ORIGINAL ARTICLE

Role of Stress Echo on the Prognosis of Hypertrophic Cardiomyopathy

Rol del eco estrés en el pronóstico de la miocardiopatía hipertrófica

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ABSTRACT

Background: Patients with hypertrophic cardiomyopathy (HCM) frequently present with confusing and misleading symptoms. In these instances stress tests may help to stratify the risk of future events.

Objective: The purpose of this study was to assess the prognostic usefulness of the different variables obtained with exercise stress echo (ESE) in patients with HCM.

Methods: A retrospective and observational study was performed in 110 patients evaluated with ESE. Patients were divided into 3 groups according to their left ventricular outflow tract obstruction level (LVOTO): 1) persistent LVOTO (peak instantaneous gradient at rest obtained by continuous Doppler ≥ 30 mmHg), 2) latent LVOTO (gradient ≥ 50 mmHg with exercise); and no LVOTO.

Median follow-up was 2.7 years. The primary endpoint was the composite of death, sudden death, sustained ventricular tachycardia or hospitalization for heart failure.

Results: Persistent LVOTO was present in 19.1% of cases, latent LVOTO in 31.8% and no LVOTO in 49.1%. Ventricular function, wall thicknesses and diameters were similar for the three groups. Poor prognostic variables were significantly higher for persistent LVOTO. The latent LVOTO group developed more symptoms, electrocardiographic changes and mitral regurgitation after exercise than the group without LVOTO, although it was not associated with a higher number of events.

Variables that were associated with increased rate of events during follow-up were the presence of gradient ≥ 30 mmHg at rest ($p=0.07$), electrocardiographic changes during the test ($p=0.020$) and the inverse relationship of METs ($p=0.07$).

Conclusions: Patients with HCM who achieved a high exercise capacity, expressed as METs ≥ 7, showed excellent mid- to long-term outcomes. LVOTO at rest and electrocardiographic changes during maximal stress exercise were associated with an increased number of events during follow-up.

Key words: Ventricular Outflow Obstruction - Cardiomyopathy, Hypertrophic - Hypertrophy, Left Ventricular - Echocardiography, Stress - Exercise Test - Prognosis

RESUMEN

Introducción: Los pacientes con miocardiopatía hipertrófica (MCH) presentan con frecuencia síntomas confusos y equívocos. En estas instancias, las pruebas de esfuerzo pueden ayudar a la estratificación de riesgo de eventos futuros.

Objetivo: Evaluar el valor pronóstico de las diferentes variables obtenidas mediante el eco estrés con ejercicio (EEE) en pacientes con diagnóstico de MCH.

Material y métodos: Estudio retrospectivo y observacional. Se evaluaron 110 pacientes mediante EEE, los cuales se dividieron según el grado de obstrucción a nivel del tracto de salida del ventrículo izquierdo (OTSVI) en: 1) OTSVI persistente (gradiente máximo instantáneo obtenido en reposo mediante Doppler continuo ≥ 30 mm Hg), 2) OTSVI latente (gradiente ≥ 50 mm Hg ante el ejercicio) y 3) sin OTSVI.

La mediana de seguimiento fue de 2,7 años. Se definió punto final primario a la ocurrencia de muerte, muerte súbita, taquicardia ventricular sostenida o internación por insuficiencia cardíaca.

Resultados: El 19,1% de los pacientes presentaron OTSVI persistente, el 31,8% OTSVI latente y el 49,1% no presentaban OTSVI. La función ventricular, los espesores parietales y los diámetros fueron similares para los tres grupos. Las variables de mal pronóstico fueron significativamente mayores para la OTSVI persistente. El grupo con OTSVI latente desarrolló más síntomas, alteraciones electrocardiográficas e insuficiencia mitral posejercicio que el grupo sin OTSVI, aunque no se asoció con un número mayor de eventos.

Las variables que se asociaron con más eventos en el seguimiento fueron la presencia de gradiente ≥ 30 mm Hg en reposo ($p = 0,07$), alteraciones electrocardiográficas durante la prueba ($p = 0,020$) y los MET en su relación inversa ($p = 0,07$).

Conclusiones: Los pacientes con MCH que alcanzaron una alta capacidad de ejercicio, expresada como MET ≥ 7, presentaron excelentes resultados a mediano-largo plazo. La OTSVI en reposo y los cambios del electrocardiograma durante el esfuerzo máximo se asociaron con más eventos en el seguimiento.

Palabras clave: Obstrucción del flujo ventricular externo - Miocardiopatía hipertrófica - Hipertrofia ventricular izquierda - Ecocardiografía Doppler - Ecocardiografía de estrés - Prueba de esfuerzo - Pronóstico

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Abbreviations

ABPBE	Abnormal blood pressure behavior during exercise	**LVOTO**	Left ventricular outflow tract obstruction
ECG	Electrocardiogram	**LVEF**	Left ventricular ejection fraction
ESE	Exercise stress echo	**MET**	Metabolic equivalent
FC	Functional Class	**MR**	Mitral regurgitation
GXT	Graded exercise test	**NYHA**	New York Heart Association
HCM	Hypertrophic cardiomyopathy		

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic disease, with a prevalence of approximately 0.2%. (1-3) The range of its natural evolution varies from asymptomatic to stages of progressive and terminal heart failure. (1-4)

Disease progression is partly due to diastolic dysfunction, mitral regurgitation (MR) and left ventricular outflow tract obstruction (LVOTO) at rest, resulting in decreased functional capacity, progression to heart failure, systolic function impairment and death. (5-6)

Patients with HCM often present confusing and misleading symptoms. In these instances, stress tests may help to stratify risk of future events.

The purpose of this study was to determine the prognostic value of the different variables obtained by exercise stress echo (ESE) in a population of patients diagnosed with HCM in Argentina.

METHODS

Study Population

The diagnosis of HCM was performed by cardiologists, according to current guidelines, based on clinical and electrocardiographic findings and on echocardiographic or cardiac magnetic resonance demonstration of wall thickness >15 mm in the absence of hypertension or other abnormal loading conditions that might produce that degree of hypertrophy in any segment. (1-3)

Among a total of 786 patients diagnosed with HCM who are followed-up at our institution, 191 patients were excluded due to follow-up discontinuation. Patients with left ventricular ejection fraction (LVEF) ≤50%, NYHA functional class (FC) ≥II, moderate-severe MR, under 16 and over 75 years of age, with motor disorders (due to previous stroke) and patients with known history of concomitant symptomatic coronary disease were also excluded.

This was a retrospective observational study with 128 patients evaluated with ESE. Sixty seven patients had been previously excluded for presenting ESE from other centers with incomplete data. Another 18 patients were additionally excluded for having been previously treated with surgery, alcohol septal ablation, or pacemaker or cardioverter defibrillator implantation. Thus, 110 patients remained for the analysis who were divided into three groups: a group with persistent LVOTO (peak instantaneous gradient at the left ventricular outflow tract level obtained at rest by continuous Doppler ≥30 mmHg); a second group with latent LVOTO (gradient ≥50 mmHg at the level of the left ventricular outflow tract with exercise); and finally a third group with no obstruction. Clinical, ergometric, and echocardiographic variables between groups were compared. The clinical variables compared were age, gender, family history of heart disease, history of hypertension, syncope, nonsustained ventricular tachycardia on Holter monitoring, atrial fibrillation, pharmacological treatment, beta-blocker treatment, anticoagulation, and pacemaker and cardioverter defibrillator implantation. The echocardiographic variables compared at rest were ejection fraction, interventricular septum and posterior wall thickness, LVOT gradient and left atrial anteroposterior diameter.

Procedure

The echocardiographic studies were performed with a Hewlett Packard Sonos 5500 ultrasound imaging system (HP, Andover, Massachusetts, USA). Images were obtained with patients in left lateral decubitus position. Ventricular and atrial dimensions and the maximum velocity at the level of the left ventricular outflow tract were measured with continuous Doppler (7), at baseline and during the pressure phase of the Valsalva maneuver. The gradients were estimated using the simplified Bernoulli equation. Systolic anterior motion and regional wall motion disorders were assessed.

All measurements were performed according to the guidelines of the American Society of Echocardiography. (8)

Exercise stress echo

The studies were conducted in a treadmill with Bruce protocols. During exercise the following variables were assessed: deficient performance of graded exercise test (GXT), submaximal GXT, double-product and maximum heart rate achieved, changes in electrocardiogram (ECG) during the test, blood pressure responses, atrial or ventricular arrhythmias, presence of symptoms on exertion and metabolic units estimated in MET. Left ventricular ejection fraction, motility disorders, MR and LVOTO were evaluated immediately after exertion.

Electrocardiographic recordings were taken at each stage of treadmill exercise according to the GXT guidelines of the American Society of Sports Medicine at rest and in the first, third and sixth minute of recovery. Abnormal ECG was considered for ST-segment depression ≥2 mm in patients with leveled ST at baseline ECG or ST-segment depression ≥4 mm in patients with baseline ST-segment depression. (9)

Criteria for test interruption were muscular exhaustion, severe arrhythmias, reactive hypertension (systolic pressure ≥240 mmHg or diastolic pressure ≥110 mmHg), and hypotension with exercise or limiting symptoms. Abnormal blood pressure behavior during exercise (ABPBE) was defined as blood pressure increase ≤25 mmHg or decrease ≥10 mmHg during exercise.

Endpoints

The primary endpoint was the presence of death, sudden death, sustained ventricular tachycardia or hospitalization for heart failure during follow-up. Sudden death included resuscitated sudden death and proper discharge of cardioverter defibrillator in case it was implanted after ESE completion.

Patients with implantable cardioverter defibrillator prior to the study were excluded from the study.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and comparisons between groups were made using the Mann-Whitney test when two groups were compared, and the Kruskall-Wallis test when 3 groups were compared (the post-hoc Conover test was used if the difference was significant). Dichotomous and ordinal variables were expressed as integers (percent of total) and compared with the chi-square test (using the post-hoc z test if the difference between groups was significant) or Fisher's exact test as appropriate. Survival curves (freedom of events) were built with variables showing significant differences on univariate analysis (Kaplan-Maier). The curves were compared using the log-rank test (Mantel-Cox). Data were analyzed using SPSS Statistics version 21 (IBM Corp, Chicago, Illinois) software package.

Ethical considerations

This work was approved by the Bioethics Committee of the Hospital Universitario Fundación Favaloro. Follow-up was conducted by clinical visits, review of medical records or telephone interviews. All patients gave verbal consent to use the data for analytical and anonymous study purposes.

RESULTS

In the total study population, 19.1% of patients presented with persistent LVOTO, 31.8% latent LVOTO and 49.1% no LVOTO. The persistent LVOTO group showed differences with respect to the other two groups in some evaluated clinical variables; they were older, presented with higher percentage of hypertension and received more pharmacological treatment (Table 1). No significant differences were found in other clinical variables between groups. Median baseline gradient was 58 mmHg in patients with persistent LVOTO, 15 mmHg in patients with latent LVOTO and 9 mmHg in those with no LVOTO.

Variables associated with poor prognosis in the stress test were significantly higher for patients with persistent LVOTO. These patients presented with more symptoms (referred to as angina or dyspnea) and ECG changes; they reached lower double-product at maximal exercise and higher incidence of moderate to severe MR at the end of the test with respect to the other two groups (Table 2). Univariate analysis findings are shown in Table 3.

The difference found in the MET values achieved is remarkable. Patients with persistent LVOTO reached a median of 7.9 METs, with latent LVOTO 12 METs,

Table 1. Baseline population characteristics according to left ventricular outflow tract obstruction

	Persistent LVOTO	Latent LVOTO	No LVOTO	p
n	21	35	54	
Gender (M), %	52	82	72	0.061
Age, years	55 (46-64)	42 (34-52)	46 (31-59)	0.066
History of disease				
HTN, %	43	24	13	0.031
Risk factors, syncope, %	19	9	9	0.478
Family history of heart disease, %	10	27	22	0.251
NSVT (Holter), %	10	9	11	0.936
AF/AF (OAC), %	19	9	6	0.233
Treatment				
Pharmacological treatment, %	90	79	64	0.046
Betablockers, %	70	67	53	0.272
Pacemaker , %	0	3	2	0.619
Implantable cardioverter defibrillator, %	10	15	11	0.824
OAC, %	15	9	9	0.769
Baseline echocardiogram				
Baseline EF	65 (60-69)	66 (61-70)	65 (60-68)	0.18
IVS	19 (17-22)	18.3 (16-26)	19 (16-22)	0.79
PW	13 (12-15)	12 (10-13)	11.9 (10-13)	0.124
LA (mm)	46.7 (42-51)	42 (39-46)	43 (38-48)	0.128
Peak baseline intraventricular gradient	58 (33-94)		9 (7-12)	< 0.0001

Values expressed as percentage or median. The interquartile range (0.25 to 0.75) is indicated in parentheses LVOTO: Left ventricular outflow tract obstruction. n: Number of patients. M: Male. HTN: Hypertension. NSVT: Nonsustained ventricular tachycardia. AF/AF: Atrial fibrillation/Atrial flutter. OAC: Oral anticoagulation. EF: Ejection fraction. IVS: Interventricular septum. PW: Posterior wall. LA: Left atrium.

and those that did not present obstruction 13 METs (with no difference between the latter two groups in post-hoc analysis).

When patients with latent LVOTO and with no LVOTO were compared, it was seen that patients with latent LVOTO significantly presented with more symptoms, ECG changes, and higher post-exercise MR, although these findings were not associated with greater number of events during the follow-up period.

When freedom of events according to the presence of gradient ≥30 mmHg at rest was compared with gradient ≤30 mmHg, the curves separated very early, even before 6 months, with the presence of significant gradient at rest associated with worse prognosis, (p=0.07) (Figure 1 A). When the evolution of the three groups of patients according to LVOTO were compared, no differences were found between the curves of latent LVOTO and no LVOTO (p=0.375). Conversely, there were differences in the freedom of events between the group with persistent LVOTO compared with latent LVOTO (p=0.026) and no LVOTO (p=0.02) groups (Figure 1 B), evidencing early curve separation.

The functional capacity achieved during the test was associated with greater freedom of events. Completing at least ≥7 METs during the test was associated with a better prognosis compared to patients who did not reach this value (Figure 1 C).

Electrocardiographic changes during the test (presence of ST-segment depression) were also associated with higher number of events during follow-up (p=0.020) (Figure 1 D).

Only 4 patients presented wall motion disorders.

Table 2. Stress-echo variables according to left ventricular outflow tract obstruction

Stress-echo	Persistent LVOTO	Latent LVOTO	No LVOTO	p
Deficient GXT, %	57	37	33	0.164
Submaximal GXT, %	14	3	6	0.268
Post exercise TTI	17,160	25,950	24,805	0.004
	(15,210-23,630)	17,200-30,440	(21,035-28,630)	
Post exercise HR, bpm	123 (113-143)	155 (118-174)	154 (136-171)	0.011
ECG changes, %	48	37	17	0.012
Arrhythmias, %	1	6	0	0.054
ABPBE, %	1	0	6	0.116
Symptoms, %	57	31	17	0.002
MET	7.9 (6-10)	12 (8-13)	13 (8-16)	0.002
Post exercise EF, %	70 (63-75)	75 (68-79)	70 (65-75)	0.106
Post exercise MR (> 1), %	86	71	28	< 0.001
Peak post-exercise gradient*	116 (92-165)	78 (56-107)	20 (12-23)	< 0.001

Values expressed as percentage or median. The interquartile range (0.25 to 0.75) is indicated in parentheses LVOTO: Left ventricular outflow tract obstruction level. GXT: Graded exercise test. TTI: Tension–time index. HR: Heart rate. bpm: Beats per minute. ECG: Electrocardiogram. ABPBE: Abnormal blood pressure behavior during exercise. MET: Metabolic equivalent. EF: Ejection fraction. MR: Mitral regurgitation. * Peak post-exercise gradient in the left ventricular outflow tract.

Table 3. Univariate analysis of stress echo variables

Stress-echo	NO (n=95) n (%)	YES (n=10) n (%)	p
Baseline gradient* >30 mm Hg	15 (15.8)	6 (60)	0.001
Post-exercise gradient** >50 mm Hg	43 (45.3)	8 (80)	0.037
Deficient GXT	34 (35.8)	7 (70)	0.045
Arrhythmia	4 (4.2)	0 (0)	0.500
ABPBE	3 (3.2)	0 (0)	0.170
Post exercise MR III/IV	15 (12.8)	4 (40)	0.059
Symptoms	24 (25.3)	6 (60)	0.021
ECG changes	25 (26.3)	6 (60)	0.026
MET >7	90 (94)	5 (50)	0.003

* Peak baseline gradient in the left ventricular outflow tract. ** Peak post-exercise gradient in the left ventricular outflow tract. GXT: Graded exercise test. ABPBE: Abnormal blood pressure behavior during exercise. MR: Mitral regurgitation. ECG: Electrocardiogram. MET: Metabolic equivalent.

They were evaluated with cardiac catheterization and in one patient only significant coronary lesions were documented.

DISCUSSION

This study demonstrates the added value of MET as a finding of great importance in assessing the functional capacity of these patients, since it unmasks their real risk. Effectively, the limit functional capacity expressed in METs was a predictor of events during follow-up. Patients who made an effort equal to or greater than 7 METs had better outcome despite being minimally symptomatic (NYHA FC I).

In a recently published study (10), it was found that if patients achieved 100% of the predicted METs for age and gender, the event rate was 1%, while those who managed 85% of the expected METs had an event rate of 12% during follow-up.

Another poor prognostic variable is the persistent LVOTO. It was documented that these patients had worse outcome regardless the severity of the obstruction both at rest and with exercise. (11) Exercise intolerance is related with the inability to increase systolic volume due to a decreased contractile reserve when afterload increases in patients with LVOTO. (5, 6, 12, 13). Although patients with latent LVOTO developed more symptoms, ECG changes and post-exercise MR than the group with no obstruction, they did not have more cardiac events during follow-up. Previous studies have neither been able to establish a direct relationship between latent gradient and poor prognosis. (12, 14, 15)

Finally, another defining element was ECG changes. This proves that with greater ST-segment depression on exercise testing patients have worse outcomes. As already described in former publications, myocardial ischemia in HCM is multifactorial (16). The probable mechanisms are related with systolic compression of small intramural vessels, elevated end-diastolic left ventricular pressure, arteriolar density reduction relative to myocardial mass increase with impaired vasodilator capacity, imbalance between oxygen supply and demand due to increased myocardial mass, fibrosis and myocyte disarray. Severe microvascular dysfunction is often present in asymptomatic or mildly symptomatic patients and this might precede clinical deterioration in successive years, being an important prognostic marker.

It is noteworthy that in our study the ABPBE was not associated with higher number of events. Some

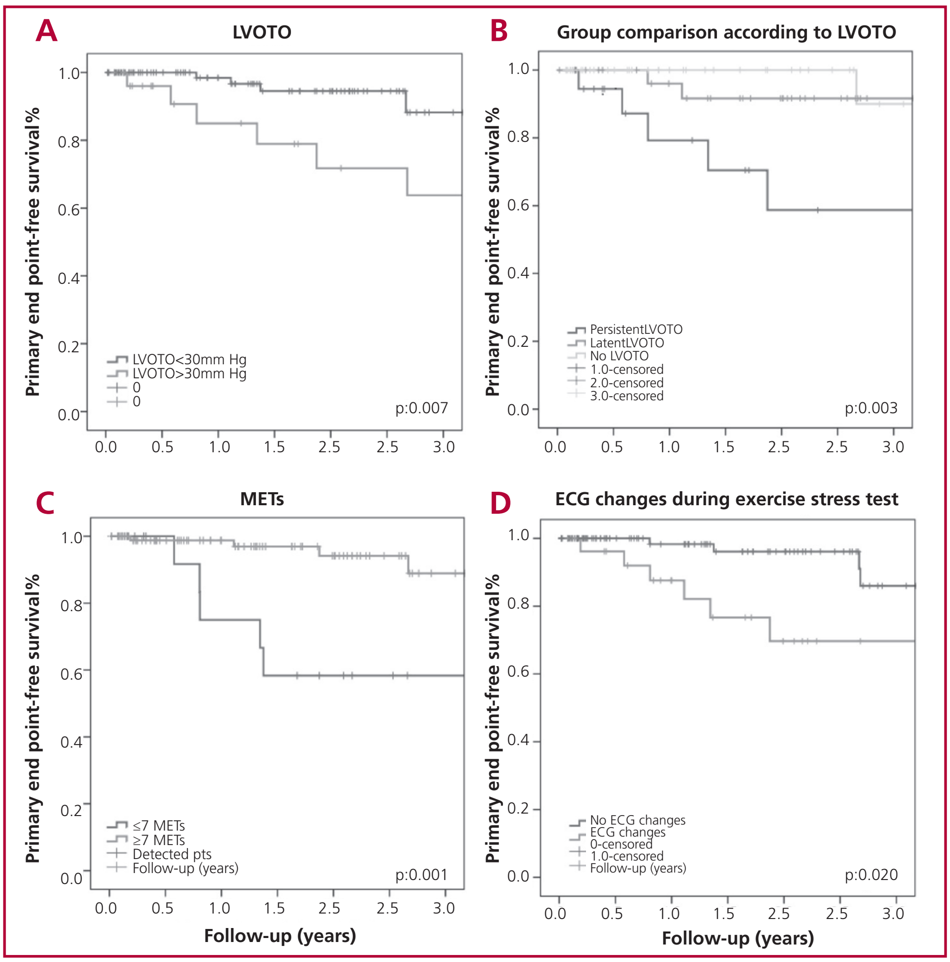

Fig. 1. Primary endpoint-free survival curves according to different variables analyzed in exercise stress-echo. **A** Survival curve comparing patients with left ventricular outflow tract obstruction (LVOTO) >30 mm Hg and <30 mm Hg. **B.** Comparison between the three groups of patients with persistent LVOTO, latent LVOTO, and with no LVOTO. **C.** Patients achieving ≥7 METs and ≤7 METs. **D.** Presence or absence of change in the ECG during stress.

authors demonstrated that the flat intra-exertion or hypotensive blood pressure response is an independent risk factor for sudden death. (17-18) Although in our study patients with worse outcome (those with persistent LVOTO) presented with higher percent ABPBE, no statistical significance was found for this variable, probably due to the very low number of patients who developed ABPBE and having analyzed less sick patients.

The study could establish the importance of ESE in HCM. It is a complementary safe and useful method for evaluating patients with this heart disease. (18)

Limitations

This is a retrospective study with a small sample of patients.

Due to the short follow-up period and the few events recorded, it was not possible to perform a multivariate analysis. Probably in the future, with more follow-up time, more events will be added and the possibility of performing this type of analysis will be considered, thus enriching the work.

Other echocardiographic measurements such as volume assessment of the left atrium, diastolic dysfunction or systolic pressure of the pulmonary artery were not uniformly documented and therefore were not analyzed in this study.

CONCLUSIONS

In our study, patients with asymptomatic or minimally symptomatic HCM, who performed ESE and achieved a high functional capacity, expressed as ≥7 METs, showed excellent mid-to long-term outcomes. Left ventricular outflow tract obstruction at rest and ECG changes during maximal exercise were associated with higher number of events during follow-up.

Conflicts of interest

None declared

(See authors' conflict of interest forms in the web/ Supplementary Material).

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