

The Prognostic Importance of Left Ventricular Outflow Obstruction in Hypertrophic Cardiomyopathy Varies in Relation to the Severity of Symptoms

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OBJECTIVES	The aim of this study was to investigate whether the prognostic importance of left ventricular (LV) outflow obstruction in hypertrophic cardiomyopathy (HCM) is influenced by other predictors of morbidity and mortality.
BACKGROUND	It remains unknown whether the effect of outflow obstruction on clinical outcome in HCM is influenced by other determinants of survival.
METHODS	We assessed the impact of severity of symptoms, LV wall thickness, atrial fibrillation, and age on the prognostic importance of outflow obstruction in a large HCM population.
RESULTS	Of 526 consecutive HCM patients, 141 (27%) had outflow obstruction. During a follow-up of 4.5 ± 4.1 years, 34 patients died of HCM. The incidence of cardiovascular death was significantly higher among patients with LV obstruction than among those without obstruction (relative risk [RR] = 2.14; $p = 0.02$). The prognostic power of the outflow gradient changed in relation to severity of symptoms ($p = 0.024$). At initial evaluation, LV obstruction was a significant predictor of cardiovascular mortality only in New York Heart Association (NYHA) functional class I to II patients (hazard ratio [HR] = 2.38; $p = 0.025$). During follow-up, at time of development of severe symptoms, the outflow gradient lost its prognostic significance (HR = 1.18; $p = 0.66$), whereas NYHA functional class III to IV was associated with an eight-fold increase in risk of cardiovascular mortality (HR = 7.90; $p < 0.001$).
CONCLUSIONS	In patients with HCM, the prognostic importance of LV outflow obstruction varies in relation to the severity of symptoms. In patients with mild or no symptoms, obstruction is an important predictor of cardiovascular death. After development of severe symptoms, NYHA functional class becomes the dominant marker of prognosis independently of the presence of an outflow gradient. (J Am Coll Cardiol 2005;45:1076–80) © 2005 by the American College of Cardiology Foundation

Left ventricular (LV) outflow obstruction is present in 20% to 25% of patients with hypertrophic cardiomyopathy (HCM) (1–3). Despite the frequency of this functional abnormality, its clinical and prognostic implications have remained controversial for more than 30 years (1,2,4–6). Recently, a study performed in a large HCM cohort has shown that LV obstruction is an important predictor of disease progression and cardiovascular death (7). However, it remains unclear whether and to what extent the prognostic power of the gradient is influenced by other determinants of morbidity and mortality, including severity of symptoms, magnitude of LV wall thickness, and atrial fibrillation (AF). Clarification of the prognostic importance of LV obstruction in different subgroups is also acquiring particular relevance because of the rapidly increasing number of HCM patients undergoing non-

pharmacologic interventions for relief of the outflow gradient (8–10). In the present study, we assessed the effect of LV outflow obstruction on clinical outcome in a consecutive HCM population including more than 500 patients and, in particular, we investigated whether the prognostic importance of the gradient is influenced by other predictors of survival.

METHODS

Study population. Each of the 543 HCM patients consecutively evaluated at the Ospedali Galliera in Genoa from June 1983 (329 patients) and at the Università “La Sapienza”, in Rome, from December 1980 (214 patients) were initially considered for inclusion in the study. Four patients with a single evaluation and 13 with myectomy operation or alcohol septal ablation before initial evaluation were excluded from the investigation. Therefore, the final study population comprised 526 patients. Follow-up started at first evaluation at the two centers. In patients who underwent heart transplantation (three patients), myectomy operation (four patients), and alcohol septal ablation (eight patients), follow-up was terminated at the time of the

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Abbreviations and Acronyms

- AF = atrial fibrillation
- CI = confidence interval
- HCM = hypertrophic cardiomyopathy
- HR = hazard ratio
- LV = left ventricular
- NYHA = New York Heart Association

procedure. None of the 19 patients with a cardioverter-defibrillator experienced ventricular fibrillation. No patient received a pacemaker to reduce the gradient.

Definitions. The diagnosis of HCM was based on echocardiographic criteria previously described (11). Sudden cardiac death, heart failure or stroke-related death, and family history of sudden death were defined as previously reported (11–14). Left ventricular wall thickness, cavity dimension, and left atrial size were assessed using echocardiographic criteria previously described (11,12). Outflow obstruction under basal conditions was considered present when a peak gradient ≥ 30 mm Hg was identified by Doppler echocardiography (7,11–14). Echocardiographic measurements were obtained by a single investigator in each of the patients evaluated in Genoa (P.S.) and in Rome (C.A.).

Statistical methods. Mortality rates were estimated by dividing the number of deaths by the number of person-years accumulated during follow-up. For calculation of rates of each cause-specific mortality, patients who died from other causes were censored as alive at time of death. Rates were compared using the chi-square test for heterogeneity; the chi-square test for trend was used for ordinary variables, and the Fisher exact test was used when events were < 5 . To assess LV obstruction role as an independent predictor of cardiovascular mortality, a multivariate Cox proportional hazard model was fitted to the data, and the following variables were included: age, gender, New York Heart

Association (NYHA) functional class I to II or III to IV, obstruction, sudden-death family history, AF, LV maximal wall thickness, cavity dimension, and left atrial size. Variables not significantly associated with outcome were removed from the model using a step-down procedure based on the likelihood-ratio test.

The modifying effect (interaction) that the variables retained in the final model could have on the obstruction prognostic power was assessed by introducing in the model, one at a time, the appropriate interaction terms, and by evaluating the change in the likelihood of the model. To further explore the combined effect of NYHA functional class and obstruction on mortality, the term denoting functional class was removed from the model and replaced by a time-dependent covariate indicating class at each point in time. The NYHA functional class I to II patients were assigned a 0 value until deterioration to class III to IV, and 1 thereafter. The NYHA functional class III to IV patients at initial evaluation were assigned a 1 value for the entire follow-up. An interaction term between obstruction and the time-dependent covariate was also included in the model to assess the effect of obstruction on cardiovascular mortality after progression to NYHA functional class III to IV. All p values are two-sided.

RESULTS

LV obstruction and prognosis. Of the 526 study patients, 141 (27%) had LV obstruction. Baseline characteristics are summarized in Table 1. Mean follow-up was 4.5 ± 4.1 years and was similar in patients with and without obstruction (mean 4.4 ± 4.3 years and 4.5 ± 4.1 years, respectively). During follow-up, 49 (9%) patients died: 15 (31%) of noncardiac causes, and 34 (69%) of cardiovascular causes, of whom 15 (44%) died suddenly, 10 (30%) died of heart failure, and 9 (26%) died of stroke. Mortality due to stroke appeared to contribute importantly to the excess in cardio-

Table 1. Baseline Characteristics in the Overall Study HCM Population, and in Patients With and Without LV Outflow Obstruction

Variable	Overall HCM Population	Patients With LV Outflow Obstruction	Patients Without LV Outflow Obstruction	p Value
Number of patients	526	141	385	
Age (yrs), mean (median)	47 (49)	49 (50)	47 (48)	0.194
Male gender, no. (%)	343 (65)	79 (56)	264 (69)	0.01
Family history of sudden death, no. (%)	115 (22)	25 (18)	90 (23)	0.191
NYHA functional class III or IV, no. (%)	40 (8)	18 (13)	22 (6)	0.009
Atrial fibrillation,* no. (%)	86 (16)	23 (16)	63 (16)	0.989
Maximal LV wall thickness (mm)	20 ± 5	22 ± 4	19 ± 5	< 0.001
LV end-diastolic cavity dimension (mm)	46 ± 5	45 ± 5	46 ± 5	0.001
Left atrial dimension (mm)	44 ± 7	47 ± 6	43 ± 7	< 0.001
Treatment, no. (%)				
None	186 (35)	24 (17)	162 (42)	< 0.001
Beta-blockers	158 (30)	63 (45)	95 (25)	< 0.001
Calcium antagonists	164 (31)	58 (41)	106 (27)	0.004
Amiodarone	43 (8)	11 (8)	32 (8)	0.9
Diuretics	77 (15)	31 (22)	46 (12)	0.006

*Either paroxysmal or chronic.

HCM = hypertrophic cardiomyopathy; LV = left ventricular; NYHA = New York Heart Association.

Table 2. Incidence of Cardiac Death, Development of Severe Heart Failure, or Atrial Fibrillation During Follow-Up in HCM Patients With or Without LV Outflow Obstruction

Outcome	Patients With LV Outflow Obstruction		Patients Without LV Outflow Obstruction		Relative Risk (95% CI)	p Value
	No. of Patients (%)	Incidence per 100 Person-Yrs (95% CI)	No. of Patients (%)	Incidence per 100 Person-Yrs (95% CI)		
Cardiovascular death	15 (10.6)	2.40 (1.34-3.96)	19 (4.9)	1.11 (0.66-1.73)	2.14 (1.10-4.20)	0.02
Progression to NYHA functional class III to IV	24 (20.0)	4.44 (2.84-6.60)	30 (8.0)	1.87 (1.26-2.68)	2.40 (1.34-4.18)	0.002
Atrial fibrillation*	24 (20.0)	4.45 (2.85-6.62)	25 (8.0)	1.71 (1.11-2.52)	2.60 (1.44-4.61)	0.001

*Either paroxysmal or chronic.

CI = confidence interval; other abbreviations as in Table 1.

vascular mortality in patients with obstruction (relative risk [RR] 3.44, 95% confidence interval [CI] 0.92 to 12.81; $p = 0.06$). Incidence of cardiovascular death, severe heart failure, or AF was significantly higher in patients with obstruction (Table 2). At 10-year follow-up, cumulative risk of cardiovascular death, severe heart failure, or AF were, respectively, 27%, 34%, and 43% in patients with obstruction, and 9%, 15%, and 18% in those without obstruction (Figs. 1 to 3).

Analysis of mortality rates in patients with a different magnitude of outflow gradient (30 to 60 mm Hg in 73 patients, and >60 mm Hg in 68 patients) did not show any increase in the risk of cardiovascular death with increasing level of obstruction, with the incidence per 100 patient-years being 2.68% (95% CI 1.28 to 4.93) and 2.51% (95% CI 0.81 to 5.86), respectively, in the two groups.

Univariate and multivariate analyses. The results of the univariate and multivariate analyses are summarized in Table 3. In particular, in the multivariate model, outflow obstruction was associated with a 68% increase in cardiovascular death (hazard ratio [HR] 1.68, 95% CI 0.83 to 3.40), age showed borderline significance ($p = 0.07$), and wall thickness, NYHA functional class III to IV, and AF were strongly associated with cardiovascular mortality.

Of the 15 patients who died suddenly, 5 (33%) had extreme LV hypertrophy (maximal wall thickness ≥ 30 mm). At multivariate analysis, extreme wall thickness showed a strong association with sudden death (HR = 6.99, 95% CI 2.37 to 20.65; $p = 0.0001$).

Prognostic interaction between LV obstruction and other clinical features. In a multivariate Cox model, the appropriate interaction terms were introduced to assess whether the prognostic implications of LV obstruction were either more marked, or exclusively present in particular patient subgroups. Age, wall thickness, and AF did not modify the prognostic power of obstruction (test for interaction $p = 0.80$, $p = 0.92$, and $p = 0.91$, respectively) (Table 4). Conversely, a highly significant interaction was identified between prognostic power of obstruction and NYHA functional class at initial evaluation ($p = 0.024$). As a consequence of this interaction, LV obstruction remained a significant predictor of cardiovascular mortality only in patients in NYHA functional class I to II (HR = 2.38; $p = 0.025$).

The combined effect of LV obstruction and functional class on cardiovascular mortality was further evaluated by assessing the prognostic significance of obstruction after progression to NYHA functional class III to IV during follow-up. In patients who developed severe symptoms, obstruction lost any prognostic significance (HR = 1.18; $p = 0.66$), whereas NYHA functional class III to IV was associated with an eight-fold increase in risk of cardiovascular mortality (HR = 7.90; $p < 0.001$) (Table 4). The limited number of events precluded the application of these analyses to specific modes of cardiovascular death (heart failure, stroke, or sudden death).

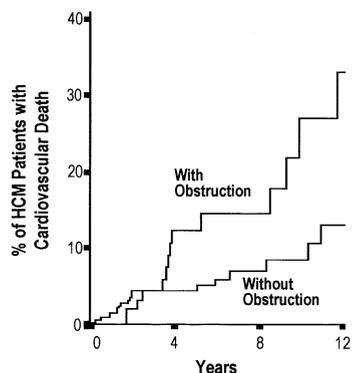


Figure 1. Kaplan-Meier estimates of the proportion of patients with or without left ventricular obstruction who died of cardiovascular causes, among the overall 526 hypertrophic cardiomyopathy (HCM) study patients.

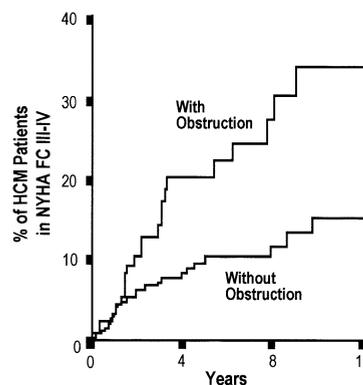


Figure 2. Kaplan-Meier estimates of the proportion of patients who progressed to New York Heart Association (NYHA) functional class (FC) III to IV, among the 486 patients with hypertrophic cardiomyopathy (HCM) in FC I or II at initial evaluation.

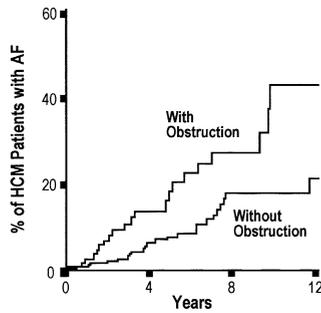


Figure 3. Kaplan-Meier estimates of the proportion of patients with or without left ventricular obstruction who developed either paroxysmal or chronic atrial fibrillation (AF), among the 440 hypertrophic cardiomyopathy (HCM) patients without AF at initial evaluation.

DISCUSSION

Our results confirm recent observations indicating that LV outflow obstruction is associated with an increased risk of progression to severe heart failure, AF, and cardiovascular death in patients with HCM (7). Our findings, however, show that the prognostic importance of outflow obstruction varies in relation to the severity of symptoms. At initial evaluation, LV obstruction was a significant predictor of prognosis only in patients with mild or no symptoms of heart failure (HR = 2.38), whereas it showed no predictive significance in patients in NYHA functional class III to IV.

We also evaluated the potential variations in the prognostic importance of LV obstruction in relation to progression of symptoms during follow-up. After development of severe heart failure, the outflow gradient lost its predictive significance, whereas NYHA functional class III or IV acquired a strong prognostic power associated with an eight-fold increase in risk of cardiovascular mortality. The results of this latter analysis suggest that outflow obstruction exerts its negative prognostic effect by favoring progression to severe functional limitation. Our analysis also showed that the prognostic power of obstruction is not influenced by

other features known as markers of morbidity and mortality in HCM, including AF, wall thickness, and age.

Clinical implications of findings. Myectomy operation or alcohol septal ablation by relieving the outflow gradient and usually associated mitral regurgitation decrease wall stress, myocardial ischemia, and left atrial size, and may lessen the risk of AF and stroke (1–3,8–10,15). At present, definitive evidence is lacking that such interventions prolong survival. Therefore, these procedures are principally recommended to improve quality of life in patients with severe symptoms, unresponsive to medical treatment (1–3,16). However, recent retrospective studies performed in large HCM populations suggest that surgery (myectomy operation) may reduce mortality (10,17).

In light of these recent surgical data, our findings that outflow obstruction loses its prognostic importance after development of severe heart failure raise the question of whether a more aggressive approach should be adopted in selected patients with obstructive HCM, without waiting for development of severe symptoms. An important difficulty would come from uncertainties regarding the appropriate candidates for early surgical intervention. A potential criterion could be the co-existence of all those clinical features considered most unfavorable for the long-term outcome of patients with obstructive HCM, including a young age, an outflow gradient under basal conditions, important mitral regurgitation, and a progressively dilating left atrium (1–3). However, the risks associated with septal myectomy (although low at centers with particular experience with this operation) impose caution, and additional evidence on the long-term outcome of surgery in patients with less severe symptoms is required before this treatment strategy can be generally adopted.

Additional observations. The cumulative risk of AF at 10 years after initial evaluation was more than two times higher in patients with LV obstruction. A clear trend was also identified toward an increased rate of death due to stroke in

Table 3. Univariate and Multivariate Relation Between Cardiovascular Mortality and Baseline Clinical Variables*

Variable	Univariate Analysis	Multivariate Analysis	Multivariate Analysis
	p Value†	p Value§	Hazard Ratio (95% CI)
Age	0.035	0.074	1.02 (1.00–1.04)
NYHA functional class (III to IV)	0.0001	0.022	3.07 (1.17–8.05)
LV outflow obstruction	0.022	0.146	1.68 (0.83–3.40)
Atrial fibrillation	0.0001	<0.001	4.33 (1.94–9.64)
LV wall thickness (mm)	0.004	<0.001	1.12 (1.05–1.20)
LV diastolic diameter (mm)	0.634	0.93	‡
Left atrial size (mm)	0.0001	0.61	‡
Gender	0.099	0.49	‡
Family history of sudden death	0.422	0.80	‡

*The subgroups for each variable were as follows: age was grouped in four classes, <20, 20 to 39, 40 to 59, and ≥60 years. New York Heart Association functional class was grouped in two classes: I to II vs III to IV. Wall thickness was grouped in four classes, <15, 15 to 19, 20 to 24, 25 to 29, and ≥30 mm. †Estimated from a Cox model in which the covariates were individually included one at a time. §Estimated from the final Cox model obtained by means of a step-down procedure, based on the likelihood ratio test, starting from the initial model in which all covariates were included. ‡Excluded from the final model. Abbreviations as in Tables 1 and 2.

Table 4. Modifying Effect (Interaction) of NYHA Functional Class, Atrial Fibrillation, LV Wall Thickness, and Age on the Prognostic Power of LV Outflow Obstruction

Variable	Hazard Ratio (95% CI)	p Value
Interaction of LV outflow obstruction with		
NYHA functional class	0.07 (0.01–0.70)	0.024
LV wall thickness		0.92
Atrial fibrillation		0.91
Age		0.80
Prognostic power of		
LV obstruction in NYHA functional class I to II patients	2.38 (1.12–5.09)	0.025
LV obstruction in NYHA functional class III to IV patients	1.18 (0.57–2.43)	0.66
Presence or development of NYHA functional class III to IV in patients with or without LV obstruction	7.90 (3.72–16.79)	<0.001

A multivariate Cox model was fitted to the data, and the potential influence of other variables on the prognostic power of the outflow gradient was investigated by introducing into the model the appropriate interaction terms. *All p values are derived from the likelihood ratio test. For variables with more than two groups, p values refer to the test of the trend of increasing (or decreasing) risk across the categories of the variable.

Abbreviations as in Tables 1 and 2.

patients with a gradient. These findings confirm previous observations suggesting that obstruction favors a cascade of complications, including left atrial dilatation, AF, and embolic stroke (12,18). In addition, in agreement with previous studies, magnitude of LV hypertrophy was independently and directly related to cardiovascular mortality (11,19). In particular, extreme wall thickness (≥ 30 mm) was associated with a more than five-fold increase in sudden death risk.

Conclusions. Our results show that the prognostic importance of LV outflow obstruction in HCM is strongly influenced by the severity of symptoms of heart failure. In patients with mild or no symptoms, outflow obstruction is a predictor of cardiovascular death. However, after development of severe symptoms, NYHA functional class becomes the dominant marker of prognosis, independent of the presence or absence of a gradient. These findings, together with recent observations suggesting that myectomy operation prolongs survival, raise the question of whether surgery should be performed in selected patients with outflow obstruction, without waiting for the development of severe symptoms. Additional data on the risk-versus-benefit ratio are required, however, before this novel approach can become a generally accepted strategy.

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