European Heart Journal (2009) **30**, 2599–2605
doi:10.1093/eurheartj/ehp327

Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy

Juan R. Gimeno, Maite Tomé-Esteban, Carla Lofiego, José Hurtado, Antonios Pantazis, Bryan Mist, Pier Lambiase, William J. McKenna, and Perry M. Elliott*

The Heart Hospital, University College London, 16–18 Westmoreland Street, London W1G 8PH, UK

Received 29 October 2008; revised 11 July 2009; accepted 23 July 2009; online publish-ahead-of-print 17 August 2009

See page 2558 for the editorial comment on this article (doi:10.1093/eurheartj/ehp307)

Background Non-sustained ventricular tachycardia (NSVT) during ambulatory electrocardiographic monitoring (typically occurring at rest or during sleep) is associated with an increased risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. The prevalence and prognostic significance of ventricular arrhythmias during exercise is unknown.

Methods and results This was a cohort study, with prospective data collection. We studied 1380 patients, referred to a cardiomyopathy clinic in London, UK [mean age 42 years (SD 15); 62% male; mean follow-up 54 (SD 49) months]. Patients underwent two-dimensional and Doppler echocardiography, upright exercise testing, and Holter monitoring. Twenty-seven patients [mean age 40 (SD 14) years (18–64); 22 (81.5%) male] had NSVT (24) or ventricular fibrillation (VF) (3) during exercise. During exercise, 13 (54.2%) had more than one run of NSVT (maximum 5) with a mean heart rate of 221 (SD 48) b.p.m. Patients with exercise NSVT/VF had more severe hypertrophy (22.6 vs. 19.5 mm, $P = 0.009$) and larger left atria (47.3 vs. 43.7 mm, $P = 0.03$). Male gender was significantly associated with exercise NSVT/VF [22 (81.5%) vs. 832 (61.5%), $P = 0.03$]. Eight (29.6%) of the exercise NSVT/VF patients died or had a cardiac event (SD/ICD discharge/transplant) compared with 150 (11.1%) patients without exercise NSVT/VF, $P = 0.008$. Patients with NSVT/VF had a 3.73-fold increase in risk of SD/ICD discharge (HR 95% CI: 1.61–8.63, $P = 0.002$). Exercise NSVT alone was associated with a 2.82-fold increased risk (HR 95% CI: 1.02–7.75, $P = 0.049$). In multivariable analysis with other risk markers, exercise NSVT/VF (but not NSVT alone) was independently associated with an increased risk of SD/ICD [HR 3.14 (95% CI: 1.29–7.61, $P = 0.01$)].

Conclusion Ventricular arrhythmia during symptom limited exercise is rare in patients with hypertrophic cardiomyopathy, but is associated with an increased risk of sudden cardiac death.

Keywords Non-sustained ventricular tachycardia • Sudden death • Hypertrophic cardiomyopathy

Introduction

Non-sustained ventricular tachycardia (NSVT) during ambulatory ECG monitoring occurs in ~25% of patients with hypertrophic cardiomyopathy (HCM).[1–4] While it is usually asymptomatic, typically occurring during periods of heightened vagal tone, numerous studies have shown that its presence is associated with an increased risk of sudden cardiac death, particularly in young adults and children with the disease.[1–5] Only one study has reported on the prevalence of ventricular tachycardia during exercise, but this was unable to determine its prognostic significance.[6] The primary aims of this study were to determine the frequency of exercise-induced ventricular arrhythmia in a large referral population and its relation to the risk of sudden cardiac death. Secondary aims were to compare the clinical characteristics of patients with and without exercise-induced ventricular arrhythmia, to determine the relation between exercise-induced ventricular arrhythmia and conventional sudden death risk factors, and to

* Corresponding author. Tel: +44 207 573 8888, Fax: +44 207 573 8838, Email: pelliott@doctors.org.uk

determine the association between exercise-induced ventricular arrhythmia and all-cause mortality.

Methods

Study population

One thousand seven hundred and forty-two patients [40 (SD 18) years old, 1030 (59%) male] with HCM were assessed at St. George's Hospital and The Heart Hospital, London, UK between 1988 and 2004. Hypertrophic cardiomyopathy was defined by the presence of unexplained left-ventricular hypertrophy more than two standard deviations from normal age and size corrected values,[7] or by the presence of unexplained electrocardiographic and echocardiographic abnormalities in relatives of patients with unequivocal disease.[8] Patients with other disorders known to cause left-ventricular hypertrophy were excluded from the study. For the purposes of this study, patients were selected from the cohort of 1742 patients using the following criteria: (i) age more than 15 and $<$ 75 years; (ii) successful completion of symptom limited upright exercise testing on a treadmill or bicycle ergometer. This was a cohort study, with prospective data collection. The study complied with the Declaration of Helsinki.

Clinical assessment

A detailed family pedigree and clinical history were obtained from all patients. Chest pain was classified as exertional or atypical if it occurred at rest or lasted more than 30 min in the absence of myocardial infarction. Dyspnoea was coded according to the New York Heart Association classification. A history of syncope and palpitation was recorded.

Echocardiography

Two-dimensional and M-mode echocardiography were performed using standard methods.[9–11] Left-ventricular end-diastolic (LVEDd) and end-systolic (LVESd) dimensions were recorded from M-mode images obtained in the parasternal window at the level of the mitral leaflet tips. End-diastolic left-ventricular wall thickness was recorded in the anterior and posterior septum and in the lateral and posterior left-ventricular wall using short-axis two-dimensional images at the level of the mitral valve and papillary muscles. Anterior and posterior wall thickness at the apex was measured in the two chamber and short-axis apical views. Left-ventricular outflow tract velocities were measured from the apical five and three chamber views using continuous wave Doppler and left-ventricular outflow tract gradient (LVOTG) was calculated using the modified Bernouilli equation.

Ambulatory electrocardiography

Two or three channel ambulatory ECG monitoring (24–48 h) was performed while patients performed routine daily activities (Marquette Electronics, Milwaukee, WI, USA). Non-sustained ventricular tachycardia was defined as three or more consecutive ventricular beats at a rate of $\geq$120 b.p.m., lasting for $<$30 s.[3]

Exercise testing

Patients were exercised to exhaustion or the development of symptoms on a treadmill using the Bruce or modified Bruce protocols (1988–94), or on an upright bicycle ergometer (Sensormedics ergometrics 800S) using an incremental ramp protocol (1994 onwards). Arterial blood pressure was measured by auscultation of the brachial artery during deflation of a mercury sphygmomanometer at rest, every minute during exercise and for the first 5 min of recovery. Blood pressure response during exercise was considered abnormal when the systolic blood pressure failed to increase by more than 25 mmHg from baseline, or when there was a decrease of 10 mmHg or more in systolic blood pressure during exercise.[12,13]

Continuous 12-lead ECG monitoring (Marquette Max 1, Marquette Electronics, Milwaukee, WI, USA), and heart rate measurements were performed throughout exercise. Exercise-induced ventricular tachycardia was defined as the presence of three or more consecutive ventricular beats at a rate of $\geq$120 b.p.m.

Sudden death risk factors in hypertrophic cardiomyopathy

Family history of sudden unexpected death under 40 years of age, unexplained syncope, severe hypertrophy (maximum left ventricular thickness $\geq$30 mm), severe left-ventricular outflow tract gradient ($>$90 mmHg), abnormal blood pressure response to exercise (in patients under 40 years of age), NSVT on Holter were coded as risk factors for sudden death.[1,12–17]

Survival analysis

Survival data were collected between July 1997 and September 2004 at routine clinic visits and by direct communication with patients and their physicians or general practitioners. For the purposes of the survival analysis, follow-up started with the date of the first exercise test with a documented episode of exercise ventricular arrhythmia or from the first evaluation at our institution in patients that did not develop exercise ventricular arrhythmia. First evaluation included complete cardiac examination, ECG, echocardiogram, Holter, and cardiopulmonary exercise test. 'Lost to follow-up' was defined as no clinical review for $\geq$1.5 years.

The following end-points were used in the survival analysis:

(1) Sudden cardiac death: Witnessed sudden cardiac death within 1 h of new symptoms. Nocturnal deaths with no antecedent history of worsening symptoms were also coded as sudden.
(2) Aborted sudden cardiac death: successfully resuscitated from sustained ventricular tachycardia or ventricular fibrillation (VF) (including appropriate shock from an internal cardioverter defibrillator).
(3) Progressive heart failure: Death preceded by signs and or symptoms of heart failure of more than 1h duration, and/or cardiogenic shock.
(4) Orthotopic heart transplantation.
(5) Other cardiovascular death: Stroke, pulmonary or systemic embolism, myocardial infarction.
(6) Non-cardiovascular death: Death secondary to non-cardiovascular events or of unknown cause.

Primary outcome (sudden cardiac death) was considered when (1) and (2) occurred. Secondary outcome was coded when all cause mortality or transplant occurred (1–6).

Statistical analysis

Clinically relevant variables and results from echocardiography, Holter, and exercise test were stored prospectively in a dedicated database. Details on exercise ventricular arrhythmias (morphology, rate, etc.) were reviewed retrospectively. Variables related to sudden death risk factors were defined a priori and follow-up

information was collected prospectively for survival analysis. Further analyses were explanatory.

Continuous variables are presented as mean (SD) and qualitative variables are expressed as count (%). Two-tailed Student *t*-test, χ^2 test, or Fisher exact test was used when appropriate to compare group data. Kaplan–Meier method was used for survival curves and for calculations of 5 year survival estimations. The magnitude of risk was calculated using the Cox regression model with 95% confidence intervals defined as $\pm 1.96 \times$ standard error. Variables associated with the defined outcomes ($P \leq 0.1$) were included in the multivariable analysis. All *P*-values were two-sided. SPSS for PC statistical program (version 11.0) was used for the analysis.

Results

One thousand three hundred and eighty patients [mean age 42 (SD 15), male 854 (61.9%)] fulfilled the selection criteria for the study (*Table 1*). One hundred and ten (8.0%) patients were lost to follow-up; 42 (3.1%) patients were evaluated only once within the last year of the study period. Twenty-seven patients had ventricular arrhythmia during exercise [40 (SD 14) years (18–64), 22 (81.5%) males]. Ventricular fibrillation occurred during exercise in three (0.2%) patients (female aged 29, and 2 males aged 33 and 64). No patient developed sustained ventricular tachycardia during exercise test. Twenty-four [mean age 40 (SD 14) years (18–60), 20 (83.3%) male] patients had NSVT during exercise. In all cases this was asymptomatic. Original ECG recordings were available for review in 19 cases. Thirteen patients (54.2%) had more than one run of NSVT (maximum five episodes). Runs varied from 3 beats up to 15 beats, with a mean heart rate of 221 (SD 48) b.p.m. Five of these 24 patients (20.8%) with exercise NSVT had $\geq$2 mm ST depression during exercise (one with normal angiogram and four aged under 40 years of age) (*Table 2*).

The clinical and echocardiographic characteristics of patients with exercise ventricular arrhythmias are summarized in *Table 1*. Compared with patients without exercise ventricular arrhythmias, patients with exercise NSVT/VF had more severe hypertrophy and larger left atria. Male gender was significantly associated with exercise NSVT/VF [22 (81.5%) vs. 832 (61.5%), $P = 0.03$]. A greater proportion of patients with exercise NSVT/VF had NSVT during ambulatory ECG monitoring [11 (40.7%) vs. 232 (17.1%), $P = 0.002$].

Table 1 Baseline characteristics of the study population in relation to the presence of ventricular arrhythmia during exercise

	Exercise NSVT/VF	No exercise NSVT/VF	*P*-value
n	27 (2.0)	1353 (98.0)	
Male/Female	22/5	832/521	0.03
Age (years)	40 (14)	42 (15)	0.6
Follow-up (months)	68 (45)	53 (49)	0.1
Prior VF	0 (0.0)	27 (2.0)	—
AF	5 (18.5)	119 (8.8)	0.08[a]
Chest pain	10 (37.0)	363 (26.8)	0.3
NYHA			
I	19 (70.4)	875 (64.7)	0.5
II	8 (29.6)	440 (32.5)	0.7
III–IV	0 (0)	38 (2.8)	0.9[a]
FHSCD	9 (33.3)	391 (28.9)	0.5
Palpitations	5 (18.5)	324 (23.9)	0.5
Syncope	3 (11.1)	191 (14.1)	0.8
ABPR	6 (22.2)	292 (21.6)	0.9
ABPR (<40 years of age)	4 (14.8)	175 (12.9)	0.8[a]
Peak VO_2 (%)	70.1 (20.9)	74.7 (24.1)	0.4
Holter NSVT	11 (40.7)	232 (17.1)	0.002
MLVWT (mm)	22.6 (6.0)	19.5 (6.2)	0.009
LVOTO	9 (33.3)	357 (26.4)	0.4
Pattern			
ASH	21 (77.8)	839 (62.0)	0.1
Concentric	6 (22.2)	351 (25.9)	0.6
Apical	0 (0)	84 (6.2)	0.4[a]
Other	0 (0)	79 (5.8)	0.5[a]
LVED (mm)	42.3 (6.6)	44.2 (6.3)	0.1
LVES (mm)	23.3 (6.3)	25.6 (6.3)	0.07
FS (%)	45.3 (9.7)	42.6 (9.2)	0.1
LA (mm)	47.3 (8.4)	43.7 (8.4)	0.03

VF, ventricular fibrillation; AF, atrial fibrillation; chest pain, exertional chest pain; NYHA, New York Heart Association dyspnoea class; FHHCM, family history of hypertrophic cardiomyopathy; FHSCD, family history of sudden cardiac death; ABPR, abnormal blood pressure response during upright exercise; Peak VO_2 (%), percentage of predicted peak VO_2 during exercise; NSVT, non-sustained ventricular tachycardia; MLVWT, maximal lest ventricular wall thickness (mm); ASH, asymmetrical septal hypertrophy; LVED, left-ventricular end-diastolic diameter (mm); LVES, left-ventricular end-systolic diameter (mm); FS, fractional shortening (%); LA, left atrial diameter (mm); LVOTO, left-ventricular outflow tract gradient ($\geq$30 mmHg); ICD, implantable cardioverter defibrillator.
[a]Fisher exact test.

Exercise-induced ventricular arrhythmias and survival from sudden death

Three patients with exercise-induced NSVT died suddenly and one patient had a syncopal sustained ventricular tachycardia requiring resuscitation. Two of the three patients with VF during exercise (female aged 29 and a male aged 33 years old) that were managed medically in accordance with standard practice in 1994 died suddenly at 11 and 150 months following the exercise test. The third (64 year old male) received an implantable cardioverter defibrillator (ICD) and had no appropriate shocks after 66 months of follow-up (*Table 2*).

When exercise NSVT and VF were considered together, patients with ventricular arrhythmias had a 3.73-fold increase in risk of SD/ICD discharge compared with patients with no ventricular arrhythmias during exercise (HR 95% CI: 1.61–8.63, $P = 0.002$). Exercise NSVT alone was associated with a 2.82-fold (HR 95% CI: 1.02–7.75, $P = 0.049$) increased risk of sudden death or resuscitated ventricular arrhythmia.

Five year survival from sudden death or ICD discharge was significantly lower in patients with exercise NSVT/VF [(81.6% (95%

Table 2 Electrocardiographic characteristics of patients with exercise-induced ventricular arrhythmias

Age	Sex	Number of runs	Beats longest	Max HR	VT morphology	Sym	Stage of exercise[a]	ABPR	Medication	ST depression	Angiogram
18	F	1	5	250	RBBB	SOB	Rec	N	Amio	Y	NP
20	M	1	3	150	RBBB	SOB	Rec	Y	N	Y	NP
20[b]	M	1	3	166	Polym	None	2	N	N	N	NP
22	M	1	3	NA	NA	SOB	3	Y	N	NA	NP
25	M	4	5	250	LBBB	Palp	3	Y	Amio	N	NP
29[c]	F	1	3	250	Polym	SOB	Rec	N	N	N	NP
30[c]	M	5	10	230	RBBB	Presyn	4	N	BB	N	Normal
32	M	4	7	270	Polym	None	4	N	N	Y	NP
34	M	2	6	150	LBBB	SOB	2+rec		Sotalol	N	Normal
36	M	1	NA	NA	NA	None	4	N	N	N	NP
37	M	1	9	200	RBBB	None	Rec	N	BB	Y	NP
39[c]	M	2	3	230	RBBB	None	3	N	N	Y	Normal
43	F	5	4	250	RBBB	SOB	2	N	N	N	NP
43	M	4	4	272	Polym	Presyn	4	N	N	N	Normal
43	M	4	13	300	LBBB+Polym	None	4+rec	N	N	N	Normal
47	M	1	11	180	LBBB	None	Rec	N	N	N	NP
49	M	1	4	190	Polym	None	Rec	N	Amio	N	Normal
50	F	2	5	250	RBBB	SOB	2+rec	N	Amio	N	NP
54	M	4	4	188	LBBB	SOB	3	Y	BB+amio	N	Normal
56	M	2	3	150	Polym	None	2	N	BB	N	Normal
59	M	1	3	NA	NA	None	4	N	Diso	N	Normal
59	M	1	NA	NA	NA	None	1		N	NA	Normal
60	M	NA	NA	NA	NA	None	2	N	N	NA	Normal
60	M	2	15	280	Polym	None	4	N	N	N	NP
29[c]	F				VF		4	Y	BB	Y	Normal
33[c]	M				VF		4	N	Fleca	N	NP
64	M				VF		3	Y	BB	NA	NP

NA, original ECG recordings not available; HR, maximal heart rate of ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; Polym, polymorphic; sym, symptoms leading to stop the test or end exercise; SOB, short of breath; palp, palpitations; rec, recovery; ABPR, abnormal blood pressure response; amio, amiodarone; BB, beta-blocker; fleca, flecainide; diso, disopyramide; NP, not performed.
[a]Each stage represents a 3 min interval.
[b]Syncopal sustained VT that required cardioversion.
[c]Sudden death

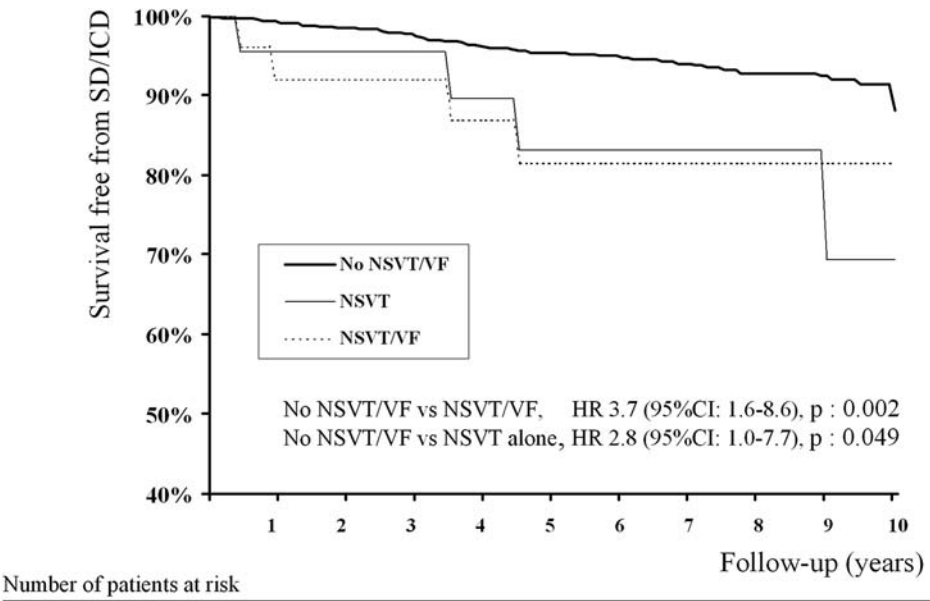
CI: 64.6–98.5) vs. 94.4% (95% CI: 92.7–96.1), $P = 0.002$)] (*Figure 1*). Five year survival from sudden death or ICD discharge was also significantly lower in patients with exercise NSVT alone [(83.3% (95% CI: 65.3–100) vs. 94.4% (95% CI: 92.7–96.1), $P = 0.049$)], (*Figure 1*).

Relation of exercise non-sustained ventricular tachycardia/ventricular fibrillation to other risk factors for sudden death

One patient (33.3%) with exercise VF had NSVT on Holter, one (33.3%) had an abnormal blood pressure response during exercise, and another had family history of sudden cardiac death. Two patients (66.6%) had severe left-ventricular outflow tract obstruction (92 and 100 mmHg) and one (33.3%) had severe hypertrophy (30 mm) (*Table 3*).

Exercise NSVT/VF was associated with a 3.03-fold increase in risk of SD/ICD discharge (HR 95% CI: 1.30–7.08, $P = 0.01$) after adjusting for the number of other described sudden death markers. In this model, the hazard ratio for every increase in the number of risk factors was 1.71 (HR 95% CI: 1.37–2.14, $P < 0.0001$). In multivariable analysis, including the predefined risk factors (*Table 4*), exercise NSVT/VF was independently associated with an increased risk of SD/ICD [HR 3.14 (95% CI: 1.29–7.61, $P = 0.01$)].

Nine (37.5%) patients with exercise NSVT had two or more risk factors compared with 269 (19.9%) patients without exercise NSVT, $P = 0.049$. When the number of risk factors was taken as a continuous variable, there was no significant difference in patients with and without exercise NSVT [mean number of risk factors 1.17 (SD 0.24) vs. 0.88 (SD 0.02), respectively; $P = 0.2$)]. Hazard ratio for SD/ICD for exercise NSVT alone (i.e. excluding the three patients with exercise induced VF) in the presence of other risk factors was 2.33 (95% CI: 0.84–6.47, $P = 0.103$).



Number of patients at risk

No NSVT/VF	1353		854		590		426		271	161
NSVT	24		19		15		11		8	2
NSVT/VF	27		21		17		12		9	2

Figure 1 Cumulative survival free from sudden death, appropriate implantable cardioverter defibrillator discharge, and resuscitated ventricular arrhythmia in patients with and without exercise ventricular arrhythmia.

Exercise ventricular arrhythmias and all-cause survival

Coded events in the exercise NSVT/VF group were five SD, one sustained syncopal VT, one heart transplantation, and one non-cardiac related death. Eight (29.6%) of the 27 patients with exercise NSVT/VF patients died, were transplanted, had an ICD discharge, or experienced syncopal sustained VT compared with 150 (11.1%) patients without exercise NSVT/VF, $P = 0.008$.

There was a significant association between exercise NSVT/VF and the composite of all-cause death, aborted SD, and cardiac transplantation [2.18-fold increase (HR 95% CI: 1.07–4.45, $P = 0.03$)]. When modelled with exercise NSVT alone, there was no difference in risk of the composite end-point [HR 1.86 (95% CI: 0.82–4.22, $P = 0.13$)].

Five year survival from any death, ICD shock, resuscitated ventricular arrhythmia, and transplantation was lower in patients with [81.6% (95% CI: 64.6–98.5) vs. without exercise NSVT/VF 89.3% (95% CI: 87.0–91.6), $P = 0.03$]. When exercise NSVT alone was analysed, 5 year survival from all-cause combined event was similar in patients with and without exercise NSVT [83.3% (95% CI: 65.3–100) vs. 89.3% (95% CI: 87.0–91.6), $P = 0.14$].

Discussion

This study shows that while ventricular arrhythmias during exercise are rare in HCM, they are associated with an increased risk of sudden cardiac death. These findings emphasize the importance of exercise testing in risk stratification in patients with HCM and suggest that exercise-induced NSVT should be taken into account when assessing the need for an ICD.

While sudden death rates in HCM populations are remarkably low, the fact that sudden death frequently occurs without warning in young and often asymptomatic people provides a powerful stimulus to pre-emptively identify individuals at high risk.[18–19] Numerous clinical features are associated with an increased risk of sudden cardiac death, but with the exception of prior cardiac arrest, most associations are relatively weak with low predictive power.[1,3,13–17] This limitation is partly overcome by considering the 'global risk burden' in individual patients using a small number of easily assessed clinical features. This approach (enshrined in consensus guidelines) identifies the majority of patients that are at very low risk of sudden death and the much smaller number of patients at very high risk.[20] Patients with only a single risk factor continue to pose a dilemma and are, for the present, managed empirically.

Non-sustained ventricular tachycardia during ambulatory monitoring is common in patients with HCM. Its prevalence is age-dependent, with a very low frequency in children and adolescents, rising to 25% or more in patients over the age of 40 years.[3] A number of studies have suggested that there is a circadian variation in the frequency of NSVT with a mid-morning peak in one study.[21] The biological basis for the circadian pattern is unknown, but the timing of most events suggests an influence of vagal tone. Numerous studies have indicated that NSVT during Holter monitoring is associated with a 2–2.5-fold increase in sudden death risk.[2–4] There is very little evidence that the

Table 3 Risk stratification of the 27 patients with exercise-induced ventricular arrhythmia (24 NSVT+3 VF)

Age	Sex	MaxLVH	Gradient	NSVTHolter	Syncope	FHSCD	ABPR	Num of RF
18	F	29	19	Y	Y	N	N	2
20	M	34	7	Y	N	Y	Y	4
20[a]	M	25	21	N	N	N	N	0
22	M	33	41	N	N	Y	Y	3
25	M	26	9	Y	N	N	Y	2
29[b]	F	24	50	Y	Y	N	N	2
30[b]	M	24	31	N	N	N	N	0
32	M	18	9	Y	N	Y	N	2
34	M	12	4	NA	N	N	NA	0
36	M	20	6	N	N	Y	N	1
37	M	20	100	NA	N	N	N	1
39[b]	M	12	49	Y	N	N	N	1
43	F	16	12	N	N	N	N	0
43	M	21	36	Y	N	N	N	1
43	M	13	3	Y	N	Y	N	2
47	M	19	5	Y	Y	N	N	2
49	M	17	21	N	N	N	N	0
50	F	24	6	N	N	Y	N	1
54	M	25	3	N	N	N	Y	0
56	M	28	18	N	N	N	N	0
59	M	22	13	N	N	N	N	0
59	M	22	9	N	N	Y	NA	1
60	M	32	6	Y	N	Y	N	3
60	M	22	58	N	N	N	N	0
29[b]	F	21	100	N	N	N	Y	2
33[b]	M	22	19	N	N	Y	N	1
64	M	30	92	Y	N	N	Y	3

NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; ABPR, abnormal blood pressure response; FHSCD, family history of sudden cardiac death. Num of RS, number of risk factors; NA, not available.
Maximal LVH ≥30 mm and severe gradient (≥90 mmHg) were taken as risk factors for number of risk factors calculations. ABPR was considered as a risk factor only in patients under 40 years of age.
[a]Syncopal sustained VT that required cardioversion.
[b]Sudden death.

duration, frequency, or rate of runs influence prognostic significance, but the relative risk of sudden death is much higher in younger patients.[3]

In this study, patients with exercise-induced ventricular arrhythmias had significantly more hypertrophy, but in contrast with previous reports, severe LVH was not associated with SCD in the multivariable analysis, probably reflecting the influence of more powerful clinical markers not included in previous models. This finding should be examined in future studies with larger populations of patients.

We are aware of only one other study that has examined the frequency of ventricular tachycardia during exercise in patients with HCM.[6] In a cohort of 86 patients, haemodynamically stable ventricular tachycardia was observed in 1.2%, a very similar proportion to that seen in this study. However, the small size of the cohort meant that no conclusions could be drawn on the prognostic significance of exercise-induced NSVT. In this study, the presence of VF or exercise-induced NSVT was associated with a 3.73-fold increase in the risk of sudden cardiac death or haemodynamically compromising sustained ventricular tachycardia during follow-up. When modelled with other risk factors, a history of exercise-induced NSVF/VT was associated with a 3.14-fold increase in SD/ICD risk (*Table 4*). Non-sustained ventricular tachycardia alone was associated with an additive risk in univariable analysis, but did not reach statistical significance in the multivariable analysis, probably reflecting the small size of the cohort with exercise induced NSVT.

There are many potential mechanisms for NSVT in HCM, including abnormal automaticity, early after-depolarizations, and micro- and macro-reentry caused by myocyte disarray, fibrosis, and disruption of gap junctions. In addition, many patients have evidence for myocardial ischaemia and abnormal autonomic function that may trigger or modulate the susceptibility to ventricular arrhythmia. The fact that exercise-induced ventricular tachycardia is so rare suggests that the increased adrenergic tone during exercise in HCM optimizes myocyte-to-myocyte coupling and reduces

Table 4 Predictors of sudden death, appropriate implantable cardioverter defibrillator discharge, and resuscitated ventricular arrhythmia (multivariable analysis, Cox regression model)

	HR	95% CI	*P*-value
Exercise NSVT/VF	3.14	1.29–7.61	0.01
Holter NSVT	2.57	1.55–4.26	0.0001
Severe LVOTO	2.41	1.08–5.53	0.03
Syncope	2.08	1.21–3.56	0.008
FHSCD	1.79	1.09–2.94	0.02
ABPR	1.43	0.86–2.36	0.2
Severe LVH	0.90	0.42–1.93	0.8

NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; Severe LVH, maximal left ventricular hypertrophy of ≥30 mm; Severe LVOTO, left ventricular outflow tract obstruction of ≥90 mmHg; ABPR, abnormal blood pressure response (in patients under 40 years of age); FHSCD, family history of sudden cardiac death.

the dispersion of repolarization that promotes the initiation of ventricular tachycardia and fibrillation. Whatever the mechanism, the findings in this study suggests that exercise VT may be a novel marker for sudden death risk in HCM that should be considered in the overall risk profile.

Limitations

Patients who were unable to exercise or who did not successfully complete the symptom limited upright exercise testing were excluded from the study. Thus, selection of participants could be biased towards the less symptomatic or a lower risk profile group.

Status at the end of the study could not be assessed in 8.0% of patients, but none of the 27 patients with exercise-induced ventricular arrhythmia were lost to follow-up. We did not systematically conduct an evaluation of the national registry of deaths for technical (lack of NHS number) and financial reasons.

The calculated statistical power of the study for the value of exercise-induced ventricular arrhythmia as marker for sudden death was 85.5% (α: 10%).

Conclusions

This study confirms the importance of exercise testing in the assessment of patients with HCM and suggests that ventricular arrhythmias during exercise may be a novel marker of sudden death risk.

Conflict of interest: none declared.

References

1. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;**36**:2212–2218.
2. Spirito P, Rapezzi C, Autore C, Bruzzi P, Bellone P, Ortolani P, Fragola PV, Chiarella F, Zoni-Berisso M, Branzi A. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and non-sustained ventricular tachycardia. *Circulation* 1994;**90**:2743–2747.
3. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;**42**:873–879.
4. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 h ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. *Am J Cardiol* 1981;**48**:252–257.
5. Elliott PM, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;**363**:1881–1891.
6. Bunch TJ, Chandrasekaran K, Ehrsam JE, Hammill SC, Urban LH, Hodge DO, Ommen SR, Pellikka PA. Prognostic significance of exercise induced arrhythmias and echocardiographic variables in hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**99**:835–838.
7. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarfas I, Martin I, Nordet P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation* 1996;**93**:841–842.
8. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart* 1997;**77**:130–132.
9. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1983;**2**:437–444.
10. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. A wide angle, two dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981;**48**:418–428.
11. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, Williams WG. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Prog Cardiovasc Dis* 1985;**28**:1–83.
12. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation* 1990 **82**:1995–2002.
13. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation* 1997;**96**:2987–2991.
14. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;**342**:1778–1785.
15. Elliott PM, Gimeno JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:420–424.
16. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303.
17. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left Ventricular Outflow Tract Obstruction and Sudden Death Risk in Patients with Hypertrophic Cardiomyopathy. *Eur Heart J* 2006;**27**:1933–1941.
18. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical Trends in Reported Survival Rates in Patients with Hypertrophic Cardiomyopathy. *Heart* 2006;**92**:785–791.
19. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 2000;**102**:858–864.
20. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *Eur Heart J* 2003;**24**:1965–1991.
21. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:697–704.