts of NSVT ranged in length from 3 to 26 beats/min (mean 6 beats/min) at an average rate of 150 beats/min; NSVT also occurred more commonly in patients with advanced symptoms (NYHA functional classes III or IV) (chi-square, $p = 0.04$) (Fig. 4). Of the 56 patients with NSVT runs, only 2 (3%) of patients reported palpitations during the arrhythmia, and none had syncope. Also, there was no association between occurrence of NSVT and prior syncopal episodes.

FREQUENT AND/OR COMPLEX ARRHYTHMIAS. Of the 178 study patients, 97 (54%) had complex ventricular arrhythmias on 24-h Holter, including couplets, NSVT, or both. Eighty patients (45%) were judged to have particularly frequent or complex ventricular arrhythmia consisting of ≥1 NSVT run or ≥5 couplets or ≥200 PVCs. Of note, 16 (9%) had all 3 of these arrhythmias: ≥1 NSVT and ≥5 couplets and ≥200 PVCs (Fig. 2). Patients who had ≥1 PVC were more likely to have couplets ($p < 0.0001$). Similarly, patients who had couplets were more likely to have NSVT ($p = 0.001$).

DIURNAL VARIABILITY. Nonsustained ventricular tachycardia occurred in a circadian pattern with a peak at 8 AM and a trough at 11 PM ($p = 0.001$), while the couplets showed two peaks at 2 AM and 2 PM and troughs at 6 AM and 6 PM ($p = 0.01$). A circadian distribution was not identified for PVCs.

DRUGS. Number of PVCs, couplets, or NSVT was not related to whether or not cardioactive drugs were taken by patients at the time of the Holter ECG. For example, PVCs occurred in 99 of the 116 patients (85%) who were taking beta-adrenergic or calcium channel blockers compared with 57 of the 59 patients (96%) who were not taking drugs (p = NS). Similarly, NSVT occurred no more frequently in patients who were taking beta-adrenergic or calcium channel blockers compared with those not taking drugs (37 of 116; 32% vs. 19 of 59; 32%; p = NS).

Supraventricular tachyarrhythmias. Of the 178 study patients, 67 (38%) had runs of SVT (range 1 to 557; mean 16 ± 71), including 32 patients (18%) with ≥3 runs and 24 patients (13%) with ≥5. Bursts of SVT ranged from 3 to 93 beats/min (mean 12 beats/min) with an average rate of 134 beats/min; SVT was significantly more common in older patients ($p < 0.0001$) and patients with LV outflow obstruction (gradient ≥30 mm Hg at rest) ($p = 0.02$) (Fig. 4). Atrial fibrillation was detected in 16 (9%) of the 178 patients, and its occurrence correlated with older age ($p = 0.004$), advanced symptoms (NYHA functional classes III or IV) ($p < 0.0001$) (Fig. 4), and enlarged left atrium ($p < 0.0001$).

Bradyarrhythmias. Of the 178 patients, 25 (14%) had evidence of sinus bradycardia (average heart rate <60 beats/min in 24 h). Patients with sinus bradycardia had significantly less frequent PVCs than those patients with average heart rate ≥60 beats/min (42 ± 72 PVCs vs. 392 ± 819 PVCs, respectively; Mann-Whitney test, $p = 0.004$).

Conduction abnormalities. Forty-one patients (23%) had ≥1 conduction abnormalities. Specifically, 31 (17%) had first degree atrioventricular (AV) block, 6 (3%) had second degree AV block, and 12 (7%) had sinus pauses >2 s.

Relation of arrhythmias to LV hypertrophy. Left ventricular wall thickness was significantly greater in patients with NSVT (23.2 ± 5.7 mm) than those without NSVT (21.3 ± 4.9 mm, $p = 0.01$), and the likelihood of NSVT increased with respect to greater LV wall thickness (Pearson correlation, $p = 0.02$) (Fig. 5). Also, NSVT was more common in patients with extreme LV hypertrophy (wall thickness ≥30 mm) than in patients with mild hypertrophy (wall thickness ≤20 mm) (11 of 21; 52% vs. 9 of 57; 16%, respectively; $p = 0.01$). Conversely, SVT was less common in patients with extreme hypertrophy compared with other patients ($p = 0.001$) (Fig. 5).

Relation of ventricular arrhythmia to outcome. Over the 5.5 ± 3.4 year follow-up period, 15 (8%) of the 178 study

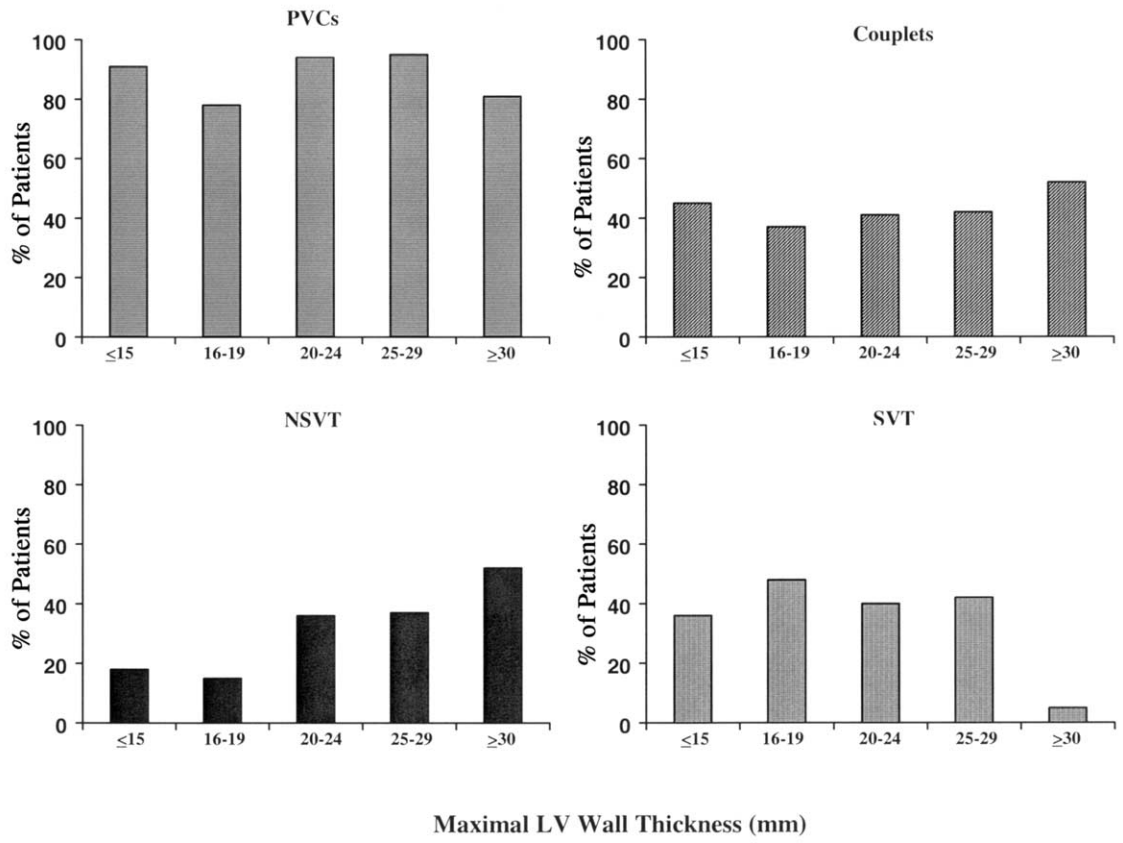

Figure 5. Relation between maximum left ventricular (LV) wall thickness and occurrence of various tachyarrhythmias on 24-h ambulatory (Holter) electrocardiogram recording in 178 hypertrophic cardiomyopathy patients. Nonsustained ventricular tachycardia (NSVT) increased progressively and in direct relation to maximal LV thickness ($p = 0.02$ by the chi-square test for trend). Supraventricular tachycardia (SVT) was less common in patients with maximal LV thickness ≥30 mm vs. <30 mm ($p = 0.001$). PVCs = premature ventricular complexes.

patients died of HCM-related causes, including 11 (6%) suddenly and 4 (2%) of heart failure or stroke (Fig. 1). Other deaths included 6 patients (3%) of coronary heart disease and 16 (9%) of noncardiac or unknown causes. Total mortality, HCM-related mortality, and HCM-related sudden death were 3.8%, 1.4%, and 1.1% per year, respectively. Moreover, the estimated rate for sudden death was 1.8% per year in patients with NSVT on Holter ECG, compared with 0.8% per year in those without NSVT.

Patients with sudden death, all HCM-related deaths, and survivors were compared with respect to several demographic or arrhythmia parameters (Table 2). There were no significant differences between patients who died suddenly and the survivors with regard to arrhythmia profile on 24-h Holter ECG. Although odds ratio for sudden death by logistic regression was 1.9 (95% confidence interval: 0.5 to 6.5) in patients with NSVT and 2.4 (95% confidence interval: 0.5 to 12.4) in patients with combined NSVT and ≥5 couplets and ≥200 PVCs, neither of these associations achieved statistical significance ($p > 0.05$). However, those patients who died of all HCM-related causes (including sudden death) had greater numbers of PVCs ($p = 0.05$) when compared with survivors (Table 2).

Predictive values, sensitivity, and specificity of ventricular arrhythmias on Holter for predicting sudden death (Table 3) consistently showed low positive predictive value and a high negative predictive value. For example, NSVT on Holter had 9% positive predictive value and 95% negative predictive value, as well as 45% sensitivity and 69% specificity (Table 3).

DISCUSSION

The present study demonstrates a broad spectrum of ventricular and supraventricular arrhythmias occurring with particular frequency on ambulatory (Holter) ECG in a nontertiary-based, low-risk HCM cohort. For example, almost 90% of our patients had PVCs with an average of >300 per patient in 24 h of ECG recording (ranging up to >5,000). More than one-half of the cohort showed complex ventricular arrhythmias in the form of couplets, NSVT, or both. Furthermore, almost one-half of the patients had a combination of frequent and/or complex arrhythmia with NSVT or ≥5 couplets or ≥200 PVCs. Of particular note, NSVT occurred with similar frequency in our relatively low-risk and nontertiary-based cohort as in previously reported tertiary center HCM populations disproportionately comprised of high-risk patients (20,21,24). For example, in selectively referred cohorts (20,21,24), NSVT was

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Table 2. Comparison of Clinical Outcome, Demographic Variables, and Arrhythmia Profile on 24-h Ambulatory ECG Monitoring in 178 HCM Patients

	HCM-Related Sudden Death (n = 11)	All HCM-Related Death (n = 15)	Survivors (n = 141)	p Value Sudden Death vs. Survivors	p Value Any HCM Deaths vs. Survivors
Age at Holter	48 ± 19	52 ± 20	48 ± 18	NS	NS
Male gender	4 (36%)	5 (33%)	85 (60%)	NS	0.04
NYHA functional class I–II	7 (64%)	8 (53%)	122 (87%)	0.03	0.001
LV outflow gradient ≥30 mm Hg	3 (27%)	5 (33%)	28 (20%)	NS	NS
Maximal LV wall thickness (mm)	26.7 ± 7.7	25.6 ± 7	21.7 ± 5	0.01	0.02
≥1 NSVT (n = 56)	5 (45%)	7 (47%)	38 (27%)	NS	NS
≥1 couplet (n = 74)	5 (45%)	6 (40%)	60 (43%)	NS	NS
≥1 PVC (n = 157)	8 (73%)	11 (73%)	128 (91%)	NS	NS
≥1 SVT (n = 67)	2 (18%)	4 (27%)	55 (39%)	NS	NS
Atrial fibrillation (n = 16)	1 (9%)	1 (7%)	9 (6%)	NS	NS
≥5 couplets (n = 26)	3 (27%)	4 (27%)	17 (12%)	NS	NS
≥3 NSVT (n = 18)	2 (18%)	3 (20%)	10 (7%)	NS	NS
≥200 PVCs (n = 40)	3 (27%)	4 (27%)	29 (21%)	NS	NS
≥500 PVCs (n = 21)	2 (18%)	2 (13%)	14 (10%)	NS	NS
AV block	1 (9%)	3 (20%)	24 (17%)	NS	NS
Bradycardia	0	1 (7%)	20 (14%)	NS	NS
No. of PVCs	520 ± 880	431 ± 759	263 ± 620	NS	0.05
No. of couplets	10 ± 10	10 ± 9	22 ± 83	NS	NS
No. of NSVT runs	2.5 ± 1.7	3.3 ± 2.2	4.3 ± 10	NS	NS
NSVT length (beats)	7 ± 2.6	7.3 ± 3.8	5.8 ± 4.5	NS	NS
NSVT rate (beats/min)	176 ± 43.7	166 ± 36	153 ± 27	NS	NS

AV = atrioventricular; HCM = hypertrophic cardiomyopathy; LV = left ventricular; NS = not significant; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular complex; SVT = supraventricular tachycardia.

identified on Holter ECG in 20% to 30% of patients compared with about 30% in our patient population.

However, despite the high prevalence of frequent and/or complex tachyarrhythmias in our population, sudden deaths as well as all HCM-related deaths (1.1% per year and 1.4% per year, respectively) were uncommon, demonstrating a mismatch between the arrhythmogenic substrate and outcome. Of note, our HCM mortality rates are substantially lower than the 3% to 6% per year previously reported from tertiary-referred HCM cohorts (2,10,14) but are consistent with reports from other less-selected HCM populations similar to the present cohort (3,22,23). On the other hand, the rate of sudden death in our study cohort was 10-fold and 100-fold higher than that in the general population for adults and children, respectively (i.e., 0.1% per year for adults; 0.01% per year for children) (30).

In other respects, the presence of arrhythmias on 24-h Holter appeared to be a manifestation of severe disease expression. For example, NSVT and couplets were more common in HCM patients with advanced symptoms (NYHA functional classes III or IV), and NSVT was significantly more common in association with extreme LV hypertrophy (31). The latter finding is relevant to recent observations that relate extreme LV hypertrophy to a greater likelihood of sudden death in HCM (14,27,32). Moreover, the circadian distribution for NSVT with a midmorning peak demonstrated here, coincided with the previously reported diurnal pattern of sudden cardiac death in HCM (33). However, the significance and biological basis for the circadian pattern we observed for couplets is uncertain. In addition, bradyarrhythmias were uncommon (<15%), not linked to demographic variables or clinical outcome, and were associated only with infrequent PVCs.

In the present relatively low-risk HCM cohort, the odds ratio and annual mortality rate for sudden death in patients with NSVT on Holter ECG was about two times that of patients without NSVT. However, these associations did not achieve statistical significance, largely due to the low

Table 3. Sensitivity, Specificity, and Predictive Value of Ventricular Arrhythmias on 24-h Ambulatory ECG as Predictors of Sudden Death in HCM

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
≥1 NSVT	45%	69%	9%	95%
≥1 couplet	45%	59%	7%	94%
≥1 PVC	73%	11%	5%	86%
≥3 NSVT	18%	90%	11%	94%
≥500 PVCs	18%	89%	10%	94%
≥1 NSVT or ≥1 couplet	64%	46%	7%	95%

HCM = hypertrophic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex.

event rate in our study population. Similarly, an earlier study from a low-risk HCM population also showed a relative risk for sudden death of >2 in patients with NSVT (which also did not achieve statistical significance) (22). Therefore, in this regard our findings are, in fact, consistent with previously reported data.

On the other hand, three other studies from higher risk tertiary-based HCM cohorts reported statistically significant relationships between NSVT on Holter ECG and sudden death (20,21,24). We believe that if our cohort had a higher event rate, larger sample size, or was followed for a longer period of time, it is likely that the association between NSVT and sudden death may well have achieved statistical power. Indeed, it is possible that nontertiary-based HCM cohorts (such as the present one) implicitly lack the statistical power to unequivocally demonstrate a significant relationship between arrhythmias on Holter ECG and outcome.

The ambulatory Holter ECG has been an important component of the outpatient evaluation and risk stratification of HCM patients (19–24). In the present study, ventricular arrhythmias on ambulatory Holter showed low positive and high negative predictive values for sudden death (9% and 95%, respectively). Therefore, while the presence of these arrhythmias did not consistently identify high-risk HCM patients, their absence more reliably defined those patients at low risk who deserve reassurance regarding their prognosis.

Study limitations. Since this is a retrospective clinical investigation, we acknowledge the possibility of some patient selection bias. On the other hand, the low annual sudden death rate in our cohort suggests that the selection of HCM patients for Holter ECG probably did not influence our findings substantially. For example, comparison of those 178 study patients with a Holter ECG to 118 HCM patients without a Holter ECG (who were not analyzed as part of the primary study population) with respect to demographic, clinical, echocardiographic, and outcome variables revealed no measurable differences with the exception of somewhat younger age and slightly increased left atrial size in the Holter group. Sudden death rate was 1.1% per year for patients with Holter ECG versus 1.0% without Holter ECG. Also, very young patients and those of advanced age may have been underrepresented in our study population, thereby reducing the power of generalizing our findings to HCM patients in these age groups. In addition, due to clinical care considerations, it was not possible to routinely withdraw patients from obligatory cardioactive medications before obtaining the Holter recordings. Nevertheless, we found no differences in arrhythmia frequency between those patients with or without drug therapy. Finally, the low incidence of sudden death may have influenced our sensitivity and predictive value calculations and reduced the power to detect a significant relationship between arrhythmias on Holter and outcome.

In conclusion, in our nontertiary-based population, HCM was associated with a particularly high frequency of a wide variety of ventricular and supraventricular tachyarrhythmias on ambulatory (Holter) ECG. Nevertheless, sudden death events proved to be relatively uncommon and frequent and/or complex ventricular arrhythmias had low positive but relatively high negative predictive value for HCM-related sudden death. Although the power of the Holter ECG in reliably assessing prognosis appears to vary among different HCM cohorts, based on the available data (including those presented here), it has sufficient clinical value to merit a continuing routine role in the outpatient evaluation of HCM patients.

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