Prognostic relevance of exercise testing in hypertrophic cardiomyopathy. A systematic review

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ABSTRACT

Background: Cardiopulmonary exercise test (CPET) is indicated as part of the assessment in hypertrophic cardiomyopathy (HCM) patients and stress echocardiography is often used to assess symptoms. However, the role of exercise testing for prognostic stratification in HCM is still not established.

Aims: To systematically review the evidence on the role of exercise testing for prognostic stratification in hypertrophic cardiomyopathy.

Methods: A systematic review was conducted for eligible publications, between 2010 and 2020, that included evaluation of outcomes and prognosis. In these studies, patients underwent exercise echocardiography and/or cardiopulmonary exercise testing, performed according to predefined protocols. Diverse parameters were assessed in order to determine which were relevant for the prognosis. Analyzed outcomes included death from any cause, sudden cardiac death (SCD) and equivalents, cardiovascular death, heart failure requiring hospitalization or progression to New York Heart Association classes III or IV, cardiac transplantation, non-sustained ventricular tachycardia, stroke, myocardial infarction and invasive septal reduction therapy.

Results: Eighteen publications were included, corresponding to a total of 7525 patients. The mean follow-up period varied between 1 and 8 years. The main findings of these studies revealed that the major predictors of outcomes were abnormal heart rate recovery, abnormal blood pressure response exercise induced wall motion abnormalities, lower peak VO\textsubscript{2}, higher VE/VC\textsubscript{O2}, and pulmonary hypertension/exercise-induced pulmonary hypertension.

Conclusion: Although most studies concluded that exercise test results are useful to determine prognosis in HCM, further investigation is needed regarding whether it adds independent value to the current risk stratification strategies.

1. Introduction

Hypertrophic Cardiomyopathy (HCM) affects approximately 0.2% of the adult population worldwide. It is characterized by left ventricular hypertrophy (LVH) in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy seen; a causal sarcomere (or sarcomere-related) variant might be identified, or a genetic etiology may remain unresolved \cite{1,2,3}. It is a cause of sudden cardiac death (SCD), heart failure (HF) and arrhythmias including atrial fibrillation \cite{1}.

Patients frequently present with reduced exercise capacity \cite{1,2,3}, which can be explained by diverse mechanisms, including left ventricular outflow tract obstruction (LVOTO), myocardial ischemia and left ventricular systolic and diastolic dysfunction \cite{1}. Chest pain is also a common presenting symptom.

Cardiopulmonary exercise testing (CPET) is recommended as part of the initial evaluation of patients with a diagnosis of HCM, when they report change in symptoms or when considering therapy to reduce
LVOTO [1,2,3]. It allows the measurement of peak oxygen consumption (VO2), minute ventilation relative to CO2 production (VE/VO2) slope, aerobic threshold (first ventilatory threshold - where the lactate production rate is higher than the lactate elimination rate) [4,5]. It may clarify equivocal symptoms, evaluate functional capacity prior to corrective therapeutic procedures, help distinguish between cardiac and pulmonary etiologies of functional impairment [1,6]. In addition, it was suggested it may allow a possible incremental prognostic role in the low-intermediate SCD risk categories over the contemporary strategies [3].

Exercise echocardiography allows evaluation of systolic anterior motion of the mitral valve, mitral regurgitation, left ventricular outflow tract (LVOT) or mid-cavity pressure gradients, diastolic and systolic function while on cycloergometer or treadmill exercise, providing valuable information to explain and assess the degree of severity of some of the symptoms [1,6]. Overall, ECG exercise testing, CPET and exercise echocardiography have been reported to predict multiple aspects of the prognosis in HCM patients. However, current guidelines do not incorporate any type of exercise testing for risk stratification strategies in HCM [1].

The aim of this work was to systematically review the current evidence concerning the relevance of these three forms of exercise testing for prognostic assessment in hypertrophic cardiomyopathy.

2. Methods

2.1. Search strategy and study selection

A systematic search was made on December 2020, using the Medline/PubMed and Embase databases, years 2010–2020, as well as searching for the publications included in the bibliography of the selected articles. The keywords used were: ‘prognosis AND (exercise OR stress OR cardiopulmonary) AND hypertrophic cardiomyopathy’.

This systematic review of the literature was conducted using the methodology suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [7]: a comprehensive search of the literature to identify all potentially relevant studies; systematic selection of studies based on inclusion and exclusion criteria; and extraction of relevant data from eligible studies.

The following inclusion criteria were applied: prospective or retrospective studies; performed in humans; participants older than 18 years; published in English; study population fulfilling the diagnostic criteria for HCM; making use of electrocardiography, echocardiography or cardiopulmonary exercise tests; evaluation of outcomes and prognosis.

Primary search was performed by two authors, who independently reviewed each reference (title and abstract) identified by the literature search, applied the inclusion and exclusion criteria listed above and decided on whether to include or exclude the publication at that stage. Any disagreement was solved by the senior author.

2.2. Data extraction

2.2.1. Patients and baseline assessment

Inclusion of patients required a diagnosis of HCM based on guidelines criteria [1]. Baseline patient characteristics that were analyzed were: age [8–25]; the presence of cardiovascular symptoms (dyspnoea, pre-syncpe, syncope, angina, palpitations) [8,10,11,13–24] or disease (coronary disease, hypertension, arrhythmia, valve disease) [8–12,14–16,20,22,24,25], as well as other systemic diseases (genetic, metabolic) that could cause myocardial hypertrophy [9,10,13,14,16,21]; family history of premature sudden death or HCM [8–12,14–17,21,24]; medication at the time of the study [8–12,14–16,20–25]; history of cardiac surgery and/or medical therapy to relieve LVOTO [9–11,15,21,25]; an adequate acoustic window [14,21] for echocardiographic studies and the ability and will to undergo exercise testing [14,21].

Other relevant initial baseline assessments included New York Heart Association (NYHA) functional class of HF [8,9,11–13,15–24], 12-lead ECG at rest [8,10,12,15,17,20] and 24 h-ECG [8].

2.2.2. Resting and exercise echocardiography

In some studies [8–25], patients underwent resting transthoracic echocardiography, including M-Mode, bi-dimensional (2D) and, in some cases, Doppler evaluation, followed by symptom-limited exercise echocardiography in a treadmill in four studies [12,14,17,20,21].

Regarding exercise echocardiography [12,14,17,20–22], medications were not generally withdrawn before the test. Heart rate (HR) and blood pressure (BP) were measured during the test and afterwards, and ECG was monitored.

2.2.3. Cardiopulmonary exercise testing

In those studies in which patients were submitted to CPET [10,11,13–16,20,22,24], the tests were performed with regular HR and BP measurements and ECG monitoring, according to standard protocols (e.g. Bruce), with gas exchange measurement.

Heart rate recovery (HRR), defined as a drop in heart rate (HR) from peak to 1 min post-exercise [26] was measured in two of the studies [12,15], to ascertain the fraction of patients with abnormal HRR (<12 beat drop over 1 min in recovery). Abnormal BP response (defined as progressive hypotension or a failure to increase the systolic blood pressure > 20 mmHg during exercise [27]) was also recorded in eight studies [10–13,15,17,18,20,22,23].

2.2.4. Follow-up and outcomes

Patients were followed up with a defined regularity, so as to determine the occurrence of events. Death certificates were also analyzed in three of the studies [12,14,22].

Primary outcomes of relevance were death from any cause [8–10,12,14,16,18,20,21,23], sudden death (defined as an unexpected sudden collapse occurring <1 h from the onset of symptoms in patients who had previously experienced a relatively stable course [18,23,24]), death due to progressive HF or “other” [8,9,11,14,16,20,21,23], sudden death equivalents (successful resuscitation from cardiac arrest and appropriate implantable cardioverter defibrillator (ICD) discharge), heart failure (HF) requiring hospitalization [9,11,16,20,21] or progression from NYHA class I or II to class III or IV of HF and cardiac transplantation [14,15,20,23,24].

Secondary outcomes of relevance were sustained ventricular tachycardia [8,12,14,18,21]; stroke in the context of atrial fibrillation (AF) [12,14,16,21]); myocardial infarction [14] and clinical deterioration leading to need of therapy to relieve LVOTO (including septal reduction) [14].

3. Results

3.1. Study selection

1368 unique publications were found and analyzed. 1236 of these publications were excluded for not fulfilling the age, date of publication and language criteria. The remaining 132 were analyzed by reading the abstract, and 114 of them excluded for not fulfilling the remaining criteria. Therefore, 18 studies were selected for this systematic review [8–25] (Fig. 1), corresponding to a total of 7525 patients.

3.2. Design of the studies and baseline characteristics of the patients

Most studies (16 out of 18) were single-centre and observational. Only two studies included over 1000 patients [15,17]. The mean follow-up was between 1.6 ± 0.95 years and 8.7 ± 3 years. Mean age of the patient populations varied between 44 ± 14 and 59 ± 21 years. A
Table 1
Demographic characteristics of the patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Period</th>
<th>Overall population, n</th>
<th>Mean follow-up, years</th>
<th>Mean age, years</th>
<th>Men, n (%)</th>
<th>Family history of HCM, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efthimiadis et al, 2010</td>
<td>Thessaloniki, Greece</td>
<td>2007-2009</td>
<td>68</td>
<td>2</td>
<td>44.8 ± 14.6</td>
<td>45 (67.1)</td>
<td>32(47)</td>
</tr>
<tr>
<td>Sorajja et al, 2012</td>
<td>Rochester (Minnesota), USA</td>
<td>1991-2008</td>
<td>182</td>
<td>4 ± 3.2</td>
<td>53 ± 15</td>
<td>119 (65)</td>
<td>43(24)</td>
</tr>
<tr>
<td>Peteiro et al, 2012</td>
<td>A Coruña, Spain</td>
<td>–</td>
<td>239</td>
<td>4.1 ± 2.6</td>
<td>52 ± 15</td>
<td>145 (61)</td>
<td>76(32)</td>
</tr>
<tr>
<td>Reant et al, 2014</td>
<td>Bordeaux-Pessac, France</td>
<td>2009-2012</td>
<td>115</td>
<td>1.6 ± 0.95</td>
<td>51.9 ± 15.2</td>
<td>76 (66)</td>
<td>59(51)</td>
</tr>
<tr>
<td>Desai et al, 2014</td>
<td>Cleveland (Ohio), USA</td>
<td>1997-2007</td>
<td>426</td>
<td>8.7 ± 3.0</td>
<td>44 ± 14</td>
<td>310 (73)</td>
<td>105(25)</td>
</tr>
<tr>
<td>Finocchiaro et al, 2015</td>
<td>Stanford (California), USA</td>
<td>2007-2012</td>
<td>156</td>
<td>2.25 ± 0.92</td>
<td>51 ± 14</td>
<td>96 (62)</td>
<td>–</td>
</tr>
<tr>
<td>Reant et al, 2014</td>
<td>Bordeaux-Pessac, France</td>
<td>2009-2012</td>
<td>115</td>
<td>1.6 ± 0.95</td>
<td>51.9 ± 15.2</td>
<td>76 (66)</td>
<td>59(51)</td>
</tr>
<tr>
<td>Peteiro et al, 2015</td>
<td>A Coruña, Spain</td>
<td>–</td>
<td>148</td>
<td>7.1 ± 2.7</td>
<td>51 ± 15</td>
<td>97 (65.5)</td>
<td>44(29.7)</td>
</tr>
<tr>
<td>Marri et al, 2015</td>
<td>Cleveland (Ohio), USA</td>
<td>1997-2012</td>
<td>1005</td>
<td>5.5 ± 4</td>
<td>50 ± 14</td>
<td>643 (64)</td>
<td>201(20)</td>
</tr>
<tr>
<td>Feneon et al, 2015</td>
<td>Rennes and Tours, France</td>
<td>2009-2013</td>
<td>126</td>
<td>2.4 ± 2.0</td>
<td>47.41 ± 15.48</td>
<td>99 (78.1)</td>
<td>42(34.1)</td>
</tr>
<tr>
<td>Coats et al, 2015</td>
<td>London, United Kingdom</td>
<td>1998-2010</td>
<td>1898</td>
<td>5.6</td>
<td>46 ± 15</td>
<td>1278 (67)</td>
<td>778(42)</td>
</tr>
<tr>
<td>Ciampi et al, 2016</td>
<td>Italy, Spain, Portugal and Serbia</td>
<td>1984-2015</td>
<td>706</td>
<td>4.1</td>
<td>50 ± 16</td>
<td>381 (54)</td>
<td>–</td>
</tr>
<tr>
<td>Moneghetti et al, 2017</td>
<td>California, USA</td>
<td>2007-2012</td>
<td>131</td>
<td>4.6</td>
<td>52 ± 13</td>
<td>83 (63)</td>
<td>–</td>
</tr>
<tr>
<td>Lu et al, 2017</td>
<td>Baltimore, USA</td>
<td>2005-2015</td>
<td>536</td>
<td>2.1</td>
<td>52 ± 15</td>
<td>359 (67)</td>
<td>110(20.5)</td>
</tr>
<tr>
<td>Rigopoulos et al, 2018</td>
<td>Athens, Greece</td>
<td>2005-2011</td>
<td>21</td>
<td>2.4 ± 1.08</td>
<td>48.8 ± 13.7</td>
<td>14 (67)</td>
<td>–</td>
</tr>
<tr>
<td>Smith et al, 2018</td>
<td>Michingan, USA</td>
<td>–</td>
<td>589</td>
<td>4.3 ± 3.3</td>
<td>50.7</td>
<td>361 (61.3)</td>
<td>–</td>
</tr>
<tr>
<td>Magri et al, 2018</td>
<td>Italia</td>
<td>2007-2017</td>
<td>681</td>
<td>4.2</td>
<td>48 ± 16</td>
<td>463 (68)</td>
<td>80 (12)</td>
</tr>
<tr>
<td>Hamatani et al, 2019</td>
<td>Osaka, Japan</td>
<td>–</td>
<td>42</td>
<td>2</td>
<td>59 ± 21</td>
<td>14 (33)</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 1. Study selection flow chart.
percentage between 33 and 78.1 were men, with a positive familial history of HCM present in at least 20% up to 51% of the study population. Up to 22% of the patients were in class NYHA>II at baseline. Between 5% and 20.5% of patients had a diagnosis of AF and 20% to 42% had hypertension. The assessment and reporting of “classical” risk factors for sudden death, i.e. defined according to the 2003 ESC/American College of Cardiology (ACC) [1] and 2011 ACC/AHA (American Heart Association) guidelines [2] such as syncope, family history of non-sustained ventricular tachycardia (NSVT), abnormal BP response to exercise, and LV wall thickness ≥ 30 mm varied, but were generally present in less than 20% of the study population in almost all studies. The ESC clinical risk prediction model for sudden cardiac death in HCM patients considers eight different predictors (age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope) to provide individualized 5-year risk for sudden cardiac death. In the analyzed studies these characteristics were underreported, limiting calculation of this score for the studies published [1,28]. The percentage of patients under β-blockade was between 33.1% and 90%. A minority of patients had, at baseline, a permanent pacemaker (5 to 21% of the population in the different studies) or an ICD (0 to 39% of the population). Baseline characteristics of the patients included in the studies are summarized in Tables 1 and 2; and supplementary Tables 1 and 2.  

3.3. Resting and exercise echocardiography

Resting and exercise echocardiography main measurements are summarized in Table 3. Exercise echocardiography was the only exercise test performed in eight studies [10–12,14,16,18,21,25], and it was executed along with CPET in three other studies [8,13,15,20].

For resting echocardiography, maximal wall thickness was between 17 ± 5 and 22 ± 6 mm. LVEF was preserved (>50%) in all studies, according to the current reference values [29], and in general was minimally (slight increase between 0 and 6% in 4 studies) or not changed with exercise. Mean LVOT pressure gradient at rest was >30 mmHg in six of the studies [9,11,15,21–23], which is diagnostic of LVOTO [2], and during exercise it was >50 mmHg in five studies [10,12,15,20,21]. When evaluated both at rest and during exercise it worsened by, at least, 5 mmHg. Regional wall motion abnormalities (WMAs) appeared de novo or worsened with exercise in the three studies evaluating this parameter; this is around four times more patients, when compared with the same parameter evaluated on resting echocardiography [10,14,18]. Not all studies that evaluated mitral regurgitation (MR) at rest repeated this evaluation in exercise echocardiography and one study [16] only reported it with exercise. MR at rest was present in between 10% and 95.4% of patients in all studies evaluating this parameter and between 24% and 93% of patients had MR during exercise, since it appeared de novo in some cases. In others, MR progressed to higher degrees of severity. Between 25% and 49.1% of patients had SAM at rest, defined as any contact of the leaflet with the septum during systole [11,12,15]. In the studies that also evaluated this parameter during exercise it was shown that it generally appeared in patients who did not have it at rest and worsened in the ones who had [12,15].

3.4. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed in isolation in seven studies [8,9,17,19,21–24] and together with exercise echocardiography in three [13,15,20]. Main measurements regarding CPET are summarized in Table 4.

Among the evaluated parameters in CPET, peak VO2 and VE/VCO2 were the ones that were consistently analyzed in all the studies that performed CPET, and also those that demonstrated a higher correlation with outcomes, as discussed below. Mean peak VO2 varied between

<table>
<thead>
<tr>
<th>Study</th>
<th>Angina n (%)</th>
<th>NYHA class &gt; II n (%)</th>
<th>AF n (%)</th>
<th>HT n (%)</th>
<th>Diabetes n (%)</th>
<th>CAD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efthimiadis et al, 2010 [8]</td>
<td>15 (22.0)</td>
<td>9(13.2)</td>
<td>14 (20.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Soraja et al, 2012 [9] n = 182</td>
<td>– (0.0)</td>
<td>24 (13)</td>
<td>49 (27)</td>
<td>6(3)</td>
<td>7(4)</td>
<td></td>
</tr>
<tr>
<td>Petreio et al, 2012 [10] n = 220</td>
<td>90(38)</td>
<td>– (13)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Desai et al, 2014 [12] n = 426</td>
<td>– (0.0)</td>
<td>65 (15)</td>
<td>125 (32)</td>
<td>21(5)</td>
<td>27(6)</td>
<td></td>
</tr>
<tr>
<td>Finocchiaro et al, 2015 [13] n = 156</td>
<td>–</td>
<td>22(14)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Petreio et al, 2015 [14] n = 148</td>
<td>50 (33.8)</td>
<td>14 (9.4)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Matri et al, 2015 [15] n = 1005</td>
<td>150(15)</td>
<td>221(22)</td>
<td>191 (19)</td>
<td>422 (42)</td>
<td>80(8)</td>
<td>150 (15)</td>
</tr>
<tr>
<td>Coats et al, 2015 [17] n = 1898</td>
<td>–</td>
<td>47(7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ciampi et al, 2016 [18] n = 706</td>
<td>–</td>
<td>37(6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Moneghetti et al, 2017 [20] n = 131</td>
<td>–</td>
<td>191 (35.6)</td>
<td>68 (12.7)</td>
<td>(15.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rigopoulos et al, 2018 [22] n = 21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Smith et al, 2018 [23] n = 589</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Magri et al, 2018 [24] n = 681</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Hamatani et al, 2018 [25] n = 42</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CAD: coronary artery disease; HT: hypertension; NYHA: New York Heart Association functional class.

17.7 ± 6 and 28.3 ± 8.7 and mean VE/VCO2 varied between 20 ± 17 and 32.6 ± 7.3. In a study that compared HCM patients to a control population [20], it was shown that in the HCM population peak VO2 was lower and VE/VCO2 slope was higher than in controls. Percentage of predicted peak VO2 (generally based on age and sex) was <80% on average.

3.5. Other resting and exercise parameters

Other resting and exercise parameters are summarized in Table 5. Mean HRR was, in the two studies [8,12] that reported this parameter, over 12 beats per minute (bpm), the threshold below which is considered abnormal, although this parameter demonstrated to be
<table>
<thead>
<tr>
<th>Study</th>
<th>MWT mm</th>
<th>Resting LVEF, %</th>
<th>Exercise LVEF, %</th>
<th>LAAD mm</th>
<th>LAIV ml/m²</th>
<th>LVOT gradient at rest*</th>
<th>LVOT gradient with exercise*</th>
<th>RWMA at rest, n (%)</th>
<th>RWMA with exercise, n (%)</th>
<th>MR at rest, n (%)</th>
<th>MR with exercise, n (%)</th>
<th>SAM at rest, n (%)</th>
<th>SAM with exercise, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efthimiadis et al, 2010</td>
<td>21.4</td>
<td>75.0 ± 6.5</td>
<td>11.2</td>
<td>42 ± 8</td>
<td></td>
<td>-</td>
<td>(LVOT at rest, n(%) - 27 (39.7))</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ciampi et al, 2012</td>
<td>19.9</td>
<td>-</td>
<td>-</td>
<td>46.6 ± 8.1</td>
<td></td>
<td>25 ± 32</td>
<td>(LVOT at rest, n(%) - 60 (25))</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peteiro et al, 2012</td>
<td>20 ± 5</td>
<td>69 ± 9</td>
<td>73 ± 10</td>
<td>44 ± 7</td>
<td></td>
<td>50 ± 54</td>
<td>(LVOT at rest, n(%) - 60 (25))</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reant et al, 2014</td>
<td>21.3</td>
<td>71.0 ± 4.8</td>
<td>71.2 ± 6.8</td>
<td>35.1 ± 18.1</td>
<td></td>
<td>30.7 ± 33.5</td>
<td>(LVOT at rest, n(%) - 42 (43))</td>
<td>-</td>
<td>51(45)</td>
<td>49(43)</td>
<td>30(26)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Desai et al, 2014</td>
<td>20 ± 5</td>
<td>61 ± 5</td>
<td>-</td>
<td>42 ± 8</td>
<td></td>
<td>28 ± 32</td>
<td>(LVOT at rest, n(%) - 60 (25))</td>
<td>-</td>
<td>381(89)</td>
<td>381(89)</td>
<td>105(25)</td>
<td>233(55)</td>
<td>-</td>
</tr>
<tr>
<td>Finocchiaro et al, 2015</td>
<td>17 ± 5</td>
<td>67 ± 11</td>
<td>-</td>
<td>44 ± 19</td>
<td></td>
<td>-</td>
<td>(LVOT at rest, n(%) - 40 (271))</td>
<td>-</td>
<td>15(10)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peteiro et al, 2015</td>
<td>20 ± 5</td>
<td>71 ± 9</td>
<td>73 ± 10</td>
<td>44 ± 6</td>
<td></td>
<td>10(9–25)</td>
<td>(LVOT at rest, n(%) - 25(24))</td>
<td>3(2)</td>
<td>13(9)</td>
<td>23(15.5)</td>
<td>36(24)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maoui et al, 2015</td>
<td>21 ± 5</td>
<td>62 ± 6</td>
<td>-</td>
<td>44 ± 24</td>
<td></td>
<td>41 ± 39</td>
<td>(LVOT at rest, n(%) - 66 (45))</td>
<td>92 ± 51</td>
<td>-</td>
<td>958(95.4)</td>
<td>934(93)</td>
<td>391(39)</td>
<td>763(76)</td>
</tr>
<tr>
<td>Feneon et al, 2015</td>
<td>-</td>
<td>66 ± 8</td>
<td>72 ± 15</td>
<td>52 ± 8</td>
<td></td>
<td>7[8]</td>
<td>(LVOT at rest, n(%) - 107 (15))</td>
<td>12[12]</td>
<td>-</td>
<td>22(20.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coats et al, 2015</td>
<td>19 ± 5</td>
<td>65 ± 11</td>
<td>-</td>
<td>44 ± 8</td>
<td></td>
<td>-</td>
<td>(LVOT at rest, n(%) - 107 (15))</td>
<td>-</td>
<td>221(12)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ciampi et al, 2016</td>
<td>20 ± 5</td>
<td>66 ± 9</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>(LVOT at rest, n(%) - 107 (15))</td>
<td>-</td>
<td>35(6)</td>
<td>92(13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magri et al, 2016</td>
<td>20 ± 5</td>
<td>63 ± 7</td>
<td>-</td>
<td>42 ± 7</td>
<td></td>
<td>12[7–34]</td>
<td>(LVOT at rest, n(%) - 107 (15))</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Monegheetti et al, 2017</td>
<td>-</td>
<td>64 ± 9</td>
<td>-</td>
<td>44 ± 17</td>
<td></td>
<td>57 ± 52</td>
<td>(LVOT at rest, n(%) - 41(31))</td>
<td>-</td>
<td>-</td>
<td>48(37)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(continued on next page)
output; RER: respiratory exchange ratio.

### Cardiopulmonary exercise testing findings.

#### Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>MWT mm</th>
<th>Resting LVEF, %</th>
<th>Exercise LVEF, %</th>
<th>LAD mm</th>
<th>LAIV ml/m²</th>
<th>LVOT gradient at rest*</th>
<th>LVOT gradient with exercise*</th>
<th>RWMAs at rest n (%)</th>
<th>RWMAs with exercise, n (%)</th>
<th>MR at rest n (%)</th>
<th>MR with exercise, n (%)</th>
<th>SAM at rest n (%)</th>
<th>SAM with exercise, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al, 2017 [21] n = 536</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rigopoulos et al, 2018 [22] n = 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al, 2018 [23] n = 589</td>
<td>18.8 ± 4.9</td>
<td>– – – – – – – –</td>
<td>49 ± –</td>
<td>6</td>
<td>67.1 ± 25.8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15(71)</td>
<td>–</td>
</tr>
<tr>
<td>Magri et al, 2018 [24] n = 681</td>
<td>20 ± 5</td>
<td>63 ± 6</td>
<td>–</td>
<td>42 ± 7</td>
<td>12 (6–35) (LVOT at rest, n (%) = 339 (57.5))</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

LAD: left atrial diameter; LAIV: left atrial indexed volume; LVOT: left ventricular outflow-tract; LVOTO: LVOT obstruction; MWT: maximal wall thickness; RWMAs: regional wall motion abnormalities; MR: mitral regurgitation; SAM: systolic anterior motion of the mitral valve; SD: standard deviation. *mean ± SD or median (interquartile range).

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relevant in terms of prognosis, as discussed below. Abnormal BP response, which has been considered a risk factor for SCD, occurred in between 1% and 43% of the patients.

#### 3.6. Follow-up and outcomes

Adverse events during follow-up were previously defined (see methods). The main predictors of worse outcomes were abnormal HRR [12], chronotropic incompetence [8,24], abnormal blood pressure response [23], AF at rest [12], low global longitudinal strain on echocardiogram [11], high left atrium volume [13], exercise WMAs [10,14], higher VE/VCO2 slope, lower peak VO2 [13,17] and pulmonary hypertension (PH) (defined as a mean pulmonary arterial pressure ≥ 25 mmHg at rest/exercise-induced pulmonary hypertension (EIPH) defined as pulmonary artery systolic pressure ≥ 60 mmHg during exercise [25]). The primary endpoints of most studies were combined and highly variable between the different publications. Table 6 summarizes the outcome data.

#### 3.7. Limitations of the included studies

The limitations were common to the majority of the studies and included studies being performed by only one centre [16], mostly referral centres for HCM, which means that the sample might not have been representative of the overall HCM population [8,12,13]. Additional selection biases were present, such as only including patients who were able to undergo exercise echocardiography [12] and exclusion of patients in NYHA class IV and with a prior LVEF < 50%. It was also noted either a tendency to include more symptomatic patients, because of clinical indication, in some studies [8,13,17] or, in one study, not including more symptomatic patients, since they were referred to surgery before undergoing stress testing [14]. Another limitation of some of the included articles was a small sample size [8,22,25].

In some of the studies, the patients did not withdraw medications (because it was considered unethical), such as beta-blockers and calcium channel blockers, which obviously influenced the hemodynamic response to exercise, diminishing the accuracy of defining an abnormal BP response, an abnormal chronotropic response and blunting the exercise-induced LVOT gradient [11,16].

Many studies were limited due to having a short follow-up period
report a group of parameters, obtained from either exercise echocardiography or cardiopulmonary testing, that revealed to be predictors of worse outcomes. These parameters are summarized in Fig. 2.

The relevance of performing exercise echocardiography to study LVOTO during exercise was firstly reported in 2006 [30] but only few groups have investigated the prognostic implications. The data correlating peak VO2 and other parameters obtained from cardiopulmonary exercise testing and prognosis have also been scarce.

As expected, some of the parameters evaluated both at rest and with exercise echocardiography in the included studies, including SAM, LVOTO and MR, appeared de novo or worsened with exercise, due to the cardiac response to stress.

Correlation of exercise-evaluated parameters with events was the main aim of this systematic review. One of these parameters was an abnormal BP response to exercise [11] has been previously considered a risk factor for SCD, although not included in the risk score evaluation from the latest ESC guidelines [1]. It was correlated with worse outcomes regarding heart failure hospitalization and with no increase in sudden cardiac death; this association was independent of LVOTO [28].

Abnormal BP response to exercise seemed to be a clinical indicator of a lack of cardiac reserve, rather than an independent risk factor for SCD. Exercise echocardiogram is also relevant to identify important subgroups of patients without gradients at rest (or with Valsalva) who nevertheless developed hemodynamically significant LV outflow obstruction only with exercise, including some with severe gradients, ≥50 mmHg. Indeed, a substantial proportion of these patients have limiting heart failure symptoms; therefore, identification of latent, exercise-triggered obstruction not only defines the probable mechanism limiting heart failure symptoms; therefore, identification of latent, exercise-triggered obstruction not only defines the probable mechanism of heart failure worsening, but it might also offer options for their relief [9].

AF in patients with HCM is considered to be a risk factor for cardiovascular death, heart failure, and stroke [31,32]. However there are no data regarding the prognostic impact of AF induced by exercise.

Regional exercise WMAs [10], probably explained by myocardial ischemia, were associated with a worse prognosis for HCM patients [11,13,21,25] and/or a reduced number of events [11,13,14,16].

Finally, some of the parameters were not uniformly assessed and hence not reported [12], which related to the fact that exercise echocardiography protocols are not standardized in HCM (some are performed in treadmill and others in semi-supine position, and the latter tends to require lower workload). Therefore, it might be challenging to compare different works.

Some of the studies were performed by the same authors and at the same centre, so there might be some overlap of study populations.

In general, the heterogeneity of the methods, reported parameters and outcomes precluded a meta-analysis.

A Downs and Black checklist is provided in supplementary material.

### 4. Discussion

We hereby present an up to date systematic review of contemporary studies evaluating the prognostic value of exercise testing in HCM and report a group of parameters, obtained from either exercise echocardiography or cardiopulmonary exercise testing, that revealed to be predictors of worse outcomes.

These parameters are summarized in Fig. 2.

Exercise testing, either echocardiographic or cardiopulmonary, allows the evaluation of diverse clinically relevant parameters in the assessment of HCM patients. The role of exercise testing is well defined for symptom evaluation and management. However, its utility in the prediction of outcomes, in order to obtain a more accurate risk stratification and improve the prognostic models, is less well established.

Table 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Heart rate at rest, bpm</th>
<th>Peak heart rate, bpm</th>
<th>HRR, bpm or % of patients with abnormal HRR</th>
<th>Systolic BP at rest, mmHg</th>
<th>Peak systolic BP, mmHg</th>
<th>ABPR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eftymiadis et al, 2010 [8] n = 68</td>
<td>74.9 ± 14.9</td>
<td>150.5 ± 24.5</td>
<td>–</td>
<td>123.9 ± 16.9</td>
<td>162.1 ± 29.9</td>
<td>–</td>
</tr>
<tr>
<td>Finocchiaro et al, 2015 n = 156</td>
<td>68 ± 13</td>
<td>139 ± 27</td>
<td>–</td>
<td>118 ± 20</td>
<td>222 ± 78</td>
<td>–</td>
</tr>
<tr>
<td>Ciampi et al, 2016 [18] n = 706</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>141(23)</td>
</tr>
<tr>
<td>Rigopoulos et al, 2018 [22] n = 21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9(43)</td>
</tr>
<tr>
<td>Smith et al, 2018 [23] n = 589</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>152.2 ± 24</td>
<td>192(33)</td>
</tr>
<tr>
<td>Magri et al, 2018 [24] n = 681</td>
<td>74 ± 15</td>
<td>131 ± 26</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ABPR: abnormal blood pressure response; HRR: Heart Rate Recovery; BP: blood pressure; bpm: beats per minute.
Predictors of outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Composite endpoint (CE)</th>
<th>Predictor of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desai et al, 2014 [12] n = 426</td>
<td>Death, appropriate ICD discharges, resuscitated sudden death, and admission for CHF</td>
<td>Abnormal heart rate recovery at 1 min in recovery: HR 0.89 (0.82–0.97), p = 0.007 &lt; 35 vs. 8% (p &lt; 0.001) meeting the CE</td>
</tr>
<tr>
<td>Eftimiadis et al, 2010 [8] n = 68</td>
<td>Cardiovascular death, ventricular tachycardia/ventricular fibrillation, and ICD discharge</td>
<td>Chronotropic incompetence group - low heart rate reserve (53.0 ± 4.0 bpm) - &gt; 15 vs 0% (p = 0.05) meeting the CE</td>
</tr>
<tr>
<td>Magri et al, 2018 [24] n = 681</td>
<td>HF endpoint (death from HF, cardiac transplantation, progression to NYHA class III-IV, admission for CHF, and septal reduction procedure)</td>
<td>pHr equal to 70% as the best cut-off value in predicting the HF endpoint HR 2.9 (p &lt; 0.001) (sensitivity: 62%; specificity: 72%; AUC: 0.68)</td>
</tr>
<tr>
<td>Arhythmia endpoint (SCD, aborted SCD and appropriate ICD shock)</td>
<td>pHr% equal to 65% as the best cut-off value in predicting the SCD end-point (sensitivity: 40%; specificity: 80%; AUC: 0.56)</td>
<td></td>
</tr>
<tr>
<td>Smith et al, 2018 [23] n = 589</td>
<td>HF endpoint (first heart failure hospitalization)</td>
<td>AbpR at baseline testing were more likely to have a subsequent heart failure hospitalization (p = 0.002). The presence or absence of LVOTD did not alter this association.</td>
</tr>
<tr>
<td>Arhythmia endpoint (SCD, aborted SCD and appropriate ICD shock)</td>
<td>The adverse arrhythmia endpoint was not associated with ABPR (p = 0.270)</td>
<td></td>
</tr>
<tr>
<td>Reant et al, 2014 [11] n = 115</td>
<td>Death related to HCM (SCD, death from HF, or stroke related to AF), SVT, appropriate cardiac shock or resuscitated cardiac arrest, and progression NYHA III or IV</td>
<td>Global longitudinal strain &lt;15%, HR 3.29 (p = 0.028); (sensitivity of 77%, and AUC 0.754)</td>
</tr>
<tr>
<td>Peteiro et al, 2012 [10] n = 220</td>
<td>Cardiac death, cardiac transplantation, appropriate ICD shock, SVT, stroke related to AF, myocardial infarction, and HF requiring hospitalization</td>
<td>Exercise WMAs were more frequent in patients who developed hard events (31.5% vs 5.9%, P &lt; 0.001)</td>
</tr>
<tr>
<td>Peteiro et al, 2015 [14] n = 148</td>
<td>Cardiac death, cardiac transplantation, appropriate ICD shock, SVT, stroke related to AF, myocardial infarction, and HF requiring hospitalization</td>
<td>Exercise WMAs were more frequent in patients who developed hard events (57 vs. 6%, P &lt; 0.001)</td>
</tr>
<tr>
<td>Finocchiaro et al, 2015 [13] n = 156</td>
<td>Overall mortality, heart transplantation, and functional deterioration leading to hospitalization for septal reduction</td>
<td>Peak VO &lt; 80% of predicted (HR: 4.11; 95% confidence interval [CI]: 1.46 to 11.59; p = 0.008)</td>
</tr>
<tr>
<td></td>
<td>Peak VO/VO2 &gt; 34 (HR: 3.14; 95% CI: 1.26 to 7.87: p = 0.014)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left atrial volume &gt; 40 ml/m2 (HR: 3.32; 95% CI: 1.08 to 10.16; p = 0.036)</td>
<td></td>
</tr>
<tr>
<td>Coats et al, 2015 [17] n = 1898</td>
<td>All-cause mortality or cardiac transplantation.</td>
<td>Peak VO2 (adjusted HR 0.85, 95% CI 0.77–0.92, P &lt; 0.001) and VE VO2 slope (adjusted HR 0.85, 95% CI 0.77–0.92, P &lt; 0.001) were both independent predictors of the CE</td>
</tr>
</tbody>
</table>

[14,33], having incremental prognostic value over clinical and resting echocardiographic variables.

Lower peak VO2 (as well as lower percentage of predicted peak VO2) and higher VE/VO2 slope, that reflects ventilatory inefficiency, are parameters of exercise intolerance and associated with a worse prognosis [13,17,20]. However, two of the studies [13,17] concluded that these were only related with some of the outcomes, namely heart failure and heart transplantation, and not with sudden cardiac death, probably because mechanisms for ventricular arrhythmia and loss of contractile function are different, suggesting the importance of defining prediction parameters for specific outcomes. The largest study [17] concluded that CPET was useful for the risk stratification of patients with both obstructive and non-obstructive forms of the disease. Lower anaerobic threshold was not as much predictive of worse outcomes as peak VO2 and VE/VO2.

Exercise capacity reflected as NYHA class is part of the criteria used to refer a patient to invasive septal reduction therapy, but a specific VO2 value/threshold is not currently used in this regard [1]. Recently Alashi et al [34] suggested that earlier myomectomy by surgery guided by VO2 had better long term survival, raising a new topic for discussion.

PH and/or EIPH appear to be the consequence of the increase of LV filling pressure secondary to diastolic dysfunction, LV obstruction, or mitral regurgitation, which could promote the occurrence of ventricular tachycardia [24]. Moreover, increased LV filling pressure results in atrial overload and remodeling, which might promote the occurrence of HF and AF. Indeed, PH in HCM patients was significantly associated with increased morbidity and EIPH also showed a significant association with HCM-related morbidity, perhaps because EIPH represents the downstream effect of the hemodynamic derangements that increase LV filling pressure during exercise [25].

Some of the assessed parameters were not consistently considered predictors of outcomes by all the studies. For example, indirect indices of diastolic dysfunction, such as LA diameter, were considered a predictor in two studies [13,16], but not in another one [10].

Severity and worsening of LVOTD (i.e. higher LVOT gradient at peak exercise) was predictive of outcomes in two studies [9,16], as well as in previous work [30,6], and not associated with events in two other [12,14]. One of the studies pointed out that peak LVOT gradient ≥50 mmHg was more predictive of outcomes than rest LVOT gradient ≥50 mmHg and that peak LVOT gradient was a better predictor than post-exercise measurement [11]. There is still conflicting evidence regarding the prognostic impact of exercise-induced LVOTD in HCM.

MR has been described in patients with HCM since the first reports of the disease and it is commonly associated with LVOTD and SAM. Since it is a dynamic phenomenon, it is important to evaluate this parameter during exercise. Exercise-induced MR was associated with adverse cardiovascular events in two studies [11,16], although in one of them [16] the result was not considered significant. As such, the increase in the degree of MR and its appearance de novo with exercise also seems to be of prognostic relevance.

Chronotropic incompetence (i.e. a blunted increase in heart rate during exercise, defined as a maximal HR during exercise that is less than 65–80% of the predicted value) is a predictor of clinical outcome in...
coronary artery disease, congenital heart disease and healthy populations [35–37]. In HCM, it is possibly explained by autonomic dysfunction, sino-atrial electrophysiological remodeling, altered beta-receptors function and density as well as impaired intracellular calcium signaling and was considered an independent predictor of exercise intolerance in one study [8], and an independent predictor of heart-failure related events in another study [24] – defined as a single exercise derived parameter.

In supplementary Table 3 we summarize all the current recommendations regarding the various forms of exercise stress testing in HCM, comparing 2014 ESC guidelines and 2020 AHA/ACC guidelines [1,3].

5. Conclusion

Data derived from exercise, which can be assessed with exercise echocardiography and/or cardiopulmonary exercise testing, is able to objectively evaluate functional status but also to risk stratify HCM patients, refining prognostic assessment. Further investigation in this area is warranted, namely larger, multi-center studies with longer follow-up and standardized stress protocols to evaluate whether exercise testing adds independent value to the current risk stratification strategies in HCM.

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Declaration of Competing Interest

None declared.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.06.051.

Fig. 2. Summary of the main findings of the systematic review. Legend: AF: atrial fibrillation, HF: heart failure, HCM: hypertrophic cardiomyopathy, ICD: implantable cardioverter-defibrillator, SVT: supraventricular tachycardia.

References


