Supplementary Online Content 1


Study Protocol
Abstract

The overall goal of this project is establish the safety profile and potential benefits of exercise training in patients with hypertrophic cardiomyopathy (HCM). HCM is the most common genetic cardiovascular disease with a broad spectrum of disease severity. HCM accounts for >30% of cases of sudden cardiac death in young athletes. This has appropriately led to the establishment of national guidelines for participation in recreational exercise, with the consensus of expert opinion being that moderate aerobic activities are generally allowable. However, data on safety of recreational fitness, useful parameters for risk stratification, and methods of devising individual exercise prescriptions are completely lacking. There is compelling animal data that voluntary exercise is not only safe, but can prevent or even reverse many of the pathologic features of HCM. There is an urgent need is to address the paradox of exercise in HCM; that is, striking a reasonable balance between potential acute risk of sudden death and the many well-established long term health and cardiovascular benefits of a regular exercise program. Large clinical trials of exercise training in patients with atherosclerosis and heart failure with equivalent acute risks, have shown safety, improved functional capacity, lower mortality, and reduced hospitalizations. We propose a pilot randomized controlled trial to determine the safety and efficacy of moderate intensity exercise in HCM patients. Aim 1 is designed to determine the safety of moderate intensity exercise in patients with HCM. The focus of this aim will be on devising individualized training protocols based on parameters derived from baseline cardiopulmonary exercise testing. A secondary goal will be to assess for exercise induced arrhythmias. Aim 2 examines whether exercise training improves functional capacity, clinical phenotypic characteristics, and quality of life in patients with HCM. Pilot data will greatly enhance the competitiveness of this proposal for extramural funding.

Specific Aims

The goal of this randomized clinical pilot trial is to establish the safety profile and potential benefits of moderate intensity exercise in patients with HCM. Participation in competitive athletics is associated with an increased risk of sudden cardiac death (SCD) in individuals with structural heart disease, most commonly HCM. This has appropriately led to the establishment of national guidelines based on expert opinion that discourage participation in high intensity competitive sports, burst exertion (e.g., sprinting), or isometric exercise (e.g., heavy lifting). Non-competitive, low to moderate intensity exercise is allowable, although many physicians and HCM patients are still understandably apprehensive. Data on the safety of a recreational exercise program, and how to gauge appropriate intensity level, are desperately needed so that HCM patients can reap the well established health benefits of regular physical activity. Limited, but compelling animal data suggest that moderate intensity exercise is not only safe, but may also prevent or even reverse cardiac hypertrophy, fibrosis, myocellular disarray, and apoptosis associated with HCM. There are no published studies on exercise in patients with HCM, although large clinical trials in heart failure have shown exercise training to be safe, to improve functional capacity and quality of life, and to lower cardiovascular mortality. The pilot randomized control trial proposed here is the first to determine the safety of moderate intensity exercise training and explore its potential benefits in patients with HCM. Pilot data will greatly enhance the likelihood of extramural funding for a larger randomized clinical trial intended to establish the long-term effects of exercise on HCM pathophysiology.

Specific Aims:

Aim 1: To determine the safety of a moderate intensity exercise training program in patients with HCM.
A. Randomize patients to home exercise training or usual activity.
B. Devise an individualized exercise training protocol using a percentage of heart rate reserve and rating of perceived exertion as the targets for exercise intensity.
C. Monitor for exercise induced arrhythmias using a 30 day ambulatory electrocardiographic monitor, and for other symptoms (i.e., dizziness, chest pain, syncope) recorded in a daily log.

**Hypothesis:** Exercise parameters derived from a baseline cardiopulmonary exercise test will target an appropriately safe level of exercise intensity that will not cause significant arrhythmias or exacerbate symptoms.

**Aim 2:** To determine whether exercise training improves functional capacity, clinical phenotypic characteristics, and quality of life in patients with HCM.
A. Compare peak oxygen consumption by cardiopulmonary exercise testing before and after 4 months of exercise training.
B. Quantitatively determine effects of exercise on hypertrophy, left ventricular obstruction, left ventricular mass and fibrosis using echocardiography and cardiac magnetic resonance imaging.
C. Administer quality of life questionnaires before and after exercise intervention.

**Hypothesis:** Exercise training in HCM patients for 4 months will result in significant improvements in peak oxygen consumption and quality of life, with neutral effects on the clinical phenotype.

**Background and Significance**

HCM is the most common genetic cardiovascular disease, affecting approximately 1:500 individuals.\(^1\) It is characterized by a hypertrophied, non-dilated left ventricle in the absence of another cardiac or systemic disease capable of producing the degree of hypertrophy present. HCM is a progressive disease with highly variable phenotypic expression with regard to age of onset, magnitude of hypertrophy, presence/degree of left ventricular outflow obstruction, presence and severity of symptoms and inherent risk of sudden cardiac death. Large-scale controlled and randomized study designs, such as those that have provided important answers regarding the management of coronary artery disease and congestive heart failure (CHF), have generally not been available in HCM. Thus, the level of evidence governing management decisions has often been derived from non-randomized and retrospective studies. Importantly, there are no therapeutic strategies or lifestyle modifications that have been shown to impact the progression of disease. This provides the rationale for the current proposal with the long-term goal of exploring the possibility that habitual exercise can improve outcomes in HCM patients.

**Well established health benefits of exercise**

While the link between physical activity and health benefits has been intuitively known for decades, physical inactivity still remains a major health problem. A staggering 200,000 deaths annually in the United States are attributable to a sedentary lifestyle.\(^2\) Conversely, observational studies show that regular exercise confers a significant survival benefit.\(^3, 4\) Habitual exercise significantly decreases the risk of coronary heart disease (CHD), cardiac events and cardiovascular death,\(^5-6\) and improves outcomes in patients with established CHD.\(^5-12\)

The benefits of regular exercise on CHD risk may be mediated, in part, by the favorable influence on plasma lipoproteins, systemic blood pressure, obesity, diabetes mellitus, and psychosocial well-being. Endurance exercise training significantly lowers total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and raises high-density lipoprotein cholesterol independent of diet, baseline body fat, or change in body fat.\(^13\) Long-term aerobic exercise also lowers systemic blood pressure,\(^14, 15\) reduces body fat and preserves body lean mass compared to a weight loss diet alone,\(^16\) and prevents
Additionally, regular exercise has been shown to reduce stress, anxiety and depression,\textsuperscript{21} which are major CHD risk factors.

In patients with chronic HF, both chronic hypoperfusion and physical inactivity lead to skeletal muscle dysfunction and exercise intolerance. Numerous studies have demonstrated the safety and efficacy of exercise training in patients with HF.\textsuperscript{22-30} Randomized controlled trials have shown that exercise training can lessen symptoms, increase exercise capacity, improve quality of life,\textsuperscript{31, 32} reduce hospitalization and increase survival\textsuperscript{36, 37} over and above traditional medical therapy such as ACE inhibitors and beta blockers. Exercise also lowers lifetime risk of developing heart failure.\textsuperscript{33}

Given these convincing data, it is imperative to understand how HCM patients can safely attain the well established, lifelong health benefits of regular exercise.

**Basic studies relevant to effects of exercise on HCM pathology**

There are compelling animal data that support the concept that moderate voluntary exercise is not only safe, but can prevent or even reverse many of the pathologic features of HCM. Transgenic mice expressing a mutant myosin heavy chain that develop pathology by 6 to 8 months of age were exposed to voluntary cage wheel running.\textsuperscript{34} As in human HCM, these mice display an increase in heart to body weight ratio and histopathologic changes such as myofibrillar disarray and fibrosis. Transgenic mice exhibited similar exercise performance and physiologic cardiac adaptation to exercise as non-transgenic mice (NTG). There was no difference in mortality between HCM and NTG exercised mice, proving the safety of moderate intensity exercise in HCM mice. Voluntary exercise led to lessened hypertrophic gene induction, myocyte disarray, and apoptotic signaling regardless of whether exercise was initiated before or after HCM pathology was established. Interestingly, a reduction in fibrosis was only observed when exercise was initiated in the pre-pathologic mice. Another study of a transgenic mouse model of dilated cardiomyopathy (DCM) showed that chronic swim training significantly improved survival and cardiac function, suppressed expression of cardiac hypertrophic markers, and enhanced signaling pathways involved in effective metabolic energy handling.\textsuperscript{35} These data suggest a role for exercise as a therapeutic strategy that can prevent or delay the onset of pathology in this disease process.

The potential role of exercise as a therapeutic strategy to prevent or delay the onset of pathology in HCM has yet to be explored in human studies.

**Relevance of sudden death risk associated with competitive exercise to the proposed studies**

Participation in competitive athletics confers an increased risk of SCD. In one Italian study, the relative risk of cardiovascular SCD in athletes (12-35 years of age) was 2.45 compared to non-athletes.\textsuperscript{36} The acute, physiological, emotional, and psychological effects of exercise, along with often extreme or unpredictable environmental conditions are thought to be the primary triggers of life threatening arrhythmias in individuals with underlying cardiovascular conditions. This is supported by the fact that SCD in athletes most often occurs during or shortly after intense training or competition.\textsuperscript{37, 38} Although the overall annual rate of SCD in US athletes is fortunately relatively low at 1 in 50-200,000,\textsuperscript{38} the impact of each and every young athlete’s death is immeasurable.

HCM accounts for >30% of cases of SCD among athletes.\textsuperscript{37} The incidence of HCM-related SCD is much higher in high-intensity sports, such as basketball and football.\textsuperscript{37, 39, 40} Nevertheless, significant concern about the safety of any form of exercise has prompted establishment of national guidelines discouraging participation in virtually all competitive sports. Although no data on safety of recreational exercise exist, a consensus of expert opinion is that many recreational activities of low-moderate aerobic intensity (i.e. walking, bicycling, light jogging, swimming) are generally safe.\textsuperscript{41}
While SCD risk with vigorous exercise in HCM patients is not to be minimized, in considering the risks of an exercise intervention in HCM patients it is also important to bear in mind the following three points. First, that habitual exercise substantially lowers the relative risk of sudden death in the general population. Second, several large clinical studies over the past decade in patients with chronic stable heart failure demonstrate the safety and many benefits of habitual exercise. Finally, ventricular arrhythmias during symptom-limited exercise are extremely rare in patients with HCM.

**Value of cardiopulmonary stress testing**

Cardiopulmonary exercise testing with metabolic monitoring is an essential component of the objective assessment of functional ability in chronic heart failure. Its value in HCM is less well studied. There are no published reports on the role of cardiopulmonary exercise testing as a means of risk stratification or for guiding exercise recommendations in patients with HCM, as shown in the heart failure population. The key measurement is peak oxygen uptake (peak VO$_2$), whose usefulness as a prognostic marker in heart failure is widely accepted. Peak VO$_2$ and anaerobic threshold have been shown to be compromised in patients with HCM, but prognostic implications are not as well understood. For heart failure patients, well-tolerated exercise programs associated with such favorable training responses have targeted exercise intensity ranges below anaerobic threshold, at 50-70% of maximum oxygen consumption which corresponds to 60-80% of maximum heart rate reserve, and/or a rating of perceived exertion of 12-14 on the Borg scale.

**Use of cardiopulmonary testing parameters to provide exercise prescriptions for HCM patients has not been studied.**

In summary, there are convincing data that exercise training in heart failure patients improves outcomes, and compelling studies in animal models of HCM show benefits of exercise training in prevention and even regression of many pathologic features. Furthermore, patients with HCM are in no way immune to developing other forms of cardiovascular disease, and thus stand to reap equal benefit from a regular exercise program well documented to reduce risks for acquiring coronary heart disease risk factors, myocardial infarction, stroke, heart failure and premature death in the general population. However, there are no data on safety and potential benefits of recreational fitness, useful parameters for risk stratification, or methods of devising individual exercise prescriptions in individuals with HCM. The pilot randomized study proposed here will begin to address these important questions.

**Previous Related Work**

We perform cardiopulmonary exercise echocardiography on virtually all HCM patients and collect this data in our Velos registry, created and managed by MICH. In preparation for initiating an exercise training study, we designed a voluntary survey drawing questions from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) to ascertain exercise practices and administered it to a national HCM population (HCMA). In a preliminary analysis, data from HCM patients (n=835) were compared to published data from eligible NHANES participants (n=9,465) using Chi$^2$ analysis or student t-tests to compare demographics and exercise practices. Compared to NHANES respondents, fewer HCM patients participate in vigorous recreational activity (23% vs 45% respectively, P <0.001), although more HCM patients exercised moderately (62% vs 59%, HCM vs NHANES respectively, P <0.05). Mean age (46 vs 31 y, P<0.001), gender (53 vs 49% male, P=0.02), race (90 vs 69% Caucasian, P<0.001) and body mass index (29 vs 27, P<0.001) were significantly different in HCM vs eligible NHANES populations, respectively. Demographic differences limit comparisons to the general population and future analysis will use propensity matching to account for...
these differences between groups. Nevertheless, we can conclude that few HCM patients perform vigorous exercise and ~1/3 are not engaging in moderate exercise recommended for overall health benefit. In addition, sixty one percent of respondents indicated that exercise restrictions impact their emotional well being. This highlights the need for further investigation into the many potential benefits of exercise in the HCM population.

Research Design and Methods

**Overall study design**
We propose to study 128 patients (see power calculation below) between 18 and 80 years of age with HCM who are not participating in a regular exercise regimen (i.e., ≤ 30 minutes of exercise, ≤ 1 day per week for the previous 3 months) and randomize them to a moderate intensity exercise regimen or usual activity. All patients will be administered a pre-screening questionnaire in order to determine eligibility based on baseline physical activity. This will be a collaborative effort with investigators from Stanford University who will secure their own funding. Target enrollment is 64 patients at each of the two centers. This project has already received IRB approval.

**Inclusion criteria:**
1. Age ≥ 18 years and ≤ 80.
2. Diagnosis of hypertrophic cardiomyopathy, defined by the presence of unexplained left-ventricular hypertrophy ≥ 13 mm in any wall segment.
3. Agreement to be a participant in the study protocol and willing/able to return for follow-up.

**Exclusion criteria:**
1. Opposition to refraining from competitive or organized sports (such as basketball, ice hockey, soccer, and football), burst activity (such as sprinting, racquetball/squash, singles tennis), or heavy isometric exercise (such as body building or bench-pressing) for the duration of the study (1 year).
2. History of exercise-induced syncope or arrhythmias.
3. Medically refractory LV outflow tract obstruction being evaluated for septal reduction therapy.
4. Less than 3 months post septal reduction therapy (surgery or catheter based intervention).
5. Hypotensive response to exercise (> 20 mmHg drop in systolic blood pressure from peak blood pressure to post exercise blood pressure).
7. Worsening clinical status in the last 3 months, advanced heart failure (NYHA IV) or angina (CCS IV).
8. Left ventricular systolic dysfunction (LVEF<55%).
9. ICD placement in last 3 months or scheduled.
10. Life expectancy less than 12 months.
11. Inability to exercise due to orthopedic or other non-cardiovascular limitations.

At our center, the average peak VO2 for patients with HCM is 24 ml/kg/min, which is in agreement with published measurements from our Stanford collaborators. Previous studies in patients with chronic heart failure have demonstrated an approximately 20% increase in peak oxygen consumption with 8 – 12 weeks of exercise. Assuming a similar effect in the HCM population, we plan to enroll 117 patients to have 90% power to detect a significant difference in peak VO2 between the two groups, at a two-tailed significance level of 0.05 or less. Assuming that 10% of patients will not complete the study protocol, we have increased our planned recruitment to a total of 128 patients.
Adherence will be tracked by completion of physical activity logs, telephone follow-ups including the Stanford 7-day recall (7-DR), downloadable data from heart rate monitors and pedometers, and self-reported percentage of time at or exceeding the prescribed training program. The 7-DR has been widely used and validated to assess physical activity levels. It assesses both work and leisure-time activities for the previous seven days. Subjects are asked to recall the number of hours spent sleeping and engaged in moderate [4 metabolic equivalents (METs)], hard (6 METs), and very hard (10.0 METs) physical activity for weekend and week days separately. The time spent performing light activity (2 METs) is determined by subtracting the time included in sleep, moderate, hard, and very hard activity from 24 hours. The physical activity data will be computed as min/d and MET min/d (calculated as the MET intensity times the minutes reported for each type of activity). Energy expenditure will then be computed as follows: MET minutes x (body weight in kilograms/60).

**Aim 1: To determine the safety of a moderate intensity exercise training program in patients with HCM.**

Participants will be randomized to a moderate intensity home exercise regimen or usual activity. The exercise group will undergo 4 months of training, 4-7 days per week with a minimum of 20 minutes per day. The exercise training protocol will be custom designed in consultation with an exercise physiologist after the initial cardiopulmonary exercise testing data have been gathered, such that patients begin exercising at a low intensity (60% of the heart rate reserve = resting heart rate + 0.6 [peak heart rate – resting heart rate]). A rating of perceived exertion on the Borg scale will be used as a secondary measure to help determine goal exercise intensity. The goal of the first week of the protocol is at least 20 minutes of exercise at 60% of the heart rate reserve during each of 3 days. From that point, the exercise prescription will be designed to first increase duration of exercise by 5-10 minutes every week up to 60 minutes of exercise per day and incrementally increase training intensity to a goal of 80% of the heart rate reserve only during the 1st month of the study protocol, and then maintain the same program for months 2-4. The modes of exercise will include cycling (stationary or routine), walk-jog protocols, and elliptical training. No strength training or burst activity will be prescribed and all activities will fall well within the recommended national guidelines for recreational exercise. Participants will be counseled to hydrate adequately during exercise, and to be alert to warning signs that should prompt them to stop exercising and contact the study coordinator. All study participants will keep an exercise log and be provided with heart rate monitors and pedometers. All patients will wear auto-triggered arrhythmia detection monitors for the first month of study initiation and keep a log of any symptoms they experience during exercise. Additionally, all study participants will wear a 24-hour Holter monitor at the end of the study protocol.

**Aim 2: To determine whether exercise training improves functional capacity, clinical phenotypic characteristics, and quality of life in patients with HCM.**

The following testing will be performed at study initiation and termination (4 months).
1. Cardiopulmonary exercise testing in combination with echocardiography.
2. Cardiac magnetic resonance imaging in patients without implantable devices.
3. Serum biomarkers of stretch activation (i.e., BNP).
4. Minnesota Living with Heart Failure, Quick Inventory of Depressive Symptomatology (Self-Report) and SF36v questionnaires.

Patients will be given new exercise logs at the end of the 4-month protocol period and these logs will be reviewed 2 months later (6 months after study initiation). They will also take the three quality of life questionnaires again at this time. Additionally, they will be asked to complete a survey about the research study itself. Finally, all patients will be asked to repeat a cardiopulmonary exercise test 1 year after study initiation and take the quality of life questionnaires again at that time.
The primary outcome measure will be the change in peak oxygen consumption and anaerobic threshold. 

Secondary outcomes will include changes in:
1. Magnitude or distribution of cardiac hypertrophy or left ventricular chamber dimensions.
2. Degree of left ventricular outflow obstruction.
3. Systolic or diastolic function.
4. Scar volume by MRI.
5. Injury and stretch activation markers.
6. Rates of collagen synthesis or degradation.
7. Quality of life indicators.

Statistical Analysis
Clinical data will be collected, coded and entered into Velos, an ongoing database generated and managed in conjunction with MICHR. Descriptive statistics will be reported as mean ± SD. All major treatment comparisons between the randomized groups will be performed according to the intention-to-treat principle: that is, patients will be analyzed — and end points will be attributed — according to the treatment arm to which patients are randomized regardless of non-adherence. Comparisons between groups will be performed by unpaired t tests for continuous variables and χ² or Fisher’s exact test for categorical variables. Changes in continuous variables over time within each group, and between groups, will be assessed by paired t-tests. The bivariate correlations procedure will be used to compute Pearson’s correlation coefficients with the significance levels. For all subjects, multiple linear regression analysis will be performed for change in the peak VO2 at month 4 from baseline as the dependent variable, with baseline demographic and clinical characteristics (age, sex, genetic status, and site) as independent variables. Results will be reported as means with 95% confidence intervals. Two-sided P values will be calculated for all statistical analyses. Significance will be defined as P less than 0.05.

If the analysis of the primary endpoint is not significant, this may reflect noncompliance with the randomization assignment. As we expect that some subjects in the usual activity will initiate an exercise program, and conversely that some subjects in the exercise arm will be non-adherent to their prescribed exercise, we intend to perform a secondary analysis where patients will be divided into quartiles based on total energy expenditure. Linear regression will be used to compare differences in peak VO2 from baseline to month 4 among patients in each quartile of energy expenditure, controlling for the same variables as above (age, sex, race, etc). We will use SAS statistical software for statistical analysis. These statistical methods were prepared under the consultation of MICHR Statistical Core.

Expected Results and Limitations
Our overall expectation is that moderate intensity exercise training will be safe in HCM patients over a broad age range and spectrum of disease severity. We do not anticipate that exercise training at this level will provoke or exacerbate symptoms of heart failure or angina, or promote arrhythmias. We expect that exercise training will be feasible in the majority of study participants and result in a significant increase in functional capacity, as measured by the primary outcome of mean change in peak oxygen consumption. However, there is a possibility that we may identify a subgroup(s) of HCM patients who do not tolerate or respond to advancement of an exercise protocol. There are data from our Stanford collaborators and others that exercise intolerance in HCM patients is related to parameters of diastolic dysfunction. Impaired diastolic filling will limit stroke volume augmentation with exercise, thereby limiting contractile reserve. Additional potential mechanisms of exercise intolerance include provokable LV outflow tract obstruction and abnormal vasomotor or chronotropic responses. What is not known, that our study will address, is whether exercise intolerance related to any of the above mechanisms can be partly overcome by exercise training, or whether certain hemodynamic profiles will be self-limiting and unresponsive to an exercise training regimen.
We fully acknowledge the likelihood that our study will be underpowered to definitively detect any effect (beneficial or harmful) of an exercise intervention on secondary outcomes related to clinical phenotype. The primary reason for this is the insensitivity of clinical imaging and circulating biomarkers to detect early phenotypic changes in a 4 month period in a disease that develops and progresses over a lifetime. We obviously are unable to examine changes in myocardial histology, biochemistry, or signaling as would be done in animal studies. Our intention is then to use data from this pilot study as a springboard to launch a larger, multicenter exercise training study with other HCM centers across the country that will be sufficiently powered to determine effects of exercise training on HCM disease progression and long-term outcomes.
<table>
<thead>
<tr>
<th>Study Enrollment &amp; Randomization</th>
<th>Initial Testing Day</th>
<th>Exercise Physiology Consultation</th>
<th>4 Months Home Exercise Training vs Usual Activity</th>
<th>Post-Study Visit &amp; Testing Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>✅ Blood draw</td>
<td>✅ Cardiopulmonary stress test w/ echo</td>
<td>✅ Exercise prescription</td>
<td>✅ Weekly phone follow-ups</td>
<td>✅ Blood draw</td>
</tr>
<tr>
<td>✅ Physical Measures</td>
<td>✅ Cardiac MRI</td>
<td>✅ Review guidelines</td>
<td>✅ Log symptoms</td>
<td>✅ Physical Measures</td>
</tr>
<tr>
<td>✅ Quality of Life Questionnaires</td>
<td></td>
<td></td>
<td>✅ ACT-EX event monitor 1st month</td>
<td>✅ Quality of Life Questionnaires</td>
</tr>
<tr>
<td>✅ HR monitor/ pedometers</td>
<td></td>
<td></td>
<td></td>
<td>✅ Cardiopulmonary stress test w/ echo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✅ Cardiac MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✅ New Activity log</td>
</tr>
</tbody>
</table>
Post-Study Visit & Testing Day

- As Above
- Telephone Follow Up regarding activities
- Quality of Life Questionnaires
- Experience Survey
- Retrieve Activity Log

6-Month Follow-Up

- Telephone Follow Up regarding activities
- Quality of Life Questionnaires
- Experience Survey
- Retrieve Activity Log
- Cardiopulmonary stress test with echo
- Quality of Life Questionnaires

1-Year Follow-Up
I. Study Participants

A. Inclusion Criteria
1. Age $\geq$ 18 years and $\leq$ 80 years
2. Diagnosis of hypertrophic cardiomyopathy, defined by the presence of unexplained left ventricular hypertrophy $\geq$ 13 mm in any wall segment
3. Agreement to be a participant in the study protocol and willing/able to return for follow-up

B. Exclusion Criteria
1. Opposition to refraining from competitive or organized sports (such as basketball, ice hockey, soccer, and football), burst activity (such as sprinting, racquetball/squash, singles tennis), or heavy isometric exercise (such as body building or bench pressing) for the duration of the study (1 year).
2. History of exercise-induced syncope or arrhythmias (VT/VF/NSVT)
3. Medically refractory LV outflow tract obstruction being evaluated for septal reduction therapy
4. Less than 3 months post septal reduction therapy (surgery or catheter-based intervention)
5. Hypotensive response to exercise (>20 mmHg drop in systolic blood pressure from peak blood pressure to post exercise blood pressure
6. Pregnancy
7. Worsening clinical status in the last 3 months, NYHA IV, CCS IV
8. ICD placement in the last 3 months or scheduled
9. LV systolic dysfunction or diagnosis of end-stage HCM
10. Life expectancy < 12 months
11. Inability to exercise due to orthopedic or other non-cardiovascular limitations

II. Screening

A. Complete Pre-screening Questionnaire
B. Complete Inclusion/Exclusion Criteria form

III. Randomization

A. Prognostic factors identified
1. Sex (Male/Female)
2. Age (18-29, 30-49, $\geq$50)
3. LVOT gradient (≤29mmHg at rest, $\geq$30mmHg at rest)

B. Minimization method
1. SD to randomize all patients at both sites

IV. Enrollment Day Protocol for All Patients

A. Review Inclusion/Exclusion Criteria form
B. Obtain Informed Consent
C. Record Demographics on Enrollment H&P Form
1. Date of birth, age
2. Sex
3. Ethnic Category as defined by NIH: Hispanic or Latino, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black or African America, White
4. Socioeconomic status – occupation and highest level of education
5. Past medical history: DM, hyperlipidemia, CAD, CHF (systolic or diastolic), stoke, CKD/ESRD, COPD/emphysema, restrictive lung disease, osteoarthritis, atrial fibrillation/flutter/tachycardia, ventricular tachycardia/fibrillation, aborted sudden cardiac death, ICD, BiV-ICD, pacemaker
6. Current medications and doses: beta blocker, calcium channel blocker, nitrates, digoxin, ACE-inhibitor/ARB, aldosterone-receptor blocker, digoxin, amiodarone, dronedarone, lipid-lowering agents, hypoglycemic agents/insulin, aspirin/plavix/Coumadin, diuretics
7. NYHA Class
   a) NYHA Class I – No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
   b) NYHA Class II – Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
   c) NYHA Class III – Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
8. Canadian Cardiovascular Society Angina Scale
   a) Class 0: Asymptomatic
   b) Class 1: Angina with strenuous exercise
   c) Class 2: Angina with moderate exertion
   a) Class 3: Angina with mild exertion (walking 1-2 level blocks at normal pace; climbing 1 flight of stairs at normal pace)

D. Physical Examination and Measurements on Enrollment H&P
1. Height in inches/cm
2. Weight in pounds/kg
3. Waist-to-hip ratio
   a) Use a tape measure to measure the smallest circumference of the natural waist (usually just above belly button) and hip circumference at its widest part
   b) Record both waist circumference and the ratio
4. Calculate BMI
5. Record HR, SBP, DBP
6. Carotid upstroke: normal, reduced, bifid
7. Record presence/absence S3, S4
8. Record presence/absence of outflow murmur (grade 1-6, none); record maneuver response (Valsalva, squat to stand; no change, increase, decrease, not done)
9. Record presence/absence of MR murmur
10. Record presence/absence JVD
11. Record peripheral edema (none, 1-4)
12. Record lung exam findings: CTAB, decreased BS in bases, wheeze, crackles

E. Blood Draw
1. Basic Metabolic Profile (includes Na, K, Cl, HCO3, BUN, Cr, Glucose, Ca)
2. Lipid profile (total cholesterol, triglycerides, HDL, LDL)
3. BNP
4. Bank three tubes for future (one tube at enrollment for future gene testing [DNA] and one at enrollment and one at the conclusion for serum)
   a) Collect blood in PAXgene Blood DNA Tubes
      (http://www1.qiagen.com/Products/GenomicDnaStabilizationPurification/PAXgeneBloodDNASystem/PAXgeneBloodDNATubes.aspx)
   b) PAXgene Blood DNA Kit for DNA isolation
      (http://www1.qiagen.com/Products/GenomicDnaStabilizationPurification/PAXgeneBloodDNASystem/PAXgeneBloodDNAKit.aspx)
   c) Serum should be spun down and frozen in a separate aliquots for each patient.

F. Quality of Life Questionnaires
1. SF-36v2
2. Minnesota Living With Heart Failure Questionnaire
3. Quick Inventory of Depressive Symptomatology (Self-Report) - 16

G. Heart Rate monitors/Pedometers, ACT-EX Monitors and Activity Logs
1. Usual Activity Group
   a) Study team to program HR monitor and pedometer and educate on use/programming for each individual
   b) Study team to educate each individual about how to document in the activity log
2. Exercise Group
   a) Exercise Physiologist to program HR monitor and pedometer and educate on use/programming for each individual
   b) Study team to educate each individual about how to document in the activity log
3. LifeWatch ACT-EX Monitors
   a) All patients have ambulatory arrhythmia monitors for first 30 days of study protocol as exercise is being increased in frequency and intensity.
   b) Monitors are placed on enrollment day.
   c) If any ventricular arrhythmias (excluding PVCs, couplets, bigeminy), subject excluded from study.
4. LogBooks
   a) For each day, log activity and associated workload, minutes, peak HR, and peak RPE
   b) For each day, log pedometer count and symptoms
   c) Record weight at the beginning of each week
   d) Exercise group will record their target number of days, minutes, HR, and RPE for exercise that week and one-minute HR recovery on day 1/week 1 and at the end of every week

H. Review of current national guidelines for all patients
1. No burst activity (sprinting, basketball, soccer, football, squash/racquetball)
2. No static/isometric activity that would involve straining (body building, lifting free weights)
3. Recommend those activities given a score of 4/5 by AHA/ACC guidelines
   a) Treadmill/stationary bike
   b) Doubles tennis
   c) Lap swimming
   d) Modest hiking
Non-free weights
Brisk walking
Hydration before, during, and after exercise program

I. Electrocardiogram

V. Enrollment Studies For All Patients

A. Cardiopulmonary Exercise Test
1. Symptom-limited treadmill exercise testing using Ramp protocols and Borg Perceived Exertion Scale, with simultaneous respiratory gas analysis.
2. Record HR, SBP, DBP at rest, peak exercise, post exercise
3. Record RER, AT, max VO2, Ve/VCO2, Ve/VCO2 slope, % heart rate reserve
4. Record arrhythmias (PACs, PVCs, NSVT, VT, supraventricular arrhythmias, VF, AV blocks),
5. Record METs achieved, exercise time, rate-pressure product (HR x SBP), % max predicted HR achieved

B. Transthoracic 2D Echocardiography including color and tissue Doppler (Philips machine)
1. Real-time 2D images acquired in the standard parasternal (long-axis) and apical (apical 4, apical 2, and apical long) views, and 3 cardiac cycles recorded. 
Parasternal short-axis views acquired at 3 levels: basal (at mitral valve level), midpapillary, and apical (minimum cavity distal to papillary muscle level).
   a) Maximum wall thickness (IVS, PW), LVIDd, LVIDs, LA (mm) measured in parasternal long-axis view
   b) LA volume (area obtained in 2-chamber and 4-chamber views and averaged)
   c) Ejection Fraction, visual estimate and/or calculated biplane/single-plane Simpson’s calculation (%)
2. Parasternal long axis of the RV
   a) Save color tissue in the RV long axis view
3. RVOT Doppler signal
4. Peak velocity of the left ventricular outflow tract recorded from the apical 5 chamber view by pulse Doppler, used to calculate pressure gradient
   a) LVOT gradient, resting/Valsalva/post exercise (mmHg)
5. Apical 4-chamber view – RV evaluation
   a) Sector focus on RV with frame rates higher than 80 Hz (2D image) for tricuspid annular plane systolic excursion (TAPSE) and strain analysis 
   b) Tissue Doppler of lateral RV wall and septum 
   c) Tissue Doppler velocities of the tricuspid annulus 
   d) Tissue Doppler of the proximal RV wall (focus on the isovolumic phase signal) – sweep speed 150 cm/s 
   e) Doppler of the RV inflow with signals at end-expiration and end-inspiration
6. In apical 4-chamber view, mitral inflow and mitral annulus tissue Doppler velocities recorded by pulse Doppler at end expiration.
   a) E peak velocity, A peak velocity (m/s); E/A
   b) Deceleration time (ms)
   c) e’ medial and lateral mitral annulus velocities (m/s); average the two velocities
   d) Use the averaged e’ velocity to calculate E/e’

7. Peak velocity of the tricuspid regurgitation jet recorded from multiple windows by continuous-wave Doppler and used to calculate pulmonary artery systolic pressure.

8. Color Doppler and visual assessment of degree of tricuspid regurgitation in the standard parasternal and apical views (none, trivial, mild, moderate, severe).

9. Color Doppler and visual assessment of degree of mitral regurgitation in the standard parasternal and apical views (none, trivial, mild, moderate, severe).

10. Subcostal views with evaluation of inferior vena cava with respiration and hepatic vein pulse signal.
   a) RAP = 5mmHg if IVC diameter < 1.5cm and > 50% change in caval diameter with respiration.
   b) RAP = 10 mmHg if IVC diameter 1.5 – 2.5 cm and < 50% change in caval diameter with respiration.
   c) RAP = 15 mmHg if IVC diameter > 2.5 cm and little or no change change in caval diameter with respiration.

C. Cardiac MRI – 1.5 Tesla magnet (Philips Achieva) MRI at UMHS or EAA
1. All sequences acquired with cardiac gating.
2. Breath-hold cine imaging performed using a retrospectively gated segmented balanced steady-state free precession sequence in the short axis plane covering the ventricles from the apex to base, 3 LV long axis planes (horizontal, vertical, and LVOT long axis), and a coronal/oblique plane of the LVOT. Vertical and horizontal line tagging performed using a SPAMM sequence in the short axis plane (one slice each through the base, mid-portion, and apex).
   a) Cine MRI will be used to assess LV function and volume.
   b) LVEF will be measured using cine balanced SSFP images at short axis view (Simpson's method).
   c) From the endocardial and epicardial tracings, left ventricular end-diastolic volume (LVEDVd), left ventricular end-systolic volume (LVEDVs), stroke volume, EF, mass, and mass-index can be calculated.
   d) Ventricular line tagging will be analyzed by inhouse Matlab (Natick, MA) scripts for assessment of ventricular torsion.
3. Perfusion imaging performed to assess first pass perfusion during bolus injection of 0.1 mmol/kg of gadolinium contrast agent (Multihance). Phase sensitive 2D inversion recovery prepared Gradient Echo imaging to be performed 15-20 minutes post injection of Multihance to evaluate for delayed enhancement of the myocardium.
   a) Perfusion images will be assessed visually and semiquantitatively (Medis software) for presence or absence of rest perfusion defects.
b) Presence or absence of DGE will be quantified using a semiautomated gray-scale thresholding with 6 or more SDs above the mean signal intensity for the visually normal remote myocardium. This method has been shown to yield the closest approximation of the extent of DGE identified with visual assessment and is highly reproducible.

VI. Exercise Physiology Consultation Only For Patients Randomized to Exercise Group

A. Individualized exercise prescription based on the gathered cardiopulmonary exercise test data

1. Start at a low intensity (60% of the heart rate reserve = resting HR + 0.6[peak HR – resting HR]) and Borg Perceived Exertion scale 12-14
2. Goal of the first week of exercise is 3 days per week, at least 20 minutes at 60% HRR during each session
3. Devise an exercise prescription that will first increase duration of exercise by 5-10 minutes every week up to 60 minutes of exercise per day and incrementally increase training intensity to a goal of 70% of the heart rate reserve during the first month and maintain regimen for months 2-4.
4. Modes of exercise will include cycling (stationary or routine), walk-jog protocols, and elliptical.
5. Again, educate participants about the recommended national guidelines for recreational exercise, hydration, and warning symptoms that should prompt them to stop exercising and contact study coordinator (lightheadedness, chest pain, syncope).
6. Handouts provided to all exercising patients about warning symptoms and hydration.

VII. Home Exercise Training vs. Usual Activity

A. Weekly follow-ups

1. Phone call by study team member every Monday (to all patients, so as to avoid bias).
   a) Review 7-day recall and activity log.
2. Meet every Tuesday to review follow-up and make decision about whether and how to advance the exercise regimen. Communicate plan to patient.

VIII. Post Study Visit and Testing Day (within 2 weeks of end of study protocol)

A. Record Demographics

1. Current medications and doses: beta blocker, calcium channel blocker, nitrates, digoxin, ACE-inhibitor/ARB, aldosterone-receptor blocker, digoxin, amiodarone, dronedarone, lipid-lowering agents, hypoglycemic agents/insulin, aspirin/plavix/coumadin
2. NYHA Class
   a) NYHA Class I – No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
   b) NYHA Class II – Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
c) NYHA Class III – Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

d) NYHA Class IV – Unable to carry out physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

3. Canadian Cardiovascular Society Angina Scale
   a) Class 0: Asymptomatic
   b) Class 1: Angina with strenuous exercise
   c) Class 2: Angina with moderate exertion
   d) Class 3: Angina with mild exertion (walking 1-2 level blocks at normal pace; climbing 1 flight of stairs at normal pace)
   e) Class 4: Angina at any level of physical exertion

B. Physical Examination and Measurements – Same as Enrollment Day

C. Blood Draw – Same as Enrollment Day

D. Quality of Life Questionnaires – Same as Enrollment Day

E. Cardiopulmonary Exercise Test – Same as Enrollment Study

F. 2D Transthoracic Echocardiography Measurements – Same as Enrollment Study

G. Cardiac MRI – Same as Enrollment Study

H. 24-hour Holter Monitor

I. Electrocardiogram

J. Provide new exercise activity log book to all patients.

K. Exercise consultation for all patients originally randomized to the Usual Activity group.
References


18. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. 
Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J 
intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-
insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med.* 1996;156(12):1307-
1314.
Manson JE. Walking compared with vigorous physical activity and risk of type 2 diabetes in 
22. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of 
the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit 
depends on the type of training performed. *J Am Coll Cardiol.* 2007;49(24):2329-2336.
exercise training on left ventricular function and peripheral resistance in patients with chronic 
Schnellbacher K, Roskamm H. Predictors of response to exercise training in severe chronic 
moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, 
26. Whellan DJ, Shaw LK, Bart BA, Kraus WE, Califf RM, O'Connor CM. Cardiac rehabilitation 
and survival in patients with left ventricular systolic dysfunction. *Am Heart J.* 2001;142(1):160-
166.
27. McKeilve RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, Hendrican K, Yusuf 
S. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial 
Exercise training without ventricular remodeling in patients with moderate chronic 
heart failure early after acute myocardial infarction. *Int J Cardiol.* 2003;87(2-3):237-
244.
training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular 
30. Radzewitz A, Miche E, Herrmann G, Nowak M, Montanu U, Adam U, Stockmann Y, Barth M. 
Exercise and muscle strength training and their effect on quality of life in patients with chronic 
SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP. 
Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION 
32. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training 
on cardiac performance, exercise capacity and quality of life in patients with heart failure: a 
33. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime 
34. Konhilas JP, Watson PA, Maass A, Boucek DM, Horn T, Stauffer BL, Luckey SW, Rosenberg 
P, Leinwand LA. Exercise can prevent and reverse the severity of hypertrophic 


