

**Hypertrophic Cardiomyopathy****Dilated-Hypokinetic Evolution  
of Hypertrophic Cardiomyopathy****Prevalence, Incidence, Risk Factors,  
and Prognostic Implications in Pediatric and Adult Patients**

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<b>OBJECTIVES</b>	This study sought to investigate the incidence, risk factors, and prognosis of dilated-hypokinetic evolution in a large cohort of patients with hypertrophic cardiomyopathy (HCM) followed up at a cardiology center serving both the pediatric and the adult population.
<b>BACKGROUND</b>	The available data on this evolution of HCM mainly regards prevalence (rather than incidence) in adults, with very little being known about the pediatric population.
<b>METHODS</b>	A total of 222 consecutive HCM patients (65% men, 19% ≤18 years old) were prospectively evaluated for a mean follow-up of 11 ± 9 years.
<b>RESULTS</b>	A diagnosis of dilated-hypokinetic HCM was made in 12 patients at first evaluation (11 without previous septal myectomy surgery; prevalence, 4.9%). Twelve of the 210 patients with classic HCM at first evaluation underwent dilated-hypokinetic evolution (incidence, 5.3/1,000 patient-years). Patients with prevalent/incident dilated-hypokinetic evolution were younger at first evaluation (32 ± 14 years vs. 41 ± 21 years, <i>p</i> = 0.04) and more often had a family history of HCM (61% vs. 26%, <i>p</i> = 0.002) or sudden death (43% vs. 19%, <i>p</i> = 0.01) with respect to patients who maintained classic HCM. Moreover, they showed greater interventricular septum (23 ± 3 mm vs. 19 ± 6 mm, <i>p</i> = 0.004) and posterior wall (15 ± 3 mm vs. 13 ± 4 mm, <i>p</i> = 0.006) thickness. Cardiovascular death-free survival was lower among patients with dilated-hypokinetic HCM ( <i>p</i> < 0.04). Cox proportional hazards regression analysis identified left ventricular wall thickness (hazard ratio [HR] = 1.07; 95% confidence interval [CI], 1.01 to 1.14; <i>p</i> = 0.03) and end-diastolic diameter (HR = 1.08; 95% CI 1.04 to 1.11; <i>p</i> = 0.0001) as independent predictors of cardiovascular death.
<b>CONCLUSIONS</b>	Dilated-hypokinetic evolution is rare but not exceptional in HCM. Young age at diagnosis, family history of HCM, and greater wall thickness are incremental risk factors for dilated-hypokinetic HCM, which carries an ominous prognosis. (J Am Coll Cardiol 2005; 46:1543-50) © 2005 by the American College of Cardiology Foundation

Most patients with hypertrophic cardiomyopathy (HCM) have normal systolic function (in terms of left ventricular ejection fraction [LVEF] and other ejection indices) in the context of impaired diastolic function and reduced left ventricular (LV) end-diastolic volume. However, in a minority of patients HCM evolves into a phase characterized by systolic dysfunction, LV dilation, and wall thinning, resembling the morphologic and functional features of

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dilated cardiomyopathy (Fig. 1). This dilated-hypokinetic evolution of HCM is often designated as end-stage, burn-out phase (1-10), or progressive disease (11). This peculiar disease pathway, which had already been clearly described in

the 1980s (1,2,4-7,9), has recently attracted renewed scientific interest for at least two reasons. On pathogenetic grounds, it has recently been reported that mutations in sarcomere protein genes can cause either HCM or dilated cardiomyopathy, stimulating two different pathobiological events that remodel the heart (12). Clinically, dilated-hypokinetic evolution is one of the pathophysiologic substrates for heart failure in patients with HCM, among whom it is also the single most frequent indication for heart transplantation (3,13,14).

The available data on the occurrence of dilated-hypokinetic evolution of HCM mainly regards prevalence (rather than incidence) of adult cases, with very little being known about the pediatric population (15,16). In the present study, we investigated the incidence, risk factors, natural history, and prognostic implications of dilated-hypokinetic evolution of HCM in a large population of patients with HCM routinely followed up at a cardiology center serving both the pediatric and the adult population.

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#### Abbreviations and Acronyms

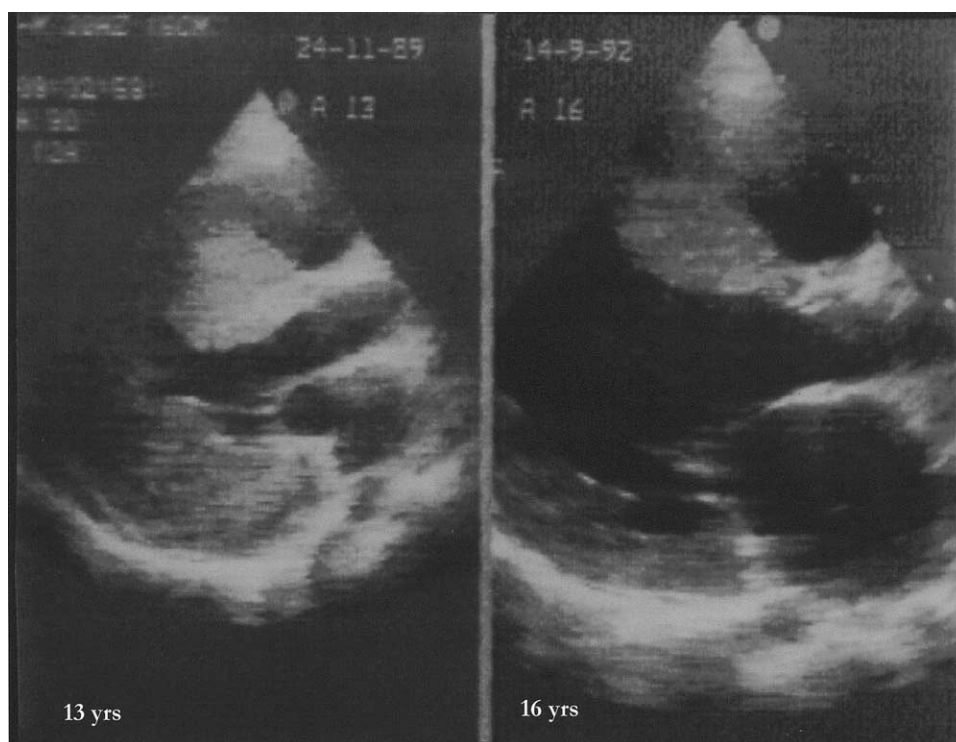
CI	= confidence interval
HCM	= hypertrophic cardiomyopathy
HR	= hazard ratio
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
NYHA	= New York Heart Association

## METHODS

**Eligibility criteria and recruitment.** The population of this observational study comprised 222 patients with a diagnosis of HCM under observation between 1964 and 2002 in the standard inpatient/outpatient clinics of our cardiology center in a public teaching hospital open to a large local and regional population. In particular, the study regarded all patients with either a de novo diagnosis of HCM made in our center or an existing diagnosis of HCM who were referred to us for follow-up purposes (all instrumental and clinical findings, including familial analysis with pedigree reconstruction, are routinely stored in an electronic database). The single inclusion criterion was diagnosis of HCM based on two-dimensional echocardiographic evidence of a nondilated and hypertrophic LV—defined as wall thickness of  $\geq 15$  mm in adults, or the equivalent with respect to body surface area in children (16)—in the absence of another cardiac or systemic disease that could produce a

similar degree of hypertrophy (17). Exclusion criteria were presence of Friedreich ataxia or Noonan syndrome (based on careful clinical analysis of phenotype), Pompe disease (clinical and enzymatic evaluation), or mitochondrial disease (exclusion of multiorgan involvement, and in selected patients, histologic evaluation of skeletal muscle biopsy or mitochondrial DNA analysis). In patients evaluated before echocardiography was introduced into our clinical practice (in 1984), the diagnosis of HCM was made by typical electrocardiographic features combined with angiographic findings (17) and was subsequently confirmed by echocardiography (18).

Those patients residing within easy distance to the clinic were regularly followed up in our outpatient clinic according to our routine institutional program, comprising two planned clinical check ups and one echocardiographic examination per year. The remainder of the population (38 patients) was recalled (by mail and then telephone) for an echocardiographic and clinical check up at the end of the study period. Data regarding time and circumstances of death were obtained from relatives and physicians (consulting clinical records and death certificates when necessary). All patients provided written informed consent to anonymous use of their data for research purposes. In line with national and European guidelines, no specific ethical approval was required for this observational study without invasive procedures.



**Figure 1.** A representative example of evolution to dilated-hypokinetic hypertrophic cardiomyopathy (HCM) in a female pediatric patient. (A) The basal echocardiogram (at age 13 years) shows HCM with massive left ventricular (LV) hypertrophy involving the intraventricular septum and the left posterior wall, accompanied by diminutive LV cavity size. (B) Three years later (at age 16 years), the LV cavity has become enlarged and the walls have thinned in the context of severe heart failure, requiring heart transplantation.

**Definitions.** Dilated-hypokinetic evolution of HCM was defined as development of hypokinetic and dilated LV, with an end-diastolic cavity dimension measured by M-mode echocardiography exceeding the reference upper 95% confidence interval (CI) for body surface area and an LVEF <50% (2,4,19). In patients who had already presented at our center with a dilated and hypokinetic LV, diagnosis of HCM always included previous echocardiographic documentation of classic HCM. "Medical treatment at first examination" refers to pharmacologic treatment ongoing/started at that time.

Other definitions were those commonly used. Sudden cardiac death was defined as unexpected sudden collapse within one hour of onset of symptoms occurring in patients who had previously experienced a relatively stable or uneventful clinical course. Heart failure-related death was defined as death occurring in the context of cardiac decompensation and progressive disease course one year or more before death.

**Statistical analysis.** The SPSS statistical package (SPSS Statistical Software Inc., Chicago, Illinois) was used for all analysis. When not otherwise specified, data are expressed as mean ± 1 SD, or as the number of patients (percentage). Prevalence of dilated-hypokinetic HCM was calculated as the ratio between patients with a diagnosis of dilated-hypokinetic HCM at the first evaluation and the total number of study patients. Analysis of incidence was performed among those patients without dilated-hypokinetic HCM at first evaluation. Incidence was calculated as the number of patients who developed dilated-hypokinetic HCM during the follow-up period divided by the total number of person-years of observation accumulated in the

study population; patients who underwent myotomy/myectomy or percutaneous transluminal septal myocardial ablation were included in the analysis only up to the time of the procedure. Differences between means were determined using the unpaired or paired Student *t* test as appropriate. Differences between proportions were determined using the chi-square test. To assess the prognostic role of dilated-hypokinetic HCM in terms of risk of cardiovascular death, a multivariate Cox proportional hazards model was fitted to the data (20). The following variables were included: gender, age at first evaluation, family history of sudden death, New York Heart Association (NYHA) functional class I to II or III to IV, medical treatment at first evaluation, nonsustained ventricular tachycardia, LV outflow obstruction, maximum LV wall thickness, posterior wall thickness, LV end-diastolic diameter, end-systolic left atrial diameter, and (as a time-dependant covariate) dilated-hypokinetic evolution. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. Probability of cardiovascular death-free survival was calculated using the Kaplan-Meier method, and survival curves were compared using the log-rank test.

## RESULTS

**Study population.** The mean age at first evaluation was 40 ± 20 years; 144 (65%) patients were men, 42 (19%) were 18 years old or younger. Baseline clinical and echocardiographic characteristics of the entire population as well as of the two groups of patients with either dilated-hypokinetic or classic HCM at first evaluation are summarized in Table 1. During a mean follow-up of 11 ± 9 years, 29 (13%) patients devel-

**Table 1.** Baseline Characteristics of the Overall Population, Patients With Classic HCM, and Patients With Dilated-Hypokinetic HCM at First Evaluation

	Overall Population (n = 222)	Dilated-Hypokinetic HCM (n = 11)*	Classic HCM (n = 210)	p Value†
Male gender	144 (65%)	8 (73%)	135 (64%)	0.8
Family history of HCM	65 (29%)	7 (64%)	58 (28%)	0.03
Family history of sudden death	47 (21%)	4 (36%)	43 (20%)	0.3
Age at diagnosis (yrs)	38 ± 18	27 ± 18	39 ± 18	0.05
Age at first evaluation (yrs)	40 ± 20	34 ± 16	40 ± 21	0.3
Pediatric age (≤18 yrs) at first evaluation	42 (19%)	3 (27%)	37 (18%)	0.6
NYHA functional class III to IV	22 (10%)	3 (27%)	19 (9%)	0.1
NYHA functional class (mean)	1.5 ± 0.7	2.1 ± 1.1	1.4 ± 1.0	0.1
Syncope	21 (9%)	1 (9%)	19 (9%)	1
Medical treatment at first examination	160 (72%)	9 (82%)	151 (72%)	0.7
Persistent atrial fibrillation	3 (1%)	0 (0%)	3 (1%)	1
Heart failure episodes	12 (5%)	3 (27%)	9 (4%)	0.01
Outflow obstruction	67 (30%)	0 (0%)	68 (32%)	0.05
Maximum left ventricular wall thickness (mm)	19 ± 6	17 ± 6	20 ± 6	0.2
Interventricular septal width (mm)	18 ± 6	16 ± 6	19 ± 6	0.2
Posterior wall thickness (mm)	13 ± 4	14 ± 4	13 ± 4	0.4
Left ventricular end-diastolic diameter (mm)	43 ± 11	61 ± 9	41 ± 10	NA
End-systolic left atrial diameter (mm)	43 ± 10	49 ± 8	42 ± 10	0.02
Left ventricular ejection fraction (%)	67 ± 8	32 ± 10	66 ± 8	NA
Apical HCM	8 (4%)	0 (0%)	8 (4%)	0.9

\*One patient with previous septal myectomy surgery was excluded from this analysis. †The p values refer to comparison between patients with dilated-hypokinetic and patients with classic HCM at first evaluation.

HCM = hypertrophic cardiomyopathy; NA = not applicable (separation into subgroups was based on these variables); NYHA = New York Heart Association.

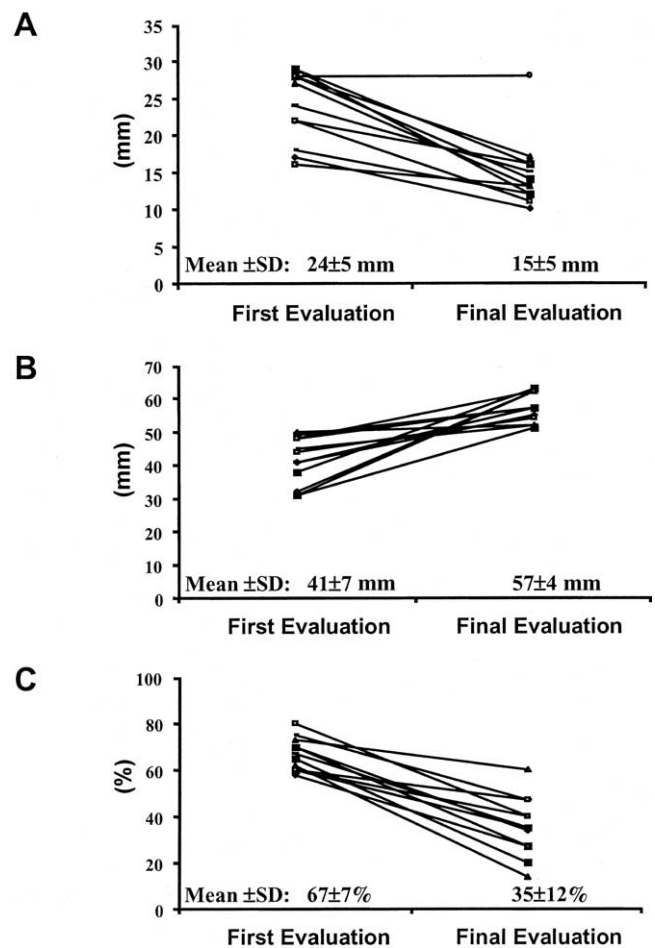
oped persistent atrial fibrillation, 65 (29%) had heart failure episodes, and 20 (9%) experienced syncope. Holter monitoring data were available for 190 (85%) patients; nonsustained ventricular tachycardia was present in 64 of 190 patients (34%). A permanent pacemaker or cardioverter-defibrillator was implanted in 10 (4%) and 11 (5%) patients, respectively. During the follow-up period, 10 patients (4%) underwent heart transplantation and 50 (23%) died. The cause of death was sudden in 20 patients (9%), heart failure-related in 13 patients (6%), stroke-related in 3 patients (1%) and due to noncardiac causes in 14 patients (6%).

**Prevalence of dilated-hypokinetic evolution of HCM.** The diagnosis of dilated-hypokinetic HCM was made in 12 patients at the first evaluation. One of these patients, who had entered this phase after septal myectomy surgery, was excluded from the analysis. Therefore, 11 patients were deemed to have dilated-hypokinetic HCM evolution at first evaluation, corresponding to a prevalence of 4.9%.

**Incidence of dilated-hypokinetic evolution of HCM.** Twelve of the 211 patients with classic HCM at first evaluation underwent dilated-hypokinetic evolution (their changes in LV cavity dimension, LVEF, and maximum wall thickness are individually represented in Fig. 2). Because all 12 of these patients belonged to the subgroup with regular follow-up data from our institutional program, an actuarial incidence curve was constructed (Fig. 3). The events (onset) were distributed rather evenly over almost the entire follow-up period (mean,  $11 \pm 9$  years; range, 4 months to 42 years). The overall incidence of development of dilated-hypokinetic HCM was 5.3 per 1,000 patient-years. Of note, a restrictive LV filling pattern was present at echo-Doppler evaluation in 3 of 12 patients at the time of detection of dilated-hypokinetic evolution.

**Characterization of patients with dilated-hypokinetic HCM and prediction of onset.** We first looked at the clinical/morphologic profile of patients with prevalent dilated-hypokinetic HCM at baseline ( $n = 11$ ). A comparison between their clinical/morphologic characteristics and those of the rest of the population at first evaluation is shown in Table 1.

To look for possible predictors of evolution, we then analyzed the baseline characteristics of patients who had prevalent/incident dilated-hypokinetic HCM ( $n = 23$ ). Table 2 shows a comparison of the baseline characteristics of patients with dilated-hypokinetic HCM and patients who maintained classic HCM (it should be noted that for those patients with prevalent dilated-hypokinetic HCM, measurements were retrieved from prior echocardiographic documentation). At the univariate analysis, the two subgroups were similar regarding gender, symptoms, LV end-diastolic volume, and LVEF. On morphologic grounds, patients with dilated-hypokinetic HCM showed greater LV parietal thickness at the posterior as well as interventricular septal level. They also more often had a family history of HCM or a family history of sudden death. They were



**Figure 2.** Changes in left ventricular (LV) maximal wall thickness (A), LV end-diastolic diameter (B), and LV ejection fraction (C) in the 12 hypertrophic cardiomyopathy (HCM) patients who underwent dilated-hypokinetic evolution during the study period. SD = standard deviation.

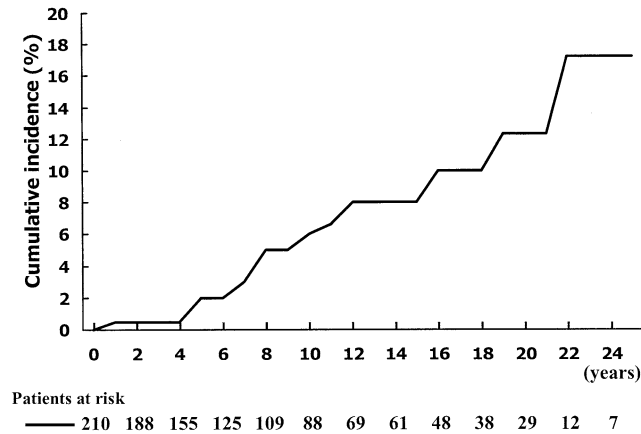
significantly younger both at the original diagnosis of HCM and at first examination. Because of the small number of patients with dilated-hypokinetic evolution, it was not possible to construct a valid multivariate model.

Of note, the 23 patients with prevalent/incident dilated-hypokinetic evolution belonged to 18 distinct families. Among these 18 nuclei, we could identify 3 pedigrees containing both sudden death in the context of nondilated HCM and death from heart failure attributable to end-stage evolution.

**Prognostic implications of dilated-hypokinetic HCM.** Figure 4 shows actuarial cardiovascular death-free survival curves for patients with prevalent or incident dilated-hypokinetic HCM ( $n = 23$ ) and the rest of the study population: patients with dilated-hypokinetic evolution had a poorer cardiovascular death-free survival ( $p = 0.04$ ). In particular, of the 23 patients with dilated-hypokinetic evolution, 4 died of congestive heart failure and 3 died suddenly.

Cox proportional hazards regression analysis identified LV wall thickness (hazard ratio [HR] = 1.07; 95% CI 1.01, to 1.14;  $p = 0.03$ ) and LV end-diastolic diameter (HR = 1.08; 95% CI, 1.04 to 1.11;  $p = 0.0001$ ) as independent predictors of cardiovascular death; dilated-hypokinetic evolution (consid-

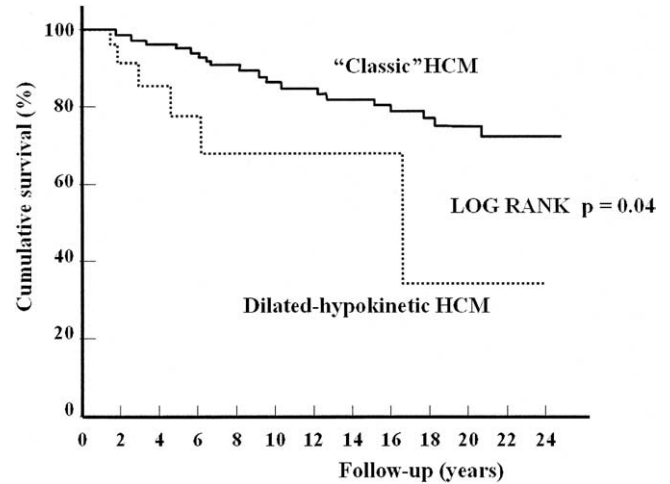
Dilated-Hypokinetic Hypertrophic Cardiomyopathy



**Figure 3.** Actuarial incidence curve of dilated-hypokinetic evolution among 210 patients with classic hypertrophic cardiomyopathy at first evaluation.

ered as a time-dependant covariate) did not independently predict cardiovascular death-free survival ( $p = 0.51$ ).

Clinical events observed during follow-up among the subgroups of patients in whom dilated-hypokinetic HCM did and did not develop during the study period are summarized in Table 3. Overall, patients in whom dilated-hypokinetic HCM developed more often had persistent atrial fibrillation, episodes of heart failure, ventricular tachycardia (on 24-h Holter monitoring), and heart transplantation. It should be noted, however, that this subgroup had a longer follow-up ( $14 \pm 6$  years vs.  $10 \pm 7$  years,  $p = 0.05$ ). The first signs of LV dilation and hypokinesis in these 12 incident patients became evident within  $13 \pm 8$  years (ranging from 5 to 33 years) after the diagnosis of HCM (mean age of patients,  $42 \pm 17$  years). The mean interval from echocardiographic appearance of LV dilation to development of heart failure (NYHA functional class III to IV) was  $3 \pm 2$  years (range, 1 to 7 years). During follow-up,



**Figure 4.** Kaplan-Meier estimates of cardiovascular death-free survival of patients with and without prevalent/incident dilated-hypokinetic hypertrophic cardiomyopathy (HCM).

two (17%) patients died and five (45%) underwent heart transplantation. The mean time between identification of dilated evolution and death or heart transplantation was  $5 \pm 3$  years and  $5 \pm 4$  years, respectively.

Five of 12 (42%) patients who experienced dilated-hypokinetic evolution during follow-up were younger than 19 years of age at first evaluation; in this subgroup, dilated-hypokinetic evolution occurred at  $8 \pm 4$  years (range, 5 to 16 years) from HCM diagnosis. After LV dilation occurred, heart failure symptoms developed earlier in these patients compared with adult patients ( $1 \pm 0.5$  years vs.  $5 \pm 3$  years,  $p < 0.05$ ). Moreover, four of five (80%) pediatric patients underwent heart transplantation (at  $5 \pm 4$  years from appearance of dilation) and one (8%) died of heart failure (at 2 years from dilation).

**Table 2.** Baseline Clinical and Echocardiographic Features of Patients With Prevalent/Incident Dilated-Hypokinetic HCM and Patients Who Maintained Classic HCM

	Dilated-Hypokinetic HCM (n = 23)	Classic HCM (n = 198)	p Value
Male gender	17 (74%)	126 (64%)	0.5
Family history of HCM	14 (61%)	51 (26%)	0.002
Family history of sudden death	10 (43%)	37 (19%)	0.01
Age at diagnosis (yrs)	$28 \pm 15$	$39 \pm 18$	0.03
Age at first evaluation (yrs)	$32 \pm 14$	$41 \pm 21$	0.04
Pediatric age ( $\leq 18$ yrs) at first evaluation	9 (39%)	34 (17%)	0.02
NYHA functional class III to IV at first evaluation	0 (0%)	19 (9%)	0.5
NYHA functional class (mean)	$1.5 \pm 0.6$	$1.4 \pm 0.7$	0.8
Syncope at first evaluation	2 (9%)	18 (9%)	0.99
Medical treatment at first examination	17 (74%)	141 (71%)	1
Outflow obstruction	4 (17%)	67 (30%)	0.2
Maximum left ventricular wall thickness (mm)	$24 \pm 3$	$20 \pm 6$	0.001
Interventricular septal width (mm)	$23 \pm 3$	$19 \pm 6$	0.004
Posterior wall thickness (mm)	$15 \pm 3$	$13 \pm 4$	0.006
Left ventricular end-diastolic diameter (mm)	$43 \pm 4$	$41 \pm 9$	0.7
End-systolic left atrial diameter (mm)	$45 \pm 7$	$42 \pm 10$	0.1
Left ventricular ejection fraction (%)	$66 \pm 4$	$66 \pm 8$	1

Abbreviations as in Table 1.

**Table 3.** Clinical Events Observed in Patients Who Underwent Dilated-Hypokinetic Evolution During Follow-Up and in Patients Who Maintained Classic HCM

	Dilated-Hypokinetic Evolution (n = 12)	Classic HCM (n = 198)	p Value
Persistent atrial fibrillation	5 (42%)	22 (11%)	0.009
Heart failure episodes	10 (83%)	48 (24%)	0.0001
Syncope	2 (17%)	19 (9%)	0.8
Sustained/nonsustained ventricular tachycardia on Holter electrocardiogram	9/12 (75%)	49/175 (28%)	0.002
Pacemaker	1 (8%)	8 (4%)	1
Implanted cardioverter-defibrillator	2 (17%)	8 (4%)	0.2
Cardiovascular death	2 (17%)	26 (13%)	0.1
Sudden death	1 (8%)	17 (9%)	1
Heart failure-related death	1 (8%)	9 (4%)	1
Stroke-related death	0 (0%)	3 (1%)	1
Noncardiovascular death	0 (0%)	14 (7%)	0.7
Heart transplantation	5 (42%)	1 (0.5%)	0.0001

HCM = hypertrophic cardiomyopathy.

## DISCUSSION

Dilated-hypokinetic evolution of HCM is responsible for severe heart-failure symptoms and is the single most frequent indication for heart transplantation among HCM patients (3,13,14). This study of a large population of HCM patients routinely followed up at a single cardiology center provides valuable data on the incidence of dilated-hypokinetic evolution among both children and adults, as well as on possible clinical and echocardiographic risk factors for development of this peculiar disease pathway.

**Prevalence and incidence of dilated-hypokinetic HCM.** Since the 1980s, dilated-hypokinetic (end-stage) evolution of HCM has become an established clinical entity, and its recognition is clearly based on the presence of cavity size enlargement and LV systolic dysfunction, commonly accompanied by ventricular wall thinning (1,2,4-7,9). Our definition of dilated-hypokinetic HCM was based on the simultaneous presence of LV cavity dilation and reduced LVEF, not necessarily associated with thinned LV walls. It is noteworthy, however, that LV wall thinning was documented during the study period in all but one patient (Fig. 2). Outside of heart transplantation centers, the prevalence of dilated-hypokinetic HCM has generally been reported to range from about 5% to 15% (4). However, these figures were produced without excluding patients who had previously undergone myotomy-myectomy, and are likely to give rise to a somewhat distorted picture [because myectomy can alter LV end-diastolic diameter as routinely measured by M-mode according to the recommendations of the American Society of Echocardiography, whereas percutaneous septal myocardial ablation can induce LV remodeling with increased volumes (21)]. After exclusion of such cases, the recorded prevalence of dilated-hypokinetic HCM in our center was 4.9%.

To our knowledge, this is the first time that the incidence of dilated-hypokinetic evolution has been studied in a large population of HCM patients not submitted to surgical/ablative myectomy. The overall incidence recorded was 5.3

per 1,000 patient-years, with a rather even distribution of onset over almost the entire follow-up period (Fig. 3).

**Prediction of onset of dilated-hypokinetic evolution.** Increased posterior wall thickness was the most peculiar morphologic trait in patients with (prevalent/incident) dilated-hypokinetic HCM (Table 2). The pathogenetic significance of this morphologic peculiarity is unclear. One attractive hypothesis is that this phenotypic peculiarity might constitute a marker of a distinct genotype (unfortunately, our study did not contemplate systematic genotyping). Alternatively, it is conceivable that a widespread distribution of LV hypertrophy might exacerbate myocardial ischemia, a very common phenomenon in HCM, and eventually lead to global LV dysfunction. The HCM characterized on echocardiography by marked thickening of the posterior LV free wall has been previously described to be associated with early (before the age of 40 years) onset of severe symptoms, such as dyspnea, syncope, chest pain, and palpitations (22). However, no relationship between this peculiar morphologic feature of HCM and dilated-hypokinetic evolution has been previously reported.

**Natural history and prognostic implications of dilated-hypokinetic evolution.** Despite the younger age at first evaluation of patients who developed dilated-hypokinetic HCM during follow-up, the interval from diagnosis to LV enlargement was rather long. However, once the dilation was established, the evolution toward heart failure and hence transplantation or death was rapid. The vast majority of our patients with dilated-hypokinetic evolution of HCM had severe symptoms (NYHA functional class IV) and were refractory to medical treatment in spite of a depression of LVEF that might be considered only moderate in comparison with heart transplantation candidates with idiopathic dilated cardiomyopathy (Fig. 2). A combination of both diastolic and systolic dysfunction could explain this apparent discrepancy.

**Pathogenesis of dilated-hypokinetic evolution in HCM.** The most likely pathogenetic mechanisms of dilated-hypokinetic evolution of HCM have been widely discussed in the

literature. Based on histology, importance has been given to small-vessel disease, myocardial disarray, or replacement fibrosis (10,11,23–26). Recently, gadolinium-enhanced cardiac magnetic resonance has provided in vivo confirmation that interstitial and replacement fibrosis is the most frequent myocardial substrate of this evolutionary pathway (11). The present study was not designed to clarify the pathogenetic mechanism of dilated-hypokinetic HCM. However, analysis of the clinical and morphologic data regarding our prevalent and incident cases can provide some hints regarding the likely pathogenesis. In our two analyses (Tables 1 and 2), dilated-hypokinetic evolution was most often already present in the third decade of life, and about one-third of the cases were actually pediatric; furthermore, age at diagnosis of HCM seemed to be lower in patients with dilated-hypokinetic evolution compared with the rest of the population. These observations make a strict aging-related mechanism seem rather unlikely. On the other hand, they fit quite well with the hypothesis that dilated-hypokinetic HCM often has a genetic basis (27–29). In some families, evolution to the dilated-hypokinetic evolution of HCM seems to occur with a particularly high frequency. A number of mutations in gene encoding proteins of the cardiac sarcomere have been reported in HCM patients in the dilated-hypokinetic evolution. It is unlikely that the propensity to develop this clinical course is exclusively attributable to any specific HCM-causing mutant gene. Interestingly, Seidman et al. (12) recently showed that mutations in the same gene (heavy-chain beta-myosin) can cause either hypertrophic or dilated cardiomyopathy. The development of LV wall thinning and systolic dysfunction probably represents a more complex phenomenon influenced by modifier genes as well as environmental factors.

**Considerations regarding the pediatric population.** Our data indicate that HCM patients diagnosed at a pediatric age are a high-risk subgroup regarding not only sudden death but also congestive heart failure. It is known that the morphologic basis for congestive heart failure in newborns with HCM is massive biventricular hypertrophy, frequently associated with right ventricular and/or LV obstruction. Our data set shows that dilated-hypokinetic evolution is another pathophysiologic substrate apparently affecting older children and adolescents. In the clinical arena, this peculiar disease pathway of classic HCM must be distinguished from other genetically determined entities that share the same phenotype of symmetrical LV hypertrophy and LV systolic dysfunction, and especially cardiomyopathies associated with mitochondrial disease. The latter, however, are generally characterized by multiorgan involvement, which should provide a valuable clue for a differential diagnosis.

## CLINICAL IMPLICATIONS AND CONCLUSIONS

The evolution toward a dilated-hypokinetic phase is rare but not exceptional in HCM, particularly among young patients

with hypertrophy not confined to the interventricular septum, but also involving the posterior wall. Recognition of this risk profile in individual patients should encourage close follow-up, aimed at timely detection and treatment of congestive heart failure. We think that the option of heart transplantation deserves consideration (and discussion with the patient) on the first appearance of heart failure symptoms, even if these occur before overt deterioration of systolic function.

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