Br Heart J 1981; **46**: 168–72

Arrhythmia in hypertrophic cardiomyopathy
I: Influence on prognosis

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SUMMARY In order to examine the association between arrhythmia and subsequent prognosis, 72-hour ambulatory electrocardiographic monitoring was performed in 86 unselected patients with hypertrophic cardiomyopathy. During monitoring 23 patients experienced at least one episode of supraventricular tachycardia and 24 had ventricular tachycardia (of whom 10 had more than three episodes). The patients were then followed for a mean of 2·6 years (range one to four). Seven patients died suddenly. Of these, five had exhibited multiform and paired ventricular extrasystoles and ventricular tachycardia. These arrhythmias were significantly associated with sudden death whereas supraventricular arrhythmias were not. The patients who died suddenly were older and had experienced more symptoms than the survivors, and three had a family history of hypertrophic cardiomyopathy and sudden death. This experience provides the basis for the assessment of treatment in patients with hypertrophic cardiomyopathy and serious ventricular arrhythmia.

The high incidence of serious ventricular arrhythmia in hypertrophic cardiomyopathy is now well recognised.[1] These arrhythmias are often asymptomatic and they are not significantly reduced by beta-adrenergic blocking drugs.[2] Those who die usually do so suddenly,[3] and are often young and asymptomatic.[4] The relation of previous arrhythmia to sudden death is, however, uncertain. We have assessed the influence of arrhythmia on prognosis in 86 patients with hypertrophic cardiomyopathy who were available for ambulatory electrocardiographic monitoring during 1976 and 1977.

Methods

Eighty-six consecutive patients with hypertrophic cardiomyopathy underwent one to 10 days (mean three) of ambulatory electrocardiographic monitoring while on no treatment other than beta-adrenergic blockers, verapamil, or digoxin. This was performed using the Oxford Medilog 1 cassette recorder and recording instrument and a Reynold's high speed Pathfinder electrocardiographic analyser. All records were analysed by a technician and reviewed by a physician. A modification of the grading system of Ryan *et al.*[5] for ventricular arrhythmia was used: grade 1, no more than 30 ventricular extrasystoles in any hour of monitoring; grade 2, more than 30 ventricular extrasystoles in any hour of monitoring; grade 3a, multiform ventricular extrasystoles; grade 3b uniform and pairs (two consecutive ventricular extrasystoles); grade 4, multiform and pairs of ventricular extrasystoles; grade 5, ventricular tachycardia (three or more ventricular extrasystoles in succession).

Patients

The diagnosis of hypertrophic cardiomyopathy was based on typical clinical features,[6] M-mode echocardiography,[7] and left ventricular angiography.[8] In 67 patients the diagnosis was established by left ventricular angiography.[8] Nineteen patients were diagnosed non-invasively: four of these patients were first degree relatives of propositi and had clinical, electrocardiographic, or echocardiographic features consistent with hypertrophic cardiomyopathy; the other 15 patients had the typical clinical and echocardiographic features of hypertrophic cardiomyopathy and left ventricular outflow tract gradient.[7 9] Patients were considered to have a significant left ventricular outflow tract gradient if the difference measured under basal conditions or with provocation (amyl nitrite inhalation or Valsalva manoeuvre) was equal to or exceeded 20 mmHg. Of the 67 patients who were

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Received for publication 17 February 1981

catheterised, 23 (34%) had a resting gradient, 15 (22%) had a gradient upon provocation, and 29 (43%) had no gradient. Mean left ventricular end-diastolic pressure was 17·6±7·6 mmHg. Sixteen of the 19 patients who were not catheterised were considered to have a gradient on the basis of echocardiographic identification of either mid-systolic closure of the aortic valve or systolic anterior motion of the anterior mitral leaflet[7 9]; these criteria were also used to confirm the presence or absence of a gradient in the 17 patients who had not undergone catheterisation within the three years before the study.

Fifty-one of the patients were male and 35 were female. The diagnosis was established one to 20 years (mean five) before the present study at which time the patients were aged between six and 66 years (mean 39). Seventy-five of the patients were then in sinus rhythm and 11 were in atrial fibrillation. Symptoms at the time of diagnosis included: palpitation, 43%; presyncope, 26%; syncope, 18%; chest pain on exertion, 46%; dyspnoea (New York Heart Association class 2), 55%, and dyspnoea (class 3 or 4), 7%. At the time of monitoring 12 (14%) of the patients were in atrial fibrillation, 25 (29%) were asymptomatic, 23 (27%) had presyncope, and nine (10%) had syncope, 28 (33%) had chest pain on exertion, 30 (35%) had dyspnoea class 2, and 15 (17%) dyspnoea class 3 or 4. Their treatment included digoxin in 11 (13%), diuretics in 16 (19%), beta-adrenergic blocking drugs in 55 (64%), and verapamil in three (3%) of the patients; no patient received any additional antiarrhythmic therapy during or before monitoring.

Patients who were found to have ventricular tachycardia on the electrocardiographic monitoring were initially treated with mexiletine, or disopyramide, either alone or in combination with propranolol. These drugs were poorly tolerated. A sustained reduction or abolition of ventricular tachycardia was achieved in only three of 14 patients. Quinidine sulphate was given to eight of the patients with ventricular tachycardia. This was better tolerated, but was successful in abolishing ventricular tachycardia in only two. The five patients in whom ventricular tachycardia was abolished on mexiletine, quinidine, or disopyramide are included in the analysis only up to the date of initiation of their successful antiarrhythmic treatment.

Statistical analysis

Where appropriate the χ^2 or Fisher's exact test were used to assess statistical significance. The two sample t test was used to test the difference between two means and the two sample Wilcoxon test was used to differentiate between the two samples when the data were not normally distributed. A stepwise discriminate analysis was also performed to compare the patients with ventricular tachycardia with the others; 12 clinical, electrocardiographic, haemodynamic, and echocardiographic features were used as independent variables.

Results

The prevalence of ventricular arrhythmias is summarised in the Fig. Ventricular arrhythmia (class 2, 3, 4, or 5) was detected in 62% of the patients. Eighteen

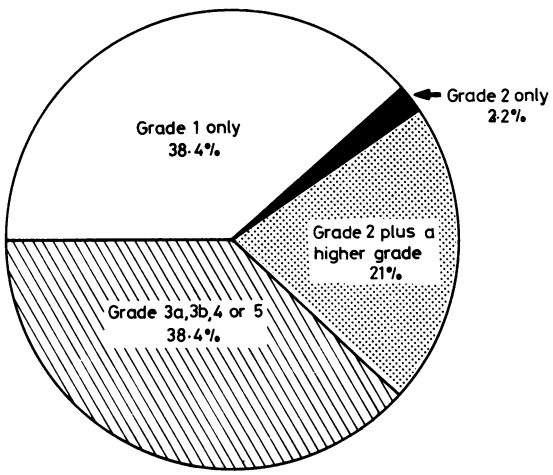

Fig. *The prevalence of ventricular arrhythmia grades in 86 patients with hypertrophic cardiomyopathy.*

of 20 patients with frequent ventricular extrasystoles (>30/hour) also had higher grade arrhythmia, but only 35% of the patients with multiform or paired ventricular extrasystoles had frequent ventricular extrasystoles. Though supraventricular arrhythmias were common (Table 1), they were not associated with poor prognosis.

Table 1 *Supraventricular arrhythmias detected during ambulatory electrocardiographic monitoring in 68 survivors and six dead patients**

	Alive (68 patients)†		*Dead (6 patients)*‡	
	No.	%	*No.*	%
Atrial extrasystoles§				
≤30/h	56	82	3	50
>30/h	12	18	3	50
*Supraventricular tachycardia***				
None	47	68	4	66
1 to 3 episodes	14	21	—	—
>3 episodes	7	10	2	33

*12 patients with atrial fibrillation excluded.
†1 to 10, mean 3 days of electrocardiographic monitoring.
‡1 to 7, mean 3·1 days of electrocardiographic monitoring.
§Maximum count/hour.
**Total number of episodes during electrocardiographic monitoring.

Table 2 *Clinical data in seven patients who died suddenly*

Case no.	*Age (y)*	*Sex*	*Year of diagnosis*	*Family history*	*Syncope*	*Dyspnoea NYHA grade*	*Haemodynamic data*			*Echocardiographic data*		
							Year of angiography	*LVEDP (mm)*	*LVOT gradient*	*IVS (mm)*	*IVS/LVPW ratio*	*SAM/MSCAV*
1	59	M	1973	HCM+SD	No	3	1977	25	None	20	2·5	No/No
2	62	M	1958	None	Yes	2	1978	19	None	44	4·4	No/Not studied
3	57	M	1975	HCM+SD	No	1	1976	22	Resting	27	1·6	Yes/Yes
4	67	F	1979	None	No	1	1979	24	Labile	22	1·6	Yes/No
5	61	F	1973	None	No	3	1978	30	Resting	19	2·1	Yes/Yes
6	38	F	1968	None	Yes	1	1973	10	None	09	1·5	No/No
7	61	F	1977	None	No	3	Not studied	Not studied	Not studied	24	1·6	Yes/Yes

HCM, hypertrophic cardiomyopathy; SD, sudden death; NYHA, New York Heart Association; LVEDP, left ventricular end-diastolic pressure; LVOT, left ventricular outflow tract; IVS, interventricular septum; LVPW, left ventricular posterior wall; SAM, systolic anterior motion of mitral valve; MSCAV, mid-systolic closure of aortic valve.
Postmortem confirmation of the diagnosis and of the electrocardiographic measurements was available in cases 2, 3, and 6.

Table 4 *Electrocardiographic data in seven patients who died suddenly*

Electrocardiographic data					*Ambulatory electrocardiographic data*						
Case no.	*Rhythm*	*Axis*	*Comment*	*Days of electrocardiographic monitoring*	*Rhythm*	*SVT (no. of episodes)*	*Ventricular extrasystoles*			*Ventricular tachycardia*	
							Peak/h	*Peak/d*	*Highest grade**	*No. of episodes*	*Beats in longest*
1	AF	+30°	LVH+ST change	6	AF	—	62	300	4	4	6
2	SR	−15°	LBBB**	4	SR	0	708	2082	4	8	10
3	SR	−30°	LVH+ST change	7	SR	0	40	103	4	1	4
4	SR	−15°	LVH+ST change	1	SR	0	4	15	1	0	0
5	AF†	−15°	LBBB	2	SR	0	47	126	4	1	3
6	SR	−60°	LVH+ST change	1	SR	>3	28	206	4	3	8
7	SR	−45°	LVH+ST change; left atrial overload	1	SR	>3	3	12	1	0	0
†Electrocardiogram recorded within three months before death					Mean±SEM for seven patients who died		127 ± 96	406 ±281			
Case 6 developed AF and LBBB subsequent to her ambulatory monitoring					79 survivors		30 ± 14	144 ± 76			
							p<0·05	p<0·05			

AF, atrial fibrillation; SR, sinus rhythm; SVT, supraventricular tachycardia; LVH, left ventricular hypertrophy; LBBB, left bundle-branch block; * grade 5 (ventricular tachycardia) excluded;
** LBBB acquired at time of septal myotomy 1959.

The duration of follow up after monitoring was one to four years (mean 2·6). Seven patients have died, all suddenly. The patients who died were older (mean 58 years) than the survivors (mean 44 years) and they had a higher incidence of family history of hypertrophic cardiomyopathy and sudden death (43%) than the survivors (11%) (Table 2). Ventricular tachycardia as well as the combination of multiform and paired ventricular extrasystoles were associated with sudden death ($p<0·05$). They were present in five of the seven patients who died suddenly (Table 3). In addition, the patients who died had significantly higher maximum ventricular extrasystolic counts (whether on an hourly or a daily basis) than the survivors ($p<0·05$) (Table 4).

Table 3 *Ventricular arrhythmias detected during ambulatory electrocardiographic monitoring in 79 survivors and seven dead patients*

	Alive (79 patients)†		*Dead (7 patients)*‡	
	No.	%	*No.*	%
*Ventricular arrhythmia grade**				
1 (≤30 VES/h)	63	80	3	43
2 (>30 VES/h)	16	20	4	57
3a (multiform VES)	15	19	0	0
3b (uniform and pairs)	8	10	0	0
4 (multiform and pairs)	19	24	5	71
5 (VT)	19	24	5	71

*Grades not mutually exclusive.
†1 to 10, mean 3 days of electrocardiographic monitoring.
‡1 to 7, mean 3·1 days of electrocardiographic monitoring.
VES, ventricular extrasystoles; VT, ventricular tachycardia.

Of the five patients who had ventricular tachycardia and died suddenly, three (cases 1, 5, and 7) were haemodynamically severe with class 2–3 functional limitation and raised left ventricular end-diastolic pressure. Two (cases 3 and 6) had no functional limitation: case 3 had a positive family history of hypertrophic cardiomyopathy and sudden death and case 6 had palpitation associated with syncopal episodes (Table 2). Left ventricular end-diastolic pressure was raised in the patients who died (mean 22 mmHg) but not significantly more so than in the survivors (mean 17 mmHg). Three of six patients who died had a gradient at rest or on provocation and case 7 who was not catheterised had echocardiographic features (systolic anterior motion of the mitral valve and mid-systolic closure of the aortic valve) associated with left ventricular outflow tract gradient.[7 9] A similar percentage (63%) of the survivors also had a gradient at rest or after provocation. The patients who died had thicker ventricular septa than the survivors, but the difference was not significant ($p=0·059$). Not only did five (71%) of the patients who died have ventricular tachycardia but so did 19 (24%) of the survivors. Tables 5 and 6 present the other ventricular and supraventricular arrhythmias detected in patients with and without ventricular tachycardia. Frequent ventricular extrasystoles (grade 2) ($p<0·001$) and multiform and paired ventricular extrasystoles (grade 4) ($p<0·0001$) were associated with ventricular tachycardia, whereas supraventricular arrhythmias were not.

Table 5 *Ventricular arrhythmia detected during ambulatory electrocardiographic monitoring in patients with and without ventricular tachycardia*

	*62 patients without ventricular tachycardia**		*24 patients with ventricular tachycardia*†	
	No.	%	*No.*	%
Ventricular extrasystoles				
1 (≤30/h)	54	87	12	50
2 (>30/h)	8	13	12	50
3a (multiform)	14	23	1	4
3b (uniform pairs)	8	13	0	0
4 (multiform and pairs)	5	8	19	79

*1 to 10, mean 3 days of electrocardiographic monitoring.
†1 to 7, mean 2·9 days of electrocardiographic monitoring.

Discriminate analysis disclosed that ventricular tachycardia was best predicted by the combination of syncope, left ventricular end-diastolic pressure greater than or equal to 20 mmHg, voltage criteria of left ventricular hypertrophy on the electrocardiogram,[10] ventricular septal thickness of 20 mm or more, and systolic anterior motion of the mitral valve on the echocardiogram. Twelve of 18 patients with ventricular tachycardia (false negative 33%) and 26 of 32 without ventricular tachycardia (false positive 19%) were correctly identified by the analysis.

Table 6 *Supraventricular arrhythmias detected during ambulatory electrocardiographic monitoring in patients with and without ventricular tachycardia**

	53 patients without ventricular tachycardia†		*21 patients with ventricular tachycardia*‡	
	No.	%	*No.*	%
Atrial extrasystoles§				
≤30/h	45	85	14	67
>30/h	8	15	7	33
*Supraventricular tachycardia***				
None	39	74	12	57
1 to 3 episodes	8	15	6	29
>3 episodes	6	11	3	14

*12 patients in atrial fibrillation are excluded.
†1 to 10, mean 3·1 days of electrocardiographic monitoring; 9 patients with atrial fibrillation excluded.
‡1 to 7, mean 2·8 days of electrocardiographic monitoring; 3 patients with atrial fibrillation excluded.
§Maximum count/hour.
**Total number of episodes during electrocardiographic monitoring.

Discussion

Our results confirm previous observations that arrhythmia is common in hypertrophic cardiomyopathy. They also disclose that in hypertrophic cardiomyopathy ventricular tachycardia is associated with sudden death, whereas supraventricular arrhythmias are not. Twenty-four patients (28%) had ventricular tachycardia, including five of seven of the patients (71%) who died suddenly. Three of those patients who died suddenly had at least three episodes of ventricular tachycardia: two had severe functional limitation with raised filling pressures and grossly thickened ventricular septa; the other patient was functionally asymptomatic but had a bad family history —both her father and a sister had died suddenly from hypertrophic cardiomyopathy. A positive family history of hypertrophic cardiomyopathy and sudden death has been associated with sudden death[4 11] and was present in two of seven of the patients who died suddenly.

In our series of 254 patients with hypertrophic cardiomyopathy 32 patients died suddenly; they were young at the time of death (seven to 67 years, (mean 37)) and were often asymptomatic.[4] The seven patients who died in the present study were, however, older (mean 58 years) and four of the seven had severe functional limitation. Patients who die suddenly from hypertrophic cardiomyopathy are not a homogeneous group. They include children[11 12] and the elderly; patients who are asymptomatic and severely limited;[4] those who have massive septal hypertrophy and minimal hypertrophy[11 13] and those with and without left ventricular outflow tract gradients and abnormal filling pressures.[4] In this study serious ventricular arrhythmia was associated with sudden death. Though a causal relation of arrhythmia and sudden death will be difficult to establish, the treatment of serious ventricular arrhythmia in hypertrophic cardiomyopathy should be explored.

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