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Research Paper

The design and rationale of the cardiac REHABilitation to improve metabolic health in Hypertrophic CardioMyopathy (REHAB-HCM) Study

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ABSTRACT

Study objective: Hypertrophic cardiomyopathy (HCM) is the most common genetic myocardial disorder increasingly characterized by concomitant metabolic syndrome. Cardiac rehabilitation (CR) has been shown to improve metabolic parameters in populations with heart failure and myocardial infarction. However, there is a paucity of data on the impact of CR in the HCM population with metabolic syndrome. We designed the REHAB-HCM study to explore the feasibility, safety, and efficacy of CR in HCM patients with metabolic syndrome.
Design: Prospective observation cohort study.
Setting: A multi-disciplinary HCM clinic and Multidisciplinary Exercise-based Cardiac Rehabilitation program.
Participants: Patients aged 18–80 years old diagnosed with HCM and metabolic syndrome, defined by the American Heart Association and American College of Cardiology guidelines, and the National Cholesterol Education Adult Treatment Panel III (NCEP-ATP III) criteria.
Intervention: A structured 3-month CR program with 6 months extended follow-up of physical activity levels.
Main outcome measures: Feasibility (e.g., attendance), safety (e.g., major adverse events and exercise-related harms), and efficacy pertaining to long term improvements in physical activity levels, metabolic health, cardiorespiratory fitness, quality of life, and systemic and cellular markers of inflammation.
Conclusion: This prospective cohort study will address an important knowledge gap by evaluating the effect of an organized CR program in HCM patients and metabolic syndrome. It is anticipated that exercise and CR will be feasible and beneficial for this complex patient population without significant exercise-related harms.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic myocardial disorder, affecting up to 1 in 500 people [1,2]. Histopathological signs of HCM typically include myocyte hypertrophy, myofibril disarray, and myocardial fibrosis [3]. These can translate into the hallmark left ventricular hypertrophy and dynamic left ventricular outflow tract obstruction which can provide anatomical substrate for arrhythmias and heart failure, as well as lead to clinical manifestations of chest pain, dyspnea, and syncope, particularly on exertion [4,5]. Exercise has long been felt to increase the risk of sudden cardiac death to a prohibitive extent in HCM patients; [6] however, contemporary evidence suggests no significant increased risk of sudden death during vigorous exercise participation in this population [7–9]. The AHA/ACC 2020 guidelines suggest that recreational moderate intensity exercise as a Class IB recommendation for most HCM patients based on its association with improved cardiorespiratory fitness, quality of life, and level of functioning [10]. Furthermore, the most recent 2024 guidelines have now stated that universal restriction from vigorous physical activity is not indicated for most patients HCM patients [11]. Despite these recommendations, many HCM patients remain sedentary [7]. An effective intervention to reduce sedentarism and improve overall health is cardiac

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rehabilitation (CR), defined as a multidisciplinary, medically supervised intervention designed to improve cardiorespiratory fitness and reduce cardiovascular risk [12]. To our knowledge, only two studies have assessed the benefits and risks of CR in HCM [9,13]. Indeed, the 2020 American Heart Association/American College of Cardiology (AHA/ACC) guideline on HCM underscores the lack of research in this area [10].

In the modern era, the leading contributor of premature death in an increasingly aging HCM population is metabolic syndrome [2,14], characterized by concurrent impaired glucose tolerance, hypertension, and dyslipidemia [14]. Data from the Human Sarcomeric Cardiomyopathy Registry demonstrated that two-thirds of HCM patients have obesity or elevated body mass index (BMI) [14]. This, in addition to increased frequencies of other comorbidities such as diabetes and hypertension, has been linked to poor outcomes in HCM patients, such as heart failure and arrhythmia [15,16]. Importantly, exercise promotes the prevention and management of these comorbidities. For instance, a meta-analysis of >19,000 patients reported that CR resulted in an impressive 25 % reduction in metabolic syndrome and significant improvements in several metabolic parameters, including cholesterol, blood pressure, glycemic control, and waist circumference [17]. However, these benefits have yet to be explored in the HCM context.

There remain substantial ***knowledge gaps*** in understanding the utility of CR in HCM patients with metabolic syndrome. Here, we report the design and rationale of the Cardiac REHABilitation to Improve Metabolic Health in Hypertrophic CardioMyopathy (REHAB-HCM) study, a hypothesis generating study that will take place at the British Columbia Hypertrophic Cardiomyopathy Program.

2. Methods

2.1. Study overview objectives, and participant recruitment

This is a prospective observational cohort study of HCM patients with metabolic syndrome that will assess 1) The feasibility of CR in HCM patients by assessing adherence to CR and exercise prescription in HCM patients with metabolic syndrome; 2) The safety of CR in this population; 3) the efficacy of CR, including improvements in metabolic risk factors, cardiorespiratory fitness, psychological well-being, physical activity levels and quality of life, and systemic and cellular markers of inflammation. The study will take place in three phases over the course of one year: 1) Participant screening, recruitment, and enrollment, which will be at the British Columbia Hypertrophic Cardiomyopathy Program (BC-HCMP) by a clinician or research coordinator, and baseline testing (0–90 days before CR initiation), 2) CR participation period (days 1–90), and 3) Post-CR follow-up period (days 91–270, i.e. 6-months monitoring after CR completion). Please see Table 2 for further details regarding the inclusion and exclusion criteria.

2.2. Cardiac rehabilitation and exercise prescription

Cardiac rehabilitation will consist of performing exercise 3× per week and will be delivered in a hybrid model. For the initial two weeks, exercise sessions will be performed in a community hospital out-patient cardiac rehabilitation center and supervised by a clinical exercise physiologist to assess patient safety and physiological responses to exercise. For weeks 3–12, patients will attend one in-person session per week, while the remaining two sessions will be performed at home. The in-person session will consist of both aerobic and strength training, while at home sessions will be aerobic exercise only. For all in person and at-home exercise training sessions, patients will be asked to wear a continuous heart rate monitor (e.g., GeneActiv watch and H9 chest strap) to monitor exercise intensity and duration and assess adherence to the exercise prescription. Patients will also be asked to record their rating of perceived exertion, dyspnea and leg fatigue pre, during and post their exercise session to the exercise physiologists overseeing their session.

The exercise prescription will consist of an individualized non-linear prescription whereby the intensity, duration and volume will be varied to target different physiological adaptations over the course of the 12-weeks. As the majority of exercise sessions will be performed at home, the prescription will follow current exercise guidelines for HCM, whereby a greater emphasis will be placed on increasing exercise duration while intensity will be prescribed at light to moderate levels (50–75%VO_{2peak}) [10]. To try and enhance physical activity behavior, patients will also be given a physical activity prescription (in addition to their prescribed exercise training sessions) that is progressive over the 12 weeks in both duration (increasing from 15 to 45 min) and frequency (1 day/ week to 3 days/week) that complements the CR program. Physical activity will be performed at a light to moderate intensity and will include activities such as walking, grocery shopping, house cleaning, etc. Patients will also meet with a registered dietician and physician and receive health education once per week on dietary targets, and lifestyle recommendations in accordance with standard guidelines as part of the standard of care community cardiac rehabilitation program [18].

This study will be conducted in strict accordance with the principles laid forth by the Providence Health Care Research Ethics Board and the Declaration of Helsinki. Informed consent was obtained by each participant prior to enrollment into the study.

2.3. Feasibility: evaluating CR adherence in HCM patients

To determine adherence to cardiac rehabilitation and to appropriately quantify exercise dose the following metrics will be documented for the 36 prescribed sessions: 1) Loss to follow up - % of patients who do not return for follow-up assessments. 2) Attendance - % of exercise sessions attended vs. planned. 3) Rescheduled sessions - % of exercise sessions rescheduled and the reason. 4) Permanent treatment discontinuation – discontinuation of exercise sessions prior to 12 weeks. 5) Treatment interruption – missing 3 consecutive exercise sessions. 6) Dose modification – at least one session requiring dose reduction during the 12 weeks. 7) Early exercise termination – at least one session requiring early termination. 8) Pre-treatment session intensity resequencing – intensity of at least one session requiring resequencing due to pre-exercise indication (e.g., fatigue). 9) Relative dose intensity - % of cumulative dose completed vs planned.

2.4. Assessing changes in physical activity levels, and attitudes, quality of life, and exercise adherence

Self-reported physical activity levels and exercise attitudes will be assessed with the International Physical Activity Questionnaire (IPAQ; short-form) and the Fear of Activity in Situations-Heart Failure Questionnaire (FActS-HF), respectively (Table 1) [21]. To monitor total physical activity levels throughout the study period, participants will wear a commercially available and validated accelerometer (e.g. GeneActiv) at baseline for at least one week prior to CR, throughout the three-month CR period, and for six months following CR completion. Data from the GeneActiv watch will be uploaded monthly to an anonymized offline database for downstream analysis to calculate total physical activity (including light, moderate, and vigorous physical activity) using established methods [22–24]. Physical activity adherence will be defined as meeting 80 % of the planned physical activity targets prescribed across the CR intervention, which will progressively increase throughout the study, and 6 months following CR completion. Accelerometer adherence will be defined as an average usage of >10 h per day and at least 21 days per month. Quality of life will be measured using the Minnesota Living with Heart Failure Questionnaire and Kansas City Cardiomyopathy Questionnaire at baselines, following completion of CR and at the 6-month time point.

Table 1
Variables of interest.

Study outcomes	Descriptors
Lipids	LDL(c) HDL(c) Non-HDL(c) Triglycerides
Glycemic control	Fasting glucose Fasting insulin Hemoglobin A1c
Resting hemodynamics	Systolic blood pressure Diastolic blood pressure Heart rate
Body composition	Body mass index DEXA scan Waist circumference
Cardiorespiratory fitness	Peak oxygen consumption Peak respiratory exchange ratio Exercise duration Peak heart rate Peak METS Heart rate reserve
Inflammation	Clinical immune/inflammatory markers: complete blood count, hsCRP Plasma and LPS-induced PBMC cytokines: IL-1β, INF-α2, INF-γ, TNF-α, MCP-1 (CCL2), IL-6, IL-8 (CXCL8), IL-10, IL-12p70, IL-17A, IL-23, and IL-33
International Physical Activity Questionnaire	Measure of health-related physical activity involvement
Fear of Activity in Situations-Heart Failure Questionnaire	Measure of kinesiophobia (fear of exercise/ movement)
Minnesota Living with Heart Failure Questionnaire	Measure of quality of life with heart failure
Kansas City Cardiomyopathy Questionnaire	Measure of quality of life with cardiomyopathy

Abbreviations: LDL(c) = low density lipoprotein cholesterol. **HDL(c)** = high density lipoprotein cholesterol. **DEXA** = Dual Energy X-ray Absorptiometry. **hsCRP** = high-sensitivity C-reactive protein. **LPS** = lipopolysaccharide. **IL** = **Interleukin**. **PBMCs** = peripheral blood mononuclear cells.

Table 2
Participant inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
Diagnosed with hypertrophic cardiomyopathy defined by the AHA/ ACC guidelines [10], and metabolic syndrome, defined by the National Cholesterol Education Adult Treatment Panel III (NCEP-ATP III) criteria requirement of three or more abnormal metabolic parameters [19], and/or by the presence of hypertension, dyslipidemia, or diabetes requiring pharmacologic treatment	Diagnosis of physical or psychological conditions that impede inclusion based on clinician assessment. These conditions are not limited to below: -Severe aortic valve stenosis -Terminal illness with life expectancy <1 year -Impairment from stroke, injury or other medical disorder that precludes participation in exercise intervention -Severe cognitive impairment/dementia that precludes ability to participate in exercise intervention and/or follow study protocols -Advanced chronic kidney disease defined as estimated glomerular filtration rate < 20 mL/min/1.73 m or on chronic or intermittent dialysis or dialysis anticipated within the next 6 months
Aged 18–80	High-risk score for sudden death (≥6 % within five years) without an ICD [20]
Receiving care from the British Columbia Hypertrophic Cardiomyopathy Program (BC-HCMP)	NYHA Class IV dyspnea
Willing to use and operate a wearable wrist device to track physical activity and heart rate during the entire study period	Already participate in at least 150 min per week of moderate-to-vigorous intensity exercise
Stable on cardiac medications for at least one month prior to enrollment	Participants who are high risk for non-adherence as determined by screening evaluation or have an inability or unwillingness to comply with the study requirements
Willing to participate in three months of a virtual/in-person hybrid cardiac rehabilitation program	

2.5. Safety considerations

While several studies show CR is safe in HCM and in metabolic syndrome, there can be serious risks [9]. Risks associated with exercise and HCM include syncope, ICD shocks, and cardiac arrest. As such, a safety committee will be formed and responsible for the adjudication of any event to determine whether exercise can be implicated in the outcome. These outcomes will be recorded and any appropriate intervention or referral to a specialist will follow suit. In addition to the safety assessment, a 5-day ECG patch monitor will be given within the first week for additional arrhythmia monitoring. In the case of an event, the panel will also determine whether the participant should be removed from the CR classes and counseled on potential exercise restrictions. Safety will be assessed during the CR intervention window by the frequency of serious (i.e., life-threatening hospitalizations, significant incapacity, important medical events) adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 questionnaire [25].

2.6. Efficacy outcomes: examination of cardiometabolic health and fitness

Evaluations of cardiometabolic health and fitness will include anthropometric measurements and cardiopulmonary exercise testing. Specifically, we will assess changes in variables that define metabolic syndrome, including cholesterol and triglyceride levels, glycemic control, waist circumference and body composition via Dual Energy X-ray Absorptiometry (DEXA), and resting blood pressure and heart rate. A cardiopulmonary exercise test (CPET) will be used to provide direct and objective evaluation of cardiorespiratory fitness, as assessed by peak oxygen consumption (VO_2peak). VO_2peak will be evaluated at the initiation of CR, at CR completion, and six months post-completion (Fig. 1) using an upright cycle ergometer with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) performed by certified exercise physiologists and with MD supervision based on established guidelines [26]. Expired gases will be analyzed continuously by a metabolic measurement system (Parvo Medics TrueOne 2400) [27]. During the test, participants will begin cycling on an upright cycle ergometer at a participant-specific intensity for 2 min. The resistance will then be increased by 5-10 W every 1 min until exhaustion and symptoms of dyspnea and leg discomfort are recorded every 2 min using the modified Borg Scale. During exercise, oxyhemoglobin saturation will be monitored continuously using finger pulse oximetry, while blood pressure will be measured every 2 min manually by auscultatory sphygmomanometer.

2.7. Evaluation of systemic and cellular markers of inflammation

A venous blood sample in EDTA vacucontainers will be collected before CR initiation, at CR completion, and six months post-completion. A complete blood count and clinical biomarkers for inflammation (e.g., hsCRP), glycemic control, and lipid panel will be performed. From remaining blood, plasma and peripheral blood mononuclear cells (PBMCs) will be isolated using SepMateTM PBMC isolation tubes within 2 h of collection (STEMCELL Technologies). Plasma will be snap frozen and stored at −80 °C, while isolated PBMCs will be cryopreserved in FBS + 10 % DMSO. Plasma will be analyzed using the Biolegend Human Inflammation Multiplex Assay, which permits simultaneous quantification of 13 human inflammatory cytokines/chemokines, including IL-1β,

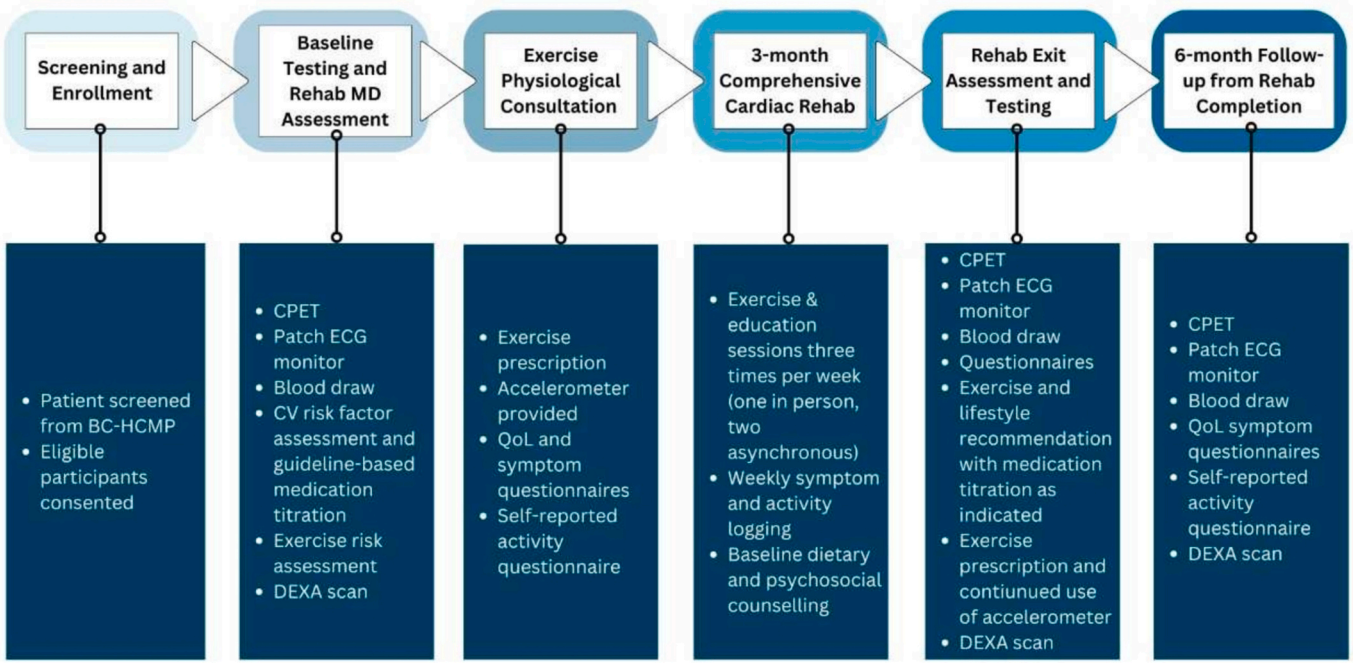

Fig. 1. Timeline of study.
Summary of study design. BC-HCMP = British Columbia Hypertrophic Cardiomyopathy Program. **CPET** = cardiopulmonary exercise testing. **CV** = cardiovascular. **QoL** = quality of life. **DEXA** = Dual Energy X-ray Absorptiometry.

INF-α2, INF-γ, TNF-α, MCP-1 (CCL2), IL-6, IL-8 (CXCL8), IL-10, IL-12p70, IL-17 A, IL-23, and IL-33. PBMCs will be thawed and plated with or without stimulation (e.g., inflammatory stimuli such as lipopolysaccharide, *S. aureus* bioparticles) for 24 h, with cytokine levels again assessed using the Human Inflammation Multiplex Assay.

2.8. Sample size and statistical plan

A pragmatic sample size of approximately 30 participants will be sought based on established guidelines for hypothesis-generating feasibility studies [28,29]. This sample size should be reasonable given the patient volumes seen at the BC-HCMP and will allow for equitable recruitment based on sex, ethnicity, and adherence. It is estimated that ~30 % of clinic patients will meet eligibility criteria and we conservatively estimate a consent rate of at least 50 % based on previous trials [30]. Based on published CR data, we expect a low drop-out rate of 10–20 % [31,32]. As approximately 50 patients are seen per month at the BC-HCMP, we expect recruitment to be completed within three months.

Descriptive analyses will include mean with standard deviation or median with interquartile range for continuous data depending on data distribution, or absolute values with percentages for categorical data. Variables will be recorded before CR initiation, at completion, and again at six months post-completion. Results will be compared across these stages. Bivariate analyses will include Student's *t*-test, Mann-Whitney *U* test, analysis of variance, and/or Wilcoxon rank-sum test depending on data distribution for continuous variables, or Chi-square, McNemar's, and/or Fisher's exact test for categorical variables. The significant level will be set at $\alpha = 0.05$. Bonferonni's correction will be used to correct for multiple comparisons as needed.

2.9. Knowledge use and future directions

This hypothesis-generating study will provide valuable information of the feasibility, safety, and magnitude of effect that will be a preliminary step in establishing an RCT across an established national, multi-centre network. If results are negative, closer evaluation as to why they are negative will have to be considered and addressed accordingly, whether due to adherence, patient factors, or study characteristics such as sample size.

3. Discussion

Exercise and HCM were previously thought to be two incompatible entities due to prior studies suggesting an association with sudden cardiac death [6]. While recent evidence suggests limited risk exists, because of this previous dogma [8], the evidence surrounding CR and HCM remains in its infancy. This initial study uniquely assesses the feasibility, sustainability and patient tolerance of CR, its safety outcomes, and its associations with markers of metabolic, physical, and mental health in HCM patients with metabolic syndrome. The results are expected to provide insights into the efficacy of CR for HCM, particularly with respect to metabolic health, systemic inflammation, cardiorespiratory fitness, and quality of life ascertained by validated questionnaires. The findings are intended to inform the development of future larger-scale studies of organized exercise interventions in patients with HCM.

Systemic inflammation is a critical pathological feature of HCM. Increased systematic inflammatory markers, including tumor necrosis factor (TNF), interleukin 6 (IL-6), and serum amyloid P (SAP), are correlates of myocardial fibrosis, diastolic dysfunction, cardiac hypertrophy, and even major adverse cardiac events [33,34]. The immune system is thought to undergo alterations in HCM that reflect a pro-inflammatory state through increased production and availability of inflammatory immune cells such as neutrophils and monocytes, as well as cytokine production generated from circulating immune cells (PBMCs) [33]. This suggests that reducing systemic chronic inflammation, innate immune cell availability, and immune cell inflammatory cytokine responses may improve HCM disease severity and cardiac events. This hypothesis is supported by the finding that exercise reduces circulating monocyte and neutrophil levels, as well as PBMC cytokine production, enabling a shift away from a pro-inflammatory state [35–38]. The impacts of targeted CR on these markers in HCM patients will be an important outcome of our work.

Two recent studies have evaluated the safety and benefits of exercise interventions in the general HCM population. The RESET HCM trial evaluated whether moderate-intensity exercise improved exercise capacity in patients with HCM [9]. The researchers randomized 136 HCM patients to a 16-week moderate-intensity exercise regimen versus usual activity, with the primary outcome of change in peak oxygen consumption from baseline. There was a modest but significant change in mean peak oxygen consumption in the exercise training arm (+1.35 ml/kg/min) than those in the usual activity arm (+0.08 ml/kg/min) ($p = 0.02$). There were no adverse outcomes, such as ICD shocks, sustained ventricular arrhythmias, sudden cardiac death, or death in either arm. Limitations of the RESET HCM study include a potential sampling bias as the majority of potential study participants declined to participate in the study, and secondly, a possible self-report bias from their quality-of-life surveys. While their study provides a useful foundation, our study will differ by having a comprehensive evaluation of objective markers for cardiometabolic health including lipids, glycemic control, anthropometric measurements, and systemic and cellular markers of inflammation in addition to cardiorespiratory fitness. This may provide us with a more comprehensive and nuanced understanding of the effect of CR and its effects on the components of metabolic syndrome in HCM patients, and its associated chronic inflammation. Furthermore, RESET HCM's observations were limited to a relatively healthy HCM population with a short period of intervention and limited follow-up data to evaluate the sustainability of CR in HCM patients. A more recent retrospective observational study published in 2019 by Wasserstrum and colleagues recruited 45 HCM patients who suffered from functional disability to participate in a 3-month CR program [13]. Primary endpoints evaluated included exercise capacity in the form of metabolic equivalents of task and NYHA class functional status, as well as self-reported quality of life measures. They reported that 56 % of their study cohort noted a statistically significant improvement in their exercise capacity and that this improvement was more pronounced in patients with a lower exercise reserve irrespective of age, NYHA functional class, HCM morphology, and outflow obstruction, and only one of the participants experienced a bout of non-lethal NSVT. Ultimately, they showed that CR was associated with an increase in exercise capacity (5.3 vs 6.7 METS, $p = 0.01$). Furthermore, no significant adverse events were seen during exercise or their short-term follow-up.

Higher quality data are now also available for HCM patients involved in more vigorous exercise, albeit not as part of a formal CR program. LIVE-HCM was designed as a multi-centre prospective observational study enrolling 1660 patients, 15 % of which were deemed as sedentary [7]. The participants were categorized to their self-reported levels of physical activity to evaluate whether engagement in vigorous exercise would result in a composite endpoint of death, resuscitated cardiac arrest, syncope from arrhythmias, and appropriate ICD shocks. They noted that patients who engaged in vigorous activity did not experience increased risk of the aforementioned composite endpoint compared to their counterparts who engaged in low-to-moderate physical activity, and that in their 3-year follow-up period, the proportion that did reach this composite endpoint was low (<5 %). Finally, HIT-HCM was a smaller RCT ($n = 15$) that evaluated the use of moderate intensity versus high intensity exercise training and its outcome on VO_2 max, cardiac remodeling, and QoL. The authors found that both moderate and high intensity exercise training unsurprisingly improved peak VO_2 max and that neither high or moderate intensity exercise were superior. Given its sample size, HIT-HCM was not powered to look at the safety profile of moderate or high intensity exercise training despite no adverse events [39].

Collectively, the existing literature supports three important themes: (1) Exercise is generally safe in most forms of HCM, (2) Exercise can prevent and treat established comorbidities that are common in HCM and lead to worse outcomes, such as diabetes, hypertension, and obesity, and (3) Inflammation plays a role in the development and potential severity of HCM. Notably, these studies are limited by their recruitment of healthier HCM patients who are examined over a short period of time and lack the follow-up on the sustainability of CR. What remains poorly understood is whether an organized exercise intervention, namely CR, can improve physical, mental and metabolic health in largely sedentary HCM population with acquired cardiovascular risk factors. This study will differ from the current body of evidence by evaluating the effects of structured CR on the diverse HCM population served by the BC-HCM and its ability to reverse acquired cardiovascular risk factors, rather than exercise intervention alone. It is well-established that acquired cardiovascular risk factors, such as obesity/elevated BMI, diabetes, and hypertension, occur in approximately 70 %, 39 %, and 10 % of HCM patients, respectively, and are independently associated with morbidity and mortality in this unique population [14]. Efforts will be dedicated towards taking a holistic bench-top-to-bedside approach on elucidating the impacts of an organized hybrid CR model on objective measures, including inflammatory pathway markers implicated in metabolic syndrome and biochemical markers of glycemic control and lipids, as well as quality of life, sustainability, and reversal of cardiovascular risk factors in an HCM population. Developing an evidence-based understanding of physical activity to improve metabolic outcomes is essential to patient-centered HCM care.

3.1. Limitations

Outcomes will be viewed as hypothesis-generating and exploratory due to the small sample being collected. For similar reasons, we will be recruiting participants from a single site, which may limit the external validity of the findings. The feasibility and benefits of exercise beyond a three-month period will be an important future area of inquiry. Finally, this study is not adequately powered to detect differences by sex or race/ethnicity. These are important considerations that affect HCM risk and outcomes. For instance, females have earlier HCM onset and are more likely to experience heart failure [40]. Patients of African/Caribbean/Black backgrounds also have higher rates of heart failure and are less likely to receive ICDs [41]. As such, sex and race/ethnicity will be considered more fulsomely in the future RCT. In the present study, these data will be recorded and exploratory analyses will be stratified by sex and/or race whenever possible. Furthermore, as CR typically takes place during regular work-hours, this may lead to underrepresentation and recruitment of non-white minority populations or those with further systemic, lower educational or socioeconomic means [42]. Patients with metabolic syndrome historically struggle to sustain increased activity levels. We will attempt to mitigate this by having a trained exercise physiologist provide the prescription to avoid decision fatigue, providing group guided and scheduled activity, and an online option via Zoom when undergoing the structured Cardiac Rehabilitation. Lastly, as patients will be recruited from a high-volume and comprehensive HCM centre, there may be bias towards preferentially enrolling those with a high engagement in care. As such, it is unknown whether the findings will be applicable to those at smaller centres or rural/remote communities.

4. Conclusions

This prospective cohort study will address an important knowledge gap by evaluating the effect of an organized CR program in patients living with HCM and metabolic syndrome. It is anticipated that exercise and CR, which previous dogma once deemed incompatible and dangerous for patients living with HCM, will be beneficial for this complex patient population.

CRediT authorship contribution statement

Matthew Cheung: Writing – review & editing, Writing – original draft, Visualization. **Nathaniel Moulson:** Writing – review & editing, Methodology, Conceptualization. **Jinelle C. Gelinas:** Writing – review

& editing, Project administration, Methodology. **Ali Daraei:** Writing – review & editing. **Sarah M. Bradwell:** Writing – review & editing. **Carolyn Taylor:** Writing – review & editing. **Neil D. Eves:** Writing – review & editing, Methodology, Conceptualization. **Graeme J. Koelwyn:** Writing – review & editing, Methodology, Conceptualization. **Thomas M. Roston:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Ethics statement

We confirm the following are true:

- the work described has not been published previously except in the form of a preprint, an abstract, a published lecture, academic thesis or registered report. See our policy on multiple, redundant or concurrent publication.
- the article is not under consideration for publication elsewhere.
- the article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- if accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Roston has received consulting honoraria from Cardurion Pharmaceuticals and Solid Biosciences.

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References

[1] B.J. Maron, J.M. Gardin, J.M. Flack, S.S. Gidding, T.T. Kurosaki, D.E. Bild, Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults, Circulation 92 (4) (1995) 785–789, https://doi.org/10.1161/01.CIR.92.4.785. https://pubmed.ncbi.nlm.nih.gov/7641357/.

[2] C.Y. Ho, S.M. Day, E.A. Ashley, M. Michels, A.C. Pereira, D. Jacoby, et al., Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe), Circulation 138 (14) (2018) 1387–1398, https://doi.org/10.1161/CIRCULATIONAHA.117.033200, https://pubmed.ncbi.nlm.nih.gov/30297972/.

[3] J.M. Bos, M.J. Ackerman, Hypertrophic cardiomyopathy in the era of genomic medicine, Genomic Precis Med Cardiovasc Dis Third Ed. (2017) 103–126, https://doi.org/10.1016/B978-0-12-801812-5.00005-6. https://mayoclinic.elsevierpure.com/en/publications/hypertrophic-cardiomyopathy-in-the-era-of-genomic-medicine-2.

[4] J.M. Bos, M.J. Ackerman, Hypertrophic cardiomyopathy in the era of genomic medicine, Genomic Precis Med Cardiovasc Dis Third Ed. (2018) 103–126.

[5] B.J. Maron, Clinical course and management of hypertrophic cardiomyopathy, N. Engl. J. Med. 379 (7) (2018) 655–668, https://doi.org/10.1056/NEJMRA1710575. https://pubmed.ncbi.nlm.nih.gov/30110588/.

[6] B.J. Maron, S.E. Epstein, W.C. Roberts, Causes of sudden death in competitive athletes, J. Am. Coll. Cardiol. 7 (1) (1986) 204–214.

[7] R. Lampert, M.J. Ackerman, B.S. Marino, M. Burg, B. Ainsworth, L. Salberg, et al., Vigorous exercise in patients with hypertrophic cardiomyopathy: results of the prospective, observational, multinational, "lifestyle and exercise in HCM" (LIVE-HCM) study, JAMA Cardiol. 8 (6) (2023) 595, https://doi.org/10.1001/JAMACARDIO.2023.1042. /pmc/articles/PMC10193262/.

[8] A.W. Snir, K.A. Connelly, J.M. Goodman, D. Dorian, P. Dorian, Exercise in hypertrophic cardiomyopathy: restrict or rethink, Am. J. Physiol. Heart Circ. Physiol. 320 (5) (2021) H2101–H2111, https://doi.org/10.1152/AJPHEART.00850.2020. https://pubmed.ncbi.nlm.nih.gov/33769918/.

[9] S. Saberi, M. Wheeler, J. Bragg-Gresham, W. Hornsby, P.P. Agarwal, A. Attili, et al., Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial, JAMA 317 (13) (2017) 1349–1357, https://doi.org/10.1001/JAMA.2017.2503. https://pubmed.ncbi.nlm.nih.gov/28306757/.

[10] S.R. Ommen, S. Mital, M.A. Burke, S.M. Day, A. Deswal, P. Elliott, et al., 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 76 (25) (2020) e159–e240, https://doi.org/10.1016/j.jacc.2020.08.045. http://www.ncbi.nlm.nih.gov/pubmed/33229116.

[11] W.C. Members, Steve R. Ommen, Carolyn Y. Ho, Irfan M. Asif, Seshadri Balaji, Michael A. Burke, et al., AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the Management of Hypertrophic Cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 2024 (2024), https://doi.org/10.1016/J.JACC.2024.02.014. https://www.jacc.org/doi/10.1016/j.jacc.2024.02.014.

[12] A.S. Leon, B.A. Franklin, F. Costa, G.J. Balady, K.A. Berra, K.J. Stewart, et al., Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation, Circulation 111 (3) (2005) 369–376, https://doi.org/10.1161/01.CIR.0000151788.08740.5C. https://pubmed.ncbi.nlm.nih.gov/15668354/.

[13] Y. Wasserstrum, I. Barbarova, D. Lotan, R. Kuperstein, M. Shechter, D. Freimark, et al., Efficacy and safety of exercise rehabilitation in patients with hypertrophic cardiomyopathy, J. Cardiol. 74 (5) (2019) 466–472, https://doi.org/10.1016/J.JJCC.2019.04.013. https://pubmed.ncbi.nlm.nih.gov/31235420/.

[14] C. Fumagalli, N. Maurizi, S.M. Day, E.A. Ashley, M. Michels, S.D. Colan, et al., Association of obesity with adverse long-term outcomes in hypertrophic cardiomyopathy, JAMA Cardiol. 5 (1) (2020) 65–72, https://doi.org/10.1001/JAMACARDIO.2019.4268. https://pubmed.ncbi.nlm.nih.gov/31693057/.

[15] Y. Wasserstrum, R. Barriales-Villa, X. Fernández-Fernández, Y. Adler, D. Lotan, Y. Peled, et al., The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy, Eur. Heart J. 40 (21) (2019) 1671–1677, https://doi.org/10.1093/EURHEARTJ/EHY625. https://pubmed.ncbi.nlm.nih.gov/30358878/.

[16] T.M. Roston, Olivotto Iacopo, S. Day, V.N. Parikh, M. Michels, J. Ingles, et al., Abstract 11709: the impact of hypertension on disease expression in hypertrophic cardiomyopathy, Circulation 144 (Suppl_1) (2021), https://doi.org/10.1161/CIRC.144.SUPPL_1.11709. https://www.ahajournals.org/doi/abs/10.1161/circ.144.suppl_1.11709.

[17] M. Sadeghi, A. Salehi-Abargouei, Z. Kasaei, H. Sajjadieh-Khajooie, R. Heidari, H. Roohafza, Effect of cardiac rehabilitation on metabolic syndrome and its components: a systematic review and meta-analysis, J. Res. Med. Sci. 21 (1) (2016), https://doi.org/10.4103/1735-1995.178757. /pmc/articles/PMC5122180/.

[18] A.H. Lichtenstein, L.J. Appel, M. Vadiveloo, F.B. Hu, P.M. Kris-Etherton, C. M. Rebholz, et al., 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association, Circulation 144 (23) (2021) E472–E487, https://doi.org/10.1161/CIR.0000000000001031. https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000001031.

[19] K.G.M.M. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K. A. Donato, et al., Harmonizing the metabolic syndrome, Circulation 120 (16) (2009) 1640–1645, https://doi.org/10.1161/CIRCULATIONAHA.109.192644. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.

[20] C. O'Mahony, F. Jichi, M. Pavlou, L. Monserrat, A. Anastasakis, C. Rapezzi, et al., A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD), Eur. Heart J. 35 (30) (2014) 2010–2020, https://doi.org/10.1093/EURHEARTJ/EHT439. https://pubmed.ncbi.nlm.nih.gov/24126876/.

[21] J.M. Hoffmann, S. Hellwig, V.M. Brandenburg, H. Spaderna, Measuring fear of physical activity in patients with heart failure, Int. J. Behav. Med. 25 (3) (2018) 294–303, https://doi.org/10.1007/S12529-017-9704-X. https://pubmed.ncbi.nlm.nih.gov/29230643/.

[22] F. Fraysse, D. Post, R. Eston, D. Kasai, A.V. Rowlands, G. Parfitt, Physical activity intensity cut-points for wrist-worn GENEActiv in older adults, Front Sport Act Living. 2 (2021) 579278, https://doi.org/10.3389/FSPOR.2020.579278. https://pmc.ncbi.nlm.nih.gov/articles/PMC7843957/.

[23] S. Zhang, A.V. Rowlands, P. Murray, T.L. Hurst, Physical activity classification using the GENEA wrist-worn accelerometer, Med. Sci. Sports Exerc. 44 (4) (2012) 742–748, https://doi.org/10.1249/MSS.0B013E31823BF95C. https://pubmed.ncbi.nlm.nih.gov/21988935/.

[24] D.W. Esliger, A.V. Rowlands, T.L. Hurst, M. Catt, P. Murray, R.G. Eston, Validation of the GENEA accelerometer, Med. Sci. Sports Exerc. 43 (6) (2011) 1085–1093, https://doi.org/10.1249/MSS.0B013E31820513BE. https://pubmed.ncbi.nlm.nih.gov/21088628/.
[25] Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP [Internet]. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
[26] ATS/ACCP Statement on Cardiopulmonary Exercise Testing, Am. J. Respir. Crit. Care Med. 167 (2) (2003) 211–277, https://doi.org/10.1164/rccm.167.2.211. https://doi.org/10.1164/rccm.167.2.211.
[27] L.W. Jones, N.D. Eves, M. Haykowsky, A.A. Joy, P.S. Douglas, Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations, Lancet Oncol. 9 (8) (2008) 757–765, https://doi.org/10.1016/S1470-2045(08)70195-5. http://www.thelancet.com/article/S1470204508701955/fulltext.
[28] J. Sim, M. Lewis, The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency, J. Clin. Epidemiol. 65 (3) (2012) 301–308, https://doi.org/10.1016/J.JCLINEPI.2011.07.011. https://pubmed.ncbi.nlm.nih.gov/22169081/.
[29] S.A. Julious, Sample size of 12 per group rule of thumb for a pilot study, Pharm. Stat. 4 (4) (2005) 287–291, https://doi.org/10.1002/PST.185. https://onlinelibrary.wiley.com/doi/full/10.1002/pst.185.
[30] L.A. Kerkhoff, J. Butler, A.A. Kelkar, S. Shore, C.D. Speight, L.K. Wall, et al., Trends in consent for clinical trials in cardiovascular disease, J Am Hear Assoc Cardiovasc Cerebrovasc Dis. 5 (6) (2016), https://doi.org/10.1161/JAHA.116.003582. /pmc/articles/PMC4937285/.
[31] B.J. Martin, T. Hauer, R. Arena, L.D. Austford, P.D. Galbraith, A.M. Lewin, et al., Cardiac rehabilitation attendance and outcomes in coronary artery disease patients, Circulation 126 (6) (2012) 677–687, https://doi.org/10.1161/CIRCULATIONAHA.111.066738. https://pubmed.ncbi.nlm.nih.gov/22777176/.
[32] B. Heindl, L. Ramirez, L. Joseph, S. Clarkson, R. Thomas, V. Bittner, Hybrid cardiac rehabilitation - the state of the science and the way forward, Prog. Cardiovasc. Dis. 70 (2022) 175–182, https://doi.org/10.1016/J.PCAD.2021.12.004. https://pubmed.ncbi.nlm.nih.gov/34958846/.
[33] L. Fang, A.H. Ellims, A.L. Beale, A.J. Taylor, A. Murphy, A.M. Dart, Systemic inflammation is associated with myocardial fibrosis, diastolic dysfunction, and cardiac hypertrophy in patients with hypertrophic cardiomyopathy, Am. J. Transl. Res. 9 (11) (2017) 5063. /pmc/articles/PMC5714791/.
[34] Y.J. Shimada, Y. Raita, L.W. Liang, M.S. Maurer, K. Hasegawa, M.A. Fifer, et al., Prediction of major adverse cardiovascular events in patients with hypertrophic cardiomyopathy using proteomics profiling, Circ Genomic Precis Med. 15 (6) (2022) E003546, https://doi.org/10.1161/CIRCGEN.121.003546. https://pubmed.ncbi.nlm.nih.gov/36252118/.
[35] V. Frodermann, D. Rohde, G. Courties, N. Severe, M.J. Schloss, H. Amatullah, et al., Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells, Nat. Med. 25 (11) (2019) 1761–1771, https://doi.org/10.1038/S41591-019-0633-X. https://pubmed.ncbi.nlm.nih.gov/31700184/.
[36] D.B. Bartlett, S.O. Shepherd, O.J. Wilson, A.M. Adlan, A.J.M. Wagenmakers, C. S. Shaw, et al., Neutrophil and monocyte bactericidal responses to 10 weeks of low-volume high-intensity interval or moderate-intensity continuous training in sedentary adults, Oxidative Med. Cell. Longev. 2017 (2017), https://doi.org/10.1155/2017/8148742. https://pubmed.ncbi.nlm.nih.gov/28656073/.
[37] K.L. Timmerman, M.G. Flynn, P.M. Coen, M.M. Markofski, B.D. Pence, Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? J. Leukoc. Biol. 84 (5) (2008) 1271–1278, https://doi.org/10.1189/JLB.0408244. https://pubmed.ncbi.nlm.nih.gov/18664531/.
[38] M.P. Noz, Y.A.W. Hartman, M.T.E. Hopman, P.H.G.M. Willems, C.J. Tack, L.A. B. Joosten, et al., Sixteen-week physical activity intervention in subjects with increased cardiometabolic risk shifts innate immune function towards a less proinflammatory state, J. Am. Heart Assoc. 8 (21) (2019), https://doi.org/10.1161/JAHA.119.013764. https://www.ahajournals.org/doi/abs/10.1161/JAHA.119.013764.
[39] J.P. Macnamara, K.A. Dias, C.M. Hearon, E. Ivey, V.A. Delgado, S. Saland, et al., Randomized controlled trial of moderate- and high-intensity exercise training in patients with hypertrophic cardiomyopathy: effects on fitness and cardiovascular response to exercise, J Am Hear Assoc Cardiovasc Cerebrovasc Dis. 12 (20) (2023) 31399, https://doi.org/10.1161/JAHA.123.031399. /pmc/articles/PMC10757533/.
[40] N.K. Lakdawala, I. Olivotto, S.M. Day, L. Han, E.A. Ashley, M. Michels, et al., Associations between female sex, sarcomere variants, and clinical outcomes in hypertrophic cardiomyopathy, Circ Genomic Precis Med. 14 (1) (2021) E003062, https://doi.org/10.1161/CIRCGEN.120.003062. https://www.ahajournals.org/doi/abs/10.1161/CIRCGEN.120.003062.
[41] L.A. Eberly, S.M. Day, E.A. Ashley, D.L. Jacoby, J.L. Jefferies, S.D. Colan, et al., Association of race with disease expression and clinical outcomes among patients with hypertrophic cardiomyopathy, JAMA Cardiol. 5 (1) (2020) 83–91, https://doi.org/10.1001/jamacardio.2019.4638. https://doi.org/10.1001/jamacardio.2019.4638.
[42] L. Mathews, L.P.C. Brewer, A review of disparities in cardiac rehabilitation: evidence, drivers, and solutions, J Cardiopulm Rehabil Prev 41 (6) (2021) 375–382, https://doi.org/10.1097/HCR.0000000000000659. https://pubmed.ncbi.nlm.nih.gov/34727556/.