

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

Wael A AlJaroudi,^{1,2} Milind Y Desai,¹ M Chadi Alraies,¹ Maran Thamilarsan,¹ Venu Menon,¹ L Leonardo Rodriguez,¹ Nicholas Smedira,¹ Richard A Grimm,¹ Harry M Lever,¹ Wael A Jaber¹

To cite: AlJaroudi WA, Desai MY, Alraies MC, *et al*. Relationship between baseline resting diastolic function and exercise capacity in patients with hypertrophic cardiomyopathy undergoing treadmill stress echocardiography: a cohort study. *BMJ Open* 2012;**2**: e002104. doi:10.1136/bmjopen-2012-002104

► Prepublication history for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-002104>).

Received 12 September 2012
Revised 12 September 2012
Accepted 11 October 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

¹Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio, USA

²Department of Cardiovascular Medicine, American University of Beirut, Beirut, Lebanon

Correspondence to

Dr Wael AlJaroudi;
wjaroudi@hotmail.com

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.

Participants: 695 consecutive patients with a diagnosis of HCM who underwent exercise stress echocardiography between 1996 and 2011.

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 (OR 3.18(1.96 to 5.14) for stage 1 versus normal, and 3.21(1.89 to 5.43) for stage ≥ 2 versus normal, $p<0.0001$ for both). 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

Article focus

- Diastolic dysfunction (DD) is often incriminated in the symptomatology of patients with hypertrophic cardiomyopathy (HCM).
- 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 metabolic equivalent (METs) achieved in patients with HCM utilising a large contemporary single institution data set.

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

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.

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,² and a more objective functional exercise capacity (metabolic equivalent (MET)) than New York Heart Association class,¹ that guide the clinician with regard to individual prognosis as well as risk stratification.^{3,4}

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.⁵ 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.⁵ The contribution of DD on the reduced functional capacity observed in HCM has been previously evaluated in several small studies with conflicting results.⁶⁻¹⁷ 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.

METHODS

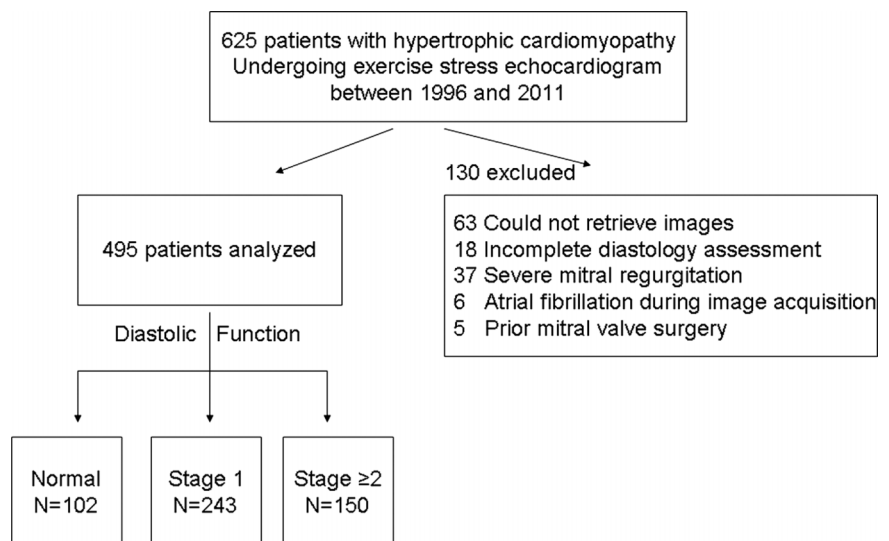
Study design

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.¹⁸ Briefly, standard protocols (Bruce, modified Bruce and Cornell) were chosen with goal test duration between 8 and 12 min. Patients were asked to hold β -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.^{19,20} Heart rate recovery was defined as the

Figure 1 Patient selection diagram.



change in heart rate between peak exercise and 1 min of recovery.¹⁸

Echocardiographic methods

Patients were imaged in the left lateral decubitus position with commercially available systems, and images were acquired per standard protocol. Continuous and 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.²¹ In studies prior to 2001 where tissue Doppler imaging was not routinely performed, DD was categorised as recently described and published:²² 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-A₂≥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)).²³ 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.²⁴ LV mass and LV mass index were calculated based on the formula: $LV\ mass\ (g): 0.8 * (1.04 ((LVDD+PWTD+IVS)^3 - (LVDD)^3)) + 0.6\ g$; $LV\ mass\ index = LV\ mass / height^{2.7} (g/m^{2.7})$.^{25, 26} Left atrial volumes were remeasured and calculated using the area-length method (most commonly used at our institution) in accordance with the guidelines.²⁴ 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 χ^2 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.²⁷ 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 R-square. 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 243 (49%) patients with stage 1 DD, 131 (26%) stage 2 DD and 19 (4%) stage 3 DD. The latter two were grouped together as \geq 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 \geq 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 \geq 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 (Nagerlkerke 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

	Normal diastolic function (N=102)	Stage 1 DD (N=243)	Stage \geq 2 DD (N=150)	p Value
Demographics				
Age, mean (SD) (years)	42 (14)	54 (13)	49 (15)	<0.0001
Female	19 (19%)	84 (35%)	58 (39%)	0.002
Race	97 (95%)	232 (95%)	137 (91%)	0.21
Height, mean (SD) (cm)	176 (9)	171 (10)	171 (11)	<0.0001
Weight, mean (SD) (kg)	91 (19)	89 (18)	87 (20)	0.26
BMI, mean (SD) (kg/m ²)	29 (5)	30 (5)	29 (5)	0.39
Comorbidities				
Hypertension	21 (21%)	109 (45%)	50 (33%)	<0.0001
Hyperlipidaemia	17 (17%)	93 (38%)	44 (29%)	<0.0001
Diabetes	5 (4%)	22 (9%)	7 (5%)	0.17
History of smoking	36 (35%)	116 (48%)	70 (47%)	0.091
COPD	0 (0%)	7 (3%)	3 (2%)	0.22
Coronary artery disease	7 (7%)	33 (14%)	15 (10%)	0.17
Prior myocardial infarction	1 (1%)	6 (2.5%)	1 (0.7%)	0.33
Prior CABG	1 (1%)	5 (2.1%)	1 (0.7%)	0.48
History of atrial fibrillation	11 (11%)	32 (13%)	32 (21%)	0.035
Stroke	0 (0%)	2 (0.8%)	3 (2%)	0.27
Syncope	30 (29%)	62 (25%)	26 (17%)	0.060
Sudden cardiac death	3 (2.9%)	8 (3.3%)	8 (5.3%)	0.51
Creatinine, mean (SD) (mg/dl)	0.73 (0.19)	0.66 (0.21)	0.62 (0.20)	<0.0001

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DD, diastolic function.

Table 2 Resting echocardiographic parameters stratified by diastolic function

Echocardiographic parameters	Normal diastolic function (N=102)	Stage 1 DD (N=243)	Stage ≥ 2DD (N=150)	p Value
LVIDD/height, mean (SD) (cm/m)	2.3 (0.3)	2.4 (0.4)	2.4 (0.4)	0.27
LVIDS/height, mean (SD) (cm/m)	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	0.53
LVEF, mean (SD) (%)	61 (5)	62 (5)	60 (5)	0.091
IVS, mean (SD) (cm)	2.1 (0.5)	2.0 (0.5)	2.2 (0.6)	0.081
PWT mean (SD) (cm)	1.3 (0.3)	1.3 (0.3)	1.4 (0.3)	0.053
LV mass, mean (SD) (g)	287 (91)	289 (103)	316 (112)	0.036
LV mass index, mean (SD) (g/m ^{2.7})	63 (19)	68 (24)	73 (23)	0.003
RVSP, mean (SD) (mm Hg)	28 (8)	30 (8)	35 (10)	<0.0001
LA size, mean (SD) (cm)	4.3 (0.7)	4.3 (0.7)	4.6 (0.8)	0.012
LA area, mean (SD) (cm ²)	21 (6)	24 (8)	25 (8)	0.002
LAVI, mean (SD) (ml/m ²)	32 (12)	43 (21)	45 (21)	<0.0001
LVOT rest gradient, mean (SD) (mm Hg)	35 (37)	42 (40)	40 (39)	0.40
LVOT gradient postamyl nitrate, mean (SD) (mm Hg)	69 (42)	79 (45)	65 (41)	0.068
Resting SAM*				0.59
Mild	93 (91%)	48 (86%)	134 (89%)	
Moderate	4 (4%)	17 (7%)	6 (4%)	
Severe	5 (5%)	17 (7%)	10 (7%)	
Mitral regurgitation				0.077
None or mild	65 (64%)	136 (56%)	74 (49%)	
Moderate	37 (36%)	107 (44%)	76 (51%)	

*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. DD, diastolic dysfunction; IVS, interventricular septum; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; LVIDD, left ventricular internal diameter, end-diastole; LVIDS, left ventricular internal diameter, end-systole; LVOT, left ventricular outflow tract; PWT, posterior wall thickness; RVSP, right ventricular systolic pressure; SAM, systolic anterior motion of the mitral valve.

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,¹ which is often reduced as compared to an age-matched and gender-matched normal cohort.⁸ Impaired LV diastolic function is prevalent in more than 50% of young patients and early in the course of the disease,⁵

Table 3 Rest and stress haemodynamics

Haemodynamics	Normal diastolic function (N=102)	Stage 1 DD (N=243)	Stage ≥ 2DD (N=150)	p Value
Bruce protocols	22 (22%)	20 (8%)	11 (7%)	<0.0001
Rest HR, mean (SD) (bpm)	65 (10)	66 (11)	64 (11)	0.20
SBP, mean (SD) (mm Hg)	122 (15)	128 (20)	120 (19)	<0.0001
DBP, mean (SD) (mm Hg)	79 (12)	81 (10)	76 (11)	<0.0001
Max HR, mean (SD) (bpm)	148 (25)	131 (24)	131 (27)	<0.0001
Peak SBP, mean (SD) (mm Hg)	157 (30)	166 (33)	149 (32)	<0.0001
Peak DBP, mean (SD) (mm Hg)	82 (12)	85 (12)	79 (13)	<0.0001
HRR, mean (SD) (bpm)	32 (10)	26 (12)	25 (13)	<0.0001
Hypotension	12 (12%)	26 (11%)	14 (9%)	0.82
Duke treadmill score				0.006
Normal	35 (34%)	67 (28%)	24 (16%)	
Abnormal	17 (17%)	56 (23%)	26 (17%)	
Uninterpretable due to abnormal baseline ST	50 (49%)	120 (49%)	10 (67%)	
METs achieved	7.7 (2.3)	6.3 (2.0)	6.2 (2.4)	<0.0001
METs _≥ 7	60 (59%)	76 (31%)	47 (31%)	<0.0001

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

Table 4 Independent predictors of achieved maximal METs <7 using binary logistic regression

	B	SE	Wald	OR	95% CI	p Value
Constant	-10.6	2.01	28			<0.0001
Age	0.034	0.014	6.39	1.035	1.008 to 1.063	0.011
Female gender	2.40	0.46	27.63	11.0	4.47 to 27.0	<0.0001
Body mass index (BMI)	0.16	0.042	15.4	1.179	1.086 to 1.280	<0.0001
LAVI	0.019	0.010	3.96	1.019	1.00 to 1.038	0.047
IVS	1.180	0.39	8.92	3.26	1.501 to 7.064	0.003
Resting LVOT gradient (per 10 mm Hg)	0.24	0.12	3.85	1.27	1.01 to 1.62	0.050

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.

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*⁹ found no correlation between maximal oxygen consumption (V_{O2}) and time to peak filling at rest in 46 patients with HCM, nor did Nihoyannopoulos *et al*⁸ between V_{O2} 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)¹⁶ and mitral E/e' was significantly higher in patients with HCM versus control (p<0.0001);¹² 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 (V_{O2}) (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.¹¹

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 tolerance¹² and similar to our findings; while another study showed that pulmonary capillary wedge pressure (a surrogate of left atrial pressure) was not predictive.⁶ 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.²²⁻²⁸ 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,²⁹ and those that correlate with exercise capacity such as aortic stiffness,¹⁷ N-terminal-pro-type natriuretic peptide,¹³ LV chamber stiffness,¹⁴ atrial systolic failure,⁷ LV systolic performance,⁷ and worsening of LV diastolic filling parameters at peak stress,¹⁵ 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.²⁷ 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.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Ethics approval Ethics approval was provided by the Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

- Sharma S, Firoozi S, McKenna WJ. Value of exercise testing in assessing clinical state and prognosis in hypertrophic cardiomyopathy. *Cardiol Rev* 2001;9:70–6.
- Wu WC, Bhavsar JH, Aziz GF, et al. An overview of stress echocardiography in the study of patients with dilated or hypertrophic cardiomyopathy. *Echocardiography* 2004;21:467–75.
- Sorajja P, Allison T, Hayes C, et al. Prognostic utility of metabolic exercise testing in minimally symptomatic patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2012;109:1494–8.
- Peteiro J, Bouzas-Mosquera A, Fernandez X, et al. Prognostic value of exercise echocardiography in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2010;25:182–9.
- Yetman AT, Gow RM, Seib P, et al. Exercise capacity in children with hypertrophic cardiomyopathy and its relation to diastolic left ventricular function. *Am J Cardiol* 2001;87:491–3, A8.
- Frenneaux MP, Porter A, Caforio AL, et al. Determinants of exercise capacity in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1989;13:1521–6.
- Chikamori T, Counihan PJ, Doi YL, et al. Mechanisms of exercise limitation in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1992;19:507–12.
- Nihoyannopoulos P, Karatasakis G, Frenneaux M, et al. Diastolic function in hypertrophic cardiomyopathy: relation to exercise capacity. *J Am Coll Cardiol* 1992;19:536–40.
- Lele SS, Thomson HL, Seo H, et al. Exercise capacity in hypertrophic cardiomyopathy. Role of stroke volume limitation, heart rate, and diastolic filling characteristics. *Circulation* 1995;92:2886–94.
- Briguori C, Betocchi S, Romano M, et al. Exercise capacity in hypertrophic cardiomyopathy depends on left ventricular diastolic function. *Am J Cardiol* 1999;84:309–15.
- Matsumura Y, Elliott PM, Virdee MS, et al. Left ventricular diastolic function assessed using Doppler tissue imaging in patients with hypertrophic cardiomyopathy: relation to symptoms and exercise capacity. *Heart* 2002;87:247–51.
- Kjaergaard J, Johnson BD, Pellikka PA, et al. Left atrial index is a predictor of exercise capacity in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2005;18:1373–80.
- Thaman R, Esteban MT, Barnes S, et al. Usefulness of N-terminal pro-B-type natriuretic peptide levels to predict exercise capacity in hypertrophic cardiomyopathy. *Am J Cardiol* 2006;98:515–19.
- Dumont CA, Monserrat L, Peteiro J, et al. Relation of left ventricular chamber stiffness at rest to exercise capacity in hypertrophic cardiomyopathy. *Am J Cardiol* 2007;99:1454–7.
- Choi EY, Ha JW, Rim SJ, et al. Incremental value of left ventricular diastolic function reserve index for predicting exercise capacity in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2008;21:487–92.
- Le VV, Perez MV, Wheeler MT, et al. Mechanisms of exercise intolerance in patients with hypertrophic cardiomyopathy. *Am Heart J* 2009;158:e27–34.
- Austin BA, Popovic ZB, Kwon DH, et al. Aortic stiffness independently predicts exercise capacity in hypertrophic cardiomyopathy: a multimodality imaging study. *Heart* 2010;96:1303–10.
- Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;341:1351–7.
- Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85:546–62.
- Jette M, Sidney K, Blumchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990;13:555–65.
- Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33.
- Kane G, Karon B, Mahoney D, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856–63.
- Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997;30:8–18.
- Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
- Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–8.
- de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992;20:1251–60.
- Weiner DA, Ryan TJ, McCabe CH, et al. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *J Am Coll Cardiol* 1984;3:772–9.
- AlJaroudi W, Alraies M, Halley C, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. *Circulation* 2012;125:782–8.
- Buakhamsri A, Popovic ZB, Lin J, et al. Impact of left ventricular volume/mass ratio on diastolic function. *Eur Heart J* 2009;30:1213–21.