Accepted Manuscript

Title: Value of Strain Imaging and Maximal Oxygen Consumption in Patients with Hypertrophic Cardiomyopathy

Author: Kegan J. Moneghetti, Davide Stolfo, Jeffrey W. Christle, Yukari Kobayashi, Gherardo Finocchiaro, Gianfranco Sinagra, Jonathan Myers, Euan A. Ashley, Francois Haddad, Matthew T. Wheeler

PII: S0002-9149(17)31132-3
DOI: http://dx.doi.org/doi: 10.1016/j.amjcard.2017.06.070
Reference: AJC 22745

To appear in: *The American Journal of Cardiology*

Received date: 5-5-2017
Revised date: 14-6-2017
Accepted date: 30-6-2017

Please cite this article as: Kegan J. Moneghetti, Davide Stolfo, Jeffrey W. Christle, Yukari Kobayashi, Gherardo Finocchiaro, Gianfranco Sinagra, Jonathan Myers, Euan A. Ashley, Francois Haddad, Matthew T. Wheeler, Value of Strain Imaging and Maximal Oxygen Consumption in Patients with Hypertrophic Cardiomyopathy, *The American Journal of Cardiology* (2017), http://dx.doi.org/doi: 10.1016/j.amjcard.2017.06.070.

Value of Strain Imaging and Maximal Oxygen Consumption in Patients with Hypertrophic Cardiomyopathy

Kegan J. Moneghetti MBBS (hons)[a,b], Davide Stolfo MD[a,c], Jeffrey W. Christle PhD[a], Yukari Kobayashi MD[a,b], Gherardo Finocchiaro MD[a], Gianfranco Sinagra MD[c], Jonathan Myers PhD[d], Euan A. Ashley MB, ChB, DPhil[a,b,e] Francois Haddad MD[a,b] * Matthew T. Wheeler MD PhD[a,b,e*].

a. Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA

b. Stanford Cardiovascular Institute, Stanford, CA

c. Cardiovascular Department, "Azienda Ospedaliero-Universitaria Ospedali Riuniti di Trieste", Trieste, Italy.

d. Division of Cardiology, Veterans Affairs Palo Alto Healthcare System, Palo Alto, CA

e. Center for Inherited Cardiovascular Diseases, Stanford Hospital and Clinics, Stanford, CA

*Equivalent senior authors of the paper

Running Head: Strain Reserve in Hypertrophic Cardiomyopathy

Corresponding Author:

Kegan James Moneghetti. Phone +1(415)9263894. Fax +1(650)725-1599. Stanford Cardiovascular Institute, Palo Alto, CA, 94304. Email:keganm@stanford.edu

Matthew T. Wheeler. Phone +1(650) 725-5921. Fax +1(650)725-1599. Center for Inherited Cardiovascular Disease, Stanford Hospital and Clinics, Stanford, CA. Email: wheelerm@stanford.edu Twitter: @MWheelerMD

Relationships with Industry: No relevant disclosures to report

Abstract

Longitudinal strain (LS) has been shown to be predictive of outcome in hypertrophic cardiomyopathy (HCM). Percent predicted peak oxygen uptake (ppVO2), among other cardiopulmonary exercise testing (CPX) metrics, is a very strong predictor of prognosis. However, there has been limited investigation into the combination of LS and CPX metrics. This study sought to determine how LS contributes to parameters of exercise performance for prognosis in HCM. One hundred and thirty-one consecutive patients with HCM who underwent CPX with simultaneous stress echocardiography were included. Global, septal and lateral LS were assessed at rest and stress. Eighty matched individuals were used as controls. Patients were followed for the composite endpoint of death and worsening heart failure (HF). All absolute LS components were lower in patients with HCM compared to controls (global 14.3±4.0% vs 18.8±2.2%, p<0.001; septal 11.9±4.9% vs 17.9±2.7%, p<0.001; lateral 16.0±4.7% vs 19.4±3.1%, p=0.001). Global strain reserve was also reduced among patients with HCM (13±5% vs 19±8%, p=0.002). Over a median follow-up of 56 months (IQR 14-69), the composite endpoint occurred in 53 patients. Global LS was predictive of outcome on univariate analysis (0.55[0.41-0.74], p<0.001). When combined with CPX metrics, lateral LS was the only independent predictor of outcome among strain variables along with indexed left atrial volume (LAVI) and $ppVO_2$. The worst outcomes were observed for patients with lateral LS<16.1%, LAVI>52ml/m^2 and $ppVO_2$<80%. Patients with HCM have decreased strain reserve when compared to controls. The combination of lateral LS, LAVI and $ppVO_2$ presents a simple model for outcome prediction.

Keywords: Hypertrophic Cardiomyopathy**,** Cardiopulmonary exercise testing**,** Contractile Reserve, Deformation imaging

Introduction

Hypertrophic Cardiomyopathy (HC) is an inherited disease characterized by a variable clinical course. Advances in primary prevention of sudden cardiac death (SCD) have simultaneously improved arrhythmic outcomes and increased the impact of chronic heart failure (HF)-related outcomes.[1, 2] Among predictors of outcome in HC, magnitude of hypertrophy, left atrial volume, left ventricular outflow tract (LVOT) obstruction, hypotensive response to exercise and peak oxygen uptake (peak VO_2) have emerged as the strongest.[3-9] Myocardial fibrosis, myocyte disarray and altered sarcomere kinetics typically affect myocardial mechanics in the early phases of HC with preserved LV ejection fraction (LVEF) which has led to an interest in strain echocardiography.[10] Longitudinal strain (LS), has demonstrated strong predictive value in myocardial diseases, including HC, which has recently been associated with a higher risk of adverse cardiovascular events.[4, 11, 12] Regional components of LS and augmentation with exercise (contractile reserve) has not been well studied in HC.[13] Moreover, there has been limited investigation into integration of CPX with strain echocardiography.[14, 15] The current study explores the implication of the complementarity of CPX and echocardiography in risk modeling of HF events in HC.

Methods

In 2007, Stanford University established the Stanford Exercise Testing (SET) Registry, where patients who have obtained simultaneous stress echocardiography with CPX are included. For this study, approved by the University's Institutional Review Board, we screened the SET registry from January 1st 2007 and January 1st 2012. Patients were included if they had a diagnosis of HC as defined by (a) the presence of significant LV hypertrophy (end-diastolic wall thickness >15 mm in M-mode or 2D echocardiography) in the absence of other etiologies, or (b) wall thickness between 13 and 15 mm in the presence

of abnormal electrocardiography or family history of inherited cardiomyopathy and (c) had simultaneous CPX and echocardiogram.[3] Patients were not included if they (a) had documented prolonged systemic hypertension, (b) previous alcohol ablation or septal myectomy, (c) poor image quality on either rest or stress echocardiography or (d) less than 12 months follow up. Data were collected during the outpatient visit on the day of CPX/echocardiography. For comparison to the HC cohort, 80 contemporary participants who underwent stress echocardiogram and had (a) normal resting LVEF, (b) normal rest and stress wall motion and (c) no hemodynamically significant valvular disease were included. [16] These controls were excluded if they had (a) left ventricular hypertrophy, (b) significant ST changes or arrhythmias, (c) exaggerated blood pressure response to exercise or (d) functional capacity less than 90% of normal.[17] The primary end-point for outcome analysis was a composite of death and worsening HF (cardiac transplantation, NYHA III-IV class progression leading to hospitalization). Outcomes were assessed by two cardiologists independently using computerized medical records.

All patients underwent baseline resting echocardiography (iE33; Philips Medical Imaging, Eindhoven, the Netherlands). Stress images were acquired immediately post-exercise, with the apical 4 chamber acquired first and thus used to calculate measures of longitudinal strain. Images were analyzed by the Stanford Cardiovascular Institute Clinical Biomarker and Phenotype Core Laboratory on Xcelera workstations in accordance with published guidelines from the American Society of Echocardiography (ASE).[16, 18] Two experienced cardiologists independently analyzed the acquired images, and were blinded to the results of the CPX metrics and clinical outcomes. LVEF was calculated by manual contouring of apical 4-chamber imaging. GLS was calculated on manual tracings of the mid-wall with the Lagrangian Strain Formula [(L1 - L0)/L0] x 100.[19] Lateral strain and septal strain

were calculated with the same technique, however, the mid-wall length was assessed from the lateral annulus to apex and mitral annulus to apex, respectively (**Figure 1**). We present strain data in absolute values.[4, 11] With tissue Doppler imaging, we used peak myocardial early diastolic velocity at the lateral mitral annulus and the assessment of trans-mitral to tissue Doppler imaging early diastolic velocity ratio (E/e'). Left atrial volume was calculated in the apical 4-chamber view at end systole then indexed to body surface area (LAVI). Systolic left ventricular gradient was quantified using the continuous-Doppler technique. A peak gradient >30mmHg at rest was considered significant.[7] Mitral regurgitation severity was assessed according to current guidelines.[20] Regarding measurement of reserve, absolute change *(peak–rest)* and relative change *[(peak-rest)/peak) x 100]* were calculated for LVEF and each component of LS.

Symptom-limited CPX was performed on a treadmill (Trackmaster by FullVision, Kansas, USA) with an integrated metabolic cart (Quark CPET, CosMed USA Inc, Concord, CA, USA), using breath-by-breath data capture and analysis with an individualized RAMP treadmill protocol.[21] Minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide production (VCO_2), and other CPX variables were acquired breath by breath and averaged over 20 second intervals for interpretation. VE and VCO_2 responses throughout exercise were used to calculate the VE/VCO_2 slope via least squares linear regression.[22] To correct for differences in age and gender, the $ppVO_2$ was calculated using the Wasserman formula.[23] The achievement of a respiratory exchange ratio (VCO/VO_2) of $\geq$1.05 and perceived exertion >16, (6-20 scale) were used to determine peak effort. A continuous 12-lead electrocardiogram was obtained with recordings at rest, each minute during exercise and for at least five minutes during recovery from exercise.

Baseline characteristics were expressed as mean ± SD for parametrically distributed values and as median and IQR for non-parametrically distributed variables. Categorical variables are presented as frequencies and/or percentages. To investigate differences between the HC cohort and the controls, independent-sample t-tests were performed. Linear regression analysis was used to determine independent associations between echocardiographic and CPX variables. The associations between clinical, echocardiographic, CPX variables and outcome were analyzed using Cox proportional hazards models. Variables significantly associated with the composite outcome from univariate analysis were selected for entry into a multivariate model and corrected age and gender. Multivariate models were performed using stepwise elimination in separate blocks (echocardiographic with global and regional strain and CPX variables). Cumulative rates of the composite endpoint as a function of time were obtained by the Kaplan-Meier method and compared using the log-rank test. Cut-offs were derived from receiver operating characteristic (ROC) curves of our cohort and compared to current population data. Inter-observer variability was quantified for echocardiographic measurements using mean differences intra class correlation coefficient and the Bland-Altman method (bias) **(Supplementary Table 1).** Analyses were performed using MedCalc version 15.8 and RStudio Version 1.0.136 – © 2009-2016 RStudio, Inc.

Results

One hundred and thirty-one consecutive patients were enrolled with baseline characteristics summarized in **Table 1**. Baseline demographics of controls are provided in **Supplementary Table 2**. Complete echocardiographic assessment was available in all patients at rest. Of the HC patients 7 (6%) had reduced image quality with stress that precluded accurate LS evaluation. **Table 2** and **Figure 2** show the values of rest and post-exercise septal, lateral and global LS with HC patients having significant lower values for all

components of strain (p<0.001). Exercise was associated with a significant increase in LS, both in the HC cohort and controls (p<0.001) however, relative strain reserve was reduced in patients with HC (13 ± 5% vs 19 ± 8%, p =0.002).

There was no correlation between septal wall thickness and septal LS (r=0.12, p=0.25) or posterior wall thickness and lateral LS (r=0.01, p=0.90). There was a moderate correlation between septal and lateral LS (r=0.51, p<0.001). LS metrics showed weak correlations **(Supplementary Figure 1)** with other echocardiographic variables and CPX metrics. Of the echocardiographic variables, e' showed the highest correlation with $ppVO_2$ (r=0.31, p<0.001).

During a median follow-up of 56 months (IQR 15-68) the composite primary outcome occurred in 53 patients (6 deaths and 47 worsening HF). Parameters significantly associated with outcome at univariate analysis **(Table 3)**, were placed in each of our multivariate models **(Table 4).** When combined with established echocardiographic metrics, of strain variables, only lateral LS was independently associated with the primary outcome. While peak strain was associated with outcome at univariate analysis these variables were not retain when combined with rest parameters in our multivariate models. Among the CPX variables, only $ppVO_2$ was statistically significantly associated with the primary end-point, whereas a borderline association was observed for the VE/VCO_2 slope. A single multivariate model incorporating lateral LS along with $ppVO_2$ and LAVI was found to be predictive of the primary outcome (x^2 = 39, p <0.001)**.** Using the variables independently associated with outcome, those patients with LAVI > 52ml/m^2, lateral LS < 16.1% and $ppVO_2$ < 80% had a poorer prognosis (p<0.001). As seen in **Figure 3** the presence of one, two, and three risk factors each increased risk of the composite outcome (log rank p<0.001). When events in

the first year of follow up were censored, the differences in outcome among patients with these risk factors remained **(Supplementary Figure 1).**

Discussion

The main findings of this paper are threefold. First, we show that LS reserve is significantly reduced in patients with HC and is only weakly associated with measures of exercise performance. Second, we validate recent findings that show LS is a major predictor of HF outcomes in HC patients. Third, our findings highlight that a simple combination of LS, LAVI and $ppVO_2$ may discriminate HF and survival outcomes in HC patients.

Contractile reserve has been poorly investigated in HC, partially due to patients often having a supranormal LVEF at rest and the LVOT flow being distorted by obstruction. Deformation imaging in HC has been investigated in recent studies, demonstrating a close relationship to clinical outcome.[4, 24, 25] Multiple pathophysiological mechanisms including hypertrophy, microvascular ischemia, myocardial fibrosis and sarcomere dysfunction may underlie reduction in GLS and ultimately contribute to overt HF.[10, 26] Our study of 131 patients has shown that high-quality assessment of GLS at peak exercise intensities is feasible. We were also able to assess reserve through the relative difference in strain, which appeared to be reduced when compared to controls. This validates the findings of Schnell et al. who in in a small cohort HC patients (n=25) found an absolute mean change in GLS of 1.9 (relative change 11%) during exercise testing.[27] Resting measures of systolic function and reserve in our cohort, as with previous studies in HF only mildly correlated with measures of exercise performance, indicating we should consider them complementary in clinical assessment or prognostication.

Despite the underlying pathophysiology, HC is often asymmetric, which led us to challenge the use of global metrics. The current study took the preferred measure of systolic

function in HC (LS) and explored the benefit of regional strain analysis. It appears that regional LS assessment at rest and immediately post exercise is feasible and reproducible in individuals with and without HC. The lower absolute mean value and standard deviation of septal strain in the HC groups reflects the predominance of septal involvement. These characteristics should make septal LS useful as a diagnostic marker, however, not necessarily as prognosticator for HF outcome. In our cohort, patients with absolute lateral LS <16.1% had a significantly higher rate of adverse events. This may be related to relative homogeneity of septal hypertrophy and decreased septal LS even among different morphologies of HC. Considering lateral LS and global LS had a similar impact on outcome, this might suggest the weight of global LS in influencing prognosis in HC might be driven by the lateral component. Further larger studies to evaluate change in lateral LS in HC over time will be needed to further support this hypothesis.

Outcome prediction in HC is complex due to the heterogeneity across recent trials. The focus of the current study is on HF outcome, not arrhythmic outcome. Doppler assessment of LVOT gradient has been used to risk stratify patients with HC.[7] However, the interpretation of gradients, particularly during exercise testing, can be complex and prone to variability. This has been complicated by the findings of a recent study by Desai et al, which showed that asymptomatic patients with greater than 100% ppVO2 had excellent outcomes regardless of the degree of LVOT obstruction.[28] A higher $ppVO_2$ has also been associated with improved outcomes in symptomatic patients (NYHA class II and NYHA III).[29] Our findings are consistent with these recent studies demonstrating that ppVO2 is independently and strongly associated with HF outcome, emphasizing the important contribution exercise capacity has to the prognosis of patients with HC. The clinical implication among the growing body of evidence in HC patients and exercise is that exercise

testing with gas analysis (where available) should be strongly considered. Left atrial volume also been a consistent marked of outcome in HC.[5, 6] It is reassuring that it performed well with regard to outcome in our cohort. One of the important contributions of the current study is that a simple combination of complementary variables may capture an important component of risk in HC. Our exploratory data suggested that (a) satisfactory exercise performance $ppVO_2$, (b) preserved lateral LS and (c) modest or absence of left atrial enlargement appears to have the most favourable prognosis.

The present study should be interpreted in the context of the methodological limitations. We did not use automated computationally-derived LS; our lab has previously shown good correlation of automated and manual assessment of strain and there was excellent inter-reader variability in measures of LVEF and strain.[30] This is a single speciality centre experience, which introduces an unavoidable selection bias with a likely over-representation of patients with advanced disease compared to other clinics. However, when events were censored during the first year of follow up, our outcome models remained unchanged. Furthermore, patients who did not undergo CPX as part their initial evaluation were excluded; however, this represented <5% of our cohort. Finally regarding outcome analyses, while the lower threshold for $ppVO_2$ has been previously described, it was necessary to derive the lower threshold for lateral LS from our dataset. Also, though we had a reasonable length of follow up, we had limited number of total events (n=53) and so these findings should be viewed as preliminary. In conclusion, strain imaging, both peak and regional appears feasible, with HC patients having reduced absolute values and strain reserve. When integrating strain and exercise testing into risk modelling, combining a structural (LAVi), functional (LS) and exercise ($ppVO_2$) metric may present a simple model for HF outcome prediction.

Acknowledgement: Nil

References

1. Maron BJ, Olivotto I, Spirito P, Casey S, Bellone P, Gohnman T, Graham K, Burton D, Cecchi F. Epidemiology of hypertrophic cardiomhopathy-related death: Revisted in a large non-referral-based patient population *Circulation* 2000;102:858-864.

2. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-Shaikh S, Rahman SM, Arnous S, Jones S, McKenna W, Elliott P. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart*. 2012;98:116-125.

3. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the American College of Cardiology foundation/American Heart Association task force on practice guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;58:e212-260.

4. Reant P, Reynaud A, Pillois X, Dijos M, Arsac F, Touche C, Landelle M, Rooryck C, Roudaut R, Lafitte S. Comparison of resting and exercise echocardiographic

parameters as indicators of outcomes in hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2015;28:194-203.

5. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the italian registry for hypertrophic cardiomyopathy). *Am J Cardiol*. 2006;98:960-965.
6. Losi M-A, Betocchi S, Barbati G, Parisi V, Tocchetti C-G, Pastore F, Migliore T, Contaldi C, Caputi A, Romano R, Chiariello M. Prognostic significance of left atrial volume dilatation in patients with hypertrophic cardiomyopathy. *J AM Soc Echocardiogr*. 2009;22:76-81.
7. Maron MS, Olivotto I, Betocchi S, Casey S, Lesser J, Losi M, Cecchi F, Maron BJ. Effects of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy *N Engl J Med*. 2003;348:295-303.
8. Finocchiaro G, Haddad F, Knowles JW, Caleshu C, Pavlovic A, Homburger J, Shmargad Y, Sinagra G, Magavern E, Wong M, Perez M, Schnittger I, Myers J, Froelicher V, Ashley EA. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: A potential role for comprehensive noninvasive hemodynamic assessment. *JACC Heart Fail*. 2015;3:408-418.
9. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, Elliott PM. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2015;8:1022-1031.
10. Chun S, Woo A. Echocardiography in hypertrophic cardiomyopathy: In with strain, out with straining? *J Am Soc Echocardiogr*. 2015;28:204-209.

11. Reant P, Mirabel M, Lloyd G, Peyrou J, Lopez Ayala JM, Dickie S, Bulluck H, Captur G, Rosmini S, Guttmann O, Demetrescu C, Pantazis A, Tome-Esteban M, Moon JC, Lafitte S, McKenna WJ. Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy. *Heart*. 2016;102:741-747.

12. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: How useful is it in clinical decision making? *Eur Heart J*. 2016;37:1196-1207.

13. Haddad F, Vrtovec B, Ashley EA, Deschamps A, Haddad H, Denault AY. The concept of ventricular reserve in heart failure and pulmonary hypertension: An old metric that brings us one step closer in our quest for prediction. *Curr Opin Cardiol*. 2011;26:123-131.

14. Wang J, Fang F, Wai-Kwok Yip G, Sanderson JE, Lee PW, Feng W, Xie JM, Luo XX, Lam YY. Changes of ventricular and peripheral performance in patients with heart failure and normal ejection fraction: Insights from ergometry stress echocardiography. *Eur J Heart Fail*. 2014;16:888-897.

15. Hensel KO, Jenke A, Leischik R. Speckle-tracking and tissue-doppler stress echocardiography in arterial hypertension: A sensitive tool for detection of subclinical LV impairment. *Biomed Res Int*. 2014;2014:472562.

16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39 e14.

17. Morris K, Myers J, Froelicher V, Kawaguchi T, Ueshima K, Hideg A. Normogram based on metabolic equivalents and age for assessing exercise capacity in men. *J Am Coll Cardiol*. 1993;22:175-182.

18. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.

19. Dumesnil JG, Shoucri RM, Sturcot J. A mathematical model of the dynamic geometry of the intact left ventricle and its application to clinical data. *Circulation* 1979;59:1024-34.

20. Zoghbi W, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.

21. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, Froelicher VF. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol*. 1991;17:1334-1342.

22. Arena R, Myers J, Aslam S, Varughese E, Peberdy M. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest* 2003;124:720-727.

23. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J, European Association for Cardiovascular Prevention & Rehabilitation, American Heart Association. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261-2274.

24. Afonso L, Kondur A, Simegn M, Niraj A, Hari P, Kaur R, Ramappa P, Pradhan J, Bhandare D, Williams KA, Zalawadiya S, Pinheiro A, Abraham TP. Two-dimensional strain profiles in patients with physiological and pathological hypertrophy and preserved left ventricular systolic function: A comparative analyses. *BMJ Open*. 2012;2.

25. Debonnaire P, Thijssen J, Leong DP, Joyce E, Katsanos S, Hoogslag GE, Schalij MJ, Atsma DE, Bax JJ, Delgado V, Marsan NA. Global longitudinal strain and left atrial volume index improve prediction of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy patients. *Int J Cardiovasc Imaging*. 2014;30:549-558

26. Haland TF, Almaas VM, Hasselberg NE, Saberniak J, Leren IS, Hopp E, Edvardsen T, Haugaa KH. Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging*. 2016;17:613-21.

27. Schnell F, Donal E, Bernard-Brunet A, Reynaud A, Wilson MG, Thebault C, Ridard C, Mabo P, Carre F. Strain analysis during exercise in patients with left ventricular hypertrophy: Impact of etiology. *J Am Soc Echocardiogr*. 2013;26:1163-1169.

28. Desai MY, Bhonsale A, Patel P, Naji P, Smedira NG, Thamilarasan M, Lytle BW, Lever HM. Exercise echocardiography in asymptomatic HCM: Exercise capacity, and not LV

outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging*. 2014;7:26-36.

29. Masri A, Pierson LM, Smedira NG, Agarwal S, Lytle BW, Naji P, Thamilarasan M, Lever HM, Cho LS, Desai MY. Predictors of long-term outcomes in patients with hypertrophic cardiomyopathy undergoing cardiopulmonary stress testing and echocardiography. *Am Heart J*. 2015;169:684-692 e681.

30. Kobayashi Y, Ariyama M, Kobayashi Y, Giraldeau G, Fleischman D, Kozelj M, Vrtovec B, Ashley E, Kuznetsova T, Schnittger I, Liang D, Haddad F. Comparison of left ventricular manual versus automated derived longitudinal strain: Implications for clinical practice and research. *Int J Cardiovasc Imaging*. 2015;32:389-98.

Figure 1- Calculation of longitudinal strain. Longitudinal strain (LS) was calculated from the four- chamber view on manual tracings of the mid wall with the formula for Langrangian Strain. Lateral and septal LS were calculated by the same technique, however, mid wall length was assessed from either septal or lateral mitral annulus to the apex.

Figure 2 – Dynamic changes in longitudinal strain. LS is shown in controls, n=80 (left) and patients with HC, n=124 (right) at rest and immediately post exercise.

Figure 3. Kaplan Meier Curve for risk factor score. Patients are stratified according to LAVI (>52ml/m^2), lateral LS (<16.1%) and $ppVO_2$ (<80%). Group 1 represents 0 risk factors, group

2, 1 risk factor, group 3, 2 risk factors and group 4, 3 risk factors. Each additional factor was associated with a significant decrement in prognosis, log rank test $p<0.001$.

Table 1 – Baseline Characteristics

Variable	Patient Cohort (n=131)
Age (years)	52 ± 13
Male	83(63%)
Body mass index (kg/m^2)	29 ± 6
Family history of sudden cardiac death	36(28%)
Syncope	34(26%)
Non sustained ventricular tachycardia	40(30%)
Atrial Fibrillation	24(18%)
Resting heart rate (bpm)	67 ± 12
New York Heart Association Class III	27(21%)
Systolic blood pressure (mm Hg)	119 ± 19
Cardiopulmonary exercise testing	
Peak heart (bpm)	138±29
Peak systolic blood pressure (mmHg)	158±27
Drop in systolic blood pressure with exercise	5 (4%)
Respiratory exchange ratio	1.10 ± 0.09
External Workload (METS)	10.3 ± 4.8
Maximal oxygen consumption (ml/kg/min)	26 ± 11
Percent predicted maximal oxygen consumption (<80%)	53 (40%)
Ventilation and carbon dioxide production slope (>32)	26 (20%)
Therapy	
Beta blocker	81(62%)
Calcium channel blocker	39(30%)

Dysopiramide (%)	5(4%)
ACE Inhibitor or ARB (%)	35(28%)
Diuretics (%)	8(6%)
Automatic implantable cardioverter-defibrillator	51(39%)

Table 2 – Echocardiographic Measures

Variable	Patient Cohort
LV interventricular septum thickness (mm)	18 ± 5
LV posterior wall thickness (mm)	11 ± 3
LV end diastolic volume (ml/m^2)	86 ± 29
LV end systolic volume (ml/m^2)	28 ± 17
LV ejection fraction (%)	64 ± 9
E/e`	12.0 ± 6.7
e` (cm/sec)	8 ± 3
Left atrial volume index (ml/m^2)	44 ± 17
Mitral regurgitation ≥2+	48 (37%)
LV gradient > 30 mmHg at rest	41 (31%)
Left ventricular outflow tract gradient post stress (mmHg)	57 ± 52
Strain assessment (rest n=131, stress n=124)	
Rest global longitudinal strain (%)	14.3 ± 3.9
Rest septal longitudinal strain (%)	12.3 ± 4.4
Rest lateral longitudinal strain (%)	16.1 ± 4.6
Stress global longitudinal strain (%)	16.8 ± 4.2
Stress septal longitudinal strain (%)	14.5 ± 4.6
Stress lateral longitudinal strain (%)	18.8 ± 5.4
Relative change global longitudinal strain (%)	13 ± 15
Relative change septal longitudinal strain (%)	13 ± 26
Relative change lateral longitudinal strain (%)	12 ± 22

Table 3 - Univariate predictors of primary outcome

Variable	HR	95% CI	p value
Rest Echocardiography (n=131)			
LV interventricular septum thickness (mm)	1.15	[1.02-1.31]	0.026
LV posterior wall thickness (mm)	1.14	[1.00-1.30]	0.059
LV end systolic volume (ml/m^2)	1.15	[0.95-1.38]	0.153
Left atrial volume index (ml/m^2)	1.70	[1.37-2.10]	<0.001
E/e`	1.49	[1.20-1.85]	<0.001
e` (cm/sec)	0.52	[0.35-0.77]	0.004
Left ventricular outflow gradient (>30mmHg)	1.57	[1.21-2.03]	0.001
Global longitudinal strain (%)	0.55	[0.41-0.74]	<0.001
Lateral longitudinal strain (%)	0.50	[0.37-0.67]	<0.001
Septal longitudinal strain (%)	0.75	[0.56-0.99]	0.043
Stress Echocardiography (n=124)			
Strain reserve	0.94	[0.69-1.27]	0.700
Global longitudinal strain (%)	0.56	[0.42-0.74]	<0.001
Lateral longitudinal strain (%)	0.56	[0.42-0.75]	<0.001
Septal longitudinal strain (%)	0.66	[0.49-0.91]	0.010
CPX (n=131)			
Peak heart rate (bpm)	0.70	[0.42-0.75]	0.026
Peak systolic blood pressure (mmHg)	0.62	[0.44-0.76]	0.002
External workload (METS)	0.55	[0.41-0.75]	<0.001
Maximum oxygen consumption (ml/kg/min)	0.57	[0.42-0.76]	<0.001

Percent predicted maximum oxygen consumption (%)	0.59	[0.46-0.76]	<0.001
Ventilation and carbon dioxide production slope	1.57	[1.25-1.96]	<0.001

Hazard ratios adjusted for standard deviation.

Table 4 – Multivariate Cox Regression Analysis for primary outcome.

	Global				Regional			
		HR	*95% CI*	*p value*		*HR*	*95% CI*	*p value*
Rest	Left atrial volume index	1.4	1.12-1.94	0.005	Left atrial volume index	1.53	1.18-1.99	0.001
	e`	0.59	0.39-0.93	0.023	e`	0.63	0.41-0.99	0.047
	Global longitudinal strain	0.70	0.49-1.03	0.072	Lateral Longitudinal strain	0.61	0.42-0.89	0.009
				x^2=23				*x^2=27*
CPX	Percent Predicted maximal oxygen consumption	0.56	0.45-0.78	0.001				
	VE/VCO_2	1.31	1.00-1.70	0.500				
				x^2=27				
Integrated Model	Left atrial volume index	1.44	1.11-1.87	0.006	Left atrial volume index	1.51	1.15-1.99	0.008
	Global longitudinal strain	1.27	0.94-1.73	0.119	Lateral longitudinal strain	0.91	0.84-0.96	0.020
	Percent Predicted maximal oxygen consumption	0.62	0.44-0.88	0.007	Percent Predicted maximal oxygen consumption	0.64	0.44-0.94	0.040
				x^2=34				*x^2=39*

All models are adjusted for age and gender. Hazard ratios adjusted for standard deviation.