Long-Term Follow-Up of Medical Versus Surgical Therapy for Hypertrophic Cardiomyopathy: A Retrospective Study

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In a retrospective analysis 139 patients with hypertrophic cardiomyopathy were followed up for 8.9 years (range 1 to 28 years). Patients were divided into two groups: Group 1 consisted of 60 patients with medical therapy and Group 2 of 79 patients with surgical therapy (septal myectomy). Groups 1 and 2 were subdivided according to the medical treatment. Group 1a received propranolol, 160 mg/day (n = 20); Group 1b verapamil, 360 mg/day (n = 18); and Group 1c, no therapy (n = 22). Group 2a received verapamil, 120 to 360 mg/day, after septal myectomy (n = 17) and Group 2b had no medical therapy after surgery (n = 62).

In Group 1, 19 patients died (annual mortality rate 3.6%) and in Group 2, 17 patients died (mortality rate 2.4%, p = NS). Of the patients who died, approximately one half to two thirds in both Groups 1 and 2 died suddenly and the other one half to one third died because of congestive heart failure. The 10 year cumulative survival rate was 67% in Group 1, significantly smaller than that in Group 2 (84%, p < 0.05). In the subgroups, the 10 year survival rate was 67% in Group 1a, 80% in 1b (p < 0.05 versus 1a) and 65% in 1c (p < 0.05 versus 1b). The 10 year survival rate was 100% in Group 2a (p < 0.05 versus 1a, 1b, 1c) and 78% in Group 2b (p < 0.05 versus 2a).

It is concluded that cumulative survival rate is significantly better in surgically than in medically treated patients. However, the survival rate among medically treated patients was better in those treated with verapamil than in those treated with propranolol or in untreated patients. The 10 year survival rate was similar in the medically treated patients receiving verapamil (80%) and the entire surgically treated group (84%, p = NS). The most favorable outcome was observed in surgically treated patients receiving long-term therapy with verapamil, probably as a result of the reduction of systolic pressure overload by septal myectomy and improvement in left ventricular diastolic function mediated by verapamil.

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Long-term follow-up of patients with hypertrophic cardiomyopathy has been reported (1–7) to be dependent on the severity of outflow tract obstruction and the degree of impairment of left ventricular diastolic function. An improved survival rate and symptomatic status has been observed after surgical treatment of the outflow tract obstruction (1,3,8–14), but more recently, medical therapy has also yielded beneficial effects on the long-term course of patients with hypertrophic cardiomyopathy (15). Before 1976 medical therapy of hypertrophic cardiomyopathy was based mainly on beta-adrenergic blocking agents, especially propranolol. Several studies (1–5,13,16,17) had documented a reduction of outflow tract obstruction and a positive effect on the clinical course and prognosis with this therapy. More recently, an improved prognosis and clinical course were reported after long-term therapy with verapamil (5–7,13,17–22).

The purpose of this study was to evaluate, in a retrospective analysis, the effect of surgical and medical therapy on survival and symptomatic status of the 139 patients with hypertrophic cardiomyopathy followed up since 1961 at the Medical Policlinic and the Clinic of Cardiovascular Surgery of the University Hospital in Zurich.

Methods

Study patients (Table 1). The study group consisted of 139 patients with hypertrophic cardiomyopathy; 26 were female and 113 male. The mean age was 37 years (range 3 to 66). The mean follow-up time was 8.9 years (range 1 to 28). Sixty patients who were managed medically (Group 1) and 79 patients underwent operation (Group 2). Group 1, which we termed the "medical group," was separated into three subgroups: Group 1a, 20 patients who received propranolol (average dose 160 mg/day range 40 to 280); Group 1b, 18 patients who received verapamil (average dose 360 mg/day, range 120 to 480); and Group 1c, 22 patients who received no treatment because they had no symptoms or showed poor

Table 1. The 139 Study Patients

	n	Age (yr)	Follow-Up (yr)
Total	139	37 ± 14	8.9 ± 6.5
Group 1a	20	42 ± 13	7.8 ± 5.9
Group 1b	18	40 ± 13	9.1 ± 7.5
Group 1c	22	32 ± 15	7.8 ± 7.1
Group 2a	17	41 ± 14	9.3 ± 5.8
Group 2b	62	36 ± 14	9.5 ± 6.2

*p < 0.05. Group 1 = medical therapy; Group 2 = surgical therapy (septal myectomy). Group 1a = propranolol treatment; Group 1b = verapamil treatment; Group 1c = no treatment; Group 2a = septal myectomy and verapamil; Group 2b = septal myectomy without verapamil. Age is given at the time of diagnosis.

compliance. In the surgical group 17 patients (Group 2a) received verapamil (average dose 360 mg/day, range 120 to 480) because of persistent symptoms after septal myectomy and 62 (Group 2b) received no medical therapy after operation (Table 1).

Patients with a systolic pressure gradient of more than 50 mm Hg or clinical symptoms that could not be influenced by medical therapy underwent septal myectomy. Patients who had only mild outflow tract obstruction (pressure gradient <50 mm Hg) with no or only mild symptoms were treated medically. Thus, in this regard the two groups are not really comparable, but because of the relatively small number of patients and the long time span of the study, randomization was not performed.

All patients were informed about the potential risk and benefit from either therapy. Patients who underwent cardiac catheterization gave informed consent.

Clinical examination. At entry into the study (time of diagnosis or preoperative evaluation), all patients were examined clinically. Functional status of the patients was described according to the New York Heart Association classification. The frequency of the most common symptoms in hypertrophic cardiomyopathy (angina pectoris, dyspnea on exertion, dizziness, syncope and palpitation) was determined. In all patients, heart rate and blood pressure were measured in the supine position. A rest electrocardiogram (ECG) was obtained routinely. The Sokolow-Lyon index was calculated as R in V_5 or V_6 + S in V_1. One hundred twenty of the 139 patients underwent exercise testing. Physical working capacity was determined by bicycle ergometry as a percentage of the age-, gender- and height-adjusted normal value. A chest roentgenogram was obtained in all patients and the cardiothoracic ratio was calculated. Because Holter ECG monitoring was performed only in a few patients, these data are not reported.

Cardiac catheterization. Of the 139 patients, 125 (all of Group 2 and 46 of Group 1) underwent cardiac catheterization for diagnostic purposes and to assess the outflow tract gradient in the pre-echocardiography era, or to determine whether coronary artery disease was present. Cardiac catheterization included right- and left-sided catheterization with

determination of cardiac output by the Fick method, biplane left ventricular angiocardiography and coronary arteriography. The systolic pressure gradient across the left ventricular outflow tract at rest and after provocation (postextrasystolic potentiation, Valsalva maneuver, isoproterenol infusion) was determined by simultaneous measurement of left ventricular (with the use of a transseptal catheter) and aortic pressures. Left ventricular volume was calculated according to the area-length method.

Echocardiography. At entry, 70 patients underwent M-mode and two-dimensional echocardiography (Diasonics model CV-3400R). Diagnosis was based on the criteria of Maron et al. (23). Before 1978, when only M-mode echocardiography was available, all patients underwent catheterization to establish the diagnosis. Nevertheless, 90% of all patients were evaluated invasively to exclude those with asymmetric hypertrophy from causes other than hypertrophic cardiomyopathy. Septal and posterior wall thickness, end-systolic and end-diastolic internal chamber diameter of the left ventricle, systolic shortening of the internal chamber diameter and end-systolic diameter of the left atrium were measured (23). After 1983, the systolic pressure gradient across the left ventricular outflow tract was assessed quantitatively (24) by Doppler ultrasound (Hewlett-Packard model 77020 AC). Hypertrophic cardiomyopathy was diagnosed exclusively by Doppler measurements in 14 of 60 patients in Group 1 and in no patient in Group 2. These patients were not evaluated invasively because symptomatic status was mild and only minimal or no outflow tract obstruction was present as determined by Doppler echocardiography.

Medical and surgical therapy. Patients were classified retrospectively into a medically and a surgically treated group. The policy for conservative (medical) or surgical treatment remained unchanged at our hospital over the years of the study and was: 1) Patients were treated medically when no or only a mild pressure gradient (<50 mm Hg) with no or mild symptoms were present. Patients with a significant pressure gradient (>25 but <50 mm Hg) or typical symptoms that responded well to medical therapy were followed up on medical treatment. 2) Patients were treated surgically if they had a resting pressure gradient of more than 50 mm Hg or a pressure gradient after postextrasystolic potentiation of more than 100 mm Hg or when clinical symptoms were present that did not respond or insufficiently responded to medical therapy. Patients who did not respond to medical therapy either by a lessening of clinical symptoms or a reduction in systolic pressure gradient were referred for surgery (n = 37). Most medically treated patients received propranolol in the years before 1978 but received verapamil after 1978. In some patients medical therapy was switched from one to the other drug when no functional improvement was observed with the first one administered. Forty-two of the 79 patients who underwent myectomy were sent directly to surgery without significant medical therapy in the presence of severe outflow tract obstruction.

Septal myectomy was performed by the transventricular

Table 2. Clinical Data of 139 Patients at Entry and at End of Follow-Up

	Sokolow-Lyon Index (mV)		CTR		PWC (% of normal)	
	Entry	End	Entry	End	Entry	End
Group 1	3.3 ± 1.3	3.2 ± 1.3	0.51 ± 0.05	0.53 ± 0.07	81 ± 19	81 ± 20
1a	3.2 ± 1.3	3.1 ± 1.3	0.51 ± 0.05	0.54 ± 0.05	78 ± 19	77 ± 25
1b	3.1 ± 1.3	2.9 ± 1.2	0.51 ± 0.05	0.54 ± 0.09	74 ± 21	84 ± 23
1c	3.5 ± 1.4	3.6 ± 1.3	0.50 ± 0.04	0.50 ± 0.06	91 ± 18	96 ± 12
Group 2	3.5 ± 1.2		0.52 ± 0.05	0.53 ± 0.06	80 ± 18	80 ± 17
2a	3.8 ± 1.1	*	0.51 ± 0.05	0.53 ± 0.06	84 ± 16	81 ± 18
2b	3.2 ± 1.2	†	0.53 ± 0.04	0.53 ± 0.06	75 ± 19	78 ± 16

*Left bundle branch block in 10 (60%) of 17 patients; †left bundle branch block in 21 (34%) of 62 patients; CTR = cardiothoracic ratio; PWC = physical working capacity; SM = septal myectomy. Groups are as defined in Table 1.

(n = 38; 1965 through 1979), the transaortic/transventricular approach (n = 7; 1973 through 1981) or the transaortic approach (n = 34) between 1966 through 1987. No patient died immediately after surgery, but one patient died 4 days after myectomy due to pericardial tamponade (perioperative mortality 1.3%).

Follow-up. In 104 patients at least one further clinical examination was performed during the follow-up period. Thirty-five patients were followed up only by questionnaire because they refused reexamination or because they had changed their domicile. Follow-up information was obtained in all patients by the end of 1986 or later. The cause of death was determined by questioning relatives or the referring physician. Autopsy was performed only in a few patients and thus, these data are not included.

Statistics. Data within each group and subgroup (entry and last follow-up data) were analyzed by the Student's *t* test for paired or unpaired variables. Differences among the subgroups were calculated by a one-way analysis of variance followed by the Scheffe test if the analysis was significant. Calculation of cumulative survival rates was performed as described by Anderson et al. (25). Relative frequencies were analyzed by the chi-square test. Annual mortality rate represents linearized rates per 100 patients per year. Values presented in the tables and figures are means ± SD.

Results

Initial findings

The patients were 3 to 66 years old. Eleven of the 79 surgically treated and 3 of the medically treated patients were ≤15 years old.

Clinical examination (Table 2, Fig. 1). At entry into the study, functional classification did not differ between Group 2 (mean 2.1) and Group 1 (mean 1.8, P = NS) but Group 2 differed significantly from Group 1c (Group 2 versus 1c, 2.1 versus 1.6, p < 0.05). Clinical symptoms, such as angina pectoris, syncope, dyspnea on exertion, dizziness and palpitation, were not observed more frequently at entry into the study in Group 1 than in Group 2. On entry into the study most of the patients in both groups were in sinus rythm (97% in Group 1 and 97% in Group 2); atrial fibrillation or flutter was observed in 3% in each group. The Sokolow-Lyon index was also similar in the two groups. Neither cardiothoracic ratio nor physical working capacity was significantly different between the two main groups and the five subgroups.

Cardiac catheterization (Table 3). Group 1 and Group 2 were not significantly different with regard to heart rate, left ventricular end-diastolic pressure, left ventricular ejection fraction and cardiac index. However, left ventricular peak systolic pressure and the pressure gradient across the left
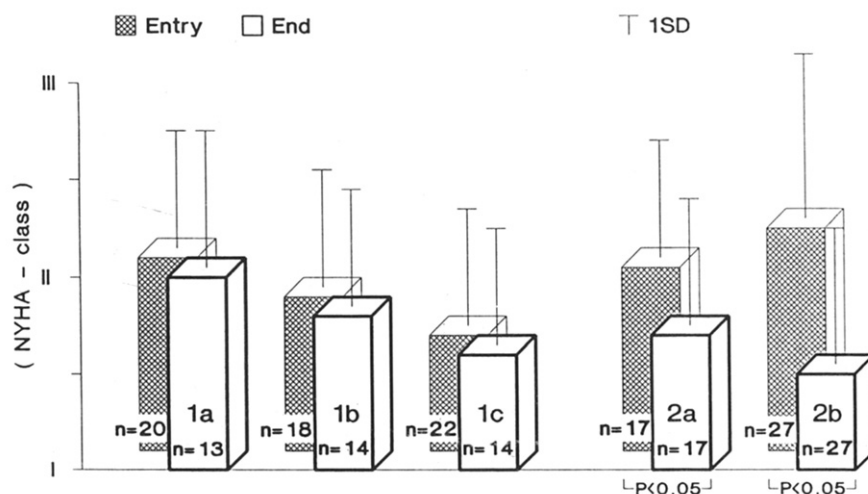

Figure 1. Functional classification according to the New York Heart Association (NYHA) at entry and at the end of follow-up in 139 patients with hypertrophic cardiomyopathy. Group 1a = 20 patients treated with propranolol; 1b = 18 patients treated with verapamil; 1c = 22 patients without any therapy; 2a = 17 patients with septal myectomy and verapamil; 2b = 62 patients with septal myectomy without any medical therapy.

Table 3. Hemodynamic Baseline Data in 93 Patients

	n	HR (beats/min)	LVEDP (mm Hg)	LVSP (mm Hg)	ΔP (mm Hg)	EF (%)	CI (liters/min/m²)
Group 1	56	72 ± 12	16 ± 8	133 ± 28 ⎤	17 ± 21 ⎤	67 ± 11	3.2 ± 0.7
1a	19	77 ± 17	15 ± 9	137 ± 24	22 ± 26	67 ± 12	3.4 ± 0.7
1b	18	70 ± 9	16 ± 8	129 ± 29 ⎟ *	11 ± 8 ⎟ *	68 ± 14	2.9 ± 0.5
1c	19	70 ± 10	18 ± 7	134 ± 30 ⎦	18 ± 28 ⎦	66 ± 7	3.4 ± 0.9
Group 2	37	71 ± 9	22 ± 7	178 ± 39 ⎤	70 ± 33 ⎤	72 ± 11	3.1 ± 0.8
2a	17	72 ± 9	22 ± 6	182 ± 40	68 ± 34	76 ± 8	3.1 ± 0.8
2b	20	70 ± 9	21 ± 7	172 ± 38	72 ± 31	68 ± 13	3.0 ± 0.7

*$p < 0.05$ for Group 1 versus Group 2. CI = cardiac index; EF = ejection fraction; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular peak systolic pressure; ΔP = pressure gradient at rest across the left ventricular outflow tract; SM = septal myectomy. Groups are defined in Table 1.

ventricular outflow tract at rest were 133 and 17 mm Hg, respectively, in Group 1 and 178 and 70 mm Hg, respectively in Group 2 ($p < 0.05$). Nine of the 125 patients who underwent cardiac catheterization were found to have coronary artery disease with significant stenosis (>50%) of one or more epicardial coronary vessels.

Echocardiography (Table 4). The echocardiographic variables (septal and posterior wall thickness, end-systolic and end-diastolic internal chamber diameter of the left ventricle, systolic shortening of internal chamber diameter and end-systolic left atrial diameter) did not show a significant difference between the two main groups and the five subgroups.

Follow-Up Data

Survival rates (Tables 5 and 6). During follow-up, 36 patients died: 19 in Group 1 (annual mortality rate 3.6%) and 17 in Group 2 (annual mortality rate 2.4%, $p = NS$). Most patients died suddenly (13 in Group 1 and six in Group 2, $p = NS$) or as a result of congestive heart failure (three in Group 1 and five in Group 2, $p = NS$) (Table 5). Among the 11 pediatric patients (3 to 15 years old) who underwent operation, four (36%) died during follow-up.

The 5, 8 and 10 year cumulative survival rates were

significantly higher ($p < 0.05$) in Group 2 than in Group 1. The 10-year survival rate was 84% in Group 2 and 68% in Group 1 (Fig. 2). In Group 1, survival rates after 5 and 8 years were significantly better in the verapamil-treated group than in the other two subgroups ($p < 0.05$): 88% and 88% at 5 and 8 years, respectively, in Group 1b (verapamil), 81% and 74% in Group 1a (propranolol) and 72% and 65% in Group 1c (nontreated). Patients treated with propranolol showed a better survival rate during the first 2 years of the study than did those without treatment ($p < 0.05$) (Fig. 3). There was no statistical difference between the 5 and 10 year survival rates of Group 2 (96% and 84%) and those of Group 1b (verapamil) (88% and 80%, respectively) (Table 6). The 17 Group 2 patients receiving verapamil (Group 2a) had the best survival rates: 100% after 5 and 8 years (maximal follow-up 16 years), compared with 92% and 85% in the 62 patients in Group 2b (both $p < 0.05$) (Fig. 4).

Clinical examination (Table 2). In Group 1, functional classification did not change significantly during the follow-up period, either in the entire medical group or in the subgroups. Group 2 showed an improvement in functional classification from preoperatively to postoperatively (2.1 versus 1.6 at the end of the observation period) ($p < 0.05$) (Fig. 1). Patients in Group 2 had angina pectoris, dizziness

Table 4. Echocardiographic Data in 139 Patients

	D_ed(cm)		Th_s(cm)		Th_p(cm)		LA (cm)		Sh(%)	
	Entry	End	Entry	End	Entry	End	Entry	End	Entry	End
Group 1	4.5 ± 0.8	4.5 ± 0.8	1.8 ± 0.4	2.0 ± 0.4	1.1 ± 0.2	1.2 ± 0.2	3.9 ± 0.8	4.6 ± 1.0	42 ± 7	43 ± 8
	n = 48	n = 43	n = 50	n = 46	n = 50	n = 44	n = 49	n = 46	n = 45	n = 44
1a	4.4	4.4	2.0	1.9	1.2	1.2	4.1	4.8	46	42
1b	4.5	4.5	1.9	2.1	1.0	1.2	3.9	4.8†	43	42
1c	4.8	4.5	1.7	2.0	1.1	1.2	3.8	4.1†	44	44
Group 2	4.5 ± 0.8	5.1 ± 0.8	1.9 ± 0.6	1.7 ± 0.3	1.2 ± 0.2	1.1 ± 0.1	4.3 ± 1.0	4.7 ± 0.9	41 ± 7	39 ± 9
	n = 20	n = 39	n = 24	n = 39	n = 22	n = 40	n = 21	n = 39	n = 21	n = 37
2a	4.6	5.2	1.9	1.7	1.1	1.2	4.1	4.8	41	40
2b	4.5	5.2	2.0	1.7*	1.2	1.2	4.5	4.6	42	39

*$p < 0.05$ versus entry; †$p < 0.01$ versus entry. D_ed = end-diastolic internal chamber diameter of the left ventricle; LA = left atrial diameter; Sh(%) = systolic percent shortening of the internal chamber diameter measured at the tip of the mitral valve; SM = septal myectomy; Th_p = posterior wall thickness; Th_s = septal wall thickness. Groups are defined in Table 1.

Table 5. Causes of Death

	Sudden Death	Heart Failure	Other
Group 1	22% (13/60)	5% (3/60)	5% (3/60)
1a	20% (4/20)	5% (1/20)	10% (2/20)
1b	17% (3/18)	0% (0/18)	6% (1/18)
1c	27% (6/22)	9% (2/22)	0% (0/22)
Group 2	8% (6/79)	6% (5/79)	8% (6/79)
2a	6% (1/17)	0% (0/17)	0% (0/17)
2b	8% (5/62)	8% (5/62)	10% (6/62)

There were no significant differences regarding cause of death. Groups are defined in Table 1.

Table 6. Survival Rates: Group 1b Versus Group 2

	n	Follow-up (yr)	5 Year Survival	10 Year Survival
Verapamil medical group (1b)	18	9.1	88%	80%
Surgical group (2)	79	9.4	96%	84%

There were no significant differences between the two groups at either 5 or 10 years of follow-up.

and syncope less frequently postoperatively than preoperatively (55% versus 44%, 28% versus 19% and 10% versus 0%, respectively, all $p < 0.05$). None of the two main groups or five subgroups had a significant change in physical working capacity or cardiothoracic ratio. The Sokolow-Lyon ECG index of ventricular hypertrophy did not change significantly during the follow-up, nor did it differ among the Group 1 subgroups at the end of the study. Because 39% of all surgically treated patients had left bundle branch block, the Sokolow-Lyon index was not determined postoperatively in Group 2.

Echocardiography (Table 4). During follow-up, left atrial diameter increased from 4.1 to 4.8 cm in subgroup 1a (propranolol) ($p < 0.01$) and from 3.9 to 4.8 cm in subgroup 1b (verapamil) ($p < 0.01$). After surgery, septal wall thickness decreased from 2.0 to 1.7 cm in Group 2b (surgical therapy, no verapamil, $p < 0.05$). Between Groups 1 and 2 only one echocardiographic variable showed a significant difference at the end of the study: left ventricular end-diastolic diameter was larger in Group 2 than in Group 1a (5.1 versus 4.4 cm, $p < 0.05$). However, left ventricular end-diastolic internal chamber diameter was not different between the Groups 1 and 2 as a whole.

Discussion

The 1-year mortality rate in patients with hypertrophic cardiomyopathy is 3 to 8% (2,4,17,26–28), and the 5-year survival rate is 55 to 78% (4,17,29). The most common cause of death is sudden cardiac death due to arrhythmias, followed by congestive heart failure. Patients at high risk for sudden death are young, have a positive family history and have no or only mild outflow tract obstruction (5). To control symptoms and possibly to improve prognosis, several therapeutic approaches (15), including surgical resection of the hypertrophied septum (8,9) or mitral valve replacement (30,31), have been proposed. Medical therapy was based for many years on beta-adrenergic blocking drugs (2,4,32), but recently calcium antagonists have become popular (18–22).

Medical Therapy

Propranolol. Propranolol was introduced in the early 1960s (32). Its main pharmacologic effect is related to a reduction in heart rate and contractility with a concomitant decrease in outflow tract obstruction. Propranolol did not affect the survival rate in most studies (5,16,17), although Frank et al. (4) reported an improved survival rate in patients receiving very large doses (460 mg/day) (Table 7). Five-year
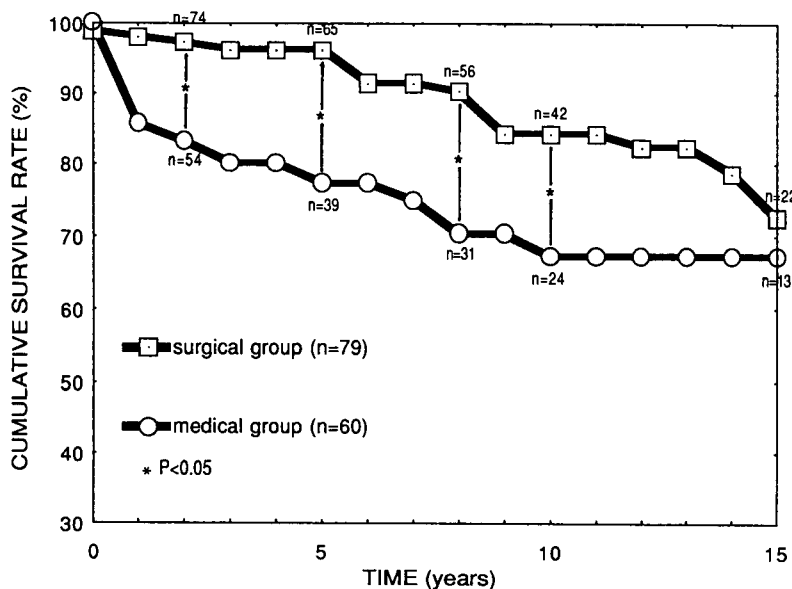

Figure 2. Cumulative survival rates of the 139 patients with hypertrophic cardiomyopathy. Group 1 = medical therapy (n = 60); Group 2 = surgical therapy (n = 79). The average follow-up was 8.9 years for the entire study group, 8.2 years for Group 1 and 9.4 years for Group 2. Group 2 had higher 2, 5, 8 and 10 year survival rates than did Group 1.

Figure 3. Cumulative survival rates of Group 1. Group 1a was treated with propranolol, 1b with verapamil, 1c received no therapy. The average follow-up time was 8.2 years for the entire medical group, 7.8 years for Group 1a, 9.1 years for Group 1b and 7.8 years for Group 1c. Group 1b had better survival rates than 1a or 1c ($p < 0.05$).
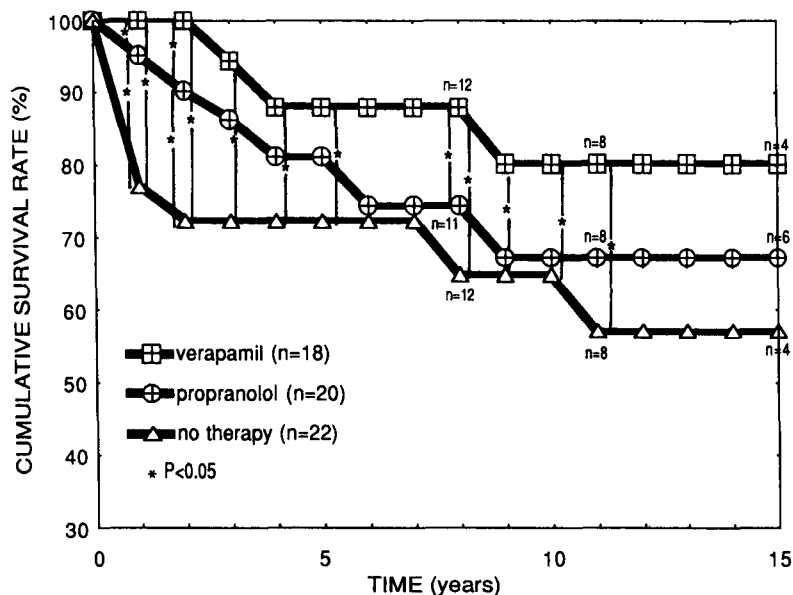
survival rates varied between 76% (16) and 90% (4), whereas in untreated patients 5-year survival varied between 55% and 78% (4,17,29). In the present study, the 2-year survival rate was better with propranolol than without medical treatment. A long-term beneficial effect of propranolol on survival could, however, not be substantiated because 5- and 10-year survival rates for patients treated with propranolol were 81% and 67%, respectively, whereas in the untreated group they were 72% and 65%, respectively (Table 7).

Verapamil. Kaltenbach et al. (33) first reported on the therapeutic effect of verapamil on symptoms and left ventricular hypertrophy in patients with hypertrophic cardiomyopathy and their findings have been confirmed by others (17,18,22). Most investigators have reported a high survival rate after chronic therapy with verapamil; Rosing et al. (21), however, reported an annual mortality rate of 6%. Their follow-up period was the shortest (1.2 years) of all studies summarized in Table 7. In the other studies (17,18,22), annual mortality rates varied between 1.8% and 2.2%. In the present analysis it was 2.3%. The 10-year survival rate was 90% in the study of Hopf and Kaltenbach (22) and 80% in the present study. Among the medically treated patients who received propranolol or verapamil and the untreated patients (Fig. 3), the best follow-up results were in the verapamil-treated patients, with a significantly ($p < 0.05$) higher survival rate after 8 years (88%) than in the propranolol-treated (74%) or untreated subgroups (65%). The mode of action of verapamil is not clear but appears to be related either to improved relaxation with an increased early filling rate (34), improved subendocardial perfusion (7), an antiarrhythmic effect (19), or a reduction in left ventricular asynchronous wall motion (34,35).

Surgical Therapy

Surgical management of hypertrophic obstructive cardiomyopathy was introduced in the late 50s by Cleland (8); he performed myotomy/myectomy of the hypertrophied septum using a transventricular approach. This technique was later adapted by others (10,11,36), and transaortic myectomy has become the treatment of choice for severely symptomatic patients with a large outflow tract pressure gradient. Mitral valve replacement as an alternative therapy for hypertrophic cardiomyopathy has been recommended (30,31), but has not been used by most surgeons except in patients with severe mitral regurgitation or clear valvular alterations (11,36). The 1-year mortality rate was low after septal myectomy, ranging between 2.6% and 4.4% (9,11,36,37); it was 2.7% in the present analysis (Table 7). Most authors have reported mortality rates between 2% and 3%, although McIntosh and Maron (11) reported a mortality rate of 4.4%/year. The perioperative mortality rate varies between 1.3% (present study) and 17.6% in the elderly (38); the average of five reports is 5%. Five- and 10-year survival rates including perioperative mortality were 96% and 84%, respectively, in the present study (Table 7). Similar data were reported by Kuhn et al. (29); however, they excluded perioperative mortality. In our study, there was a tendency toward fewer sudden cardiac deaths after surgery (Table 5) than with medical therapy ($p = NS$). The mechanism of this favorable result is not clear but may be related to regression of secondary hypertrophy with less subendocardial ischemia after removal of the pressure burden (39).

Medical Versus Surgical Therapy

Cumulative survival rates were consistently better after myectomy than after medical therapy, including untreated and treated (propranolol and verapamil) patients (Fig. 2). After 5 years the cumulative survival rate was 96% in the surgical and 78% in the medical group; the respective data after 10 years were 84% and 68%. The two survival curves approached each other after 13 years of follow-up. In absolute terms, 19 (32%) of 60 patients in the medically treated

Table 7. Literature Review of the Course of Hypertrophic Cardiomyopathy in Patients With or Without Therapy

|	n	Follow-up (years)	Deaths	Mortality (%/year)	5-/10-year survival (%)	Therapy
No therapy						
Frank 1968 (28)	98	2.9	10	3.5	—/—	—
Loogen 1978 (27)	47	6.7	11	3.5	—/—	—
Shah 1974 (2)	31	5.2	5	3.1	—/—	—
Frank 1978 (4)	10	5.0	4	8.0	74/—	—
Haberer 1983 (17)	20	6.4	8	6.3	55/—	—
Kuhn 1983 (29)	27	6.4	7	4.0	78/—	—
Present data 1990	22	7.8	8	4.7	72/65	—
Propranolol						
Shah 1974 (2)	101	4.7	19	4.0	—/—	Beta-blocking agents
Frank 1978 (4)	22	5.0	0	0	90/75	Propranolol (460 mg/day)
Kuhn 1978 (16)	168	5.2	28	3.2	76/—	Beta-blocking agents
Canedo 1981 (3)	33	5.7	1	0.5	—/—	Propranolol (460 mg/day)
McKenna 1981 (5)	170	6.0	39	3.8	—/—	Beta-blocking agents
Haberer 1983 (17)	15	7.0	4	3.8	80/—	Propranolol (175 mg/day)
Kuhn 1983 (29)	140	4.6	7	2.6	—/—	Propranolol (? mg/day)
Present data 1990	20	7.8	7	4.5	81/67	Propranolol (160 mg/day)
Verapamil						
Hopf 1982 (18)	41	2.7	2	1.8	—/—	Verapamil (500 mg/day)
Rosing 1982 (21)	42	1.2	3	6.0	—/—	Verapamil (240–640 mg/day)
Haberer 1983 (17)	15	3.7	1	1.8	93/—	Verapamil (360 mg/day)
Hopf 1987 (22)	84	4.3	8	2.2	—/90	Gallopamil (158 mg/day)
Present data 1990	18	9.1	4	2.3	88/80	Verapamil (360 mg/day)
Septal myectomy/myotomy						
Senning 1976 (9)	39	2.9	3	2.6	—/—	Septal myectomy (TV)
Maron 1983 (37)	240	35	2	2.7	—/—	Septal myectomy (TA)
McIntosh 1988 (11)	123	11.5	63	4.4	—/—	Septal myectomy (TA)
Schulte 1988 (36)	283	6.2	39	2.2	80/—	Septal myectomy (TA)
Present data 1990	62	95	17	2.7	96/84	Septal myectomy (TV/TA)
Myectomy + verapamil						
Present data 1990	17	9	1	0.6	100/00	Septal myectomy + verapamil (120–360 mg/day)

TA = transaortic approach; TV = transventricular.

group and 17 (22%) of 79 in the surgically treated group died during the follow-up of approximately 9 years. Although the absolute values are similar, only one-fifth of all patients in the surgically treated but one-third in the medically treated group died. Thus, not only are cumulative survival rates better in the surgical than in the medical group but the percent of patients who died during the follow-up period was also lower.

Role of verapamil. The survival rates of the surgically treated patients are only slightly and insignificantly better than those of the medically treated patients who received verapamil after 5 (96% versus 88%) and 10 years (84% versus 80%) (Table 6). Some investigators (18,22) have concluded that verapamil therapy is as effective as surgery and that surgical intervention is no longer necessary even in severely symptomatic patients with a high pressure gradient. On the basis of this observation (Table 6), the effect of verapamil treatment on cumulative survival rates in surgically treated patients was evaluated (Fig. 4). Surprisingly, cumulative survival rates after 5 and 8 years were 100%; the only patient

who died among the 17 treated surgically and then with verapamil (Group 2a) died after 16 years of follow-up. This excellent result must be interpreted with caution because the number of observations is relatively small. The indication for therapy was based on clinical symptoms rather than hemo-dynamic findings; nevertheless, the favorable outcome may be explained by the combined action on systole (myectomy) and diastole (verapamil). Whereas surgery is known to reduce the systolic pressure gradient and diastolic filling pressure (12,39), verapamil has been shown to improve left ventricular function (34,35). Whether improvement of impaired diastolic function was the basis of the excellent survival in Group 2a or whether primarily a reduction of arrhythmias with consecutive reduction of sudden death was the predominant mechanism remains open to discussion.

Effect of therapy on clinical and laboratory findings. An improvement in functional classification could be observed only after myectomy but not with medical therapy (Fig. 1). This effect is probably related to the reduction in systolic pressure gradient and diastolic filling pressure that is asso-

Figure 4. Cumulative survival rates of the 60 patients treated medically (Group 1) and the 79 treated surgically (Group 2). The subgroup of Group 2 patients who were subsequently treated with verapamil (120 to 360 mg/day) had the best survival rate: they were followed by the surgical group that did not receive verapamil and then by Group 1. The average follow-up duration was 8.2 years for Group 1, 9.3 years for Group 2, 9.4 years for Group 2 patients treated with verapamil and 9.5 years for Group 2 patients not treated with verapamil (p < 0.05).
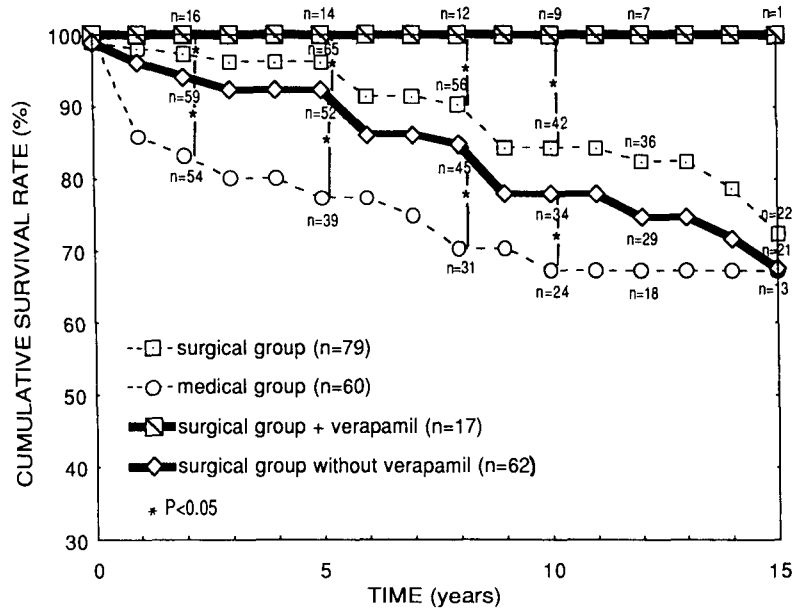
ciated with myectomy but is not seen after medical therapy (21). Cardiothoracic ratio, physical working capacity and Sokolow-Lyon ECG index (Table 2) remained unchanged in all groups throughout the follow-up period. There is a reported consensus (9,12,13,37) that myectomy/myotomy lessens cardiac symptoms and improves functional classification even over long-term follow-up.

The effect of beta-adrenergic blockers on functional status in hypertrophic cardiomyopathy is controversial. Earlier studies by Frank et al. (3,4) showed a significant lessening of symptoms with large doses of propranolol, whereas more recent studies (5,17,20) did not find improvement in functional classification during long-term therapy. Several investigators (18,19,29,40) have reported a decrease in clinical symptoms with long-term verapamil treatment. However, the present study with a mean follow-up period of 9.7 years did not show any lessening of clinical symptoms, although in most patients temporary clinical improvement with initial verapamil therapy was seen.

A decrease in septal wall thickness was observed with M-mode echocardiography in patients receiving long-term verapamil therapy (19,22), whereas posterior wall thickness remained unchanged (19) or decreased (22). Myectomy was shown (41) to be associated with a significant decrease in septal wall thickness, but at the same time left ventricular end-diastolic internal chamber diameter increased significantly. This finding could be due to the reduction in muscle mass or the occurrence of asynchrony caused by left bundle branch block or both. However, no change in septal or posterior wall thickness was observed during medical therapy in the present study.

Limitations of the study. One major limitation of the present study is that it is a retrospective analysis comparing two groups that are not necessarily comparable. In this regard, systolic pressure gradient and peak systolic pressure

were significantly different between the medically and surgically treated patients (Table 3). This is due to patient selection: patients with a large pressure gradient underwent operation and those with a small gradient did not. Because of the relatively small number of patients and the long observation period of up to 28 years, randomization could not be performed in a reasonable time span, and thus, all follow-up studies in patients with hypertrophic cardiomyopathy are based on retrospective data.

Conclusions. In severely symptomatic patients and those with hypertrophic cardiomyopathy and large pressure gradients, clinical follow-up results are best with combined treatment with septal myectomy and chronic verapamil therapy. However, mildly symptomatic patients with no or mild outflow tract obstruction probably benefit most from treatment with verapamil.

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