Published in final edited form as:

Am Heart J. 2017 February ; 184: 47–54. doi:10.1016/j.ahj.2016.10.010.

Safety Profile and Utility of Treadmill Exercise in Patients with High Gradient Hypertrophic Cardiomyopathy

Lars Lindholm Sorensen^{1,2}, Hsin-Yueh Liang^{1,3}, Aurelio Pinheiro¹, Alex Hilser¹, Veronica Dimaano¹, Niels Thue Olsen⁴, Thomas Fritz Hansen², Peter Sogaard⁵, Alexandra Nowbar¹, Chiara Pisanello¹, Iraklis Pozios¹, Susan Philip¹, Xun Zhou¹, Roselle Abraham¹, and Theodore P. Abraham¹

¹Division of Cardiology, Johns Hopkins Medical Institutions

²Department of Cardiology, Gentofte Hospital, Copenhagen Denmark

³China medical University, Taichung, Taiwan

⁴Department of Cardiology, Rigshospitalet, Copenhagen Denmark

⁵Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

Abstract

Background—Exercise echocardiography in the evaluation of Hypertrophic Cardiomyopathy (HCM) provides valuable information for risk stratification, selection of optimal treatment and prognostication. However, HCM patients with left ventricular outflow (LVOT) gradients ≥ 30 mmHg are often excluded from exercise testing because of safety considerations. We examined the safety and utility of exercise testing in high-gradient HCM patients.

Methods—We evaluated clinical characteristics, hemodynamics and imaging variables in 499 consecutive HCM patients who performed 959 exercise tests. Patients were divided on the basis of peak LVOT gradients using a 30 mmHg threshold into: obstructive (n=152), labile-obstructive (n=178) and non-obstructive (n=169) groups.

Results—There were no deaths during exercise testing. We noted 20 complications (2.1% of tests) including 3 serious ventricular arrhythmias (0.3% of tests). There was no difference in complication rate between groups. Obstructive HCM patients had a higher frequency of abnormal blood pressure response (obstructive: 53% versus labile-obstructive: 41% and non-obstructive: 37%, $p=0.008$). Obstructive patients also displayed a lower work capacity (obstructive: 8.4 ± 3.4 versus labile-obstructive: 10.9 ± 4.2 and non-obstructive: 10.2 ± 4.0 , METs, $p<0.001$). Exercise testing provided incremental information regarding sudden cardiac death risk in 19% of high

Address for correspondence: Theodore P. Abraham, Johns Hopkins University, 600 North Wolfe Street, Carnegie 568, Baltimore, MD 21287, Tel: 410 502 7974, Fax: 410 955 1509, tabraha3@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: All Authors report no conflict of interests.

gradient HCM patients and we found poor correlation between patient-reported functional class and work capacity.

Conclusion—Our results suggest that exercise testing in HCM is safe and serious adverse events are rare. Although numbers are limited, exercise testing in high gradient HCM appears to confer no significant additional safety hazard in our selected cohort and could potentially provide valuable information.

Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common cardiac genetic disorder and is characterized by left ventricular hypertrophy, myocyte, disarray and fibrosis. Other causes of LVH such as hypertension, storage diseases and athletes should be excluded. Variations in pattern of hypertrophy, systolic anterior motion of the mitral valve and left ventricular outflow tract (LVOT) obstruction are commonly seen even in patients carrying the same mutation. A significant proportion of patients diagnosed with HCM develop arrhythmias, chest pain and/or heart failure symptoms requiring interventions such as defibrillator implantation and myectomy/alcohol septal ablation.^{1–3} Exercise stress testing is widely used to evaluate patients with HCM. Exercise echocardiography is used for diagnosing patients with labile-obstruction, who despite of absence of LVOT obstruction at rest have significant LVOT obstruction at exercise⁴ and therefore need intensive medical therapy or even septal reduction procedures.⁵ Standard exercise testing helps assess the risk for sudden cardiac death (SCD) and permits an objective assessment of functional capacity.^{6, 7} Furthermore it helps in providing patients with a tailored exercise regimen and can provide information on autonomic function in HCM.⁸ While exercise has been shown to ameliorate hypertrophy in mouse models of HCM, it can also serve as a trigger for ventricular arrhythmias and sudden death.^{6, 9} Hence, in clinical practice, HCM patients with high LVOT pressure gradients, e.g. over 30 mmHg, are often excluded from exercise testing, because of safety considerations and controversy about the usefulness of the test in this group of patients.^{4, 10} In the recent ACC/AHA guidelines stress testing has IIA recommendations under the following circumstances: 1) *“Treadmill exercise testing is reasonable to determine functional capacity and response to therapy in patients with HCM”*. 2) *“Treadmill testing with monitoring of an ECG and blood pressure is reasonable for SCD risk stratification in patients with HCM”*. 3) *“In patients with HCM who do not have a resting LVOT instantaneous gradient of greater than or equal to 50 mmHg, exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction”*. However, current guidelines provide little guidance in patients with gradients >50 mmHg.¹¹

In this study we report the utility, safety and clinical profile of 499 consecutive HCM patients undergoing 959 treadmill exercise tests.

Methods

Study Population

This study was approved by the Johns Hopkins institutional review board. We enrolled 499 consecutive HCM patients referred for treadmill stress at the Johns Hopkins HCM clinic in

the period February 2005 to October 2013. All patients fulfilled the criteria for a diagnosis of HCM defined as unexplained hypertrophy with a maximal wall thickness above 15 mm in the absence of other cardiac or systemic condition capable of producing a similar degree of left ventricular hypertrophy. Patients with a maximal wall thickness of 13–15 mm were diagnosed with HCM in case of other features suggestive of HCM such as systolic anterior motion (SAM), elevated LVOT gradients, family history of HCM or positive genetic test.¹¹ Information about medical history and use of medication was collected during the initial visit in the HCM clinic. The cohort was separated according to recent guidelines into a non-obstructive group (resting peak LVOT gradient <30 mmHg and exercise peak LVOT gradient < 30 mmHg), a labile-obstructive group (resting peak LVOT gradient <30 mmHg and exercise peak LVOT gradient ≥ 30 mmHg) and an obstructive group (resting peak LVOT gradient ≥ 30 mmHg).¹¹ When evaluating baseline characteristics, clinical response to exercise and utility of exercise testing we used the initial test of the 499 patients, however when investigating the safety profile we used all the exercise tests of the 499 patients performed in the full study period (n=959).

Resting electrocardiogram

The electrocardiograms (ECG) were analyzed according to the ESC guidelines.¹² Patients with QRS width ≥ 120 ms were considered having bundle branch block and divided according to configuration into left bundle branch block and right bundle branch block. Cardiac repolarization was carefully analyzed in patients without bundle branch block, ST-depression was defined as ST-segment depression of at least 1 mm in 2 contiguous leads and T-wave inversion was defined as T-wave inversion ≥ 1 mm in at least 2 contiguous leads.

Treadmill exercise test

All patients in our HCM clinic routinely undergo treadmill exercise testing at every visit unless excluded per the conditions listed below: unable to walk on the treadmill, BP >220/120 mmHg, unstable angina, recent myocardial infarction (<1 week), decompensated heart failure, active atrial arrhythmia (resting heart rate >120 bpm).

A standard Bruce protocol is implemented unless patients reported very low exercise tolerance in which case a modified Bruce or Naughton protocols were used. Patients had continuous 12-lead ECG monitoring and blood pressure was measured at each stage. Patients were encouraged to exercise until development of symptoms limiting continuation of exercise or inability to exercise further. The test was terminated early in case of sustained ventricular arrhythmia, symptomatic drop in blood pressure, ST elevation or development of severe symptoms. Ongoing medications were continued prior to stress testing.

Data was collected regarding exercise induced symptoms, exercise capacity, ECG changes, abnormal blood pressure response (ABPR) and arrhythmias. Symptoms monitored were chest pain, dyspnea and syncope. Exercise capacity was expressed as metabolic equivalent (METs) and percentage of heart rate achieved. Significant ECG changes from baseline were defined according to ACC guidelines as either horizontal or down sloping ST-depression or ST-elevation (>1 mm in two corresponding leads 80 ms from the J point).¹³ Non-specific ST-T changes were defined as any ST-T changes not fulfilling the above criteria. Patients

with active pacemakers (n=22), LBBB (n=15) and resting ST-depressions (n=76) not allowing analysis of ST-T changes were excluded from ECG-analysis (n=113). Abnormal blood pressure response was defined as: 1) blunted blood pressure response: <20 mmHg increase of systolic blood pressure or 2) hypotensive response: >20 mmHg decrease of systolic blood pressure from baseline blood pressure or an initial rise in systolic blood pressure followed by a decrease of systolic blood pressure >20 mmHg.^{7, 14}

Arrhythmias were registered as supraventricular, non-sustained ventricular tachycardia (duration <30 seconds), sustained ventricular arrhythmia (duration >30 seconds) and ventricular fibrillation/pulseless ventricular tachycardia. The complication rate during exercise testing was evaluated as number of arrhythmias but also the combined safety endpoint, which was defined as syncope or onset of any arrhythmia.

Echocardiography

A Vivid 7 cardiac ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) with a 3.5-MHz transducer was used. Echocardiographic examinations were performed with the patient in the left lateral decubitus position.¹⁵ The following parameters were obtained and measured according to the recommendations of American Society of Echocardiography: end-diastolic and end-systolic left ventricular dimensions at the level of the mitral leaflets tips in the parasternal long axis view; LV ejection fraction (LVEF) was calculated from these LV dimensions using the Teicholz formula. Maximal wall thickness was measured in the parasternal long axis view, short axis view or in the 4 chamber image with focus on the apex.¹⁶ Peak LVOT gradients were measured in the apical long axis and 5 chamber view at rest and immediately (usually within 30 seconds) after exercise using continuous wave-Doppler technique.¹⁷ LVOT gradients were also calculated from the mitral-regurgitation jet measured during rest and after exercise with following formula: LVOT gradient= MR-gradient – systolic blood-pressure + left atrial pressure (estimated 10 mmHg).¹⁸

Statistics

All continuous data were summarized as mean and standard deviation. Categorical data was summarized as frequency and percentage with 95% Confidence Interval. ANOVA was used to compare continuous variables among the 3 groups, and intergroup differences were calculated with student t-test. X²-test was used to compare categorical data, in case of low number of events (n<5) Fischer's exact test was used. A p value of <0.05 was considered significant. Multivariate analysis was done with regards to METs. Statistical analysis was performed with Stata/IC 12.1 statistical software (StataCorp College Station Texas USA).

Results

We enrolled 499 consecutive HCM patients, at their initial evaluation with exercise testing at our HCM clinic; all the patients fulfilled our inclusion criteria. Baseline clinical and echocardiographic characteristics at the initial exercise test is presented in table 1 and 2. Nineteen patients (3.8%) had atrial fibrillation and 14 patients (3%) had a history of prior septal reduction procedures; 9 had myectomy and 5 had alcohol ablation. Family history of HCM and ICD was more common in the non-obstructive group. However, history of

coronary disease and hypertension and the use of medications was the same in all groups. Likewise, resting ECG changes were similar in the 3 groups.

The 499 patients underwent a total of 959 treadmill tests: 286(57%) patients had 1 test, 99(20%) patients had 2 tests, 51(10%) patients had 3 tests, 24 patients (5%) had 4 tests, 22 (4%) patients had 5 tests, 8 patients (2%) had 6 tests, 6 patients (1%) had 7 tests, 1 patient (0.2%) had 8 tests and 2 patients (0.4%) had 9 tests.

Clinical response of stress

The clinical response to treadmill stress in the 499 patients at their initial exercise test is summarized in table 3. The obstructive group had significantly lower exercise capacity (METs) and was more likely to develop dyspnea and ST-depression during exercise test. After adjusting for age and gender the exercise capacity expressed as METs was still significantly lower in the obstructive group (adjusted difference -1.5 , 95%CI:(-0.84 ; -2.2), $P<0.001$). The resting heart rate was similar in the 3 groups, however the obstructive group had lower max heart rate and therefore lower heart rate response to exercise. Abnormal blood pressure response in patients aged <50 was more prevalent in the obstructive group compared to the non-obstructive and labile-obstructive groups.

Safety profile

For the safety profile we evaluated all the exercise tests performed in our HCM cohort ($n=959$). There were no deaths in this cohort during treadmill stress. Complications and arrhythmias during exercise are listed in Table 4. We observed no difference in complication rate between all the sub-groups of HCM patients. In table 5 patients are divided according to a resting gradient of 50 mmHg, to investigate the safety of this subset of patients with very high gradients and there were no differences as well. We also compared the safety of exercise tests done on patients with prior myectomy ($n=106$) or alcohol ablation ($n=17$) with patients managed on a strictly medical regimen ($n=836$). The exercise tests performed on patients with prior septal reduction procedures accounts for both the patients ($n=14$) who had procedures done before inclusion in our study and patients who underwent septal reduction procedure during follow-up at our institution. We found no convincing difference between these groups. There was a significant difference in the prevalence of NSVT between the group treated with myectomy compared to alcohol ablation group and the medically managed group (3.8% vs. 0% vs. 0.7%, $p=0.04$), however all the serious ventricular arrhythmias were seen in the medically treated group. Also no difference was seen in the combined safety endpoint.

The patients who had a safety event are described in detail in table 6. A total of 20 events were noted corresponding to a total event rate of 2.1%, the rate of ventricular arrhythmia was 1.4%. There were 3 incidents of potentially life-threatening arrhythmic events (overall rate of 0.3%). All the patients recovered without complications, however one patient required external defibrillation and one patient received a shock from his implantable cardioverter-defibrillator. Two events, one case of ventricular fibrillation and one case of ventricular tachycardia, occurred in the non-obstructive group and one case of ventricular tachycardia occurred in the obstructive group (see table 6).

Utility of exercise test in high gradient HCM

The utility of exercise testing was evaluated at the initial test in the cohort of 499 patients. Exercise testing provided an objective assessment of exercise capacity and symptoms in all HCM patients. The relationship between NYHA-class and the METs achieved during exercise test is illustrated in figure 1. It shows substantial overlap between the different NYHA-classes, illustrating the inaccuracy of the clinical NYHA-class evaluation. Additionally, exercise testing gave information regarding risk stratification of SCD in a substantial amount of HCM patients. We could retrieve information about blood pressure response in 97% of the HCM patients and we evaluated exercise-induced arrhythmias in all patients.

In the entire cohort of HCM patients, the initial exercise test gave information regarding SCD risk stratification in 95 patients (19%) - 89 patients (age ≥ 50 years) developed ABPR and 6 patients had exercise induced ventricular arrhythmia.^{6, 7} In patients with obstructive HCM, information regarding risk stratification was obtained in 31 patients (20%); 30 patients (age ≥ 50 years) developed ABPR and 1 patient had exercise induced ventricular arrhythmia.

Discussion

The main result of our study is that incidence of complications and life-threatening arrhythmias during exercise testing are low in HCM patients. Likewise, subgroup analysis, with lower number of patients, indicates that exercising high gradient HCM pose no additional risk of adverse events. We find exercise testing capable of providing potentially important information in a substantial amount (19%) of patients with high gradient HCM. Patients with obstructive HCM had lower exercise capacity, higher incidence of ABPR and ECG changes during exercise.

In our study we evaluated differences in safety according to degree of LVOT obstruction, because it is traditionally presumed that exercising high gradient HCM patients bear a higher risk of adverse effects. Also, previous studies have been unclear about the incremental information provided by exercise testing in high gradient HCM patients.¹¹ In our study we found no increased risk of adverse events when exercising obstructive HCM patients. However, these results are based on a subset of the total exercise tests (LVOT gradients >30 mmHg (n=246) and LVOT gradients >50 mmHg (n=149)) and should therefore be interpreted with caution. In our study we also found no increased risk, when exercising patients with prior septal reduction procedures. However, these results are based on a small number of tests (alcohol ablation n=17, myectomy n=106) and should be confirmed in larger studies. The overall incidence of ventricular arrhythmias and complications in our study is comparable with a previous study by Gimeno et al, which found the overall incidence of ventricular fibrillation to be 0.2% and the incidence of ventricular arrhythmias to be 2%.⁶ Also the overall rate of serious arrhythmias is comparable with several smaller studies by Drinko et al (0.4%),¹⁹ Bunch et al (1.2%)²⁰ and Sadoul et al (0.6%).¹⁴ The small discrepancies seen between these studies may arise because of coincidence and the small sample sizes. However, none of these studies have examined the risk of complications according to LVOT obstruction.

Despite the low rate of complications during exercise test in HCM, the risk of ventricular arrhythmias and complications is higher than the complication rate of 1:2500 seen during exercise test in an unselected general population.¹³ This warrant that any echo lab doing exercise testing in HCM patients take sufficient safety precautions regarding monitoring and availability of trained personal.

Another aim of this study was to evaluate the utility of exercise testing in a group of high gradient HCM patients. We find exercise testing capable of giving accurate information about functional class and helpful in assessing prognosis and risk of SCD in a substantial number of patients. Clinical NYHA-class evaluation is subjective, has substantial inter-observer variability and a poor correlation with functional class calculated from exercise time.^{21, 22} Accordingly we found substantial variation in the METs achieved during exercise among patients who are evaluated to be in the same NYHA class see figure 1. Therefore, exercise testing of obstructive HCM patients is reasonable especially in cases where an accurate assessment of function class is important, such as before invasive septal reduction therapy.¹¹

The overall risk assessment of sudden cardiac death in HCM and the subsequent selection of patients for defibrillator-therapy can be difficult.¹¹ Traditionally several exercise related parameters such as ABPR and exercise induced ventricular tachycardia have been linked to increased risk of SCD in HCM.^{6, 7, 14} Likewise a new study from Desai et al found exercise capacity to be a predictor of SCD in HCM patients.²³ All these parameters are also relevant in high gradient HCM and in our cohort of obstructive HCM the exercise testing provided information useful in risk stratification in a substantial amount of patients.

Clinical Implications

Based on our results we suggest exercise testing with assessment of exercise capacity, exercise induced gradients, exercise induced arrhythmia and blood pressure response should be considered in the evaluation of all HCM patients irrespective of gradients. In our study, although on a limited number of patients, the presence of LVOT obstruction was not associated with an increased risk of complications. Diligent electrocardiographic and hemodynamic monitoring and availability of trained critical care personnel during the test is mandatory given the serious nature of the potential adverse events.

Limitations

The Johns Hopkins HCM Center is a tertiary referral center and our cohort may not be reflective of or be extrapolated to the general population. Because of the relative low number of complications during exercise testing and the rare nature of HCM, it's difficult to achieve statistical power to address the question about safety differences according to gradients. So, even though this study is one of the largest studies regarding exercise testing in HCM, minor differences in complications might be missed. As in other database studies we have missing data, in our study the majority of the variables have only 0–2% missing data, however some variables have a slightly higher rate of missing data between 3–5%, these are family history of HCM, interventricular diameters and abnormal blood pressure response. These number

are in accordance with the missing data in other retrospective studies. In our clinic VO2 test is not used routinely, however this data could have provided a more accurate assessment of exercise capacity. When determining LVOT gradients we used both direct measurements with CW Doppler and supplemented with indirect calculations from mitral regurgitation jet velocity. The latter method has limitations in the assumption of LA pressure as 10 mmHg and especially after exercise where blood pressure drop occurs, there can be uncertainty linked with this method.

Conclusion

Our study suggests that exercise testing HCM patients is associated with a low risk of adverse events. Furthermore, this study, although in a selected cohort and in a limited number of patients, indicates that exercise testing in high gradient HCM pose no additional risk of complications and provides potential important information about symptoms, functional class and SCD risk stratification. We therefore suggest that HCM patients irrespective of gradients should be considered for exercise testing unless strong contraindications are present.

Acknowledgments

This work was supported in part by a grant from the National Institutes of Health (HL098046) and the John Taylor Babbit Foundation. Lars L. Sorensen is supported in part by a grant from Ingenor August Wedell Erichsens legat, Snedkermester Sophus Jacobsen og Hustru Fond and Direktor Jacob Madsen & Olga Madsens Fond.

We would like to express our gratitude to the sonographers and nurses of the Johns Hopkins Echocardiography Laboratories for their technical expertise and contributions to data collection. We appreciate the support received from the Dr. Lawrence and Sheila Pakula Foundation. We thank Glenn Lie and Gunnar Hansen (GE Ultrasound, Horten Norway) for providing us analysis software.

References

1. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007; 298(4):405–412. [PubMed: 17652294]
2. Maron MS, Olivetto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med*. 2003; 348(4):295–303. [PubMed: 12540642]
3. Ho CY. Genetics and clinical destiny: Improving care in hypertrophic cardiomyopathy. *Circulation*. 2010; 122(23):2430–2440. discussion 2440. [PubMed: 21135371]
4. Maron MS, Olivetto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*. 2006; 114(21):2232–2239. [PubMed: 17088454]
5. Schaff HV, Dearani JA, Ommen SR, Sorajja P, Nishimura RA. Expanding the indications for septal myectomy in patients with hypertrophic cardiomyopathy: Results of operation in patients with latent obstruction. *J Thorac Cardiovasc Surg*. 2012; 143(2):303–309. [PubMed: 22154797]
6. Gimeno JR, Tome-Esteban M, Lofiego C, et al. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2009; 30(21):2599–2605. [PubMed: 19689975]
7. Olivetto I, Maron BJ, Monterege A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1999; 33(7):2044–2051. [PubMed: 10362212]

8. Efthimiadis GK, Giannakoulas G, Parcharidou DG, et al. Chronotropic incompetence and its relation to exercise intolerance in hypertrophic cardiomyopathy. *Int J Cardiol.* 2011; 153(2):179–184. [PubMed: 20851477]
9. Konhilas JP, Watson PA, Maass A, et al. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res.* 2006; 98(4):540–548. [PubMed: 16439687]
10. Morise AP. Exercise testing in nonatherosclerotic heart disease: Hypertrophic cardiomyopathy, valvular heart disease, and arrhythmias. *Circulation.* 2011; 123(2):216–225. [PubMed: 21242508]
11. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation.* 2011; 124(24):2761–2796. [PubMed: 22068435]
12. Corrado D, Pelliccia A, Heidbuchel H, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010; 31(2):243–259. [PubMed: 19933514]
13. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: Summary article: A report of the american college of cardiology/american heart association task force on practice guidelines (committee to update the 1997 exercise testing guidelines). *Circulation.* 2002; 106(14):1883–1892. [PubMed: 12356646]
14. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation.* 1997; 96(9):2987–2991. [PubMed: 9386166]
15. Nagueh SF, Bierig SM, Budoff MJ, et al. American society of echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: Endorsed by the american society of nuclear cardiology, society for cardiovascular magnetic resonance, and society of cardiovascular computed tomography. *J Am Soc Echocardiogr.* 2011; 24(5):473–498. [PubMed: 21514501]
16. 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(12):1440–1463. [PubMed: 16376782]
17. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography. American society of echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr.* 2007; 20(9):1021–1041. [PubMed: 17765820]
18. Klein, AA. Clinical echocardiography review; A self-assessment tool. Lippincott Williams & Wilkins; 2011. Craig.
19. Drinko JK, Nash PJ, Lever HM, Asher CR. Safety of stress testing in patients with hypertrophic cardiomyopathy. *Am J Cardiol.* 2004; 93(11):1443–1444. A12. [PubMed: 15165938]
20. Bunch TJ, Chandrasekaran K, Ehram JE, et al. Prognostic significance of exercise induced arrhythmias and echocardiographic variables in hypertrophic cardiomyopathy. *Am J Cardiol.* 2007; 99(6):835–838. [PubMed: 17350377]
21. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol.* 1972; 30(7):757–762. [PubMed: 5084774]
22. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. *Circulation.* 1981; 64(6):1227–1234. [PubMed: 7296795]
23. Desai MY, Bhonsale A, Patel P, et al. Exercise echocardiography in asymptomatic HCM: Exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging.* 2014; 7(1):26–36. [PubMed: 24290569]

Figure 1.

Achieved METs according to NYHA class.

METs: metabolic equivalent, NYHA class: New York Heart Association class. *Line: median, box: 25th-75th percentile, whiskers: higher 75th + 1.5*(25th-75th), lower 25th – 1.5*(25th-75th). Dots: outliers*

Table 1

Baseline clinical characteristics of HCM patients referred for exercise test.

Group	Non-obstructive n=169	Labile-obstructive n=178	Obstructive n=152	Total n=499	P-value
Age (years)	49±14	49±16	55±12 ^{*†}	51±14	<0.001
Male n(%)	117(69%)	130(73%)	101(66%)	348(70%)	0.42
Medical history:					
Family history of HCM	47(29%) [#]	32(19%)	18(12%)	97(20%)	0.001
ICD	30(18%) [#]	15(9%)	15(10%)	60(12%)	0.01
Hypertension	66(40%)	79(45%)	77(51%)	222(45%)	0.17
CAD	13(8%)	18(10%)	14(9%)	45(9%)	0.74
Presenting symptoms:					
Angina n(%)	31(19%)	37(21%)	50(33%) ^{*†}	118(24%)	0.01
Dyspnea n(%)	73(45%)	79(45%)	98(64%) ^{*†}	250(51%)	<0.001
Syncope n(%)	20(12%)	26(15%)	18(12%)	64(13%)	0.68
NYHA functional Class	1.4±0.6	1.5±0.6	1.8±0.7 ^{*†}	1.5±0.7	<0.001
NYHA class 1 n(%)	104(63%)	105(60%)	60(39%) ^{*†}	269(55%)	<0.001
NYHA class 2 n(%)	50(30%)	56(32%)	69(45%) ^{*†}	175(36%)	
NYHA class 3 n(%)	10(6%)	14(8%)	23(15%) ^{*†}	47(10%)	
Medications:					
Beta-blockers	114(68%)	124(70%)	113(75%)	351(71%)	0.37
Ca-blockers	36(22%)	46(26%)	45(30%)	127(26%)	0.23
Ace/ARB inhibitors	32(19%)	26(15%)	26(17%)	84(17%)	0.55
Diuretics	29(17%)	25(14%)	29(19%)	83(17%)	0.46

^{*} P<0.05 between Obstructive and Non-obstructive.

[†] P<0.05 between Obstructive and Labile-obstructive.

[‡] P<0.05 between labile obstructive and non-obstructive. Comparison between groups: ANOVA, χ^2 -test, intergroup difference T-test, χ^2 -test.

Table 2

Baseline ECG and echocardiography characteristics.

Group	Non-obstructive n=169	Labile-obstructive n=178	Obstructive n=152	Total n=499	P-value
Atrial fibrillation n(%)	9(5%)	5(3%)	5(3%)	19(4%)	0.44
Pace-rhythm	9(5%)	7(4%)	6(4%)	22(4%)	0.78
LBBS	4(2%)	6(3%)	5(3%)	15(3%)	0.84
RBSB	7(4%)	15(8%)	7(5%)	29(6%)	0.18
T-wave inversion	59(35%)	54(30%)	54(36%)	166(34%)	0.53
ST-depression	31(18%)	19(11%)	26(17%)	76(15%)	0.10
LVESD (mm)	27±5	25±6 [#]	24±5 [*]	25±5	<0.001
LVEDD (mm)	43±6	41±6 [#]	41±6 [*]	42±6	0.003
LVEF (%)	67±11	69±11	70±11 [*]	69±11	0.03
Max wall thickness (mm)	21±6	21±6	22±5	21±5	0.43
Rest gradient (mmHg)	8±5	15±7	69±35	29±33	
Peak gradient (mmHg)	18±6	71±43	115±42	66±52	

^{*} P<0.05 between Non-obstructive and Obstructive.[†] P<0.05 between Obstructive and Labile-obstructive.[#] P<0.05 between labile obstructive and non-obstructive. Comparison between groups: ANOVA, X²-test, intergroup difference student t-test, X²-test.

Table 3

Symptoms, work capacity and ECG changes during exercise-test.

Group	Non-obstructive n=169	Labile-obstructive n=178	Obstructive n=152	Total n=499	P-value
Dyspnea (%)	75(44%)	81(46%)	94(62%) ^{*†}	250(50%)	0.002
Angina (%)	18(11%)	19(11%)	27(18%)	64(13%)	0.09
ABPR(%)	61(37%)	71(41%)	77(53%) [*]	209(43%)	0.008
ABPR, age<50 (%)	28(34%)	31(36%)	30(54%) ^{*†}	89(39%)	0.04
METs	10.2±4.0	10.9±4.2	8.4±3.4 ^{*†}	9.9±4.0	<0.001
Resting Heart Rate	67±13	65±14	65±12	66±13	0.28
Max Heart Rate	146±30	148±29	135±26 ^{*†}	144±26	0.0001
% of Max Predicted Heart Rate	86±15	87±14	82±14 ^{*†}	85±15	0.02
Non-specific ST-T changes n(%)	10(8%)	12(8%)	14(12%)	36(9%)	0.48
Significant ST depression n(%)	25(20%)	32(22%)	38(33%) [*]	95(25%)	0.05

ABPR: Abnormal blood pressure response.

^{*} P<0.05 between Non-obstructive and Obstructive.[†] P<0.05 between Labile-obstructive and Obstructive.. Comparison between groups: ANOVA, X²-test, intergroup difference student t-test, X²-test.

Table 4

Safety profile. Complications and arrhythmic events during exercise tests.

Group	Non-obstructive n=333	Labile-obstructive n=379	Obstructive n=246	Total n=959	P-value
Syncopal n(%)	0(0%)	0(0%)	2(0.9%)	2(0.2%)	0.07
SVT n(%)	1(0.3%)	2(0.5%)	2(0.8%)	5(0.5%)	0.74
NSVT n(%)	6(1.8%)	3(0.8%)	1(0.4%)	10(1.0%)	0.30
Sustained VT/VF n(%)	2(0.6%)	0(0%)	1(0.4%)	3(0.3%)	0.36
Safety Endpoint (any complication)	9(2.7%)	5(1.3%)	6(2.4%)	20(2.1%)	0.39

SVT: supraventricular tachycardia, NSVT: non-sustained ventricular tachycardia, VT: ventricular tachycardia, VF: ventricular fibrillation. Comparison between groups: χ^2 -test and Fisher's exact test.

Table 5

Safety profile in patients with resting gradients above 50 mmHg

Group	Gradient <50 mmHg N=810	Gradient ≥ 50 mmHg N=149	P-value
Syncope n(%)	2(0.3%)	0(0%)	1.00
SVT n(%)	5(0.6%)	0(0%)	1.00
NSVT n(%)	9(1.1%)	1(0.7%)	1.00
Sustained VT/VF n(%)	3(0.4%)	0(0.0%)	1.00
Safety Endpoint n(%)	19(2.3%)	1(0.7)	0.34

SVT: supraventricular tachycardia, NSVT: non-sustained ventricular tachycardia, VT: ventricular tachycardia, VF: ventricular fibrillation.
Comparison between groups: Fisher's exact test.

Table 6

Characteristics of the patients with adverse events during exercise testing.

Case	Test	Age	Sex	CAD	Medication	Max wall	Resting gradients	Exercise gradients	ECG changes	Arrhythmia	Runs	Max HR	Symptoms
1	1	58	M	0	0	21	5	13	PM	a.fib	1	122	dyspnea
2	1	45	M	0	CA	15	6	38	No	a.fib	1	118	none
3	3	59	M	0	0	20	32	131	No	a.fib	1	151	none
4	1	69	M	0	BB,CA	22	37	75	No	a.fib	1	173	none
5	1	58	M	0	BB	28	23	93	Yes	a.fib	4	151	none
6	1	53	F	0	BB	16	33	89	No	syncope	-	-	syncope
7	2	66	F	0	BB,CA	16	46	96	No	syncope	-	-	syncope
8	3	59	M	0	BB	16	2	16	No	NSVT	>10	214	dyspnea
9	4	60	M	0	BB	16	12	13	No	NSVT	4	250	none
10	1	55	M	0	BB,CA,DP	18	10	33	Yes	NSVT	8	188	none
11	2	40	M	0	BB	14	5	15	Yes	NSVT	1	300	none
12	6	43	M	0	BB	15	16	43	No	NSVT	8	167	chest fluttering
13	1	32	M	0	BB	35	6	17	No	NSVT	1	150	none
14	1	37	M	0	BB	31	4	11	No	NSVT	3	231	none
15	1	76	M	0	BB,CA	20	60	120	Yes	NSVT	3	214	none
16	3	53	M	0	0	16	8	23	PM	NSVT	3	115	none
17	1	19	M	0	0	15	6	34	Yes	NSVT	1	125	none
18	3	20	M	0	BB	18	8	12	No	VF	1	-	collapse
19	3	29	F	0	BB	30	40	N/A	Yes	VT	1	230	collapse
20	1	57	F	0	BB, ACE	27	5	14	Yes	VT	1	144	dyspnea

M: Male, F: Female, Hx CAD: Coronary artery disease, BB: Beta-blocker, CCB: Calcium channel blocker, PM: pacemaker, DP: disopyramide, NSVT: Non-sustained ventricular tachycardia, VT: Ventricular tachycardia, a. fib: Atrial fibrillation, VF: Ventricular fibrillation, VT: Ventricular tachycardia.