ORIGINAL ARTICLE

Long-term Outcome of Patients with Hypertrophic Cardiomyopathy

Evolución a largo plazo de pacientes con miocardiopatía hipertrófica

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ABSTRACT

Background: Hypertrophic cardiomyopathy is a complex disease that for years has been associated with high rates of morbidity and mortality. However, most of the available information on its outcome is based on data generated from centers including selected, mainly high risk patients.
Objective: The purpose of this study was to evaluate the rate of events at follow-up of patients with hypertrophic cardiomyopathy in our setting.
Methods: A retrospective cohort of patients with hypertrophic cardiomyopathy was studied, assessing functional class and clinical event occurrence from echocardiographic and cardiac magnetic resonance imaging studies.
Results: A total of 259 patients with median follow-up of 3.5 years (2-10) were included in the study. Mean age was 56±16.8 years and 38.2% had obstructive forms of the disease. Sixty-seven percent of patients were in functional class I at follow-up onset. During the follow-up period, overall mortality rate was 1.6% with 1.1% sudden death or appropriate defibrillator shock and 6.6% of patients developed atrial fibrillation. The rate of in-hospital admission for acute heart failure was 5.8% and 14.3% of patients had functional class worsening. A total of 22 alcohol septal ablation and 15 myectomy procedures were performed with significant symptom improvement.
Conclusions: Follow-up of patients with hypertrophic cardiomyopathy showed low morbidity and mortality rate. The main adverse event was functional class worsening, followed by the development of atrial fibrillation and heart failure, with a low rate of sudden death.

Key words: Hypertrophic Cardiomyopathy - Prognosis - Follow-up Study - Atrial Fibrillation

RESUMEN

Introducción: La miocardiopatía hipertrófica es una enfermedad compleja que se ha asociado durante años con tasas altas de morbimortalidad. Sin embargo, mucha de la información que tenemos en relación con su evolución proviene de centros en los que se incluyeron pacientes seleccionados, principalmente de riesgo alto.
Objetivo: Evaluar los eventos en el seguimiento de pacientes con miocardiopatía hipertrófica en nuestro medio.
Material y métodos: Se evaluó una cohorte retrospectiva de pacientes con diagnóstico de miocardiopatía hipertrófica. Se analizó la evolución de la clase funcional junto con la ocurrencia de eventos clínicos. Se recabaron datos del ecocardiograma y de la resonancia magnética cardíaca.
Resultados: Se incluyeron 259 pacientes, con una mediana de seguimiento de 3,5 años (2-10). La edad promedio fue de 56 ± 16,8 años y el 38,2% de los pacientes tenían formas obstructivas de la enfermedad. Al inicio del seguimiento, el 67% se encontraban en clase funcional I. En la evolución, la mortalidad global fue del 1,6%, con el 1,1% de muerte súbita o choque apropiado de desfibrilador y el 6,6% de los pacientes presentaron fibrilación auricular. La tasa de internación por insuficiencia cardíaca resultó del 5,8% y en el 14,3% de los pacientes empeoró la clase funcional. Se realizaron 22 procedimientos de ablación septal y 15 miectomías, con mejoría significativa de la sintomatología.
Conclusiones: El trabajo muestra que en el seguimiento de esta cohorte de pacientes con miocardiopatía hipertrófica la tasa de morbimortalidad fue baja; el principal evento adverso fue el empeoramiento de la clase funcional, seguido por el desarrollo de fibrilación auricular y la insuficiencia cardíaca, con una tasa baja de muerte súbita.

Palabras clave: Miocardiopatía hipertrófica - Pronóstico - Estudios de seguimiento - Fibrilación auricular

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Abbreviations

FC	Functional class	**ICD**	Implantable cardioverter defibrillator
HCM	Hypertrophic cardiomyopathy	**NYHA**	New York Heart Association

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most frequent genetic heart disease, with an estimated prevalence of 1 case per 500 inhabitants. (1) It is a complex entity, presenting at different ages and with different clinical manifestations, with patients who spend their whole life asymptomatic and others who progress with dyspnea, heart failure, atrial fibrillation, stroke and even sudden death.

There is discordant information on its natural evolution depending on the reporting centers. In general, historical data come from centers mainly involving high-risk patients referred for invasive procedures, which could overestimate the risk of complications and prognosis, as they concern more complex patients.

For this reason, the aim of our study was to evaluate the clinical outcome and the presence of functional class (FC) progression predictors in a population of patients with HCM from a center that receives both referral patients and outpatients from the same center with close follow up through a Cardiomyopathy Unit.

METHODS

Clinical histories of patients with HCM followed-up at the Cardiomyopathy Unit of the Instituto Cardiovascular de Buenos Aires were analyzed from 1997 to the present.

Clinical, electrocardiographic, echocardiographic and medication data were collected, as well as family history of the disease.

Patients were clinically evaluated at the Cardiomyopathy Unit of our center, where a clinical cardiologist established the FC according to the New York Heart Association (NYHA) classification.

The diagnosis of HCM was performed following international guideline recommendations, as the presence of ventricular hypertrophy in the absence of cardiac or systemic cause to justify it. The morphological types were defined by Doppler echocardiography. Septal asymmetric HCM was considered when the interventricular septum thickness was ≥15 mm and the ratio ≥1.5 with respect to the inferolateral wall. Apical HCM was defined for thickness ≥15 mm at the apical segment level, with ratio ≥1.5 ratio with respect to basal segments, and obstructive HCM when the maximum baseline gradient obtained by Doppler echocardiography was ≥30 mmHg. (2)

Two-dimensional echocardiography was used to define maximum myocardial thickness, hypertrophy distribution, atrial diameter measured in the long parasternal axis and atrial area measured from the apical four-chamber view. The study of diastolic function was based on the analysis of diastolic mitral flow and the velocity of longitudinal cardiac fibers assessed by tissue Doppler imaging. Mitral regurgitation was evaluated by color Doppler echocardiography and quantitatively graded as mild, moderate, moderate-severe and severe. (3) Presence of dynamic obstruction and maximum gradient, calculated by the Bernouilli equation were also evaluated. (4, 5) Early diastolic peak velocity analysis was performed at the septal and lateral annulus, as the average of these two values. The ratio between mitral E wave velocity and tissue Doppler e' wave velocity (E/e') was calculated. (6)

Cardiac magnetic resonance imaging was performed, as well as laboratory tests to rule out Fabry's disease and other diseases mimicking HCM, and even an endomyocardial biopsy.

Exercise echocardiography was indicated to all patients able to perform it, to evaluate blood pressure behavior, exercise arrhythmias, gradients, wall motion and mitral regurgitation. (5)

Patient retrospective follow-up was performed through electronic clinical records and whenever necessary, by telephone contact or personal interview. The follow-up purpose was to record events and patients' clinical outcome. All patients underwent at least one 24-hour electrocardiographic Holter monitoring study every year.

The following events were defined: all-cause death, cardiovascular death, non-cardiovascular death, atrial fibrillation, ventricular tachycardia, sudden death, implantable cardioverter defibrillator (ICD) insertion, pacemaker implantation, appropriate and inappropriate ICD shocks, septal myectomy, alcohol septal ablation, hospitalization for acute heart failure, heart transplantation and stroke.

Functional class worsening was defined as dyspnea and angina deterioration, regardless of the symptom limiting physical capacity.

Statistical analysis

Discrete variables were expressed as percentages and continuous variables, according to their distribution, as mean or median with their corresponding standard deviation or interquartile range. The Kolgomorov Smirnov test was used to define normal sample distribution. Discrete variables were compared with the chi-square test and continuous variables using Student's t test or the Mann-Whitney test according to sample distribution. The t test or the Kruskal-Wallis test for multiple samples was used for multiple comparisons. A two-tailed p value <0.05 was considered as statistically significant. Logistic regression analysis was performed to detect predictors, and variables with $p \leq 0.10$ in the univariate analysis entered a multivariate analysis. ROC curves were used to define sensitivity and specificity of continuous variables and Kaplan Meier curves to define the follow-up median. All the data were analyzed with SPSS 21 IBM software package.

Ethical considerations

The Institutional Ethics and Teaching Committee approved the study, in compliance with the declaration of Helsinki principles.

RESULTS

The study included 259 patients with a median follow-up period for all the events of 3.5 years. (2-10) Mean

age was 56±16.8 years and 67% were men (Table 1). In order of prevalence, the septal obstructive form represented 35% of cases, same as the septal non-obstructive form, followed by the apical form with 27% of cases. In the overall analysis, 38.2% of the patients presented with dynamic obstruction at follow-up initiation. Two hundred and fifty patients underwent exercise echocardiography, and only 6 of them evidenced abnormal blood pressure behavior

Regarding symptoms, 67% of the patients were asymptomatic at follow-up onset, while the rest presented with dyspnea (25%), chest pain (10%), or either of them (33%). Ten percent of the population had family history of sudden death, only 1.2% had ICD implantation and only 4 patients had undergone prior septal ablation o myectomy at other institutions. Fifty-five percent of the patients were treated with betablockers, 19.32% with calcium blockers and 5.43% with amiodarone and anticoagulation.

Follow-up analysis showed that overall mortality was 1.6%, with 0.81% of cardiovascular origin and only 1 patient presenting sudden death, though another 2 received appropriate ICD shocks (Table 2).

During follow-up, 6.6% of the study population developed atrial fibrillation. All patients received anticoagulation and one episode of stroke and two episodes of peripheral embolism were recorded. The rate of admission for heart failure was 5.8% and 1 patient required heart transplantation. Fifteen ICDs were implanted with two resynchronization devices, all as primary prevention.

Functional class worsened in 14.3% of the patients with 17% attaining FC III-IV, and 52% remained asymptomatic. This led to 22 septal ablation procedures and 15 myectomies were performed, which significantly improved the FC of these patients (p=0.011 for ablations and p=0.022 for myectomies) (Figures 1 and 2). (7) At the end of the follow-up period, and after the invasive procedures, 32% of the patients were asymptomatic, with only 7 patients in FC III-IV, 3 for refusing myectomy or ablation procedures and 4 for ventricular dysfunction with heart failure. The univariate analysis of factors related to FC deterioration showed association among female gender, left ventricular outflow tract obstruction, maximum septal thickness, left atrial enlargement, dynamic gradient, E/e' ratio and pulmonary artery systolic pressure (Table 3). In the multivariate analysis, LV outflow tract obstruction (OR 3.76, 95% CI 1.18-11.89) and maximum septal thickness (OR 1.23, 95% CI 1.09-1.38) were statistically significant. The ROC curve for gradient was 0.747 with a cut-off point of 19.5 mmHg, 71% sensitivity and 69% specificity. The ROC curve for thickness was 0.683, with a cut-off point of 17.5 mm, 82.82% sensitivity and 51.51% specificity.

Table 1. Baseline population characteristics.

Variable	n=259
Age, years	56 ±16
Male gender, %	67
HTN, %	31
Prior AMI, %	2.71
Diabetes %	5.42
Chronic kidney failure (CrCl<60 ml/min), %	5
AF, n (%)	14 (5.4)
Form, n (%)	
Septal obstructive	92 (35.5)
Septal non-obstructive	91 (35.1)
Apical	70 (27)
Medioventricular	4 (1.5)
Concentric	2 (0.8)
Maximum gradient, mmHg	12 (10-44)
Functional class, n (%)	
I	173 (67)
II	62 (24)
III-IV	24 (9)
Syncope, %	23 (8.9)
EF, %	64 (60-68)
Maximum thickness by echocardiography, mm	18 (16-20)
Maximum thickness by magnetic resonance, mm	17.5 (15-21)
LA diameter, mm	38 (28-48)
LA area, cm2	23 (20-28)
MR, n (%)	
I. Mild	88 (34)
II. Moderate	20 (7.7)
III. Moderate-severe	12 (4.6)
IV. Severe	5 (1.9)
E wave, m/seg	85 (45-110)
A wave, m/seg	50 (31-72)
E/A ratio	1.10 (0.8-1.3)
E/e' ratio	10 (8-15)
Positive late gadolinium enhancement (n=180),	47/180 (26)
n (%)	
Obstructive, n (%)	99 (38.2)
Abnormal blood pressure behavior (n=250), n (%)	6/250 (2.4)
Family history of sudden death, n (%)	26 (10)
Prior ICD, n (%)	3 (1.2)
Prior ablation, n (%)	2 (0.8)
Prior myectomy, n (%)	2 (0.8)

HTN: Hypertension. AMI: Acute myocardial infarction. CrCl: Creatinine clearance. AF: Atrial fibrillation. EF: Ejection fraction. LA: Left atrial. MR: Mitral regurgitation. ICD: Implantable cardioverter defibrillator

DISCUSSION

This study shows that in the close follow-up of a cohort of HCM patients, the morbidity and mortality rate was low, with FC worsening as the main event, followed by the development of atrial fibrillation and heart failure. On the other hand, the rate of sudden death was very low.

Since its original description more than 40 years ago, HCM has been associated with increased risk of early sudden death and morbidity, with high rates,

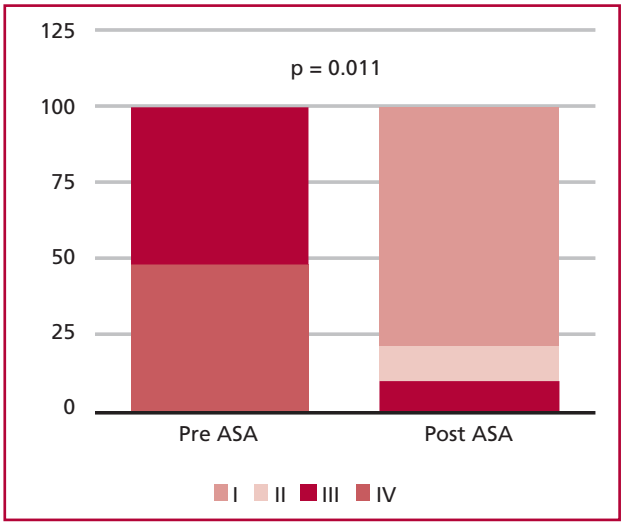

Fig. 1. Functional class improvement with alcohol septal ablation (ASA)

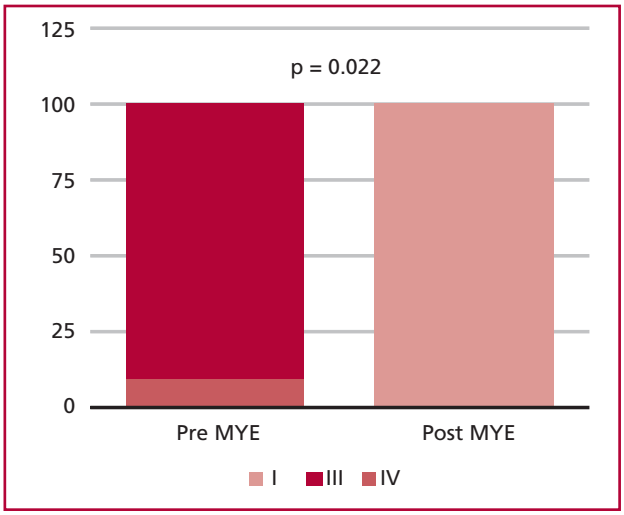

Fig. 2. Functional class improvement post myectomy (MYE)

Table 2. Follow-up events

Variable	n=259
AF at follow-up, n (%)	17 (6.6)
Heart failure, n (%)	15 (5.8)
Overall death, n (%)	4 (1.6)
Sudden death or appropriate shock, n (%)	3 (1.2)
Cardiovascular death, n (%)	2 (0.8)
ICD at follow-up, n (%)	16 (6.2)
Stroke at follow-up, n (%)	1 (0.4)
Functional class worsening, n (%)	37 (14.3)
Septal ablation, n (%)	22 (8.5)
Myectomy, n (%)	15 (5.8)
Heart transplantation, n (%)	1 (0.4)

AF: Atrial fibrillation. ICD: Implantable cardioverter defibrillator.

close to an annual mortality rate of 3-6%. However, we understand that this information was obtained from centers mostly with referral patients, which carries a bias selection, as they are higher risk patients. When analyzing more updated information, with a less selected cohort of patients and with current pharmacological and non-pharmacological treatments, sudden death figures are around 0.5% per year. (8) In our work, the rates were also low.

Dyspnea upon exertion is the most common symptom in patients with HCM, occurring in 90% of symptomatic patients as reported in most series. (9) There are multiple mechanisms leading to it: increased myocardial stiffness, intraventricular dynamic obstruction, mitral regurgitation, supraventricular arrhythmias and, in fewer cases, systolic failure. Dyspnea progression to NYHA class III-IV occurs in a very low proportion of HCM patients and this entails worse prognosis. (10-12) In their study of the Minnesota population, Maron et al. found that, with a mean follow up of 8.1 years, 25% of the population worsened their FC, with 14% developing FC III-IV. (13) In our work, the percentage of patients with exacerbated dyspnea was similar, and the associated parameters were left ventricular outflow tract obstruction and maximum septal thickness, as reported in previous studies. (14-16) We understand that obstruction is an important conditioning factor of increased left ventricular end-diastolic pressure, while ventricular hypertrophy causes diastolic failure. In these patients, the decrease of obstructive gradient, either by pharmacological or invasive methods such as myectomy or alcohol septal ablation, was associated with a substantial improvement of symptoms and life expectancy. (17-21) In this regard, we believe it is important to have a multidisciplinary working team to allow deciding the best treatment option for each patient.

Regarding the development of atrial fibrillation, the reported prevalence is 4 to 6 times greater than in the general population of the same age. (22) The incidence found in our population is similar to that reported by Elliot et al. who in the literature review found an annual incidence of 3.08%. (23) The development of this arrhythmia has direct impact on morbidity and mortality, as revealed in the work of Olivotto et al., where patients with atrial fibrillation had lower follow-up survival and higher rate of hospital admissions at the expense of more episodes of heart failure and embolic events, but not of sudden death. (17)

Limitations

Since this is a retrospective study we were exposed to biases in data collection, although the fact that all patients were followed up in the same center by a selected group of cardiologists reduces that possibility.

It is important to highlight that all the data reported in the study represents the evolution of a group of closely monitored patients at an institution with excellent results in invasive treatments, which differs

Table 3. Factors associated to functional class worsening. Univariate analysis

Variable	With symptom worsening n=37	Without symptom worsening n=222	p
Age, years	59 ±17	56 ±16	0.196
Male gender, n (%)	13 (35)	160 (72)	0.001
Obstructive, n (%)	26 (72)	73 (32)	0.001
AF, n (%)	2 (5.4)	12 (5.4)	0.980
Form, n (%)			0.001
Septal obstructive	32 (86,3)	60 (27)	
Septal non-obstructive	4 (11)	87 (39)	
Apical	0	70 (31)	
Concentric	0	2 (0.9)	
Medioventricular	1 (2.70)	3 (2.1)	
Maximum thickness, mm	19 (18-24.5)	17 (15-20)	0.001
LA area, cm2	27 (24-30)	22 (19-27)	0.001
Maximum gradient, mmHg	57 (15.5-75)	10 (10-30)	0.001
E/e'	15 (13-19)	9.5 (7-14)	0.001
EF, %	62 (59-68)	64 (60-68)	0.885
PASP, mmHg	35 (29-45)	30 (26-32)	0.004

AF: Atrial fibrillation. La: Left atrial. EF: Ejection fraction. PASP: Pulmonary artery systolic pressure

from the natural evolution of the disease. (7)

For reasons of availability, a genetic test was conducted in only a small number of our patients.

CONCLUSIONS

Based on data obtained from patients of our institution, we can confirm that most present with a benign, asymptomatic or with mild limitation evolution, with very rare sudden death. The development of atrial fibrillation in this population is worrying and close attention to its diagnosis and treatment should be paid in order to prevent cardioembolic events. In the cases where progression of symptoms occurs, medical treatment associated with invasive treatment, selecting the best option case by case, improves patients' FC.

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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