Prevalence, Clinical Profile, and Significance of Left Ventricular Remodeling in the End-Stage Phase of Hypertrophic Cardiomyopathy

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Background—End stage (ES) is a recognized part of the hypertrophic cardiomyopathy (HCM) disease spectrum. Frequency, clinical profile and course, and treatment strategies in these patients remain incompletely defined.

Methods and Results—Three HCM cohorts comprised 1259 patients, including 44 (3.5%) characterized as ES with systolic dysfunction (ejection fraction <50% at rest; range 15% to 49%). ES developed at a wide age range (14 to 74 years), with 45% of patients ≤40 years old. Although 29 patients (66%) died of progressive heart failure, had sudden death events, or underwent heart transplantation, 15 (34%) survived with medical management over 3±3 years. Duration from onset of HCM symptoms to ES identification was considerable (14±10 years), but ES onset to death/transplantation was brief (2.7±2 years). ES occurred with similar frequency in patients with or without prior myectomy (P=0.84). Appropriate defibrillator interventions were 10% per year in patients awaiting donor hearts. Most ES patients (n=23; 52%) showed substantial left ventricular (LV) remodeling with cavity dilatation. Less complete remodeling occurred in 21 patients (48%), including 5 with persistence of a nondilated and markedly hypertrophied LV. Pathology and magnetic resonance imaging showed extensive (transmural) fibrosis in 9 of 11 ES patients. At initial evaluation, patients who developed ES were younger with more severe symptoms, had a larger LV cavity, and more frequently had a family history of ES than other HCM patients.

Conclusions—ES of nonobstructive HCM has an expanded and more diverse clinical expression than previously appreciated, including occurrence in young patients, heterogeneous patterns of remodeling, frequent association with atrial fibrillation, and impaired LV contractility that precedes cavity dilatation, wall thinning, and heart failure symptoms. ES is an unfavorable complication (mortality rate 11% per year) and a sudden death risk factor; it requires vigilance to permit timely recognition and the necessity for defibrillator implantation and heart transplantation. **(*Circulation*. 2006;114:216-225.)**

Key Words: cardiomyopathy ■ echocardiography ■ heart failure ■ heart transplantation ■ hypertrophy ■ magnetic resonance imaging

The end stage (ES) phase of hypertrophic cardiomyopathy (HCM), characterized by systolic dysfunction, has previously been regarded as a not uncommon disease complication with a distinctively homogeneous clinical profile.[1–5] Previous characterization of ES has been based largely on single cases or small groups of patients.[4,6–17] More recently, it has been our impression that the clinical spectrum of this HCM subset may be more diverse than previously appreciated and that its frequency may have been overestimated. Therefore, it is a particularly opportune time to offer a large measure of clarity to our understanding of the clinical profile, prognosis (including risk for heart failure or sudden death), and treatment strategies for the ES of HCM by revisiting this subset of the HCM disease spectrum in a large, multicenter population.

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Methods

Selection of Patients

The study population was composed of 1259 consecutively enrolled HCM patients, from 1983 to 2005, analyzed retrospectively at 3

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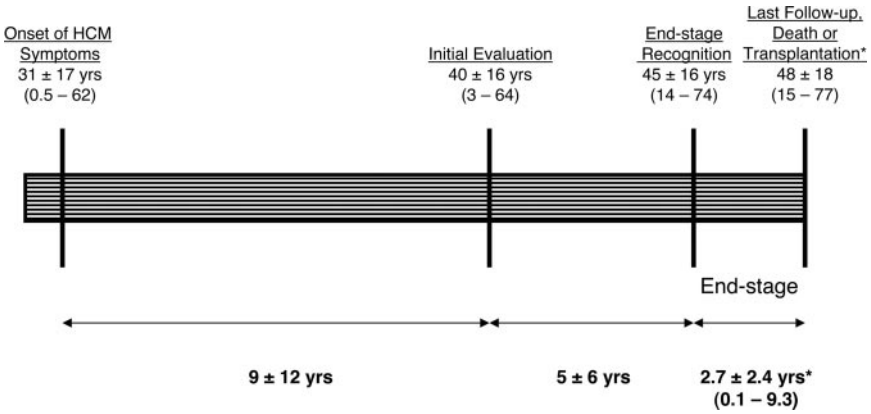

Figure 1. Time line with patient ages describing evolution of 44 HCM patients to ES. *Also includes 5 patients with appropriate ICD intervention.

centers: Minneapolis Heart Institute Foundation, Minneapolis, Minn (n=752); Ente Ospedaliero Ospedali Galliera, Genoa, Italy (n=354); and Tufts-New England Medical Center, Boston, Mass (n=153). Initial evaluation was the first clinical assessment of heart disease for which an echocardiogram was obtained or first visit to a participating institution. Most recent evaluation, 2.3±3.8 years (range 0.5 to 22) after initial assessment, was ascertained in patients while they were in the hospital or by telephone interview.

Definitions

Diagnosis of HCM was based on echocardiographic documentation of a hypertrophied nondilated left ventricle (LV) in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident at some time during the natural course of the disease.[18] The ES phase of HCM was defined as an LV ejection fraction <50% at rest, reflecting global systolic dysfunction, at study entry or during follow-up, by 2D echocardiography.

Echocardiography

Echocardiograms were performed with commercially available instruments. Magnitude of LV hypertrophy and outflow obstruction were assessed as described previously.[18,19] Mitral regurgitation was graded semiquantitatively (1 to 4+ scale), and scores were averaged.[20] Ejection fraction was calculated from 2D echocardiographic images with the modified Simpson's rule formula or area-length method.[21]

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) imaging was performed on Siemens Sonata-Avanto (Erlangen, Germany) or Philips Gyroscan ACS-NT (Best, the Netherlands) 1.5T whole-body scanners with dedicated cardiac coils. Breath-hold cine images were acquired in multiple short-axis and 3 long-axis slices with steady-state free precession sequences. Ventricular coverage was achieved with contiguous 10-mm-thick slices or 7-mm slices (3-mm gap). A delayed enhancement protocol was used 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering; Berlin, Germany) with breath-held segmented inversion-recovery sequence (inversion time=240 to 300 ms) acquired in the same views.

Statistical Analysis

Data are expressed as mean±SD. Two-tailed paired or unpaired Student *t* tests compared normally distributed data. χ^2 Tests compared noncontinuous variables expressed as proportions. Incidence of ES phase was calculated (for patients with normal ejection fraction at study entry) as the ratio of new cases (n=33) to the total number of HCM patients in the cohort over the follow-up period.

Occurrence of the ES phase in patients with or without a history of surgical septal myectomy was compared by calculating average annual occurrence rates over the follow-up period and expressing those as relative risk with *z* test with Yates correction. Confidence intervals (95% CIs) were calculated with the Poisson distribution and standard methods. Probability values were significant when ≤0.05.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Occurrence

ES of HCM was identified in 44 (3.5%; 95% CI 2.54% to 4.69%) of 1259 study patients, and this proportion was similar (P=0.18) among the 3 centers: Minneapolis (3%), Genoa (5%), and Boston (3%). Eleven (25%) of 44 patients had ES at initial evaluation; the other 33 patients (75%) evolved into ES during follow-up. Incidence was 33 cases per 2946 person-years of follow-up (1.12 cases per 100 person-years; 95% CI 0.77 to 1.54).

Clinical Profile of ES

Age and Gender

The 44 ES patients were 40±16 years old (range 3 to 63) at initial evaluation and 48±18 years at the most recent evaluation, death, heart transplantation, or appropriate implantable cardioverter-defibrillator (ICD) intervention for ventricular tachycardia/fibrillation (Figure 1). ES was identified at a wide range of ages, ie, 14 to 74 years (mean 45±16 years): Twenty patients (45%) were ≤40 years old, 9 (21%) were ≤30 years old, and 11 (25%) were ≥60 years old. Twenty-seven patients (61%) were male.

Seven of 44 patients had undergone surgical myectomy[1,2] many years before ES onset (18±5 years of age; Table). ES occurrence in patients with myectomy was 7 of 89 (8% over 45 person-years), and in patients without myectomy, it was 37 of 1170 (3% over 288 person-years), which produced a relative risk for ES after myectomy of 1.21 (95% CI 0.51 to 2.26; P=0.84). Also, myectomy and nonmyectomy patients did not differ with respect to adverse disease consequences, including death, transplantation, or appropriate ICD shocks (5/7 [71%] versus 26/39 [67%]; P=0.9). Atherosclerotic coronary artery disease (≥50% narrowing of at least 1 major artery) was excluded by angiography or pathological examination in 17 patients. One patient (patient 20) had an incidental finding of 95% focal narrowing of the left anterior descending coronary artery at autopsy.

Clinical and Demographic Data From 44 Patients in the End Stage of HCM

Patient No.	Gender	Age Sx, y	Age I, y	Age II, y	Time (I to II), mo	NYHA FC I	NYHA FC II	LVED II, mm	VS II, mm	LVEF† II, %	Myectomy	Survived Cardiac Arrest	AF in ES	ICD Shock in ES	Age at ES Recognition, y	Outcome	Age at Transplantation, y	Age at Death, y
Nondilated																		
1	M	N/A	38	39	14	1	1	50	13	48	0	0	0	0	39	Alive	N/A	N/A
2	F	11	30	30	1	1	4	49	15	30	0	0	+	0	28	TP; alive	31	N/A
3	M	12	30	37	84	1	4	(45)	(28)	49	+	0	+	0	37	TP; alive	38	N/A
4	F	16	16	27	137	2	4	38	39	47	0	0	0	0	26	TP; alive‡	28	N/A
5	M	16	43	44	39	4	4	53	12	32	0	0	+	0	46	TP; died	47	65
6	M	16	37	39	22	2	3	(54)	(19)	23	+	+	+	0	39	Died; HF	N/A	42
7	M	18	43	44	13	2	3	38	24	49	0	0	0	0	45	TP; alive	46	N/A
8	F	18	25	27	25	2	3	48	20	40	0	0	0	0	26	TP; alive‡	28	N/A
9	F	20	47	48	10	2	3	42	17	40	0	0	+	0	47	TP; alive	49	N/A
10	F	22	34	36	25	2	3	47	11	39	0	0	0	0	36	Alive	N/A	N/A
11	M	26	27	38	138	1	3	46	27	28	0	0	+	0	37	Alive	N/A	N/A
12	M	28	54	56	18	3	2	(54*)	(14)	30	+	0	+	0	54	Alive	N/A	N/A
13	M	31	22	36	181	2	2	44	17	33	0	0	+	0	36	Alive‡	N/A	N/A
14	F	34	57	65	99	1	4	54	15	42	0	0	+	0	64	Died; HF	N/A	66
15	F	36	36	37	1	2	2	54	14	25	0	0	+	0	36	Died; SCD	N/A	37
16	M	38	30	38	98	1	2	50*	20	40	0	0	0	0	38	Alive	N/A	N/A
17	M	39	39	42	44	3	3	52*	15	34	0	0	0	0	41	Died; HF	N/A	43
18	M	41	44	51	80	2	2	51*	17	40	0	0	+	0	50	Alive	N/A	N/A
19	F	44	44	53	106	3	4	48	10	40	0	0	+	0	44	Alive	N/A	N/A
20	M	44	46	48	22	2	4	53	20	40	0	0	+	0	49	TP; alive	49	N/A
21	F	57	58	75	213	2	3	50*	17	49	0	0	0	0	70	Died; HF	N/A	75
Dilated																		
22	M	0.5	32	33	8	3	3	57	25	38	0	0	+	+	33	Died; SCD	N/A	34
23	F	3	3	25	21	2	3	(68)	(11)	45	+	+	0	+	25	Alive‡	N/A	N/A
24	F	12	12	14	25	1	4	65	17	33	0	0	0	0	14	TP; alive	15	N/A
25	F	12	51	67	196	2	4	(57)	(12)	41	+	+	+	0	65	Died; HF	N/A	67
26	M	14	16	24	100	1	2	72	22	30	0	0	0	0	23	Died; SCD	N/A	24
27	M	15	15	19	45	2	2	74	28	43	0	0	0	0	19	Alive	N/A	N/A
28	M	15	16	23	79	1	3	66	12	48	0	0	0	0	20	TP; alive	23	N/A
29	M	16	17	23	80	2	3	63	15	35	0	0	+	0	21	Died; SCD	N/A	23
30	F	18	44	47	44	2	3	61	10	40	0	0	0	+	47	TP; died	48	54
31	M	22	41	41	4	1	2	(55)	(18)	15	+	0	+	0	40	Alive	N/A	N/A
32	M	30	59	60	9	1	4	58	19	32	0	0	0	0	59	TP; alive‡	62	N/A
33	M	31	31	47	194	2	2	62	13	33	0	0	0	+	44	Alive	N/A	N/A
34	F	38	38	39	8	2	3	60	12	25	0	0	0	0	33	TP; alive	38	N/A
35	M	39	53	60	85	1	2	60	14	49	0	0	0	0	58	Alive	N/A	N/A
36	M	44	44	65	243	1	3	62	17	49	0	0	0	0	65	Alive	N/A	N/A
37	M	46	49	70	250	1	2	70	13	22	0	0	0	+	62	Alive	N/A	N/A
38	M	47	63	64	6	3	3	56	18	33	0	0	+	0	63	Alive	N/A	N/A
39	F	48	51	62	135	3	3	56	13	40	0	0	+	0	60	Died; HF	N/A	62
40	M	56	58	72	163	2	4	63	17	49	0	0	+	0	67	Died; HF	N/A	76
41	F	57	57	66	109	1	2	63	30	28	0	0	0	0	63	Alive	N/A	N/A
42	M	57	61	73	101	3	3	(58)	(16)	35	+	0	+	0	74	Died; HF	N/A	77
43	M	58	58	61	30	3	3	57	16	29	0	0	0	0	58	Alive	N/A	N/A
44	F	62	62	69	84	2	3	60	19	36	0	0	0	0	69	Died; SCD	N/A	75

Sx indicates symptom onset; I, initial evaluation; II, most recent evaluation; NYHA FC, New York Heart Association functional class; LVED, LV end-diastolic dimension; VS, ventricular septum; LVEF, LV ejection fraction; AF, atrial fibrillation; M, male; F, female; N/A, not applicable; TP, transplant; HF, heart failure; SCD, sudden cardiac death; +, present; and 0, absent.

*Enlargement of LV cavity >20% between first and most recent evaluation but with absolute transverse cavity dimension <55 mm.

†Calculated from the 2D echocardiographic image with the modified Simpson's rule formula or area-length method.

‡Trial of biventricular pacing (cardiac resynchronization therapy).

Values for LVED II and VS II are in parentheses in patients with a history of myectomy.

Family History

Of 44 ES patients, 31 (70%) had a family history of HCM, including 20 families in which at least 1 relative died suddenly of HCM. Nine patients (20%) had at least 1 other relative with ES (Table). Three probands were genotyped to HCM-causing sarcomere protein mutations: β-myosin heavy chain in 2 ($Gly^{716}Arg$; patients 5 and 28) and myosin-binding protein C in 1 (patient 25; ins G-791).[2]

Morphology

Most Recent Evaluation

LV end-diastolic cavity dimension was 55±9 mm, including 23 patients (52%) with enlarged cavities and 21 (48%) with nondilated LVs within the normal partition value (ie, ≤54 mm); 15 patients (34%) showed marked LV dilatation (≥60 mm). ES patients with and without LV cavity enlargement did not differ with regard to clinical outcome, including cardiac death, transplantation, or ICD shocks (16/23 [70%] for dilated; 13/21 [62%] for nondilated; $P=1.0$). Ventricular septal thickness was 18±6 mm, including 10 patients (23%) with thickness ≥20 mm and 19 (43%) with thickness ≤15 mm; posterior LV free-wall thickness was 14±7 mm.

Serial Observations

Paired echocardiograms, available in 31 patients without myectomy, showed significant dimensional increase over 7±6 years (Figures 2 and 3): LV end-diastolic cavity 47±8 to 56±9 mm ($P<0.001$), with an average rate of progressive enlargement of 1.7 mm for each patient per year of follow-up; end-systolic cavity 30±9 to 40±10 mm ($P<0.001$); and left atrium 46±9 to 53±9 mm ($P=0.0001$). Septal thickness decreased 23±7 to 18±6 mm ($P<0.001$), with rate of thinning of 1.4 mm per year. Ejection fraction decreased from 58±11% to 39±8%, or 6.1% per year ($P<0.001$).

Remodeling Patterns

Four patterns of LV remodeling were identified: (1) Twenty-three patients (52%) showed the most complete remodeling, with LV cavity enlargement (≥55 mm end-diastolic) and/or increase in size, associated with relatively mild hypertrophy (<20 mm), and/or regression in septal thickness (Figure 4); (2) 5 patients (11%) demonstrated enlarged and/or progressively increasing LV cavity dimension with preserved hypertrophy (≥20 mm); (3) 11 patients (25%) had normal LV cavity size but relatively mild increase in septal thickness (<20 mm) and/or decrease during follow-up; and (4) 5 patients (11%) showed persistence of nondilated and markedly hypertrophied LV (septal thickness 20 to 39 mm; Figure 5). On initial evaluation, resting LV outflow gradients of 25 to 70 mm Hg due to mitral valve systolic anterior motion were evident in 5 patients (11%; patients 7, 21, 33, 36, and 42); no patient had a gradient at most recent evaluation. Mitral regurgitation scores increased from 1.0±0.9 to 1.5±1.1 at most recent evaluation ($P=0.003$), when 20 (45%) of 44 patients showed moderate to severe regurgitant jets.

Clinical Course and Management

ES was identified 5±6 years after initial evaluation (at or near HCM diagnosis; Figure 1). Time from onset of HCM symptoms to ES recognition was considerable (14±10 years). In contrast, the interval from ES identification to death or transplantation was relatively brief (2.7±2 years; Figure 1).

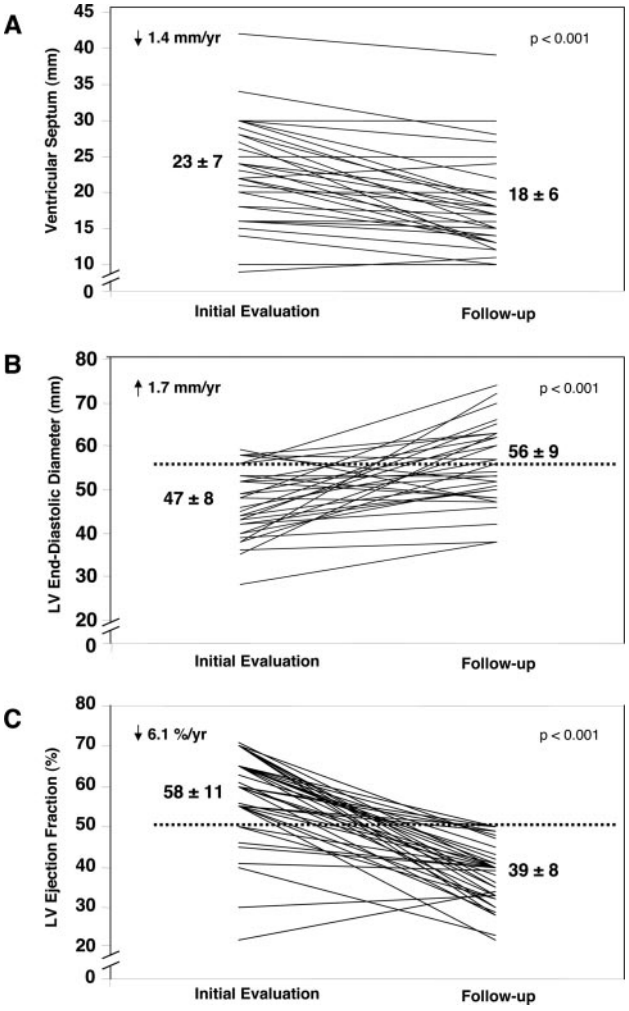

Figure 2. Changes in ventricular septal thickness (n=31; A), LV end-diastolic cavity dimension (n=31; B), and ejection fraction (n=38; C). Data were obtained in ES patients with serial (paired) echocardiographic studies obtained over 7±6 years. Seven study patients who underwent septal myectomy are excluded from analysis of septal thickness and cavity dimension because this therapeutic intervention is known to affect LV geometry and remodeling.

At study entry, 15 (34%) of 44 ES patients were asymptomatic in New York Heart Association functional class I, 20 (45%) had mild symptoms (class II), and 9 (21%) were severely limited due to exertional dyspnea (classes III/IV); of the 35 class I and II patients, 8 already showed systolic dysfunction.

In the presence of preserved LV systolic function, patients initially received standard medications for HCM, most commonly β-blockers and verapamil. After systolic dysfunction developed, patients were treated with afterload-reducing agents (64%; ACE inhibitors or angiotensin II receptor blockers), diuretics (68%), and β-blockers (50%), as well as digitalis (11%), spironolactone (11%), and warfarin when indicated.

Fifteen (34%) of the 44 patients have survived free of events with maximal medical treatment over 3±3 years, including 9

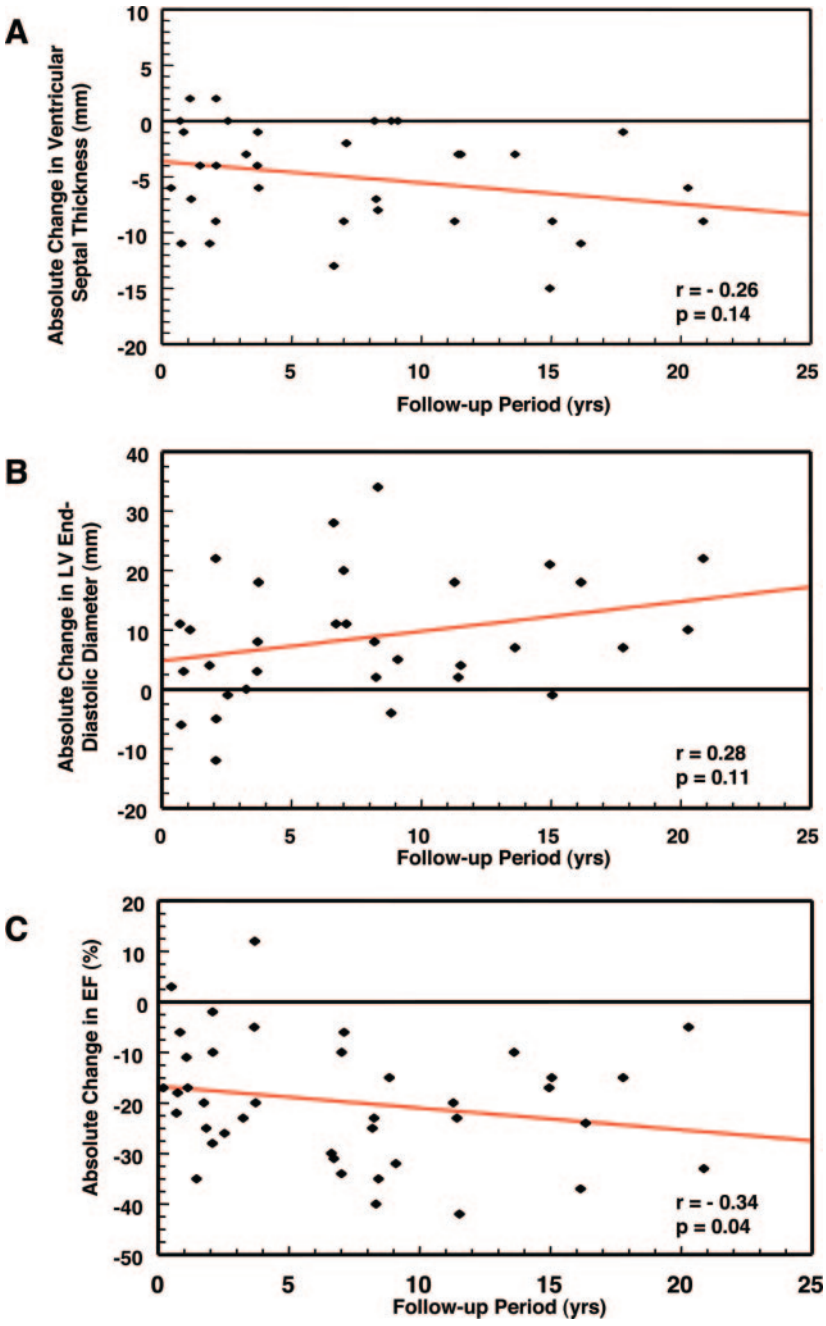

Figure 3. Regression analysis of absolute changes in ventricular septal thickness (n=31; A), LV end-diastolic dimension (n=31; B), and ejection fraction (EF; n=38; C) over follow-up period. Seven study patients who underwent septal myectomy are excluded from analysis of septal thickness and cavity dimension because this therapeutic intervention is known to affect LV geometry and remodeling.

who remain in classes I/II (Table). The other 29 patients (66%) have died either of progressive, unrelenting heart failure (n=8) or of sudden cardiac death (n=5) or have had ICD interventions (n=5; 2 subsequently died) or heart transplantation (n=13; 2 later died; Table; Figure 6). Annual adverse event rate of ES patients was 11% (95% CI 7.27% to 15.6%).

Five patients (28%) among 18 with ICDs experienced appropriate device interventions, including 4 who survived to present or to transplantation; all patients with ICD shocks had LV dilatation (Table; Figure 6). Appropriate intervention rate was 10% per year (95% CI 3.3% to 24.3%). Four patients had cardiac resynchronization therapy for 1 to 2 years before transplantation, with modest symptom improvement in 1 and none in the other 3.

Comparison of ES and Other HCM Patients

Compared with non-ES HCM patients, the 33 patients who developed ES after study entry were diagnosed at an earlier age (32±18 versus 42±20 years; $P=0.002$), and at initial evaluation had more severe symptoms (New York Heart Association class 1.8±0.8 versus 1.4±0.6; $P=0.009$), larger LV cavity (48±8 versus 44±6 mm; $P=0.03$), thicker septum (25±6 versus 21±6 mm; $P=0.005$), and less frequent outflow gradients ≥30 mm Hg at rest (13% versus 36%;

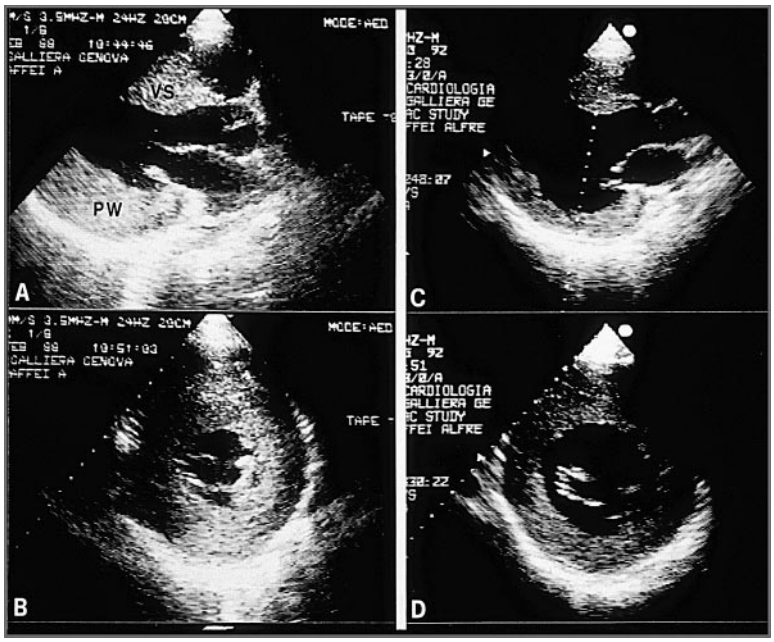

Figure 4. Evolution to ES in a male HCM patient (patient 26), shown at end diastole in parasternal long-axis (A and C) and short-axis (B and D) echocardiographic cross-sectional planes. A and B, At age 16 years, when asymptomatic, showing marked hypertrophy of anterior ventricular septum (VS) and LV free wall (PW), 32 mm thickness for both, and small LV cavity (38 mm); ejection fraction is 70%. C and D, At age 23 years, with modest New York Heart Association class II symptoms, showing decreased thickness of septum and LV free wall and markedly increased cavity size (70 mm); ejection fraction is only 30%. Calibration marks are 10 mm apart. Ao indicates aorta; LA, left atrium.

$P=0.04$). In addition, ES patients more often experienced atrial fibrillation (48% versus 14%; $P=0.002$) and showed more symptom progression (to New York Heart Association class 3.0±0.9 versus 1.7±0.8; $P<0.001$).

CMR Imaging

Postgadolinium contrast CMR imaging was obtained in 6 ES patients (1, 2, 4, 13, 18, and 27; Table and Figure 7). Each showed large isolated or confluent areas of delayed hyperenhancement indicative of fibrosis, frequently transmural, and distributed diffusely throughout ventricular septum and LV free wall. These areas of fibrosis predominantly involved midepicardial and subepicardial portions of the LV wall.

Pathological Findings

Native explanted hearts were available for examination in 6 patients. Two distinctive morphological patterns were evident. Two hearts showed dilated ventricular chambers associated with only mild ventricular septal thickening (ie, 15 and 13 mm; heart weights 320 and 350 g, respectively). Each showed diffuse or transmural scarring of septum and LV free wall, resulting in wall thinning.

The 4 other hearts (patients 4, 7, 8, and 20) had nondilated ventricular chambers associated with marked septal LV thickening (20 to 39 mm; weights 470 to 525 g; Figure 5). Two of these showed diffuse transmural scarring of septum and LV free wall (patients 4 and 8; Figure 5B, 5C, 5D, and 5F), whereas the other 2 had diffusely distributed, patchy areas of nontransmural fibrosis (patients 7 and 20). In each of 6 hearts examined, histopathology showed cardiac muscle cell disorganization (Figure 5E) and abnormal intramural coronary arteries typical of HCM[1,22,23] (Figure 5C and 5E).

Discussion

The clinical expression of HCM has proved to be particularly heterogeneous, and awareness of the diverse disease spectrum and clinical course has expanded substantially over the last decade.[1–3,18,24,25] A patient subset characterized by clinical progression, and largely known as the ES phase, has been described.[3–17,26,27] Much of the prior literature about ES is, however, confined to isolated or small groups of patients.[4,6–17] Therefore, we have revisited the ES in a multicenter cohort of >1200 HCM patients, which included the largest group of ES patients reported to date. The present study represents an opportunity to investigate occurrence, diagnosis, pathophysiology, and prognosis of this unique HCM subset, information that ultimately impacts management strategies.

The data in the present study expand the clinical profile of the ES and differ considerably from previous accounts in several important respects. First, ES frequency was 3.5%, which suggests that reliance on earlier reports from tertiary HCM referral centers (prevalence up to 15%)[3,5] may have overestimated the occurrence of ES, probably largely because of patient selection biases.[3,5]

The relative infrequency with which ES occurs only underscores the importance of a high index of clinical suspicion. For example, the transition from a hypertrophied and nondilated state (with intact contractility) to one of systolic dysfunction appears to evolve gradually over substantial time periods often associated with development of atrial fibrillation (eg, average 14 years), which, if recognized, allows important alterations in management strategies to be readily instituted. These include transition of standard HCM medical therapy to drugs for systolic pump failure, as well as proper timing for heart transplantation evaluation, which is the only definitive treatment option for ES (when systolic dysfunction is evident with ejection fraction <50%).

The clinical course of ES proved to be variable, often unpredictable, but generally unfavorable. Overall, about two thirds of the study population have died of their disease, undergone heart transplantation, or had appropriate life-

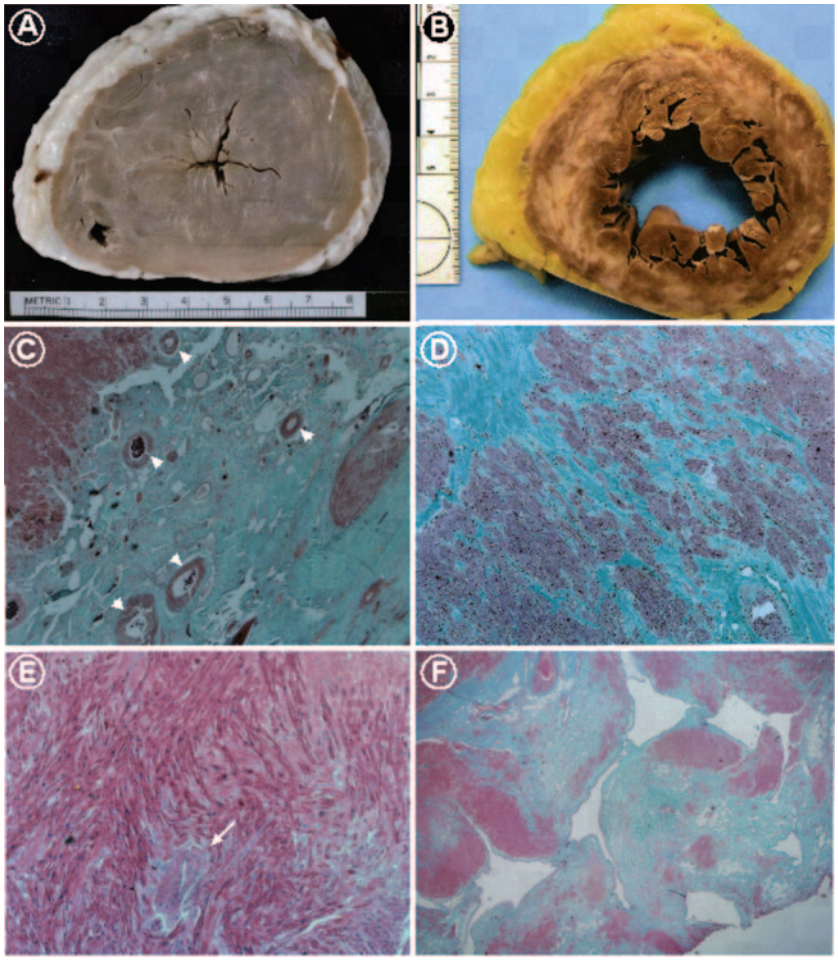

Figure 5. Selected gross (A and B) and histopathological (C through F) features of patients with ES of HCM. A and B, Distal cross-sectional views of explanted hearts from patients 7 and 8 with systolic dysfunction (ejection fraction 49% and 40%, respectively) but persistent and marked LV wall thickening in the absence of cavity dilatation in A; in B, prominent transmural scarring (white areas) is diffuse and circumferential, involving virtually the entire LV but particularly the ventricular septum and the contiguous anterior free wall. C and D, Low magnification of LV myocardium (patients 9 and 8) shows large areas of replacement fibrosis, which in C contains several abnormal intramural coronary arteries with thickened walls and narrowed lumen (arrowheads). Trichrome stain; original magnification ×40 and ×20, respectively. E, Area of cardiac muscle cell disorganization in which adjacent myocytes are arranged at perpendicular and oblique angles (patient 8); 1 abnormal intramural artery (arrow) is evident. Hematoxylin and eosin stain, original magnification ×200. F, Fibrotic area of LV myocardium and trabeculations (patient 20). Trichrome stain, original magnification ×40.

saving ICD shocks. The overall annual mortality rate of 11% per year is in sharp contrast to 1% per year for the overall HCM population.[1,2] Furthermore, after recognition of ES, patients experienced a generally precipitous course, in which on average <3 years elapsed from recognition of ES to heart transplantation or death. Therefore, once ES is in place, it usually adopts an aggressive course, and definitive management strategies may be required. However, profound clinical deterioration was not universal, given that almost one third of patients treated medically in the present study have experienced substantial periods of time with compensated heart failure (average 3 years).

Another issue that underscores the importance of timely ES recognition relates to our strategy of providing patients with prophylactic ICDs when systolic dysfunction is evident, to protect against lethal ventricular tachyarrhythmias while they await donor hearts.[24,28,29] This approach proved to be lifesaving in 5 patients who received appropriate defibrillation shocks. The appropriate intervention rate of 10% per year was similar to that reported in HCM patients implanted for secondary prevention.[24] These observational data suggest that ES can be regarded as another risk marker in HCM, and the prophylactic placement of ICDs in all ES patients is a reasonable clinical strategy.[24]

We observed ES patterns of LV remodeling to be nonuniform and variable. Global LV systolic dysfunction was, by definition, the most consistent ES feature and often preceded other evidence of remodeling, as well as severe symptoms. For example, only about 50% of patients had evidence of complete remodeling with the triad of LV wall thickness regression, cavity dilatation, and reduced ejection fraction. Of particular note, more than one third of the ES patients showed a nondilated or persistently hypertrophied LV or both, and 5 of these patients underwent heart transplantation. The latter patients represent a novel and heretofore unappreciated subset within the ES spectrum and suggest that the descriptive term "dilated HCM"[4–7,9,14–16,26] is a misnomer for describing the ES.

However, although many ES study patients did not in fact exceed the outer limits for LV cavity size by echocardiography (established for a normal population) or progress to absolute LV dilatation over the period of observation, our serial data showed evidence for considerable enlargement of the LV chamber over time. Such enlargement was often considerable, given the small chamber size characteristic of HCM patients before remodeling, even though the end-diastolic dimension that was ultimately achieved did not necessarily exceed the normal cutoff value of 55 mm. Therefore, the sine qua non of ES is a functional abnormality (ie, systolic dysfunction; ejection fraction <50%), whereas other morphological changes common in ES, such as LV cavity dilatation and wall thinning, are evident less consistently.

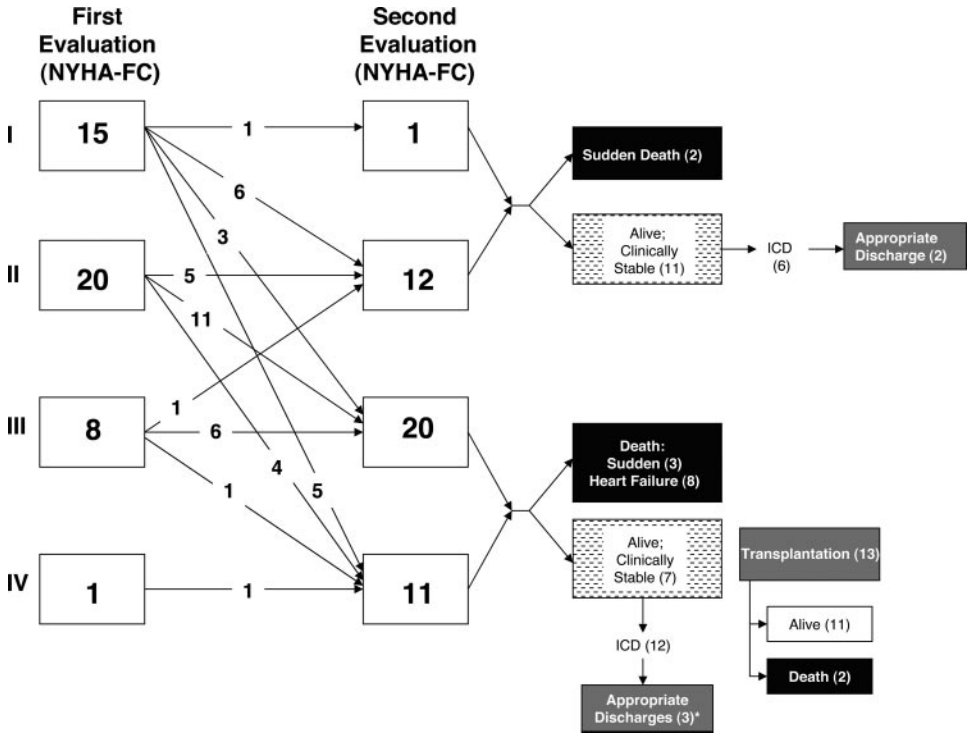

Figure 6. Flow diagram summarizing clinical course of 44 ES HCM patients. *Includes 1 patient who died suddenly and 1 who died after heart transplantation; NYHA-FC indicates New York Heart Association functional class.

Clinical and demographic markers that reliably anticipate evolution to the ES could not be defined with precision, largely owing to the retrospective nature of the study design and the broad clinical profile of ES patients. Nevertheless, certain clinical profiles were associated with a greater likelihood of developing ES. Of particular note, we found 20% of probands in the present study had at least 1 relative with the ES, which suggests that affected relatives merit close follow-up for early detection of ES. In addition, compared with the general HCM population, patients who developed ES after study entry were more symptomatic, had larger LV cavity and thicker ventricular septum, and more frequently developed atrial fibrillation. Furthermore, in ES patients, HCM diagnosis was earlier by 10 years, which suggests that disease recognition in young patients may predispose to ES later in life. We found no evidence that posterior LV free wall hypertrophy was associated with evolution to ES, as previously suggested.[26] Although ES was identified in 7 study patients many years after septal myectomy, we found no evidence that surgery predisposes to ES.

On the other hand, our observations suggest a potential role for CMR in earlier detection of the propensity to develop ES

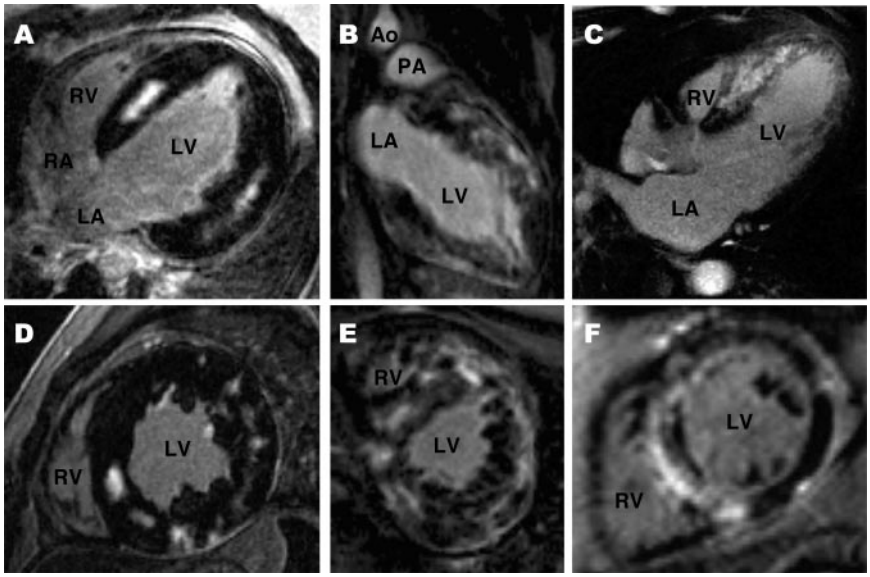

Figure 7. Delayed enhanced CMR horizontal long-axis (A, B, and C) and short-axis (D, E, and F) images from 3 ES patients. A and D, 19-year-old man (patient 27) with New York Heart Association class II symptoms; B and E, 27-year-old woman (patient 4) in class IV awaiting transplantation; C and F, 39-year-old asymptomatic man (patient 1). Each panel shows extensive areas of transmural postcontrast delayed hyperenhancement (white areas) within septal and LV free wall myocardium, indicative of scarring. Ao indicates aorta; LA, left atrium; RA, right atrium; PA, main pulmonary artery; and RV, right ventricle.

(possibly even in advance of systolic dysfunction), by post-gadolinium delayed hyperenhancement demonstrative of widespread LV nonviability.[30] These CMR patterns, presumed to represent fibrosis and replacement scarring, are consistent with our pathological observations and those of others[3,10,31] and are probably largely responsible for the striking disease process.[1,2,22,25,32]

Mechanisms responsible for transformation of typical HCM to ES are unresolved. Intuitively, the expanded collagen matrix in HCM[33] would appear to offer a structural framework for substantial ventricular stiffness and consequently, a measure of protection from the ES. This raises the alternative possibility of a unique molecular or genetic susceptibility to ES.[34,35] Clustering of ≥2 relatives with ES was evident in a significant minority of our families, and 3 were genotyped. In each case, the identified mutation was in β-myosin heavy chain or myosin-binding protein C genes, suggesting that ES does not result from a particular molecular defect. Because these are the most common HCM-causing mutant genes,[2] also known to cause the primary dilated form of cardiomyopathy,[35] it is perhaps not unexpected that such mutations would prove to be responsible for the ES phase of HCM, as well as for the frequent occurrence of both ES and sudden unexpected death in HCM families.[12]

In conclusion, HCM with ES is more heterogeneous with respect to clinical expression, symptomatic course, and patterns of LV remodeling than previously regarded. Greater clarity about the occurrence, expanded clinical profile, and features of ES will promote earlier recognition of this disease evolution. This is paramount to ensure implementation of more effective management strategies directed toward appropriate pharmacological treatment of pump failure and atrial fibrillation, defibrillator implantation, and timely evaluation for heart transplantation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The end stage (ES) of hypertrophic cardiomyopathy is a cause of progressive heart failure and a profound disease consequence, affecting a relatively small but important patient subgroup in a broad range of ages (14 to 74 years). ES is characterized by substantial cardiac remodeling and the gradual evolution from the typical hypertrophied, nondilated, and hyperdynamic state to one of systolic dysfunction due to widespread myocardial fibrosis (which can be defined with cardiac magnetic resonance imaging). It is of particular clinical relevance to the practicing cardiologist that ES is far more heterogeneous than previously regarded in terms of presentation and demographics, including frequent occurrence in the young (45% $\leq$40 years). ES diagnosis is primarily dependent on ejection fraction $<$50%, and ES commonly does not present as a dilated cardiomyopathy, with only $\approx$50% of patients showing associated left ventricular cavity enlargement or regression in wall thickness; paradoxically, a small proportion of ES patients even demonstrate persistent marked hypertrophy with nondilated left ventricle. A useful clinical clue for prospective ES diagnosis is familial occurrence of ES. Clinical course is variable and unpredictable but generally unfavorable, with heart transplantation the only definitive treatment for unrelenting progressive heart failure unresponsive to medical management. Vigilant follow-up and a high index of suspicion are required for timely identification of transition to ES and to permit early attention to its unique clinical implications. This includes, most importantly, patient access to treatment options that target ES, such as drug treatment for systolic pump failure, prophylactic implantable defibrillator for sudden death prevention, and consideration for heart transplantation.

Prevalence, Clinical Profile, and Significance of Left Ventricular Remodeling in the End-Stage Phase of Hypertrophic Cardiomyopathy

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