Functional Assessment of Patients With Hypertrophic Cardiomyopathy by Maximal Oxygen Consumption

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Introduction and objectives. Differences between anatomical severity and clinical manifestations are frequent in patients with hypertrophic cardiomyopathy. Our objective was to assess functional capacity in a consecutive group of patients with hypertrophic cardiomyopathy measuring exercise aerobic parameters, as well as clinical and echocardiographic variables.

Patients and method. We studied 98 consecutive patients with hypertrophic cardiomyopathy. All patients underwent both echocardiographic and cardiopulmonary exercise testing. The control group consisted of 22 untrained persons. We studied exercise capacity by analyzing maximal oxygen consumption and aerobic functional capacity, among other variables.

Results. Patients with hypertrophic cardiomyopathy attained significantly lower maximal oxygen consumption values than controls (24.1 ± 5.9 vs 36.4 ± 5.9 ml/kg/min; p = 0.0001). Maximal aerobic capacity was significantly different among patients with NYHA functional capacity class I, II or III (78.9 ± 13.5%; 71.9 ± 14.7%; 63.9 ± 15.7%; p = 0.009). However, considerable overlap was found between groups in maximal aerobic capacity. Functional impairment was greater in patients with left ventricular thickness > 20 mm, ejection fraction < 50%, left atrial dimension > 45 mm and pseudonormal or restrictive transmitral flow pattern.

Conclusions. Patients with hypertrophic cardiomyopathy show significant functional impairment, which is difficult to detect from their clinical manifestations. Optimal assessment requires cardiopulmonary exercise testing.

Key words: Cardiomyopathy. Exercise. Hypertrophy.

Evaluation funcional de los pacientes con miocardiopatía hipertrófica mediante análisis del consumo de oxígeno máximo

Introducción y objetivos. En pacientes con miocardiopatía hipertrófica, frecuentemente encontramos discrepancias entre la gravedad de la afección anatómica y la expresión clínica. El objetivo de nuestro estudio fue evaluar la repercusión funcional de la enfermedad mediante el análisis de gases respirados, teniendo en cuenta variables clínicas y ecocardiográficas.

 Pacientes y método. Estudiamos de forma consecutiva a 98 pacientes con miocardiopatía hipertrófica. A todos ellos se les realizó un estudio ecocardiográfico y un estudio ergométrico con análisis de los gases respirados. El grupo control estaba formado por 22 sujetos sanos, no entrenados. Como parámetros ventilatorios se estudiaron, entre otros, el consumo de oxígeno máximo y la capacidad funcional aeróbica.

 Resultados. El consumo de oxígeno máximo alcanzado por los pacientes fue significativamente menor que el alcanzado por los controles (24,1 ± 5,9 frente a 36,4 ± 5,9 ml/kg/min; p = 0,0001). Al analizar los datos de la capacidad funcional aeróbica, encontramos diferencias significativas según el paciente tuviera un grado funcional I, II o III de la New York Heart Association (NYHA) (78,9 ± 13,5%; 71,9 ± 14,7%; 63,9 ± 15,7%; p = 0,009). Sin embargo, fue notable la presencia de una importante superposición entre los grupos. Los subgrupos más afectados fueron los pacientes con hipertrofia superior a 20 mm, fracción de eyeccción < 50%, aurícula izquierda > 45 mm y los que presentaban un patrón de flujo mitral seudonormal o restrictivo.

 Conclusiones. Los pacientes con miocardiopatía hipertrófica presentan una importante limitación al ejercicio que difícilmente es valorable mediante la expresión clínica de la enfermedad. Una correcta valoración individual requiere el análisis del consumo de oxígeno máximo.


INTRODUCTION

One of the most important aspects of the daily tasks of a physician is the functional evaluation of
patients. This evaluation can affect the decision making on the degree of certain physical activities, set work limitations, suggest the introduction or modification of therapeutic measures and even affect the prognostic assessment of most types of heart disease. In patients with hypertrophic cardiomyopathy (HC), the functional evaluation is normally performed according to the clinical expression of the hypertrophy and to its degree of severity based on echocardiographic findings. However, discrepancies between the anatomic severity of hypertrophy and its clinical expression are frequently observed. Many patients remain asymptomatic for years despite presenting severely hypertrophic ventricles, while others may be very symptomatic although do not present such a severe degree of hypertrophy.

Different authors have shown that exercise testing is a useful and safe method for stratifying risk in patients with HC. Analysis of maximal oxygen consumption (VO$_2$) can provide an objective assessment of the functional capacity of the patient, which is of great importance for prognostic assessment and for making certain therapeutic decisions.

Almost all studies have been performed in referral centers for the disease in different parts of the world so we do not know if these results are reproducible in our patients. To date, no studies have been performed with unselected populations in Spain. Studies are therefore warranted to extend our knowledge of a technique that is not widely used but that is useful and safe to manage patients with this particular disease.

The objective of our study was to evaluate the functional capacity of a consecutive group of patients with HC by analysis of maximal VO$_2$ and to compare the results with clinical variables and echocardiographic findings.

PATIENTS AND METHODS

Patients

We studied 98 consecutive patients from our outpatient clinics between June 1999 and September 2001. Patients underwent echocardiographic examination and exercise testing with analysis of respiratory gases. We excluded patients who were unable to walk and those whose clinical situation precluded the interruption of all heart medication for 48 h prior to the test.

The diagnostic criterion for HC was parietal thickness of the left ventricle (LV) $\geq$15 mm with no apparent cause of hypertrophia. Patients with a family history of HM (two first-degree relatives with HC) were included if the hypertrophy was $\geq$12 mm, provided that there was no other possible cardiac or extracardiac cause.

Control group

The control group comprised 22 untrained healthy volunteers whose exercise response and oxygen consumption data were recorded.

Clinical assessment

All patients were asked about incidence of the disease in their families. Hypertrophic cardiomyopathy of familial origin was present if at least two relatives were affected. Diagnosis in such instances had to be confirmed by our own hospital or by a medical report.

The presence or absence of angina, syncope and dyspnea was assessed. The degree of clinical function was assessed in accordance with the classification of the New York Heart Association (NYHA). We recorded medication taken by the patients in the three months prior to the test and whether they had pacemakers or implantable defibrillators.

Echocardiography

All studies were performed with the Sonos 5500 ultrasound system (Philips, Andover, Massachusetts). The studies were performed a few minutes before the exercise test and the images stored on an optical disc for later analysis. Parietal thickness was measured in four segments along the short transversal axis, at the mitral valve and at the papillary muscles. Ejection fraction (EF) was calculated with the Simpson method in the apical four-chamber plane. Transmural and pulmonary venous flows and LV ejection were analyzed using continuous, pulsed color transthoracic Doppler echocardiography. Peak transmural flow, deceleration time of E velocity and isovolumic relaxation time were measured. Peak velocity of the retrograde diastolic pressure wave was measured from pulmonary venous flow. M-mode color echocardiography was used to measure the velocity of propagation of mitral flow. Peak diastolic velocities of the septal annulus, Ea and Aa, were
measured using tissue Doppler techniques. These data were used according to the criteria proposed by García et al to interpret the LV filling pattern as normal, altered relaxation, pseudonormal or restrictive. The degree of mitral regurgitation was calculated from the area of the regurgitant jet in the apical four-chamber plane. Continuous Doppler echocardiography from the apical plane was used to assess obstruction of the LV outflow tract, defines as a pressure gradient greater than 25 mm Hg.

Exercise testing

All subjects were to reach maximal exercise, limited only by the symptoms, in accordance with the Bruce protocol. Respiratory gases were analyzed using a Cx Ergometrix system, which allows ventilatory parameters to be obtained every 15 seconds. The most important parameters were VO₂, CO₂ produced (VCO₂) and the respiratory exchange ratio. In each studied subject, the maximal theoretical VO₂ was calculated as a function of age, sex and body surface area. Aerobic functional capacity (AFC) for each individual was defined as maximal VO₂ divided by the theoretical maximal value, expressed as a percentage (AFC=100 × maximal VO₂/maximal theoretical VO₂). The O₂ pulse was calculated by dividing VO₂ in mL/min, by heart rate. Anaerobic threshold (AT) was determined by detecting the beginning of excess CO₂ output using the so-called V-slope method. The echocardiogram was monitored throughout the test. Blood pressure was measured manually with a sphygmomanometer every minute throughout the exercise test and for the first three minutes of recovery.

The patients performed the test after abstaining from food or drink and from taking heart medication (except amiodarone) during the 48 h prior to the test. A test was considered a valid measure of maximal VO₂ only if the patient had: a) exceeded 85% of the maximum predicted heart rate for the age of the patient; b) no change (increase or decrease) in O₂ consumption on advancing to the next stage in the protocol, and c) reached a respiratory exchange ratio greater than 1.15 at maximal exercise or greater than 1.5 after 3 minutes of recovery.

Statistical analysis

The following variables were established from the echocardiographic data: maximum thickness >20 mm, presence of obstruction at rest, dilatation of left atrium >45 mm, EF<50%, severity of mitral regurgitation and flow pattern for mitral filling. The results were expressed as mean values (standard deviation (SD)). Continuous variables with a normal distribution were compared by an analysis of variance or Student’s t test. The degree of association between continuous variables was defined by the Pearson correlation coefficient. For categorical variables we used the χ² test. All data were analyzed with the SPSS 9.0 program.

RESULTS

Study population

The control group comprised 15 men and 89 women (35%) aged between 23 and 50 years (37±6.8 years). Of the 98 patients enrolled initially, eight were excluded because their tests were inconclusive. The tests were not conclusive because of inability to adapt to the exercise system or the mask of the gas analyzer (2 patients), premature interruption of the test by the patient without meeting the criteria for maximal exercise (2 patients), drop in blood pressure (3 patients) or paroxysmal atrial fibrillation (one patient). Age in the final group of 65 men and 25 women (28%) ranged from 13 to 73 years (43.8±15 years). Their clinical and echocardiographic characteristics are presented in Tables 1 and 2.

Data on maximal and submaximal exercise

All patients and control group subjects performed the exercise test, reached exhaustion and surpassed the anaerobic threshold in all cases. There were no serious complications. The patients showed a reduced exercise capacity compared to the control group subjects, who performed four minutes more exercise, reached higher stages in the protocol and had three times greater MET (Table 3). The maximal VO₂ reached by patients was much lower, the difference between groups being

<table>
<thead>
<tr>
<th>TABLE 1. Clinical characteristics of the patients</th>
</tr>
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<tbody>
<tr>
<td>Functional class (NYHA)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Angina grade</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Familial origin</td>
</tr>
<tr>
<td>45 (50)</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Pacemakers</td>
</tr>
<tr>
<td>DCP</td>
</tr>
<tr>
<td>IAD</td>
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</tbody>
</table>

DCP indicates dual-chamber pacemaker; IAD, implantable automatic defibrillator.
more than 10 mL/kg/min and highly statistically significant. In the submaximal exercise, both the time to AT and the maximal VO₂ reached were also much higher in the control group than in the patient group. The maximal VO₂ reached by patients and by healthy volunteers is presented in Figure 1. All subjects in the control group exceeded 70% of their maximal predicted VO₂. By contrast, only 23 patients exceeded 85% of their maximal predicted VO₂ and 41 remained below 70%. Furthermore, the VO₂ exceeded 20 mL/kg/min for all subjects in the control group while one-third of patients did not achieve this threshold.

**TABLE 2. Echographic characteristics of the patients studied**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrium, mm</td>
<td>90</td>
<td>44.2±6.4</td>
<td>28-59</td>
</tr>
<tr>
<td>TD, mm</td>
<td>90</td>
<td>44.2±5.9</td>
<td>31-61</td>
</tr>
<tr>
<td>Maximum thickness, mm</td>
<td>90</td>
<td>20.9±5.8</td>
<td>12-45</td>
</tr>
<tr>
<td>End-diastolic volume, mL</td>
<td>83</td>
<td>77.4±24.3</td>
<td>24-143</td>
</tr>
<tr>
<td>EF, %</td>
<td>83</td>
<td>62.2±7.9</td>
<td>32-76</td>
</tr>
<tr>
<td>E velocity, cm/s</td>
<td>88</td>
<td>77.4±24.3</td>
<td>18-151</td>
</tr>
<tr>
<td>A velocity, cm/s</td>
<td>88</td>
<td>65.1±21.9</td>
<td>15-139</td>
</tr>
<tr>
<td>E/A</td>
<td>88</td>
<td>1.35±0.74</td>
<td>0.38-4.8</td>
</tr>
<tr>
<td>Td, ms</td>
<td>88</td>
<td>212.9±83.9</td>
<td>100-600</td>
</tr>
<tr>
<td>IRT, ms</td>
<td>85</td>
<td>94.4±19.1</td>
<td>50-150</td>
</tr>
<tr>
<td>Gradient, mm Hg</td>
<td>39</td>
<td>60.2±32.3</td>
<td>25-130</td>
</tr>
</tbody>
</table>

*DE indicates end-diastolic diameter of the left ventricle; EF, LV ejection fraction; Td, deceleration time of mitral E velocity; IRT, isovolumic relaxation time. The image quality in seven patients was insufficient to allow assessment of the volumes, two patients presented CA due to AF and 39 patients (43.8%) presented obstructions at rest.*

**TABLE 3. Maximal and submaximal exercise data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minutes</td>
<td>8.1±2.7</td>
<td>12.3±2.5</td>
<td>.0001</td>
</tr>
<tr>
<td>Stage</td>
<td>3.1±0.9</td>
<td>4.5±0.8</td>
<td>.0001</td>
</tr>
<tr>
<td>Hₘₚ max, %</td>
<td>84.2±11.8</td>
<td>98.2±5.7</td>
<td>.0001</td>
</tr>
<tr>
<td>VO₂max, mL/kg/min</td>
<td>24.1±5.9</td>
<td>36.4±5.9</td>
<td>.0001</td>
</tr>
<tr>
<td>AFC, %</td>
<td>73.7±14.9</td>
<td>100±14.1</td>
<td>.0001</td>
</tr>
<tr>
<td>MET</td>
<td>6.9±1.7</td>
<td>10.4±1.7</td>
<td>.0001</td>
</tr>
<tr>
<td>O₂ pulse, mL/beat</td>
<td>12.9±3.5</td>
<td>14.9±4.2</td>
<td>.02</td>
</tr>
<tr>
<td>Anaerobic threshold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute</td>
<td>3.7±1.5</td>
<td>4.9±1.8</td>
<td>.001</td>
</tr>
<tr>
<td>VO₂, mL/kg/min</td>
<td>15.2±2.9</td>
<td>18.6±3.8</td>
<td>.0001</td>
</tr>
<tr>
<td>VO₂max, %</td>
<td>47.5±11.9</td>
<td>51.7±11.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*AFC indicates aerobic functional capacity, HR, heart rate; VO₂ max, maximal oxygen consumption; MET, metabolic equivalents.*

**Relationship between oxygen consumption and the clinical characteristics of the disease**

We did not find any differences between the functional capacity of patients with a family history of HC and those who presented isolated HC (74.2±14.6% vs 73.2±15.4%) or between those who or did not present angina (73.6±15.3% vs 73.4±14%). Patients with dyspnea attained a lower VO₂ and were more limited than those in a higher functional class according to the NYHA classification (Table 4). When we looked at the AFC stratified according to NYHA class (Figure 2) we found clear differences between groups, though the spread of values is high and the results extensively overlapped. For example, eight patients in functional class I had an AFC lower than...
70% and three patients in a high functional class (NYHA III) had an AFC >70%.

Functional capacity and echocardiographic data

Anaerobic functional capacity was significantly lower in patients with left atrial dilatation of more than 45 mm and parietal thickness greater than 20 mm, and in those whose ejection fraction was below 50% (Table 5). We also found significant differences dependent on the type of mitral flow filling pattern. Thus, patients with a restrictive and pseudonormal pattern were those who presented a lower AFC. There was a tendency towards a lower AFC in patients with a higher degree of regurgitation, but the differences were not statistically significant. Finally, patients with obstruction at rest presented a functional limitation similar to those with no obstruction. We did not find any association between the basal pressure gradient and AFC in patients with obstruction (r=0.1; P=NS).

DISCUSSION

Our results confirm that most patients with HC in our sociocultural environment have an important functional limitation. Only one-fourth of the patients exceeded 85% of their theoretical maximal VO2 values, while half did not exceed 70% of their theoretical maximal VO2. In our patients, this functional limitation was not related to the presence of angina, and the results were highly variable when patients were stratified by NYHA functional class. Moreover, the patients in our study with the greatest limitations were those with greater hypertrophy, lower ejection fraction and higher degrees of diastolic dysfunction.

Study population

The patients were included consecutively and taken...
from outpatient clinics affiliated to our hospital. They constituted an unselected population with a variety of clinical characteristics, ranging from asymptomatic patients (37%) to those with symptoms corresponding to NYHA class III functional capacity, or to those with an automatic defibrillator. Our patient population is therefore representative of a broad range of patients with this disease.13,23-25 Almost one-third of the patients (30%) were not taking any medication. Other medications, except for amiodarone, were suspended 48 h before the test. Amiodarone was not interrupted because of its long half-life, the questionable permissiveness of its suspension and its limited influence on the assessment of maximal VO₂.4,10

Methodology of the functional evaluation

A single exercise protocol (The Bruce protocol) was used for all patients. Eight patients (8%) failed to reach maximal VO₂ with this protocol. Half of these failures were attributed to procedural complications such as paroxysmal atrial fibrillation and drop in blood pressure. The remaining failures were due to the inability of the patient to adapt to the method, that is, to the treadmill or the gas sampling mouthpiece. Other authors have reported similar data with different protocols.3,7 Our procedure is therefore no different to those reported previously, and is effective and safe in patients with a serious obstruction at rest.

Functional capacity of the patients

Both the exercise parameters and the VO₂ data of patients at maximal and submaximal exercise were lower than those of the control group. Only the VO₂ percentage at the anaerobic threshold was similar in both groups. This parameter is related to the fitness of an individual among other factors. Fitter subjects are able to perform more extensive exercise and delay their anaerobic threshold to a VO₂ value closer to the maximum.26 This parameter may therefore be similar for patients and healthy subjects alike because subjects in the control group were not particularly fit and because the limitation for patients is continuous for any exercise, however strenuous.4,5

Functional capacity and symptoms

Our study showed that angina was not responsible for any particular functional limitation. This is in agreement with the results of Sharma et al.,7 who also did not see any relationship between angina and AFC. Anginal chest pain in patients with HC does not have any obvious cause and seems to be related to the effects on coronary artery flow of small vessel disease or an inadequate vasodilator reserve.27,28 Dyspnea was however an indicator of individuals with a lower AFC. Thus, patients in NYHA functional class I had a higher exercise tolerance and a higher VO₂ than patients in class II and, likewise, those in functional class II surpassed those in functional class III. Our results agree with those published previously by Sharma S et al.7 Their data are even more revealing, with lower values for AFC than those found in our population (70±15%, 56±15% and 35±11% for groups in functional class I, II and III, respectively, versus 79±13%, 72±15% and 64±16% in our study).

The large spread of data and overlap between different patient groups stratified by NYHA class in our study is in agreement with the results of other authors.4,5,7 Given the variability in the data, the evaluation of isolated symptoms is an unreliable method for the functional evaluation of the disease of a given individual.

Functional capacity and echocardiographic data

The patients in our study with extensive hypertrophy (>20 mm), left atrial dilatation, a pattern of pseudonormal and restrictive mitral flow and EF<50% had lower VO₂ values than those without such characteristics (Table 5).

Cardiac output has been correlated with VO₂ in patients with HC. The inability to increase the systolic volume may be responsible for the lack of increase in cardiac output.5,10,29 Diastolic dysfunction typical of patients with HC is due to mechanisms such as ventricular hypertrophy, interstitial fibrosis and ischemia.29 Patients with a higher degree of hypertrophy may correspond to those with greater impairment of ventricular filling. They would therefore be unable to increase systolic volume and VO₂. Previous studies have not managed to demonstrate an association between hypertrophy and VO₂,7 but excessive stratification of patients into subgroups of increasing hypertrophy may be the reason for this lack of association.

Eight patients in our study had an EF<50%. These patients had no striking symptomatic deterioration, but VO₂ was nevertheless considerably lower than in the remaining subjects. A progressive deterioration in systolic function occurred in 10%-15% of patients with HC, with narrowing of the walls, mild dilatation and a drop in EF.30 Such pattern of disease progression can be slow and go unnoticed,3,30 which would explain why patients in this subgroup belonged to the same functional class as other patients.

The functional capacity of patients with obstruction at rest did not differ from that of patients with no gradient. Likewise, we did not find any association between the size of the gradient and AFC in subjects with an obstruction. Other authors have also failed to find any particular limitation in these patients with an
obstruction and, although a certain association between the gradient and the AFC has been reported, this association is low (r=-0.5).

Our data indicate that both the left atrial dilatation and the pattern of mitral filling, as assessed with new echocardiographic criteria, can identify patients with a lower exercise tolerance. Left atrial dilatation and pattern of mitral filling are closely related to the diastolic properties of the left ventricle. Numerous studies have observed the importance of diastolic function as directly limiting the AFC. Diastolic function was assessed in these studies with invasive methods, nuclear medicine or echocardiographic techniques other than Doppler methods. If we try to correlate ACF with Doppler velocities of mitral flow, the results are not satisfactory. For example, Briguori et al did not find any differences in patterns of mitral flow when they compared patients with an AFC greater than or less than 70%. The filling pattern in this study was established from the peak mitral velocities and from the relaxation times and deceleration time of E velocity. Given that the Doppler parameters are highly dependent on the pre-filling and post-filling conditions, there is no clear relationship between these Doppler parameters and the diastolic properties of the left ventricle. Evaluation of the velocity of propagation of mitral flow by color M-mode Doppler echocardiography or the Doppler analysis of the velocity of the atrioventricular annulus provides more independent data on the filling conditions. These data, along with Doppler echocardiography of the pulmonary veins and mitral flow, allow a better evaluation and stratification of diastolic function, which may explain why we found a relationship between the filling pattern of the left ventricle and AFC.

Study limitations

Maximal VO₂ does not only depend on cardiac output. Peripheral factors such as hypoperfusion distal to the locomotor system or mitochondrial mutations occasionally associated with the HC gene may limit oxygen uptake by muscles and therefore lower the maximal VO₂. No genetic tests were performed with our patients, so we do not know the implications of a hypothetical mitochondrial dysfunction associated with HC.

Echocardiographic assessments were performed at rest. During exercise some parameters such as the intraventricular gradient or LV contractility may change significantly. Subsequent studies should clarify how these parameters are affected by exercise and their role in determining functional capacity.

CONCLUSION

Exercise testing, along with the analysis of respiratory gases, is a useful and safe method for functional assessment of patients with HC. Patients with HC have an important exercise limitation that is hard to assess from the clinical expression of the disease. For a correct individual evaluation, analysis of maximal oxygen consumption is necessary. In our population, patients with hypertrophy greater than 20 mm, low EF, left atrial dilatation greater than 45 mm and restrictive or pseudonormal pattern of mitral flow have the lowest exercise capacity.

REFERENCES