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Left ventricular chamber dilatation in hypertrophic cardiomyopathy: related variables and prognosis in patients with medical and surgical therapy

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Abstract

***Background*—To determine the incidence and prognosis of left ventricular dilatation and systolic dysfunction in 139 patients with hypertrophic cardiomyopathy during long term follow up.**

***Methods*—Left ventricular chamber dilatation and systolic dysfunction (both together referred to as left ventricular chamber dilatation) were determined echocardiographically. Chamber dilatation was defined as an increase in the left ventricular end diastolic diameter of >2% per year combined with a decrease in midventricular systolic fractional shortening of >2% per year of follow up [10·3 (SD 6) years]. The predictive value for left ventricular chamber dilatation of clinical, invasive, and echocardiographic variables and its prognosis were assessed.**

***Results*—In 119 of 139 individuals (86%), left ventricular chamber size and systolic function remained stable (group 1), and in 20/139 patients (14%) left ventricular chamber dilatation occurred during follow up (group 2). At baseline examination, symptoms such as dyspnoea and syncope occurred less often in group 1 than in group 2; New York Heart Association classification was lower in group 1 than in group 2 (P = 0·001). Left ventricular mass index relative to sex specific normal values was increased by 18% in group 1 and by 41% in group 2 (P = 0·04). Cumulative survival rates were slightly although not significantly higher in group 1 than in group 2. Event-free survival was significantly higher in group 1 than in group 2 (P < 0·05).**

***Conclusions*—(1) The development of left ventricular chamber dilatation and systolic dysfunction in hypertrophic cardiomyopathy occurs in approximately 1·5% of the patients per year. (2) Factors associated with left ventricular dilatation are dyspnoea, syncope, a higher functional classification, and a higher degree of left ventricular hypertrophy. (3) Patients with chamber dilatation have a worse prognosis than those without, particularly regarding quality of life.**

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Keywords: hypertrophic cardiomyopathy, left ventricular dilatation, prognosis with medical and surgical treatment

Clinical course and prognosis in patients with hypertrophic cardiomyopathy are characterised by life threatening arrhythmias and sudden cardiac death. The prognostic significance of these factors[1] has been well recognised but other factors—such as the evolution of "typical" hypertrophic cardiomyopathy into a dilated form with systolic dysfunction—have been studied only rarely, and the impact of this particular subgroup on cardiac morbidity and mortality is not precisely known (for references see table 1). This is due in part to the fact that the frequency with which left ventricular dilatation

Table 1 Left ventricular chamber dilatation and systolic dysfunction: published reports

Source	n	Age (years)	FU (years)	Incidence (%/FU)	ED_1 (mm)	ED_2 (mm)	ΔEDD %/year	EF_1 (%)	EF_2 (%)	ΔEF %/year	S_1 (mm)	S_2 (mm)	PW_1 (mm)	PW_2 (mm)
Hina K 1993[2]	8	48	6·5	15·7	44	53	3·1	72	56	−3·4	—	—	—	—
Okamoto S 1992[3]	1	—	7	—	35	68	13·5	60	11	−11·7	—	—	—	—
Bourmayan C 1990[4]	4	36	4	—	43	57	8·1	—	—	—	—	—	—	—
Pelliccia F 1990[5]	1	—	8	—	50	61	2·8	56	40	−3·6	—	—	—	—
Shimizu A 1992[6]	1	—	9	—	39	51	3·4	—	—	—	26	14	17	15
Yutani C 1985[7]	3	24	6	—	—	58	—	—	—	—	—	19	—	—
ten Cate FJ 1979[8]	2	59	4	4	—	60	—	—	—	—	—	—	—	—
Ando H 1990[9]	3	50	6	17	—	42	—	73	52	−4·8	—	21	—	15
Spirito P 1987[10]	13	—	3·6	6	44	49	3·2	40	—	—	—	—	—	—
Spirito P 1986[11]	6	—	7	—	41	47	2·1	53	31	−5·9	22	18	—	—
Fighalli S 1987[12]	5	37	8	8·1	33	46	4·8	72	43	−5	18	12	14	10
Hartmann A 1991[13]	5	56	7·8	—	53	63	2·4	60	24	−7·7	21	17	13	12
Kanemoto N 1987[14]	1	20	8	—	53	65	2·8	40	21	−5·9	20	10	21	15
Funakoshi M 1984[15]	1	52	5	—	45	65	8·9	44	33	−5	15	8	12	8
Present data 1994	20	38	10·3	14·3	43	50	2·5	68	50	−3·5	19	17	11	11
Mean (SD)	4 (5)	40 (14)	7·0 (4)	12·2 (5)	44 (6)	57 (8)	4·6 (3·2)	58 (12)	37 (13)	−5·6 (2·4)	19 (4)	15 (4)	14 (4)	12 (3)

n, number of patients; FU, time of follow up; $ED_{1,2}$, end diastolic diameter at baseline and at follow up examination; ΔEDD, mean change in end diastolic diameter in % per year; $EF_{1,2}$, left ventricular ejection fraction at baseline and at follow up examination; $S_{1,2}/PW_{1,2}$, septal and posterior wall thickness at baseline and at follow up examination; ΔEF, mean change in left ventricular ejection fraction in % per year.

and systolic dysfunction occurs in hypertrophic cardiomyopathy is uncertain.[10-12] There are only a few studies[10-12] which have provided some insight into the pathophysiological mechanisms involved in this subgroup of patients with hypertrophic cardiomyopathy. The development of progressive systolic dysfunction has been reported to occur more often in surgically treated patients than in medically treated patients.[16]

The purpose of the present retrospective study was therefore (1) to determine the incidence of the development of left ventricular dilatation and systolic dysfunction in 139 patients with hypertrophic cardiomyopathy during long term follow up; (2) to define clinical, echocardiographic, or invasive predictors for the development of ventricular dilatation; (3) to compare the incidence of ventricular dilatation and clinical course in medically and surgically treated patients; and (4) to assess the prognosis in these patients.

Methods

PATIENTS

The entire study group consisted of 139 patients with hypertrophic cardiomyopathy (113 men, age at baseline examination 38·8 (SD 13) years, ranging from 7 to 68 years; 26 women, age 31·7 (15) years, ranging from 5 to 67 years; P = 0·006). The effect of different methods of treatment on survival and clinical outcome has been reported previously.[17] The diagnosis of hypertrophic cardiomyopathy was made by means of cardiac catheterisation or M mode echocardiography, or both (from 1975 to 1979) and/or cross sectional and M mode echocardiography (from 1979 until now) The following diagnostic and inclusion criteria were required[18]: (1) asymmetric distribution of hypertrophy or systolic anterior movement of the anterior mitral leaflet, or both; (2) normal or supernormal ejection fraction; and (3) absence of other cardiac or systemic disorders. The patients were followed for 10·3 (6) years (range one to 31 years). The entire study population was divided in two groups according to the absence (group 1, n = 119) or presence of left ventricular chamber dilatation combined with systolic dysfunction (subsequently referred to as left ventricular chamber dilatation) developing during the course of the disease (group 2, n = 20).

A subgroup analysis evaluated the impact of different types of treatment on the development and prognosis of left ventricular chamber dilatation. Sixty patients were treated medically (medical group) with β blockers (mainly propranolol), calcium antagonists (predominantly verapamil), or no therapy; 79 patients received surgical treatment (septal myectomy). Patients qualified for surgical treatment if mean systolic pressure gradient across the left ventricular outflow tract exceeded 50 mm Hg or if clinical symptoms were unresponsive to or deteriorated with medical therapy. Thus patients treated medically may not be comparable to surgically treated patients, but because of the long time span of the study and the relatively rare occurrence of hypertrophic cardiomyopathy, randomisation was not performed.

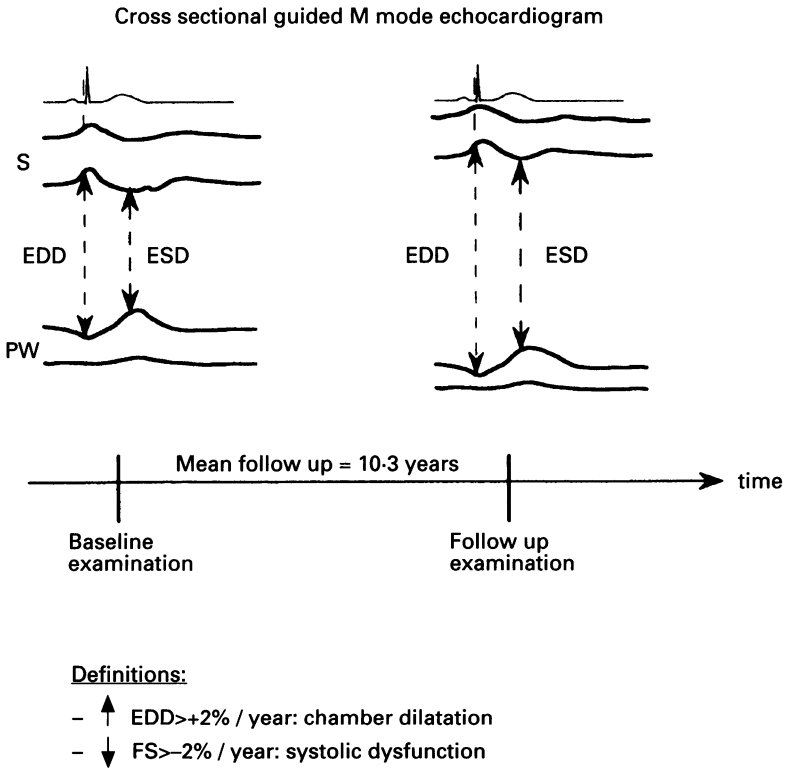

Figure 1 Determination of left ventricular (LV) chamber dilatation and systolic dysfunction in patients with hypertrophic cardiomyopathy. At baseline and follow up examination, cross sectionally guided M mode echocardiographic measurements of end systolic (ESD) and end diastolic (EDD) LV chamber diameters were obtained according to the guidelines of the American Society of Echocardiography. The change in EDD and LV fractional shortening (FS = [EDD-ESD]/EDD) during follow up was calculated as ([EDD or FS at follow up minus EDD or FS at baseline] divided by the respective baseline value) × 100. LV chamber dilatation was defined as a combined change in EDD and FS of greater than + 2% per year and greater than − 2% per year of follow up. S, interventricular septum; PW, posterior wall.

DEFINITION OF LEFT VENTRICULAR CHAMBER DILATATION AND SYSTOLIC DYSFUNCTION

Left ventricular chamber dilatation and systolic dysfunction were defined by M mode echocardiography (fig 1; M mode alone before 1979, n = 42; cross sectionally guided since 1979, n = 97) as an increase of >2% per year of follow up in end diastolic diameter (ED) combined with a decrease of >2 relative percentage points per year in left ventricular fractional shortening (FS). These numerical thresholds of the annual change of ED and FS were chosen according to published data (table 1). Values of ED exceeding the upper normal range (60 mm[19]) were not chosen as criteria for definition because it has been a controversial issue whether this is a necessary condition for the definition of left ventricular chamber dilatation in hypertrophic cardiomyopathy.

CLINICAL EXAMINATION

At entry into the study (time of diagnosis), all patients were examined clinically. Functional status according to the New York Heart Association (NYHA) was determined. The frequency of symptoms most commonly occurring in hypertrophic cardiomyopathy (dyspnoea,

angina pectoris, syncope, palpitations) was assessed. Heart rate and blood pressure were measured and a resting electrocardiogram was recorded. In 125 patients physical working capacity was determined by bicycle ergometry and was expressed as a percent of the age, gender, and height adjusted normal value. A chest *x* ray was obtained in all patients and the cardiothoracic ratio was calculated.

CARDIAC CATHETERISATION

Of the 139 patients, 125 underwent cardiac catheterisation for diagnostic purposes to assess left ventricular outflow tract gradient in the pre-echocardiography era, and to exclude coronary artery disease. Cardiac catheterisation included right and left sided catheterisation with determination of cardiac output by the Fick method, biplane left ventricular angiocardiography, and coronary arteriography. Left ventricular volume was calculated according to the area-length method.

ECHOCARDIOGRAPHY

At the time of diagnosis, 113 patients underwent M mode (n = 34) or cross sectionally guided plus M mode echocardiography (n = 79) (Diasonics model CV-3400R or Hewlett Packard model 77020 AC). In the 26 patients whose clinical follow up was longer than 18 years [mean of 21·7 (5) years], echocardiographic follow up was only 16·8 (4) years (P = 0·01). Since the definition of chamber dilatation required echocardiographic examination, all patients received two or more (n = 58) echocardiograms, and 19% (26/139) had their baseline echocardiography after the first diagnostic examination.

Serial cross sectionally guided M mode recordings (n = 97) were performed with the subject in a supine right anterior oblique position according to standard techniques.[20] Left ventricular measurements were obtained at end systole and at end diastole. End diastolic measurements were carried out according to the American Society of Echocardiography convention (fig 1).[21] Left ventricular measurements included septal thickness at end diastole, posterior wall thickness at end diastole, and left ventricular and left atrial internal dimensions at end systole and at end diastole. Regional wall motion analysis was performed visually. Left ventricular mass was calculated according to the equation of Devereux and coworkers.[22] After 1983, Doppler echocardiographic recordings were performed for determination of the left ventricular outflow tract gradient using a real time phased array sector scanner (Sonos 500, Hewlett Packard) with integrated colour Doppler facilities and a transducer containing a 2·5 MHz crystal set for imaging and continuous wave (CW) Doppler.

The diagnosis of hypertrophic cardiomyopathy was made exclusively by means of cross sectional and Doppler echocardiography in 14 of the 139 study patients. These patients were not evaluated invasively because their symptomatic status was mild or no outflow tract obstruction was present.

FOLLOW UP

Follow up for the entire study group averaged 10·3 (6) years, ranging from one to 32 years. In 104 patients at least one clinical examination took place after the baseline examination. Thirty five patients had their clinical follow up examination only by questionnaire. However, a follow up echocardiography was performed in all patients. Follow up information was obtained in all patients by the end of 1986 or later. Number of deaths was determined through the primary physicians or through relatives of the deceased. Fifty eight patients (42 in group 1, and 16 in group 2) underwent more than one follow up Doppler echocardiography. In 33 patients (22 in group 1 and 11 in group 2) a follow up cardiac catheterisation was carried out.

DATA ANALYSIS AND STATISTICS

Data were analysed (1) by determining the incidence of ventricular dilatation and systolic dysfunction during follow up, (2) by assessing the predictive value of clinical, invasive, and echocardiographic variables at baseline examination, and (3) by assessing the prognosis with regard to survival and to quality of life. "Quality of life" was assessed by measuring the event-free cumulative survival rate; "events" were defined as newly developed symptoms typical for hypertrophic cardiomyopathy such as a change in functional NYHA classification >1, onset or worsening of dyspnoea, angina pectoris, or syncope. (4) The effect of medical treatment was compared to that of surgical treatment by applying the above criteria to medically and surgically treated patients.

Determination of the predictive value of different variables for the group characteristics was performed by univariate analysis using the χ^2 test for comparison of relative frequences between groups, unpaired two tailed *t* test for comparison of continuous variables, and one way analysis of variance (ANOVA) followed by the Scheffé's test (if significant at $P < 0{\cdot}05$) for comparing continuous variables between the two study groups under different forms of therapy. Cumulative survival rates and event-free survival were calculated according to Anderson *et al.*[23] Values presented in the tables and figures are means with standard deviations.

Results

INITIAL FINDINGS

In 119 of 139 individuals of the study population (86%), left ventricular chamber size and systolic function remained stable during follow up (group 1). Twenty of 139 patients (14%) developed left ventricular chamber dilatation combined with deterioration of systolic performance (group 2) during follow up.

Patient characteristics and clinical examination (tables 2 and 3)

Patients without and with left ventricular chamber dilatation did not differ with regard to mean age or age range (5–68 years in group 1, and 23–55 years in group 2). Five of the

Table 2 Patient characteristics at baseline examination

	Group 1 (No LV chamber dilatation)	*Group 2 (LV chamber dilatation)*	*P*
Number	119/139	20/139	
Age (years)	36 ± 14	38 ± 9	NS
Men/women (% women)	89/30 (25)	10/10 (50)	NS
Type of HCM:			
HNCM (%)	33/114 (29)	3/20 (15)	NS
HOCM (%)	81/114 (71)	17/20 (85)	NS
LVOT gradient (mm Hg) (SD)	53 (40)	56 (26)	NS
MVO (%)	5/119 (4)	0/119 (0)	NS
Follow up (years) (SD)	10·6 (6·5)	9·8 (5·6)	NS
Family history of HCM (%)	7/119 (6)	4/20 (20)	0·08
Body surface area (m^2) (SD)	1·85 (0·2)	1·68 (0·2)	0·008
Body mass index (kg/m^2) (SD)	24·6 (3·1)	23·7 (2·9)	NS
Medical/surgical treatment (%)	55/64 (54)	5/15 (75)	NS

LV, left ventricular; HCM, hypertrophic cardiomyopathy; HNCM/HOCM, hypertrophic non-obstructive/obstructive cardiomyopathy; LVOT, left ventricular outflow tract; MVO, mid-ventricular obstruction.

119 patients in the control group were in the age group between 5 and 18 years. Their baseline echocardiographic examination was chosen during adulthood in order to be comparable to the rest of the study group.

There was a trend for fewer women to be in group 1 (25%) than in group 2 with chamber dilatation (50%). The significantly higher body surface area in group 1 than in group 2 was most probably related to the higher percentage of men in group 1. The type of cardiomyopathy at baseline—non-obstructive or obstructive cardiomyopathy with subvalvular or midventricular obstruction—did not predict the outcome. Time of follow up averaged approximately 10 years in both groups. There was a lower frequency of patients with a family history of hypertrophic cardiomyopathy in group 1 than in group 2. The frequency of patients treated surgically was lower in group 1 (64/119 = 54%) than in group 2 (15/20 = 75%; NS).

Of all clinical variables listed in table 3, dyspnoea and syncope occurred less often in group 1 than in group 2, and NYHA classification was lower in group 1 than in group 2.

Cardiac catheterisation

None of the indices obtained from invasive procedures (left ventricular pressure, pressure gradient across the left ventricular outflow tract, cardiac index, left ventricular ejection fraction, left ventricular end diastolic volume) predicted the development of chamber dilatation and systolic dysfunction during follow up. Only one of the 105 patients in group 1 who underwent coronary angiography had significant coronary artery disease (coronary artery diameter stenosis >50%); all patients in group 2 had normal coronary angiograms. Of the 14 patients in group 1 who were only examined non-invasively (mean age 25 years), 10 had no chest pain at baseline, and four had rare episodes with angina pectoris.

Echocardiographic data (table 4 and fig 2)

The following echocardiographic baseline variables did not differ between the two study groups: end systolic diameter, septal and posterior wall thickness, left atrial dimension, left ventricular fractional shortening, mean systolic pressure gradient across the left ventricular outflow tract, frequency of systolic anterior motion, frequency of myocardial wall motion abnormalities, left ventricular mass, and septal to posterior wall thickness ratio.

Left ventricular mass index showed a tendency to lower values in group 1 than in group 2. Left ventricular mass index relative to sex specific values[24] was a predictor for subsequently developing chamber dilatation; it was increased at baseline by 18% in group 1 and by 41% in group 2 (P = 0·04). Similarly, but without reaching statistical significance, myocardial wall thickness relative to left ventricular chamber diameter at baseline was smaller in group 1 than in group 2. There was a significant relationship between relative left ventricular mass index and the relative change in end diastolic diameter (fig 2A) and the relative increase in left ventricular fractional shortening (fig 2B), respectively during follow up.

Comparison between medical and surgical therapy

Left ventricular chamber dilatation and systolic dysfunction (group 2) occurred in 8%

Table 3 Clinical data at baseline

	Group 1 (n = 119) (No LV chamber dilatation)	*Group 2 (n = 20) (LV chamber dilatation)*	*P*
Symptoms:			
Angina pectoris (%)	63 (53)	10 (50)	NS
Dyspnoea (%)	43 (36)	20 (100)	0·0001
Syncope (%)	13 (11)	8 (42)	0·005
Palpitations (%)	39 (33)	7 (35)	NS
Heart rate (beats/min) (SD)	72 (12)	72 (10)	NS
Blood pressure (mm Hg) (SD)	125 (15)/79 (12)	122 (19)/78 (11)	NS
NYHA class (SD)	1·8 (0·7)	2·5 (0·6)	0·001
PVB (%)	13 (11)	2 (10)	NS
Working capacity (% of required) (SD)	82 (18)	76 (23)	NS
Cardiothoracic ratio (SD)	0·50 (0·05)	0·51 (0·04)	NS
Sokolow index (mV) (SD)	3·18 (1·2)	2·91 (1·4)	NS
Atrial fibrillation (%)	6 (5)	0 (0)	NS
Left bundle branch block (%)	20 (17)	0 (0)	NS

LV, left ventricular; PVB, premature ventricular beats; NYHA, New York Heart Association.

Table 4 Echocardiographic data at baseline. Values are mean (SD) except where shown as percentages

	Group 1 (n = 119) (No LV chamber dilatation)	*Group 2 (n = 20) (LV chamber dilatation)*	*P*
End systolic diameter (mm)	27·7 (7)	24·6 (4)	NS
End diastolic diameter (mm)	47·2 (7)	42·8 (7)	0·06
Septal wall thickness (mm)	18·3 (5)	18·0 (4)	NS
Posterior wall thickness (mm)	11·2 (2)	11 (9)	NS
Left atrial dimension (mm)	40·9 (9)	40·1 (9)	NS
LV fractional shortening (%)	41 (9)	42 (6)	NS
LVOT pressure gradient (mm Hg)	38 (41)	47 (32)	NS
Systolic anterior movement (%)	83/119 (70)	15 (75)	NS
Wall motion abnormality (%)	15/98 (15)	2/16 (13)	NS
Left ventricular mass (LVM, g)	294 (106)	261 (59)	NS
LVM index (g/m² of BSA)	152 (46)	162 (20)	NS
Relative LVM index*	1·18 (0·40)	1·41 (0·3)	0·04
Relative wall thickness ((S + P)/EDD)	0·64 (0·16)	0·74 (0·18)	0·06
S/P ratio (SD)	1·63 (0·38)	1·67 (0·43)	NS

LV, left ventricular; LVOT, left ventricular outflow tract; S, septal, P, posterior wall thickness; EDD, end diastolic diameter; BSA, body surface area.
*LVM index divided by gender specific normal values: ⩾109g/m² of BSA for women; ⩾134g/m² of BSA for men.

(5/60) of medically treated and in 19% (15/79) of surgically treated patients (NS).

The following baseline variables predictive of the development of chamber dilatation during follow up in the entire study group did not change their predictive value in relation to treatment: dyspnoea, functional classification, and relative left ventricular mass index. A history of syncope was predictive for subsequent left ventricular dilatation only in surgically treated patients (occurrence at baseline in the medical versus the surgical subgroup of group 2 with a frequency of 20 versus 53%, respectively; P < 0·05).

FOLLOW UP DATA

Clinical data

The following clinical variables remained unchanged during follow up in either group: body surface area, body mass index, heart rate, blood pressure, frequency of angina pectoris, premature ventricular beats, atrial fibrillation, physical working capacity, and Sokolow-Lyon index.

The occurrence of dyspnoea remained constant during follow up in group 1 (from 43/119 = 36% to 45/119 = 38%), but decreased significantly in group 2, from 20/20 = 100% to 10/20 = 50% (P = 0·03), which may be related to the fact that 15 of the 20 patients in this group had successful surgical treatment. In groups 1 and 2, the frequency of syncope decreased from 13/119 = 11% to 1/119 = 1% (NS), and from 8/20 = 40% to 3/20 = 17% (P = 0·05), respectively, during follow up. Palpitations were reported to a similar degree in group 1 (approximately 30%) and group 2 (50% at baseline and 33% at follow up examination, NS). NYHA classification did not change in group 1, but decreased during follow up from 2·5 (0·6) to 1·5 (0·5) in group 2 (P = 0·004).

Echocardiographic data

Posterior wall thickness did not change during follow up in either one of the two groups.

End diastolic diameter remained constant in relative (–0·3%/year of follow up) and absolute terms in group 1 and increased significantly in group 2 (fig 3A; relative increase

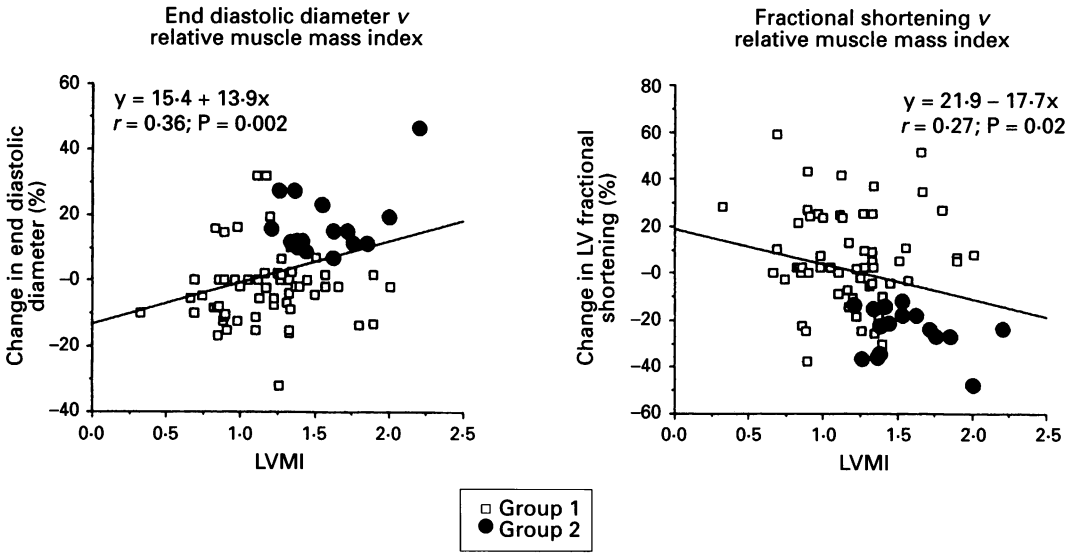

Figure 2 Relation between the change in end diastolic diameter (vertical axis, med panel A; % during the entire follow up) and left ventricular (LV) fractional shortening (vertical axis, panel B; % during the entire follow up), respectively, and the severity of LV hypertrophy (horizontal axis, relative LV mass index = LVMI divided by the gender specific upper normal value: 109 g/m² for women and 134 g/m² for men). Empty squares represent patients with HCM in the group without chamber dilatation (group 1, n = 119); filled circles represent those with chamber dilatation (group 2, n = 20). There was a direct, inverse correlation between the change in end diastolic diameter and LV fractional shortening, respectively, and the severity of LV hypertrophy.

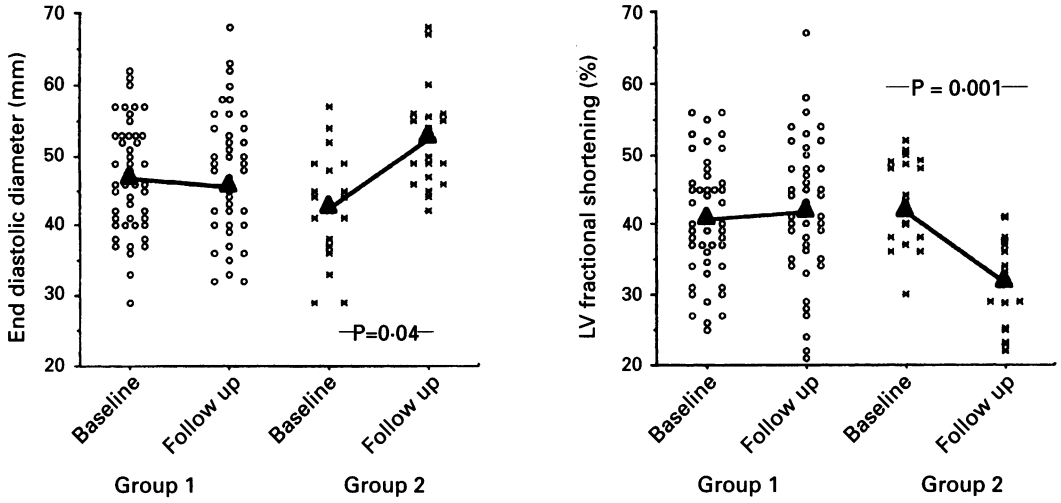

Figure 3 Change in absolute values of end diastolic diameter (panel A) and left ventricular (LV) fractional shortening (panel B) during follow up. Empty circles represent individual data of patients with hypertrophic cardiomyopathy but without LV chamber dilatation/systolic dysfunction (group 1, n = 119), "x" symbols represent those of patients with chamber dilatation (group 2, n = 20). Filled triangles are mean values. There was no significant change in end diastolic diameter and fractional shortening in the control group (group 1); patients in group 2 showed a significant increase in end diastolic diameter and a significant decrease in fractional shortening during follow up, respectively.

+2·5%/year). Three percent of all patients in group 1 showed a chamber diameter equal to or larger than 60 mm compared to 18% in group 2 (P = 0·04). Left ventricular fractional shortening did not change significantly in group 1 (+1·1%/year; fig 3B) but decreased by 3·5 relative percentage points per year in group 2 (for absolute changes see fig 3B). During follow up, end systolic diameter remained constant at approximately 27 mm in group 1, whereas in group 2 it increased to a greater extent than end diastolic diameter, from 25 (5) to 35 (7) mm (P = 0·005). Septal wall thickness increased slightly during follow up in group 1 (from 18·3 (5) to 18·8 (4) mm, NS) whereas it decreased slightly although not significantly in group 2 (from 18·7 (4) to 16·5 (4) mm, P = 0·06). Systolic anterior motion of the mitral valve occurred less often in both groups at follow up than at baseline examination (group 1, 60% to 35%, NS; group 2, 75% to 36%; P < 0·05). Left ventricular myocardial wall motion abnormalities were observed more often in group 2 at follow up (100%) than at baseline (13%, P < 0·001, n = 16) but equally as often as in group 1.

Survival and event-free survival rates (fig 4)
During follow up, 36 patients died: 33 in group 1 (annual mortality rate 2·6%) and three in group 2 (annual mortality rate 1·5%, NS). Most patients died suddenly (19 in group 1 and none in group 2). Five of the 33 deaths in group 1 (15%) and all three in group 2 (100%, P < 0·01) were due to congestive heart failure.

Cumulative survival rates were not significantly different in the two groups during 25 years of follow up (fig 4A). Five, 10, and 20 year survival rates were 95%, 94%, and 91% respectively in group 1, and 90%, 90%, and 83% in group 2 (NS). Event-free survival rates were 99%, 97%, and 92% at 5, 10, and 20 years of follow up in group 1, and 94%, 75%, and 63% in group 2 (fig 4B; P < 0·05).

Comparison between medically and surgically treated patients (table 5)
End diastolic diameter and fractional shortening showed more pronounced changes among medically treated patients than among surgically treated patients in group 2. Angiographically determined indices of left

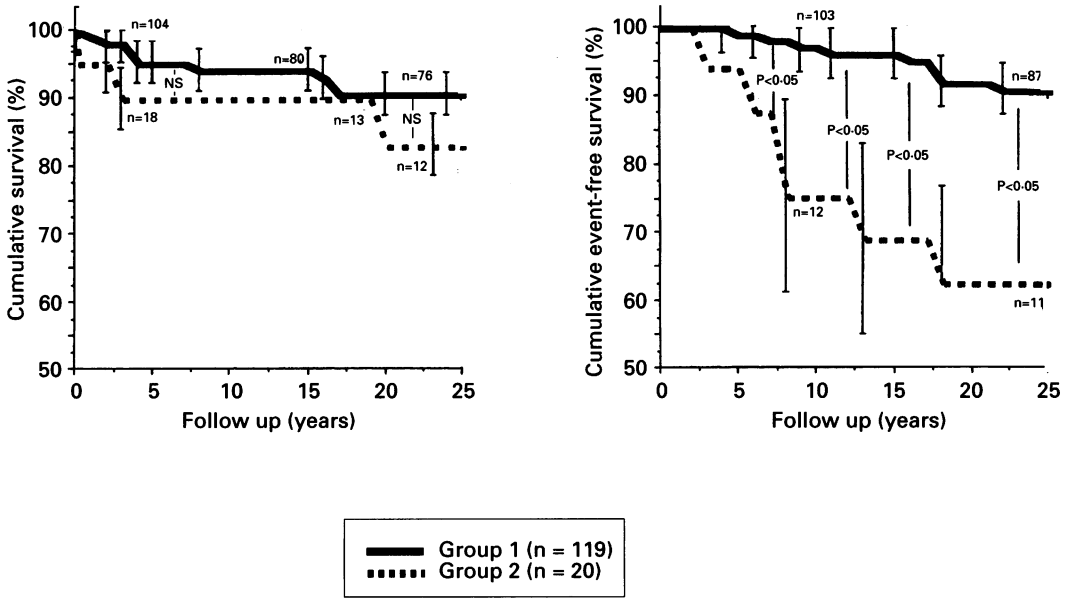

Figure 4 Cumulative survival (panel A) and event-free survival (panel B) in patients with hypertrophic cardiomyopathy without (group 1, solid line, n = 119) and those with chamber dilatation (group 2, dashed line, n = 20). There was a slightly (NS) higher survival rate in the control group compared to group 2. After five years of follow up and later, cumulative event-free survival rates in group 1 were significantly higher than those in group 2.

Table 5 Follow up in the group with left ventricular (LV) chamber dilatation and systolic dysfunction (group 2). Method of treatment. Values are means (SD) except where shown as percentages

	Medical treatment			*Surgical treatment*		
	Baseline	*Follow up*	*P*	*Baseline*	*Follow up*	*P*
Number	5	4		15	13	
ΔEDD per year/ΔFS per year (%)	+2·5 (2)/–4·1 (4)			+2·1 (1)/–2·9 (1)		
Dyspnoea (%)	5 (100)	4 (80)	NS	15 (100)	6 (46)	0·04
Syncope (%)	1 (20)	1 (20)	NS	8 (53)	2 (15)	0·04
NYHA class	2·1 (0·6)	1·6 (0·4)	0·09	2·7 (0·6)	1·5 (0·4)	0·002
LBBB (%)	0 (0)	0 (0)	NS	0 (0)	8 (63)	0·03
Working capacity (%)	75 (20)	65 (15)	0·06	76 (24)	72 (11)	NS
End diastolic diameter (mm)	41·3 (4)	49·8 (6)	0·04	43·6 (7)	52·8 (4)	0·02
LV fractional shortening	42 (6)	33 (7)	0·0009	43 (5)	35 (8)	0·04
Septal wall thickness (mm)	17·5 (5)	17·2 (7)	NS	18·3 (4)	16·9 (6)	NS
Posterior wall thickness (mm)	10·8 (8)	10·5 (4)	NS	11·1 (2)	11·3 (5)	NS
ED Volume Index (ml/m²)	78 (15)	155 (30) (n = 3)	0·002	88 (17)	150 (20) (n = 8)	0·02
EF (%)	72 (8)	54 (10) (n = 3)	0·05	70 (6)	58 (5) (n = 8)	0·04
Group 1						
ED volume index (ml/m²)	92 (35)	90 (17) (n = 14)	NS	85 (30)	100 (27) (n = 14)	NS
EF (%)	70 (10)	72 (10) (n = 8)	NS	74 (15)	68 (10) (n = 8)	NS

ΔEDD per yr/ΔFS per yr (%), mean change in end diastolic diameter and LV fractional shortening in relative percentage points per year of follow up; LBBB, left bundle branch block, EF, LV ejection fraction.

ventricular end diastolic cavity size and systolic performance (EDVI and EF) changed similarly in both groups when compared to the corresponding echocardiographic variables (ED and FS), and there was no differential change in these indices among medically and surgically treated patients (table 5). Twelve surgically treated patients in group 2 had an early postoperative Doppler echocardiogram at 3·7 (3·5) months, which showed no significant changes in left ventricular chamber size and systolic performance as compared to the preoperative examination. Left bundle branch block occurred only in surgically treated patients of group 2.

Discussion

The findings of the present study indicate that in a population with longstanding hypertrophic cardiomyopathy, approximately 14% of the patients develop left ventricular chamber dilatation with systolic dysfunction during 10 years of follow up. A high degree of left ventricular hypertrophy, and possibly surgical treatment, among other unknown factors, seems to be a determinant of this unique feature of the disease. The mortality and morbidity in this subgroup of patients with hypertrophic cardiomyopathy appear to be higher than those in patients with "ordinary" forms of hypertrophic cardiomyopathy.

DEFINITIONS AND INCIDENCE OF LEFT VENTRICULAR CHAMBER DILATATION IN HYPERTROPHIC CARDIOMYOPATHY

In 1977, the first clinical report described a 40 year old woman with myocardial histological findings typical of hypertrophic cardiomyopathy who had an acute myocardial infarct despite normal coronary arteries, and who subsequently died after progression of congestive heart failure.[25] About 40% of the more recently published studies (table 1), and the majority of the cohort studies,[4 6 9–12] have documented left ventricular chamber dilatation not exceeding normal left ventricular cavity limits[19] in hypertrophic cardiomyopathy during the course of the disease. The present study sought to optimise both the sensitivity and specificity of detecting left ventricular chamber dilatation by using *combined* changes in left ventricular chamber size and systolic function for its definition. With this approach, the incidence of left ventricular chamber dilatation in hypertrophic cardiomyopathy was similar to that given in published reports (table 1), that is, 1·4% compared to a reported 1·9% per year of follow up. In the study of Ando *et al*[9] the incidence was twice as high as in the present study and in a few other studies.[1 10] The fact that a different, qualitative rather than quantitative, approach (detection of new myocardial wall motion abnormalities) was used for the definition of left ventricular dysfunction may explain this difference. However, Fighali and coworkers,[12] using a similar definition for left ventricular dysfunction, have reported an incidence of only 1% per year. The discrepancy between the reported studies may be accounted for by different forms of hypertrophic cardiomyopathy with varying degrees of left ventricular hypertrophy; it may also be related to the fact that the present study cohort is unique in that cases undergoing myectomy were predominant. In addition, the definition of hypertrophic cardiomyopathy used in this study[18] favoured to some extent the obstructive component of the disease. Thus our study population may not be entirely representative of the overall population of patients with hypertrophic cardiomyopathy.

Another reported feature of left ventricular chamber dilatation and systolic dysfunction (table 1)—septal wall thinning during the course of hypertrophic cardiomyopathy—was observed in the present study, although it did not reach statistical significance. Given the fact that Fighali and coworkers[12] as well as Hartmann *et al*[13] also reported several patients who showed septal thickening rather than septal thinning during follow up, this property does not seem to be mandatory for the definition of left ventricular dilatation and systolic dysfunction in hypertrophic cardiomyopathy.

PREDICTORS OF LEFT VENTRICULAR CHAMBER DILATATION AND PATHOPHYSIOLOGICAL MECHANISMS

The patients described by Ando *et al* showed left ventricular dysfunction located exclusively in the apical segment.[9] Fighali and coworkers,[12] on the other hand, have found that patients with midventricular obstruction are at greater risk of developing left ventricular dysfunction. Although the present study did not confirm these findings, the development of left ventricular chamber dilatation was also related to the degree of left ventricular hypertrophy. Left ventricular mass index relative to gender specific normal values was associated with the occurrence of left ventricular dilatation and systolic dysfunction during follow up (fig 2). Individuals showing ventricular dilatation were significantly more symptomatic at baseline than those without left ventricular dilatation, and were more likely to undergo later surgical treatment in the form of septal myectomy.

Two questions arise in this context. (1) Were the variables "higher degree of left ventricular hypertrophy" and "more severely symptomatic status" independent predictors of left ventricular dilatation or were they merely related to the fact that surgically treated patients, who predominated in the group with left ventricular dilatation, showed more symptoms and more left ventricular hypertrophy than those with medical treatment? The absolute as well as relative values of left ventricular mass were both lower in group 1 than in group 2, irrespective of the kind of treatment, and they were not statistically different for those patients in group 2 treated medically and those treated surgically (data not shown). More frequent dyspnoea and higher functional classification were predictive of left ventricular dilatation irrespective of the type of treatment, whereas syncope as a predictor was related to surgical treatment. (2) Is the predominance of surgically treated patients in the group with left ventricular dilatation dependent on how the left ventricular cavity dimension was measured, that is, possibly through the area of septal myectomy? This is unlikely because two criteria were required for the definition of left ventricular dilatation, namely an increase in the cavity dimension and a decrease in fractional shortening. Moreover, left ventricular end diastolic volume index and ejection fraction in group 2, determined independently from echocardiographic measurements, showed similar changes during follow up to end diastolic diameter and fractional shortening (table 5). Finally, all of the surgically treated patients in group 2 undergoing several echocardiographic follow up examinations (n = 12) showed normal left ventricular dimensions and systolic performance three months after myectomy.

There are three possible mechanisms that might lead to left ventricular dilatation with systolic dysfunction: (1) non-transmural myocardial infarction, (2) severe left ventricular hypertrophy with replacement fibrosis, and (3) disruption of left ventricular geometry after septal myectomy.

The findings of our study suggest that non-transmural myocardial infarction(s) most probably occur, which are caused by a mismatch of oxygen supply and demand due to severe myocardial hypertrophy.[25] Several investigations have reported a reduction in myocardial perfusion in patients with hypertrophic cardiomyopathy supposedly leading to myocardial scarring.[26 27]

Severe left ventricular hypertrophy as a cause for enhanced interstitial fibrosis has been reported in patients with severe valvular disease and heart failure. The exact process which is responsible for this scarring is not yet known but is thought to be the result of the stimulation of the renin-angiotensin system or of aldosterone production in patients with congestive heart failure. Other mechanisms might be involved as well, such as immunological or inflammatory processes. It has been reported that small intramural coronary arteries are abnormal in about 80% of patients with hypertrophic cardiomyopathy and that abnormal small arteries are observed more often within areas of fibrosis.[27 28]

Another mechanism for left ventricular dilatation is a disruption of left ventricular geometry after septal myectomy.[16] This mechanism is supported by the fact that patients undergoing septal myectomy less often developed left bundle branch block in group 1 (from 37% preoperatively to 72% postoperatively) than those in group 2 (from 0% to 63%). Septal thinning after myectomy has been described previously[16] and has been attributed to the disruption of left ventricular geometry.

PROGNOSIS

The one year mortality in patients with hypertrophic cardiomyopathy has been reported to range between 3% and 8%,[1 17 29] and the five year cumulative survival rate between 55% and 75%.[17 29] The annual as well as the five and 10 year survival rates found in this study were better than those previously reported. It has been shown[17] that the relatively low mortality in our study is mainly the result of the low mortality in surgically treated patients. The apparent inconsistency that the annual mortality rate in the group with ventricular dilatation is low and even lower than that in the control group is probably related to the small number of patients and consequently to the small number of deaths in group 2. Assuming an incidence of ventricular dilatation of approximately 15% during an average follow up of 10 years, the patient population would need 1200 individuals for differences in cumulative survival between patients with and without ventricular dilatation to be detected with a statistical significance of $P < 0{\cdot}05$ at five, 10, and 20 years. Such a sample size would exceed the highest study populations presently reported (n = 600)[30] by 100%.

Despite the fact that signs and symptoms typical of hypertrophic cardiomyopathy improved more in the group with than in the group without ventricular dilatation (table 5), the event-free survival was significantly better

in the patients who did not develop ventricular dilatation than that in those who did (fig 4). This is consistent with the notion that prognosis for quality of life is worse in patients with than in those without ventricular dilatation, because patients in group 2 were significantly more symptomatic at baseline examination than those in group 1.

STUDY LIMITATIONS

One major limitation of the present study is that this was a retrospective analysis. Due to patient selection, the systolic pressure gradient across the left ventricular outflow tract was significantly different between medically and surgically treated patients. Because of the long observation period of up to 32 years and the relatively low incidence of the disease, and because for ethical reasons randomisation could not be performed, this, like all previously reported follow up studies in patients with hypertrophic cardiomyopathy, was based on retrospective data.

In 26 patients (22 in group 1 and four in group 2), entry into the study (time of diagnosis) did not coincide with the baseline echocardiographic evaluation because echocardiography was not available at that time. Analysing our data under the assumption that study entry in these 26 patients occurred at the time of their first echocardiogram did not change the findings of the present study but reduced the time of follow up for the entire study group from 10·3 to 8·8 years.

The formula for calculation of left ventricular mass[22] used in this study might cause somewhat inaccurate results because of changes in left ventricular geometry in patients with hypertrophic cardiomyopathy. The left ventricular cavity does not really resemble an ellipsoid, the shape of which is the basis for the calculation of left ventricular mass by echocardiography. Unfortunately, no alternative way of calculating left ventricular mass by echocardiography is available. The ratio of patients with or without obstruction was similar in both study groups. Therefore the error of using the formula of Troy and Devereux[22] was equally distributed among the study patients.

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