Relationship between baseline resting diastolic function and exercise capacity in patients with hypertrophic cardiomyopathy undergoing treadmill stress echocardiography: a cohort study

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ABSTRACT

Objective: Diastolic dysfunction (DD) is often incriminated in the symptomatology of patients with hypertrophic cardiomyopathy (HCM), but with limited supporting data. This study sought to assess the relationship between baseline diastolic function and exercise capacity in patients with HCM.

Design: Retrospective study.

Setting: Tertiary referral centre from Cleveland, Ohio, USA.


Primary and secondary outcome measures: Diastolic function was reassessed from the resting echocardiograms by two blinded board-certified cardiologists. Maximal metabolic equivalents (MET) were extracted from the records. Multivariate regression analysis was performed to determine independent predictors of METs achieved.

Results: Of 695 patients, 130 were excluded because of inability to assess diastolic function. There was no significant difference in maximal METs achieved between those excluded and included in the analysis (p=0.80). There were 495 remaining patients with a mean age (SD) of 50 (15) years, and 32% women among whom 102 (21%) had normal diastolic function, 243 (49%) stage 1 DD; 131 (26%) stage 2 DD and 19 (4%) stage 3 DD. Patients with advanced DD had lower maximal METs achieved compared with those with normal diastolic function. After adjustment for demographics, comorbidities, echocardiographic parameters and haemodynamics, baseline DD was not an independent predictor of maximal METs achieved.

Conclusions: Although baseline DD is common in patients with HCM, it does not predict maximal METs achieved beyond traditional risk factors.

ARTICLE SUMMARY

Key messages
- Patients with advanced DD had lower maximal METs achieved compared with those with normal diastolic function.
- After adjustment for demographics, comorbidities, echocardiographic parameters and haemodynamics, baseline DD was not an independent predictor of maximal METs achieved.
- Routine treadmill exercise stress echocardiogram should be performed in patients with HCM when clinically indicated irrespective of baseline diastolic function.

INTRODUCTION

Exercise stress echocardiography testing in patients with hypertrophic cardiomyopathy (HCM) is commonly performed, particularly among those who are asymptomatic or have minimal symptoms.1 2 It is a useful non-invasive modality that has been adopted in clinical practice for several decades in such cohort, and is currently the standard of care at our institution. It provides relevant haemodynamic assessment including rest and stress...
left ventricular outflow tract gradients (LVOT), timing, location and degree of septal leaflet contact, dynamicity and mechanism of mitral regurgitation, blood pressure and heart rate recovery, and a more objective functional exercise capacity (metabolic equivalent (MET)) than New York Heart Association class, that guide the clinician with regard to individual prognosis as well as risk stratification.

Previous studies have documented a high prevalence of diastolic dysfunction (DD) in patients with HCM, both at a young age and early in the course of the disease. It has been postulated that impairment of left ventricular (LV) relaxation with or without elevated filling pressure that lead to DD, is associated with exercise intolerance among these patients. The contribution of DD on the reduced functional capacity observed in HCM has been previously evaluated in several small studies with conflicting results. We sought to evaluate whether baseline diastolic function is an independent predictor of maximal METs achieved in patients with HCM utilising a large contemporary single institution data set.

**Figure 1** Patient selection diagram.

**METHODS**

**Study design**

The study cohort consisted of consecutive patients with clinical and echocardiographic diagnosis of HCM who underwent an outpatient rest and treadmill stress echocardiogram at the Cleveland Clinic or its satellite facilities between 1 January 1996 and 31 December 2011. For patients with more than one stress echocardiogram, only the first one was retrieved for analysis. The rest and exercise stress echocardiogram were often performed on the same day or within the same week. Patients with prior myomectomy or alcohol septal ablation at the time of the first available stress test were excluded. Of 625 patients who were identified from the stress echocardiography database, 130 were excluded because of inability to assess diastolic function for various reasons (figure 1). There were 495 patients left for analysis.

**Exercise stress echocardiogram**

The methods for exercise treadmill testing in our laboratory have been described in detail previously. Briefly, standard protocols (Bruce, modified Bruce and Cornell) were chosen with goal test duration between 8 and 12 min. Patients were asked to hold ß-blockers (if any) at least 12–24 h prior to the stress testing. All patients exercised to exhaustion, irrespective of the achieved heart rate, and were asked not to hold on to the handrails. However, the test was terminated prematurely if patients developed severe chest pain, symptomatic hypotension, systolic blood pressure >250 mm Hg, significant arrhythmia, severe ST segment changes or per patient’s request. Patients were monitored for heart rate, blood pressure, rhythm, symptoms, ECG changes and rate of perceived exertion (on a 1–10 scale, where 10 is maximum exertion) at rest and at every stage of the exercise protocol. Exercise capacity in MET (1 MET=3.5 ml/kg/min of oxygen consumption) was estimated on the basis of the protocol, speed and grade achieved. Heart rate recovery was defined as the

**ARTICLE SUMMARY**

**Strengths and limitations of this study**

- This is the largest study to our knowledge to evaluate the relationship between diastolic function and METs in patients with HCM.
- The diastolic function was evaluated by two blinded echocardiography-board certified cardiologist.
- The study has the limitations of a retrospective study from a tertiary centre with selection and referral bias.
- One-fifth of patients were excluded because of inability to assess diastolic function for various reasons.
- Additional parameters that might influence diastolic function and exercise capacity such as aorta and ventricular stiffness, as well as diastology parameters at peak stress were not available.

Diastolic dysfunction and maximal METs in HCM

Echocardiographic methods
Patients were imaged in the left lateral decubitus position with commercially available systems, and images were acquired per standard protocol. Continuous and standard pulse Doppler imaging were performed across the LVOT to assess for gradients (frame rate ~50 Hz, sweep speed 50–100 mm/s), and with Nyquist velocity ~80–100 cm/s for pulse Doppler (no limit for continuous Doppler).

Diastolic function was assessed from the rest images in our institution in a standardised method by two echocardiography board certified cardiologists (WA and WJ) who were blinded to the functional exercise capacity of the patients, and retrieved the individual resting echocardiograms. Diastolic function was labelled as normal or abnormal (DD) and classified according to the American Society of Echocardiography guidelines. In studies prior to 2001 where tissue Doppler imaging was not routinely performed, DD was categorised as recently described and published: mild (stage 1, impaired relaxation without echocardiographic evidence of increased LV end-diastolic filling pressure (E:A ratio <0.80)), moderate (stage 2, pseudo-normal with increased LV end-diastolic filling pressure (E:A 0.75–1.5), deceleration time >150 ms, plus 2 other Doppler indices of elevated end-diastolic filling pressure such as blunted pulmonary veins, Ar-A≥30 ms, and dilated left atrium) and severe (stage 3, restrictive (E:A >1.5, deceleration time <150 ms and Doppler indices of elevated filling pressures)).

Owing to the limited number of patients with stage 3 DD (N=19), patients with stage ≥2 were grouped together in the final analysis. The reported LVEF was extracted from records and was based on visual assessment or quantification using Simpson’s methods of disks in accordance with published guidelines whenever possible. LV mass and LV mass index were calculated based on the formula: LV mass (g): 0.8 *(1.04 ((LVDD+PWTd+IVS)− (LVDD)±)− 0.6 g; LV mass index=LV mass/height² (g/m²). Left atrial volumes were remeasured and calculated using the area-length method (most commonly used at our institution) in accordance with the guidelines. Specifically, at the end of LV systole and before the opening of the mitral valve, the area of the LA was obtained from the 4-chamber and 2-chamber apical views; special care was made not to foreshorten the chambers, and the LA appendage and pulmonary veins were excluded from the tracing.

The stress echocardiogram images were acquired immediately at peak exercise, and focused on LV outflow gradients, degree of mitral regurgitation and wall motion.

Clinical data
Clinical data were entered into the stress echocardiography database at the time of stress testing and were subsequently retrieved for analysis.

Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at the time of the echocardiogram or clinic visits, self-reported history or the use of antihypertensive medications. Hyperlipidaemia was defined as abnormal fasting lipid panel according to the ATP III guidelines, self-reported history or the use of statins. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl, self-reported history or the use of hypoglycaemic medications. The study was approved by the Cleveland Clinic institutional review board with waiver of consent, and complied with the declaration of Helsinki.

Statistical analysis
Continuous data were expressed as mean (1 SD), and compared using one-way analysis of variance testing. Categorical data were displayed as frequencies and percentages, and comparisons were made using χ² tests or Fisher exact tests as appropriate.

Multivariate binary logistic regression was performed to identify factors independent predictors of maximal METs achieved. Maximal METs was used as dichotomous variables with a cut-off value of 7 which has been traditionally used and shown to be predictive of outcome. Interactions between diastolic function and age, left atrial volume index, body mass index, LV mass index and LV ejection fraction were tested for. The model was adjusted for age, gender, race, diabetes, smoking, coronary artery disease, chronic obstructive pulmonary disease, stroke, syncope, hypertension, prior atrial fibrillation, mitral regurgitation, resting heart rate, resting systolic blood pressure, Bruce versus non-Bruce protocol, body mass index, left atrial volume index, LV mass index, ejection fraction, interventricular septal thickness, LVOT gradient at rest, change of LVOT gradient with amyl nitrate, systolic anterior motion of the mitral valve, right ventricular systolic pressure and baseline diastolic function. The strength of the model was expressed using Nagelkerke R². All statistical tests were two sided. A p value <0.05 was set a priori and considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences, V.11.5, for Windows (SPSS, Chicago, Illinois, USA).

RESULTS
Of 625 patients with HCM initially screened and identified from the stress echocardiography database, 130 were excluded because of inability to measure diastolic function (figure 1). Diastolic function could not be assessed in five patients with prior mitral valve surgery (three mechanical, one bioprosthetic and one valve repair), six with atrial fibrillation during image acquisition, 37 with moderately severe or severe mitral regurgitation and 18 with incomplete diastology assessment. There were 64 studies that could not be retrieved from the archives (figure 1). There was no significant difference in maximal METs achieved or heart rate recovery,
mean (SD), between those excluded versus those included in the analysis (6.6 (2.5) vs 6.5(2.2) and 26(18) vs 27 (12), p=0.80 and 0.60, respectively).

There were 495 remaining patients with a mean age (SD) of 50 (15) years, 32% women. The prevalence of coronary or atherosclerotic cardiovascular disease was relatively low; 11% with known coronary artery disease and 1% with prior stroke (table 1). Almost a quarter of patients had prior history of syncope, and 3.8% had survived sudden cardiac death.

DD was present in 393 (79%) of patients, while only 102 (21%) had normal diastolic function. There were 245 (49%) patients with stage 1 DD, 131 (26%) stage 2 DD and 19 (4%) stage 3 DD. The latter two were grouped together as ≥ stage 2 DD.

Patients’ baseline characteristics, echocardiographic parameters and rest/stress haemodynamics are stratified by baseline diastolic function and shown in tables 1–3, respectively. Patients with DD were older, had more women, hypertensive and hyperlipidaemic patients as compared with those with normal diastolic function (table 1). Also, patients with DD had increased LV mass index, left atrial volumes, pulmonary hypertension, and a trend toward more significant mitral regurgitation (table 2). There was no significant difference in LV ejection fraction, interventricular septal thickness, resting LVOT gradients or systolic anterior movement of the mitral valve.

Only 53 (11%) patients exercised using Bruce protocol (the rest with Cornell or modified Bruce protocols), and had a significantly higher proportion of patients with normal diastolic function (22% vs 8%, p<0.0001; table 3). Furthermore, patients with DD had lower peak heart rate achieved, slower heart rate recovery, more abnormal Duke Treadmill scores, lower overall METs achieved and percentage METs ≥7 as compared with patients with normal baseline diastolic function (table 3). On univariate analysis, abnormal baseline DD was associated with threefold higher odds of having exercise intolerance (METs <7) (OR 3.18(1.96 to 5.14) for stage 1 vs normal diastolic function, and 3.21(1.89 to 5.43) for stage ≥2 vs normal diastolic function, p<0.0001 for both).

Using multivariate binary logistic regression analysis, and after adjusting for demographics, comorbidities, echocardiographic parameters and possible interactions, independent predictors of low functional capacity and achieving MET <7 were age, female gender, body mass index, interventricular septal thickness, left atrial volume index and resting LVOT gradient (Nagerkerke R²=0.501). Baseline diastolic function was not an independent predictor of functional exercise capacity or maximal MET achieved (p=0.9; table 4).

**DISCUSSION**

This is the largest study to our knowledge that evaluated the association between baseline diastolic function and exercise capacity in patients with HCM. In this retrospective study, the two main findings were: (1) baseline DD is prevalent in up to 79% of the cohort; (2) patients with DD had reduced exercise capacity and worse heart

### Table 1 Baseline characteristics of patients stratified by diastolic function

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Normal diastolic function (N=102)</th>
<th>Stage 1 DD (N=243)</th>
<th>Stage ≥2 DD (N=150)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) (years)</td>
<td>42 (14)</td>
<td>54 (13)</td>
<td>49 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>19 (19%)</td>
<td>84 (35%)</td>
<td>58 (39%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Race</td>
<td>97 (95%)</td>
<td>232 (95%)</td>
<td>137 (91%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Height, mean (SD) (cm)</td>
<td>176 (9)</td>
<td>171 (10)</td>
<td>171 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, mean (SD) (kg)</td>
<td>91 (19)</td>
<td>89 (18)</td>
<td>87 (20)</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI, mean (SD) (kg/m²)</td>
<td>29 (5)</td>
<td>30 (5)</td>
<td>25 (5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (21%)</td>
<td>109 (45%)</td>
<td>50 (33%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>17 (17%)</td>
<td>93 (38%)</td>
<td>44 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (4%)</td>
<td>22 (9%)</td>
<td>7 (5%)</td>
<td>0.17</td>
</tr>
<tr>
<td>History of smoking</td>
<td>36 (35%)</td>
<td>116 (48%)</td>
<td>70 (47%)</td>
<td>0.091</td>
</tr>
<tr>
<td>COPD</td>
<td>0 (0%)</td>
<td>7 (3%)</td>
<td>3 (2%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (7%)</td>
<td>33 (14%)</td>
<td>15 (10%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>1 (1%)</td>
<td>6 (2.5%)</td>
<td>1 (0.7%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1 (1%)</td>
<td>5 (2.1%)</td>
<td>1 (0.7%)</td>
<td>0.48</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>11 (11%)</td>
<td>32 (13%)</td>
<td>32 (21%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0%)</td>
<td>2 (0.8%)</td>
<td>3 (2%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Syncope</td>
<td>30 (29%)</td>
<td>629 (25%)</td>
<td>26 (17%)</td>
<td>0.060</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>3 (2.9%)</td>
<td>8 (3.3%)</td>
<td>8 (5.3%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Creatinine, mean (SD) (mg/dl)</td>
<td>0.73 (0.19)</td>
<td>0.68 (0.21)</td>
<td>0.62 (0.20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DD, diastolic function.
rate recovery compared to those with normal diastolic function; however, DD was not an independent predictor of maximal-METs achieved beyond traditional risk factors.

HCM is a common genetic condition affecting ∼1/500 patients. Despite having preserved LV systolic function, patients may present with heart failure symptoms or could be completely asymptomatic. Exercise stress echocardiography is a non-invasive method to objectively assess function capacity of patients, which is often reduced as compared to an age- and gender-matched normal cohort. Impaired LV diastolic function is prevalent in more than 50% of young patients and early in the course of the disease.

### Table 2

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>Normal diastolic function (N=102)</th>
<th>Stage 1 DD (N=243)</th>
<th>Stage ≥ 2DD (N=150)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDD/height, mean (SD) (cm/m)</td>
<td>2.3 (0.3)</td>
<td>2.4 (0.4)</td>
<td>2.4 (0.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>LVDS/height, mean (SD) (cm/m)</td>
<td>1.3 (0.3)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>LVEF, mean (SD) (%)</td>
<td>61 (5)</td>
<td>62 (5)</td>
<td>60 (5)</td>
<td>0.091</td>
</tr>
<tr>
<td>IVS, mean (SD) (cm)</td>
<td>2.1 (0.5)</td>
<td>2.0 (0.5)</td>
<td>2.2 (0.6)</td>
<td>0.081</td>
</tr>
<tr>
<td>PWT mean (SD) (cm)</td>
<td>1.3 (0.3)</td>
<td>1.3 (0.3)</td>
<td>1.4 (0.3)</td>
<td>0.053</td>
</tr>
<tr>
<td>LV mass, mean (SD) (g)</td>
<td>287 (91)</td>
<td>289 (103)</td>
<td>316 (112)</td>
<td>0.036</td>
</tr>
<tr>
<td>LV mass index, mean (SD) (g/m²)</td>
<td>63 (19)</td>
<td>68 (24)</td>
<td>73 (23)</td>
<td>0.003</td>
</tr>
<tr>
<td>RVSP, mean (SD) (mm Hg)</td>
<td>28 (8)</td>
<td>30 (8)</td>
<td>35 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA size, mean (SD) (cm)</td>
<td>4.3 (0.7)</td>
<td>4.3 (0.7)</td>
<td>4.6 (0.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>LA area, mean (SD) (cm²)</td>
<td>21 (6)</td>
<td>24 (8)</td>
<td>25 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>LAVI, mean (SD) (ml/m²)</td>
<td>32 (12)</td>
<td>43 (21)</td>
<td>45 (21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVOT rest gradient, mean (SD) (mm Hg)</td>
<td>35 (37)</td>
<td>42 (40)</td>
<td>40 (39)</td>
<td>0.40</td>
</tr>
<tr>
<td>LVOT gradient postamyl nitrate, mean (SD) (mm Hg)</td>
<td>69 (42)</td>
<td>79 (45)</td>
<td>65 (41)</td>
<td>0.068</td>
</tr>
<tr>
<td>Resting SAM*</td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Mild</td>
<td>93 (91%)</td>
<td>48 (86%)</td>
<td>134 (89%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (4%)</td>
<td>17 (7%)</td>
<td>6 (4%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5 (5%)</td>
<td>17 (7%)</td>
<td>10 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
<td></td>
<td></td>
<td>0.077</td>
</tr>
<tr>
<td>None or mild</td>
<td>65 (64%)</td>
<td>136 (56%)</td>
<td>74 (49%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>37 (36%)</td>
<td>107 (44%)</td>
<td>76 (51%)</td>
<td></td>
</tr>
</tbody>
</table>

*None or mild SAM was defined as systolic anterior movement of the mitral valve with >1 cm separation from the interventricular septum; moderate SAM if the separation was 0.5–1.0 cm; and severe SAM if the separation was <0.5 cm or there was septal contact.

### Table 3

<table>
<thead>
<tr>
<th>Haemodynamics</th>
<th>Normal diastolic function (N=102)</th>
<th>Stage 1 DD (N=243)</th>
<th>Stage ≥ 2DD (N=150)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce protocols</td>
<td>22 (22%)</td>
<td>20 (8%)</td>
<td>11 (7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rest HR, mean (SD) (bpm)</td>
<td>65 (10)</td>
<td>66 (11)</td>
<td>64 (11)</td>
<td>0.20</td>
</tr>
<tr>
<td>SBP, mean (SD) (mm Hg)</td>
<td>122 (15)</td>
<td>128 (20)</td>
<td>120 (19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mean (SD) (mm Hg)</td>
<td>79 (12)</td>
<td>81 (10)</td>
<td>76 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Max HR, mean (SD) (bpm)</td>
<td>148 (25)</td>
<td>131 (24)</td>
<td>131 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak SBP, mean (SD) (mm Hg)</td>
<td>157 (30)</td>
<td>166 (33)</td>
<td>149 (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak DBP, mean (SD) (mm Hg)</td>
<td>25 (12)</td>
<td>26 (12)</td>
<td>25 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HRR, mean (SD) (bpm)</td>
<td>12 (12%)</td>
<td>26 (11%)</td>
<td>14 (9%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Normal</td>
<td>35 (34%)</td>
<td>67 (28%)</td>
<td>24 (16%)</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>17 (17%)</td>
<td>56 (23%)</td>
<td>26 (17%)</td>
<td></td>
</tr>
<tr>
<td>Uninterpretable due to abnormal baseline ST</td>
<td>50 (49%)</td>
<td>120 (49%)</td>
<td>10 (67%)</td>
<td></td>
</tr>
<tr>
<td>METs achieved</td>
<td>7.7 (2.3)</td>
<td>6.3 (2.0)</td>
<td>6.2 (2.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>METs≥7</td>
<td>60 (59%)</td>
<td>76 (31%)</td>
<td>47 (31%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; DD, diastolic dysfunction; HR, heart rate; HRR, heart rate recovery; Max, (maximal; MET, metabolic equivalent; SBP, systolic blood pressure.
Diastolic dysfunction and maximal METs in HCM

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Independent predictors of achieved maximal METs &lt;7 using binary logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>SE</td>
</tr>
<tr>
<td>Constant</td>
<td>−10.6</td>
</tr>
<tr>
<td>Age</td>
<td>0.034</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.40</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>0.16</td>
</tr>
<tr>
<td>LAVI</td>
<td>0.019</td>
</tr>
<tr>
<td>IVS</td>
<td>1.180</td>
</tr>
<tr>
<td>Resting LVOT gradient (per 10 mm Hg)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Nagelkerke R²=0.44.

The model was adjusted for age, gender, race, diabetes, smoking, coronary artery disease, chronic obstructive pulmonary disease, stroke, syncope, hypertension, prior atrial fibrillation, mitral regurgitation, resting heart rate, resting systolic blood pressure, Bruce protocol, body mass index, left atrial volume index (LAVI), interventricular septal thickness (IVS); left ventricular mass index (LVMI), ejection fraction (EF), left ventricular outflow (LVOT) gradient at rest, change of gradient with amyl nitrate, systolic anterior motion of the mitral valve, right ventricular systolic pressure and baseline diastolic function. Interactions between diastolic function and age, BMI, LAVI, LVMI, EF were tested and entered into the model.

Nagelkerke R²=0.44.

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and has been proposed to be the link to impaired exercise tolerance.

There have been several studies of small sample size that investigated this hypothesis, some with conflicting results. Lele et al. found no correlation between maximal oxygen consumption (V02) and time to peak filling at rest in 46 patients with HCM, nor did Nihoyannopoulos et al. between V02 and resting Doppler indices (N=40). On the other hand, lateral e' was shown to correlate with functional capacity (r=0.50, p=0.001) and mitral E/e' was significantly higher in patients with HCM versus control (p<0.0001). However, neither parameter was independently predictive of oxygen consumption nor added incremental value. Similarly, the transmitral E to lateral e' ratio was shown to negatively correlate with functional capacity (V02) (r=−0.42, p<0.0001) in 85 patients with HCM, but no multivariate regression analysis was performed to assess its independent value beyond the known covariate.

The relationship between left atrial volume index and pressure on functional capacity in HCM has also been investigated. In one study (N=93), left atrial volume index was an independent predictor of exercise tolerance and similar to our findings; while another study showed that pulmonary capillary wedge pressure (a surrogate of left atrial pressure) was not predictive. It is a bit peculiar that LAVI (a reflection of long-term LV DD) was predictive of functional capacity while DD was not. We did however adjust for possible interaction and for mitral regurgitation (which may affect LAVI) in the multivariate analysis (table 4).

Our study showed that patients with worse DD had impaired exercise tolerance with odd ratio ∼ 3.0 (table 3). However, these patients were older and had more women, LV hypertrophy, dilated left atrium and hypertension (tables 1 and 2). After adjusting for these confounders and other relevant ones (table 4), baseline diastolic function was not an independent predictor of maximal METs achieved. Routine exercise stress echocardiogram therefore should remain a valid tool in the care of patients with HCM irrespective of baseline diastolic function to assess their functional capacity.

Strengths and limitations

This is the largest study to our knowledge that assessed the association between diastolic function and functional capacity in HCM. Diastolic function was evaluated by two blinded board-certified cardiologists who reviewed all the echocardiograms. However, we acknowledge several limitations. This is a retrospective study from a single tertiary centre with likely referral and selection bias. Twenty-one per cent of patients were excluded because of inability to assess diastolic function; however, there was no difference in functional capacity between those included and excluded from the study. The relatively high number of indeterminate or missing diastolic function, however, is not unusual and is comparable to other studies. The Devereux’ formula which uses linear measurements at one level of the LV to calculate LV mass in patients with asymmetrical HCM is not accurate. While we adjusted for many of the known determinants of exercise capacity, additional parameters that have been shown to influence diastolic function such as LV volumes/mass ratio, and those that correlate with exercise capacity such as aortic stiffness, N-terminal-pro-type natriuretic peptide, LV chamber stiffness, atrial systolic failure, LV systolic performance, and worsening of LV diastolic parameters at peak stress, were not available in the database for analysis. Furthermore, maximal oxygen consumption was not available since these patients had regular treadmill stress echocardiograms; however, maximal METs is a reflection of exercise capacity and has strong prognostic value. Current study evaluating patients with HCM who had undergone metabolic stress testing is in progress.

CONCLUSION

Baseline DD is common in patients with HCM undergoing exercise stress echocardiogram, but is not an independent predictor of maximal METs achieved or
functional capacity beyond traditional factors. Routine treadmill exercise stress echocardiogram should be performed in patients with HCM when clinically indicated irrespective of baseline diastolic function.

Contributors WA, MD, NS, LR, VM, MT, HL and WJ participated in study concept and design. WA, WJ, MCA, MD, HL and MT were involved in data collection. WA, WJ and MCA participated in data analysis. WA, WJ, HL, MD, MT, LR, RG and VM participated in critical review. WA and WJ were the responsible contributors for the overall content.

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