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Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy

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KEYWORDS
Outflow tract obstruction;
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Aims Left ventricular outflow tract obstruction (LVOTO) is associated with reduced survival in patients with hypertrophic cardiomyopathy (HCM). The influence of LVOTO on survival from SD in relation to other recognized clinical risk markers is unknown.

Methods and results A total of 917 patients with HCM (554 males, 43 ± 15 years) were studied; 288 (31.4%) had LVOTO at rest (≥30 mmHg). During follow-up [median 61 (30;99) months], 54 (5.9%) patients died suddenly (SD), survived ventricular fibrillation, or had an appropriate ICD discharge; 25 (2.7%) died from heart failure or were transplanted; 17 (1.8%) died from other cardiovascular causes. Five-year survival from all-cause death or cardiac transplantation was lower in patients with LVOTO [86.5% (95% CI: 81.7–91.2) vs. 90.1% (95% CI: 87.3–92.8), $P = 0.006$], with a trend towards higher all-cause death and transplantation with increasing LVOTO [(RR per 20 mmHg = 1.24 (95% CI: 1.08–1.42), $P = 0.003$)]. In patients with obstruction, there was a significant relation between 5-year survival from all-cause death and functional limitation (NYHA class I: 91.0%; NYHA class II: 83.3%; NYHA class III/IV: 82.6%, $P = 0.002$). LVOTO was associated with reduced survival from SD and ICD discharge (SD/ICD) [91.4% (95% CI: 87.4–95.3) vs. 95.7% (95% CI: 93.8–97.6), $P = 0.0004$]. Magnitude of LVOTO was related to a higher occurrence of SD/ICD [RR per 20 mmHg = 1.36 (95% CI: 1.12–1.65), $P = 0.001$]. There was no relation between survival from SD/ICD, LVOTO, and NYHA class. The annual rate of SD/ICD in patients with LVOTO and no risk factors was 0.37% (95%CI: 0.05–1.35). There was a trend towards lower survival from SD/ICD, with increasing numbers of risk factors in patients with and without LVOTO ($P = 0.002$ and $P = 0.002$, respectively). Multivariable analysis demonstrated that LVOTO was an independent predictor of SD/ICD, with a 2.4-fold ($P = 0.003$) increase in the risk of SD/ICD.

Conclusion LVOTO is associated with an increased risk of SD/ICD that is related to the severity of obstruction and the presence of other recognized risk factors for SD. The low sudden death mortality in asymptomatic patients with LVOTO and no other SD risk markers suggests that aggressive interventions to reduce LVOTO are unwarranted in this group. Further studies are required to determine the most appropriate treatment strategies (ICD or gradient reduction) in patients with additional risk factors.

Introduction

Approximately 25% of patients with hypertrophic cardiomyopathy (HCM) have dynamic left ventricular outflow tract obstruction (LVOTO) caused by contact between the anterior mitral valve leaflet and the interventricular septum in systole.[1,2] When severe, this can cause dyspnoea, chest pain, and syncope, and predisposes to the development of atrial arrhythmias.[2] Two recent studies have shown that LVOTO is associated with an increased risk of death[3,4]; the implications of this observation for clinical risk stratification and prevention of sudden cardiac death (SD) in patients with HCM are uncertain. The aim of this study was to examine the influence of symptomatic status and the presence of other recognized risk markers for sudden death on the relation between LVOTO and the risk of sudden cardiac death.

Methods

Patients

The study population comprised all adult patients (≥16 years of age) referred to a dedicated HCM clinic at St George's Hospital, London, UK, between January 1988 and March 2002. The diagnosis of HCM was based on the presence of unexplained left ventricular hypertrophy greater than two standard deviations from the normal range[2] or on the presence of published criteria for the diagnosis of familial disease in the relatives of patients with unequivocal disease.[5,6] Patients with other disorders known to cause hypertrophy were excluded from the analysis. The presence or absence of medications was not used as a selection criterion.

All patients' medical history was analysed and they underwent physical examination. Dyspnoea was classified using the New York Heart Association system. Chest pain was classified as exertional if

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precipitated by physical activity and relieved by rest, or atypical if it occurred at rest or lasted more than 30 min in the absence of myocardial infarction. Patients were advised not to take medications 48 h prior to the first evaluation at St George's Hospital in order to avoid masking the effect of medications on LVOTO and exercise test variables.

Forty-eight-hour ambulatory electrocardiography and upright exercise on either a bicycle ergometer (Sensormedics Ergometrics 800S) or a treadmill with simultaneous breath-by-breath analysis of respiratory gases (VMax 229 Console, Sensormedics, Yorba Linda, CA, USA) and measurement of systolic blood pressure were performed in all patients in accordance with previously published protocols.[7]

Echocardiography

All patients were imaged in the left lateral decubitus position using an Acuson 128 XP/10 (Mountain View, CA, USA), GE Vingmed system V (GE Ultrasound Europe), or a Hewlett-Packard Sonos 1000 (Hewlett-Packard Corp., Andover, MA, USA). Standard techniques were used to obtain M-mode, two-dimensional, and Doppler measurements. Left ventricular cavity dimensions and left atrial size were measured in accordance with American Society of Echocardiography guidelines. The severity and distribution of left ventricular hypertrophy were assessed in the parasternal short-axis plane by dividing the left ventricle into four regions: anterior and posterior septa and lateral and posterior segments. Wall thickness was determined using two-dimensional short-axis images at the level of the mitral valve and the papillary muscles in each of the four segments. Maximal left ventricular wall thickness was defined as the greatest thickness in any single segment. Patterns of hypertrophy were defined in accordance with previously published methods.[8,9]

Left ventricular outflow gradients were determined using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients were determined using the modified Bernouilli equation: Gradient $= 4V^2$, where V is the peak aortic outflow velocity.

Clinical assessment of sudden death risk

On the basis of previously published data,[7,10–19] five clinical features were defined as risk markers for sudden cardiac death:

(i) *Non-sustained ventricular tachycardia*. Three or more consecutive ventricular extrasystoles at a rate of $\geq$120 bpm, lasting for $<$30 s.
(ii) *Abnormal exercise blood pressure response*. A rise in systolic blood pressure from baseline to peak exercise of $<$25 mmHg or a fall of $>$10 mmHg from baseline or the maximum achieved blood pressure. The presence of an abnormal response was only considered as a risk factor in patients aged $<$40 years of age.
(iii) *Family history of premature sudden death*. History of sudden cardiac death in relatives under 40 years of age.
(iv) *Unexplained syncope*. Recurrent unexplained syncope within the previous year of first evaluation.
(v) *Severe left ventricular hypertrophy*. A left ventricular wall thickness in any myocardial segment of $\geq$30 mm on two-dimensional echocardiography.

Survival analysis

Follow-up data were obtained from routine hospital attendances and by direct contact with patients' medical practitioners. For the survival analysis, the start of follow-up was defined as the first echocardiogram at St George's Hospital or the first echocardiogram to demonstrate an outflow tract gradient of $\geq$30 mmHg. In patients with obstruction who underwent septal alcohol ablation or myectomy, follow-up was censored at the time of the procedure.

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

(i) *Sudden cardiac death*. Witnessed sudden death with or without documented ventricular fibrillation, death within 1 h of new symptoms, or nocturnal death with no prior history of worsening symptoms.
(ii) *First documented internal cardioverter defibrillator discharge for sustained ventricular tachycardia or ventricular fibrillation*. Subsequent discharges in the same patient were not counted.
(iii) *Death from congestive cardiac failure*. Death preceded by progressive signs and symptoms of heart failure or cardiogenic shock.
(iv) *Orthotopic cardiac transplantation*.
(v) *Other cardiovascular deaths*. stroke, perioperative, thrombo-embolism, or myocardial infarction.
(vi) *Non-cardiovascular death*.

SPSS statistical software (SPSS Inc., Chicago, IL, USA, version 10.0) was used for the statistical analysis. Patients were divided into two groups according to the presence or absence of LVOTO ($\geq$30 mmHg). In order to assess the linear relation between gradient and survival, patients were divided into five groups on the basis of their resting left ventricular outflow tract gradient: $<$30, 30–49, 50–69, 70–89, and $\geq$90 mmHg. *A priori*, gradients $\geq$90 mmHg were defined as severe obstruction. Student's *t*-test was used for comparisons between continuous variables; Pearson's χ^2 or Fisher's exact test was used for dichotomous variables. Survival estimates were calculated using the Kaplan–Meier method, and their relation to outflow tract gradients determined using log rank for trend. The magnitude of risk was calculated using the Cox regression model with 95% CI. A *P*-value $<$0.05 was considered significant. All *P*-values were two-sided.

Results

Between January 1988 and March 2002, 1222 patients with HCM were evaluated; 126 patients under 16 years of age and 179 patients with follow-up of $<$6 months were excluded. The final study cohort comprised 917 adult patients with HCM (554 males, mean age 43 $\pm$ 15 years, range 16–88).

The baseline clinical and echocardiographic data in the study cohort are shown in *Table 1*. Two hundred and eighty-eight (31.4%) patients had a peak left ventricular outflow tract gradient $\geq$30 mmHg. The relation of baseline clinical characteristics to the presence of outflow tract obstruction is shown in *Table 1*. Patients with obstruction were older and had a higher incidence of chest pain and dyspnoea class II or more. There was no difference in the prevalence of syncope. Patients with obstruction had smaller end-diastolic and end-systolic left ventricular cavity dimensions, larger left atrial size, and greater maximum left ventricular wall thickness. The percentage of predicted peak oxygen consumption during exercise was lower in patients with obstruction, but there was no difference in the frequency of abnormal blood pressure responses. Medications of the study population during follow-up are listed in *Table 2*.

Relation between LVOTO and survival

Median follow-up in the entire cohort was 61 (30;99) months. The duration of follow-up was shorter in patients with obstruction [median 52 (26;88) months, $P = 0.004$]. The total number of deaths, cardiac transplants, ICD discharges, and episodes of resuscitated VF during follow-up

Table 1 Baseline characteristics and outcomes of the study population in relation to LVOTO (mmHg)

	<30	≥30	Total	Significant *P*-value
N	629 (68.6)	288 (31.4)	917 (100)	
Male/female	377/252	177/111	554/363	0.7
Age (years)	41 (15)	46 (16)	43 (15)	<0.0001
Age at diagnosis	36 (15)	41 (17)	38 (16)	<0.0001
Follow-up (months)	63 (31;109)	52 (26;88)	61 (30;99)	<0.001
VF	13 (2.1)	4 (1.4)	17 (1.9)	0.5
AF	47 (7.5)	20 (6.9)	67 (7.3)	0.8
Chest pain	147 (23.4)	116 (40.3)	263 (28.7)	<0.0001
NYHA				
I	442 (70.3)	133 (46.2)	575 (62.7)	<0.0001
II	175 (27.8)	132 (45.8)	307 (33.5)	<0.0001
III–IV	12 (1.9)	23 (8.0)	35 (3.8)	<0.0001
FHHCM	318 (50.6)	79 (34.6)	397 (43.3)	<0.0001
FHSCD	222 (35.3)	56 (19.4)	278 (30.3)	<0.0001
Palpitations	155 (24.6)	81 (29.2)	236 (25.7)	0.4
Syncope	99 (15.7)	43 (15.1)	142 (15.5)	0.8
ABPR	160 (25.4)	86 (29.8)	246 (26.8)	0.1
Peak VO_2 (%)	74.6 (21.7)	65.5 (17.4)	71.6 (20.8)	<0.0001
NSVT	112 (17.8)	60 (20.8)	172 (18.8)	0.3
MLVWT (mm)	19.7 (6.2)	21.9 (5.2)	20.4 (6.0)	<0.0001
Pattern				
ASH	384 (61.0)	207 (71.9)	591 (64.4)	0.001
Concentric	188 (29.9)	64 (22.2)	252 (27.5)	0.02
Apical	40 (6.4)	3 (1.0)	43 (4.7)	<0.0005
Other	17 (2.7)	14 (4.9)	31 (3.4)	
LVED (mm)	44.3 (6.4)	42.5 (5.5)	43.7 (6.2)	<0.0001
LVES (mm)	26.2 (6.5)	22.8 (5.1)	25.2 (6.3)	<0.0001
FS (%)	41.1 (8.9)	46.2 (8.3)	42.7 (9.0)	<0.0001
LA (mm)	41.8 (8.1)	46.7 (7.5)	43.3 (8.2)	<0.0001
Status				
Alive	556 (88.4)	239 (83.0)	795 (86.7)	
Sudden death	16 (2.5)	26 (9.0)	42 (4.6)	
Resuscitated VF	3 (0.5)	1 (0.3)	4 (0.4)	
Heart failure death	16 (2.5)	1 (0.3)	17 (1.9)	
Heart transplantation	7 (1.1)	1 (0.3)	8 (0.9)	
Other cardiovascular death	12 (1.9)	5 (1.7)	17 (1.9)	
Non-cardiac death	12 (1.9)	14 (4.9)	26 (2.8)	
ICD discharge	7 (1.1)	1 (0.3)	8 (0.9)	

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 on Holter monitoring; MLVWT, maximal lest ventricular wall thickness (mm); ASH, asymmetrical septal hypertrophy; LVED, LV end-diastolic diameter (mm); LVES, LV end-systolic diameter (mm); FS, fractional shortening (%); LA, left atrial diameter (mm); LVOTO ≥30 mmHg; ICD, implantable cardioverter defibrillator.

was 122 (*Table 1*). Five-year survival from any cause of death, cardiac transplantation, or appropriate ICD discharge was 89.0% (95% CI: 86.6–91.4); 5-year survival from sudden death, resuscitated VF, or ICD discharge (SD/ICD) was 94.4% (95% CI: 92.7–96.2).

Forty-nine (40.2%) of the 122 patients who died, had an appropriate ICD discharge, or were transplanted had LVOTO. Five-year survival from all-cause mortality/transplantation was lower in patients with LVOTO [86.5% (95% CI: 81.7–91.2) vs. 90.1% (95% CI: 87.3–92.8), $P = 0.006$]. There was a significant trend towards increased all-cause mortality/transplantation with increasing outflow obstruction [RR per 20 mmHg = 1.24 (95% CI: 1.08–1.42). $P = 0.003$] (*Figure 1*).

Of the 54 patients with SD/ICD, 28 (51.8%) had an outflow tract gradient ≥30 mmHg. Patients with SD/ICD had a higher gradient than those who survived (38.5 ± 38.0 vs. 26.0 ± 33.2, $P < 0.01$). Five-year survival from SD/ICD was lower in the LVOTO group [91.4% (95% CI: 87.4–95.3) vs. 95.7% (95% CI: 93.8–97.6), $P = 0.0004$]. There was a significant trend towards lower SD/ICD survival in patients with increasing outflow tract obstruction [RR per 20 mmHg = 1.36 (95% CI: 1.12–1.65), $P = 0.001$] (*Figure 2*).

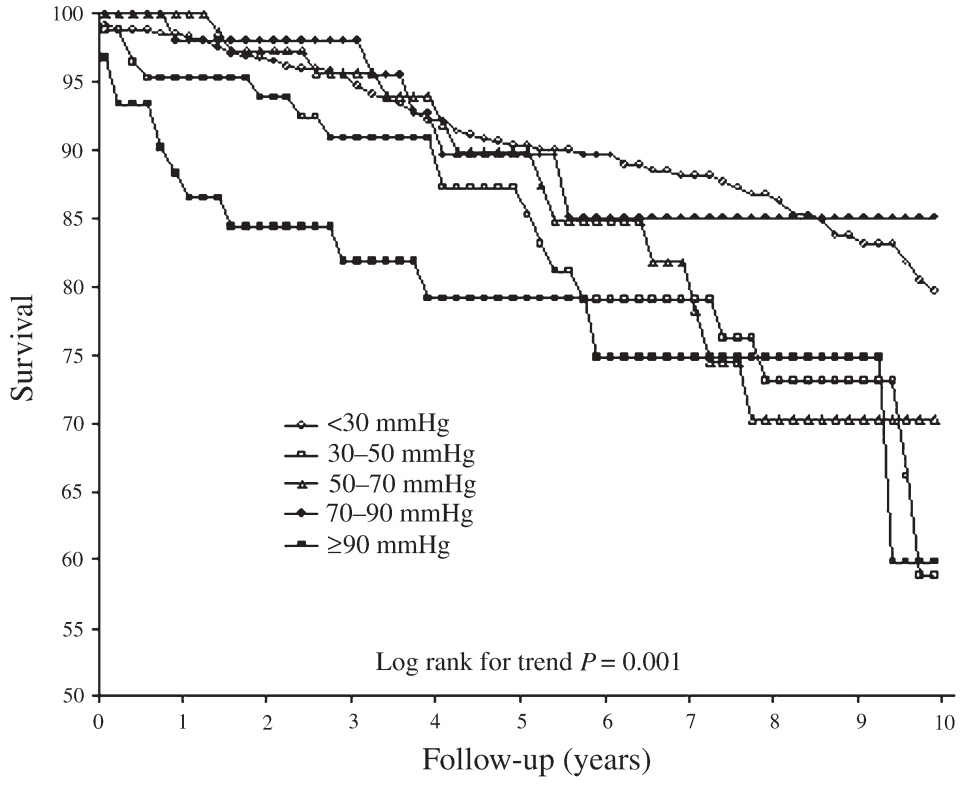
The positive predictive value (PPV) for SD/ICD in the presence of LVOTO was 9.7%; negative predictive value (NPV) was 95.9%. Similarly, PPV of the presence of severe LVOTO was 11.5% and the NPV 94.5%.

Relation between symptoms and survival in patients with obstruction

In patients with obstruction, there was a significant relation between 5-year survival from all-cause death and functional

Table 2 Medications during follow-up of the study population in relation to LVOTO (mmHg)

	<30	≥30	Total	Significant *P*-value
N	629 (68.6)	288 (31.4)	917 (100)	
β-blocker	205 (32.6)	175 (60.8)	380 (41.4)	<0.0001
Calcium antagonist	162 (25.8)	101 (35.1)	263 (28.7)	0.0004
Disopyramide	23 (3.7)	80 (27.8)	103 (11.2)	<0.0001
Amiodarone	203 (32.3)	108 (37.5)	311 (32.9)	0.1
Sotalol	50 (7.9)	26 (9.0)	76 (8.3)	0.6
Diuretic	118 (18.8)	78 (27.1)	196 (21.4)	0.004
ACE-inhibitor	66 (10.5)	23 (8.0)	89 (9.7)	0.2

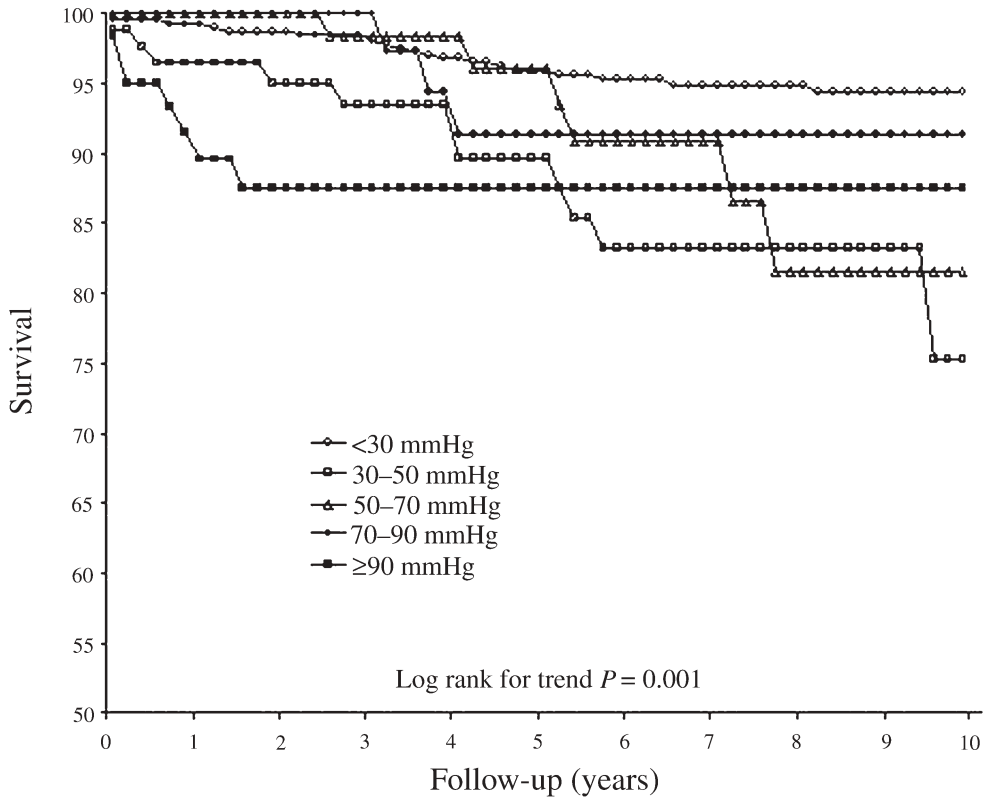


	Number of patients at risk			
	0-year follow-up	3-year follow-up	6-year follow-up	9-year follow-up
<30 mmHg	629	444	255	150
30–50 mmHg	85	59	35	15
50–70 mmHg	86	57	31	11
70–90 mmHg	56	38	14	3
≥90 mmHg	61	32	17	6

Figure 1 Kaplan–Meier estimates of the proportions of patients surviving from all-cause mortality/transplantation in relation to LVOTO.

limitation [NYHA class I: 91.0% (95% CI: 85.2–96.8%); NYHA class II: 83.3% (95% CI 75.5–91.1); NYHA class III/IV: 82.6% (95% CI: 64.2–100), $P = 0.002$]. There was no significant relation between all-cause survival at 5 years and a history of chest pain [88.6% (95% CI: 81.8–95.5) vs. 85.2% (95%CI: 78.6–91.8), $P = 0.9$] or syncope [82.6% (95%CI: 68.3–96.9) vs. 88.0% (95% CI: 83.1–92.9), $P = 0.07$].

There was no significant relation between 5-year survival from SD/ICD and functional class [NYHA class I: 93.3% (95% CI: 88.4–98.3%); NYHA class II: 89.7% (95% CI 83.1–96.3); NYHA class III/IV: 89.7% (95% CI: 76.2–100), $P = 0.1$]. There was no relation between 5-year survival from SD/ICD and a history of syncope [86.8% (95% CI: 74.2–99.3) vs. 92.2% (95% CI: 88.1–96.3), $P = 0.08$]. Patients with chest



	Number of patients at risk			
	0-year follow-up	3-year follow-up	6-year follow-up	9-year follow-up
<30 mmHg	629	444	255	150
30–50 mmHg	85	59	35	15
50–70 mmHg	86	57	31	11
70–90 mmHg	56	38	14	3
≥90 mmHg	61	32	17	6

Figure 2 Kaplan–Meier estimates of the proportions of patients surviving from sudden cardiac death, appropriate ICD discharge, or resuscitated ventricular fibrillation in relation to LVOTO.

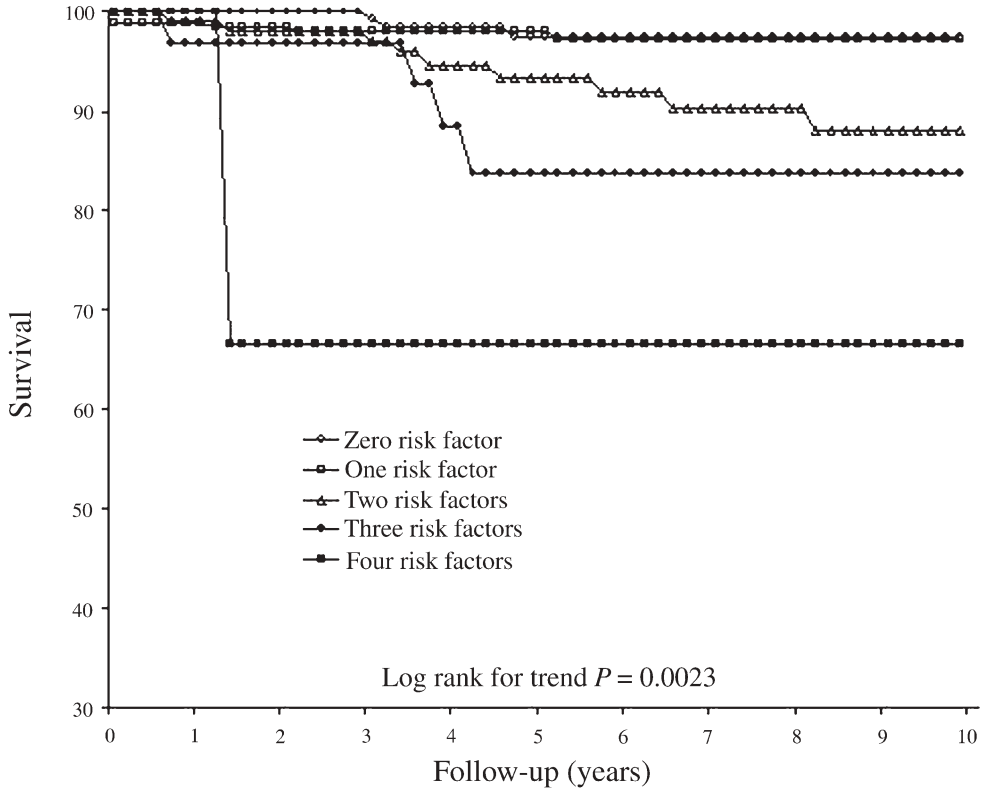
pain had a better 5-year SD/ICD survival [95.3%, (95% CI: 90.7–99.9)] compared with patients without [88.4%, (95% CI: 82.6–94.2)] ($P = 0.04$).

Relation between LVOTO and other risk factors for sudden cardiac death

The annual rate of sudden death in patients without LVOTO and none of the pre-specified risk markers for sudden cardiac death was 0.28% (95% CI: 0.06–0.81; there were no ICD discharges or successfully resuscitated VF episodes in this group). The annual rate of SD/ICD in patients with LVOTO and no risk factors was 0.37% (95% CI: 0.05–1.35). The annual rate of SD/ICD in patients with severe LVOTO and no risk factors was 0.92% (95% CI: 0.02–5.14).

The relation between survival from SD/ICD and the number of additional risk factors in patients with and without LVOTO is shown in *Figures 3* and *4*. There was a significant trend towards increased mortality, with increasing numbers of risk factors in patients with and without LVOTO. The relative risk per unit increase in number of risk factors was 1.98 (95% CI: 1.40–2.78, $P = 0.0001$) for non-obstructive and 1.76 (95% CI: 1.25–2.47, $P = 0.001$) for obstructive patients.

Multivariable analysis of LVOTO and the five pre-specified risk markers demonstrated that LVOTO was an independent predictor of SD/ICD. LVOTO of $\geq$30 mmHg was associated with a 2.4-fold ($P = 0.003$, 95% CI: 1.4–4.4) increase in the risk of SD/ICD. When patients with severe LVOTO ($\geq$90 mmHg) were compared with patients with lesser degrees or no LVOTO, the relative risk reached 3.8 ($P = 0.005$, 95% CI: 1.6–9.2). In this model, NSVT, syncope, and severe obstruction were the most important predictors of sudden cardiac death (*Table 3*). When LVOTO was included in the model as a continuous variable, the relative risk of SD/ICD for a 1 mmHg increase in gradient was 1.01 (95% CI: 1.004–1.019, $P = 0.002$).



Number of risk factors	Number of patients at risk			
	0-year follow-up	3-year follow-up	6-year follow-up	9-year follow-up
Zero	217	139	67	37
One	261	187	113	67
Two	116	90	59	34
Three	32	25	13	10
Four	3	2	2	2

Figure 3 Kaplan–Meier estimates of the proportions of patients surviving from sudden cardiac death, appropriate ICD discharge, or resuscitated ventricular fibrillation in relation to number of risk factors in patients without obstruction.

Effect of amiodarone therapy

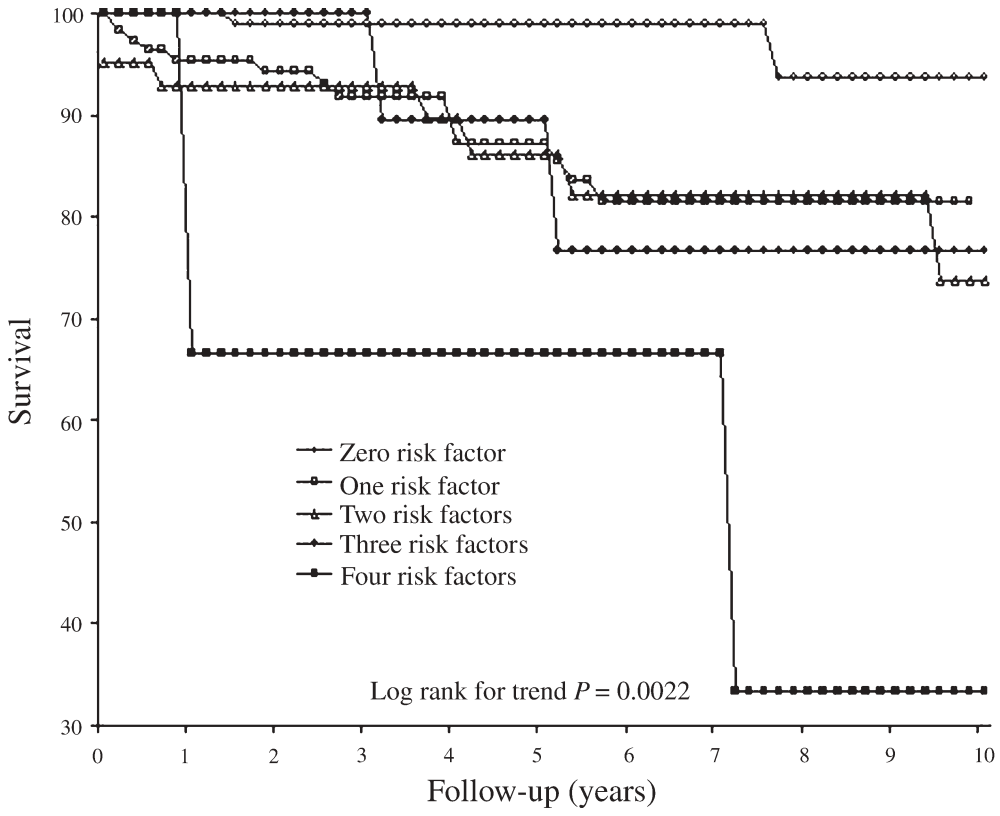
Mean outflow tract gradient in patients on amiodarone was 26.6 ± 30.9 mmHg vs. 26.8 ± 34.9 mmHg ($P = 0.9$). One hundred and eight (37.5%) patients with obstruction received amiodarone during the follow-up vs. 203 (32.3%) patients without obstruction ($P = 0.1$); 21 (6.8%) patients who had received amiodarone during the follow-up died suddenly vs. 33 (5.4%) patients who never were on amiodarone ($P = 0.4$).

Discussion

Resting LVOTO is present in only a minority of patients with HCM, but its detection and treatment are central to the clinical management of the disease. Many studies have shown that severe obstruction causes significant exercise limitation and that its relief results in an improvement in symptoms.[20–32] It is only recently, however, that there have been data showing that severe obstruction has an influence on survival from disease-related complications.[3,4] This study confirms the relation between a gradient of 30 mmHg and prognosis, but differs from previous studies in that it demonstrates a relation between the severity of obstruction and the risk of sudden cardiac death. Unlike all-cause mortality, the risk of sudden death or appropriate ICD discharge was not significantly increased in patients with moderate-to-severe functional limitation; it was, however, related to the presence of other recognized risk factors for sudden cardiac death. This difference with previous studies may be explained partly by patient selection; for example, SD rates in one multi-centre study varied substantially between centres (1.8–3.3%)[3]; it is also possible that different treatment regimens influenced outcomes.

Relation between obstruction, symptoms, and survival

The fact that all-cause mortality, but not sudden death, related to the severity of functional limitation in patients



Number of risk factors	Number of patients at risk			
	0-year follow-up	3-year follow-up	6-year follow-up	9-year follow-up
Zero	117	71	35	9
One	114	72	35	11
Two	42	31	20	12
Three	12	10	5	2
Four	3	2	1	1

Figure 4 Kaplan–Meier estimates of the proportions of patients surviving from sudden cardiac death, appropriate ICD discharge, or resuscitated ventricular fibrillation in relation to number of risk factors in patients with obstruction.

Table 3 Predictors of sudden cardiac death on multivariate analysis

	RR (95% CI)	Significance
NSVT	3.84 (2.1–7.0)	0.00001
ABPR	1.42 (0.7–2.8)	0.3
Syncope	2.27 (1.2–4.2)	0.01
FHSCD	1.88 (1.0–3.5)	0.04
Severe LVH	1.70 (0.8–3.8)	0.2
Severe LVOTO	3.82 (1.6–9.2)	0.005

Severe LVH, severe left ventricular hypertrophy (≥30 mm); Severe LVOTO, left ventricular outflow tract obstruction (≥90 mmHg).

with obstruction suggests that LVOTO influences the natural history of HCM via different mechanisms. LVOTO sufficient to cause moderate-to-severe symptoms is likely to contribute to left ventricular remodelling by increasing wall stress and predisposing to myocardial ischaemia. Sudden ventricular arrhythmia is more likely in such damaged ventricles, but it might also occur in patients without severe symptoms during periods of increased cardiac workload when wall stress and/or myocardial perfusion are abruptly disturbed. This latter mechanism could be most relevant in those patients with mild obstruction at rest, but severe provocable gradients during exercise.

Syncope is an important symptom in patients with obstructive and non-obstructive HCM. When unexplained, it is associated with an increased risk of SD; when it occurs in optimally treated patients with obstruction, it may be an indication for invasive management. Although statistically non-significant, there was a trend towards poorer survival in obstructive patients who experienced syncope. The implications of this for clinical practice require further study, but it supports the notion that obstruction-related syncope requires active treatment.

A curious observation in this study was the inverse relation between chest pain and sudden death risk in patients with obstruction. It is possible that patients who develop chest pain might limit their exercise, thereby avoiding severe myocardial ischaemia; other explanations include greater use of medication in patients with chest pain (not observed in this study) and that chest pain in many patients is unrelated to the presence of LVOTO. It is also possible that this finding is simply a chance observation arising out of multiple statistical comparisons.

Relation to other risk markers

Previous studies have shown that the risk of sudden cardiac death increases in the presence of non-sustained ventricular tachycardia,[7,12,14,15] severe left ventricular hypertrophy,[18,19] abnormal blood pressure response during upright exercise,[16,17] unexplained syncope,[11] and a family history of sudden cardiac death.[10] In common with these risk markers, LVOTO had a low positive predictive accuracy for SCD; however, there was an interaction between outflow tract obstruction and other risk markers, suggesting that LVOTO modifies the expression of the underlying arrhythmogenic substrate in patients already predisposed to sudden cardiac death.

Effect of amiodarone therapy

In the pre-ICD era, a number of papers suggested that amiodarone may prevent SCD in patients with HCM. Many patients in this study received amiodarone for some or all of the observation period for sudden death prophylaxis or for the treatment of atrial arrhythmia. Analysis of the effect of amiodarone in an observational cohort is difficult, but there was no relation between outflow obstruction, the use of amiodarone (at any time), and the number of sudden deaths, suggesting that the drug did not influence the observed association between outflow gradient and survival.

Implications for clinical practice

Current guidelines suggest that patients with a resting or provocable outflow tract gradient $\geq$50 mmHg should be considered for invasive management only when medical therapy with β-blockers, disopyramide, and calcium antagonists have failed to improve symptoms.[33] The most important question posed by this study is whether the increased risk of sudden cardiac death associated with outflow tract obstruction justifies the use of treatments such as septal myotomy–myectomy and alcohol septal ablation in asymptomatic or medically treated patients. At present, there are insufficient data to answer this question; however, the relatively low risk of sudden death in asymptomatic patients with LVOTO and none of the recognized risk factors for sudden cardiac death ($<$0.4% per year) suggests that aggressive interventions are unjustified in this group. A similar argument applies to the use of ICDs to prevent sudden death in asymptomatic patients with LVOTO when there is no other evidence for increased risk. The situation in asymptomatic patients with obstruction and additional risk factors is less clear. It is our view that the surgery and alcohol ablation are still unjustified given the mortality and morbidity associated with both procedures; however, the value of an ICD in this circumstance warrants further study.

Limitations

It is well recognized that left ventricular outflow gradients can be latent (present only during provocation manoeuvres) or labile.[34,35] In the absence of prior data to suggest that routine provocation of gradients in patients without severe symptoms is of clinical value, it has not been our policy to perform haemodynamic evaluations during amyl nitrate inhalation or Valsalva in all patients. This means that we were unable to comment on the prognostic significance of either labile or latent obstruction.

Conclusions

LVOTO is associated with an increased risk of SD/ICD that is related to the severity of obstruction and the presence of other recognized risk factors for SD. The low all-cause mortality in asymptomatic patients with LVOTO and no other SD risk markers suggests that aggressive interventions such as septal alcohol ablation and septal myotomy–myectomy are unwarranted in this group. Further studies exploring the role of intervention in patients with obstruction and additional risk factors for sudden death are necessary.

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