
Physical Activity in Tetralogy (PhiT Trial): a Randomized Trial of Interval Training Versus Moderate Continuous Training

SYNOPSIS

This study is a single center randomized controlled trial evaluating the effect of an exercise training intervention (interval training or moderate continuous training) compared to usual care (no training) on exercise capacity in patients with congenital heart disease (CHD).

Medical and surgical advances over the past six decades have resulted in over 90% of children reaching adulthood. As a result, the population of adolescents and young adults with CHD is growing exponentially¹. However, exercise capacity is significantly diminished in CHD patients when measured objectively, even in patients with simple lesions, and similar to that of patients with heart failure². Furthermore, exercise capacity in CHD is an independent predictor of hospitalization or death, irrespective of the underlying lesion². Factors contributing to low exercise capacity are diverse and include abnormal cardiac anatomy, ventricular and valvular dysfunction, pulmonary hypertension, diminished oxygen carrying capacity, blunted heart rate response and impaired pulmonary function. Psychosocial factors including parental overprotection and lack of confidence or motivation on the part of the patient with CHD³ further contribute to this reduction. Finally, as CHD patients reach middle age, an increasing number are accumulating traditional risk factors as a result of sedentary lifestyles that started in childhood and adolescence^{4, 5}. Thus patients with CHD stand to benefit from cardiac rehabilitation to improve exercise capacity, reduce coronary risk, and ultimately reduce morbidity and mortality.

Unlike acquired heart conditions⁶, there is little guidance with respect to exercise prescription in CHD. Recommendations are vague⁷ or specific to competitive sports⁸. Consequently physical activity recommendations tend to be prohibitive, if recommended at all⁹. Unfortunately, activity restriction is associated with overweight and obesity in CHD patients¹⁰. There is need for in-depth study of the acute and chronic physiological adaptations of exercise training in CHD due to varied and unique physiologic demands compared to acquired heart disease patients.

To address these knowledge gaps we have developed a novel exercise training intervention for CHD patients.

Our *primary aim* is to determine the impact of interval training (IT) compared to moderate continuous exercise training (MCT) versus controls (no exercise) on exercise capacity as measured by peak VO₂. *Secondary aims* are to: 1) assess the safety of exercise training in CHD, 2) evaluate the effect of exercise training on cardiac structure and function and 3) assess the effects of exercise training on quality of life and long-term physical activity.

BACKGROUND

Exercise capacity is reduced in CHD and carries an adverse prognosis. Although often erroneously considered “cured” after surgery to correct CHD, valvular and ventricular dysfunction are common in CHD patients, who are often asymptomatic due to chronic adaptation to their underlying abnormalities. Nevertheless, objectively measured exercise performance is reduced across the spectrum of CHD (average peak VO₂ 22 ± 9 mL/kg/min compared to 45 ± 9 in age matched normal population)². Moreover the peak VO₂ of asymptomatic CHD patients is comparable to heart failure patients, despite the latter group being an average of 20 years older². Reduction in exercise capacity is prognostically significant with higher rates of hospitalization and death in CHD patients with the lowest peak VO₂².

Data on exercise training in CHD is minimal. Numerous randomized controlled studies in large numbers of patients with acquired heart disease support the use of aerobic exercise training in individuals to increase exercise capacity, reduce mortality^{15, 16} and manage cardiovascular risk factors¹⁷. In contrast, data in CHD

consists of small studies assessing the effect of moderate continuous exercise training on exercise capacity. Of 31 published studies in a systematic review, only 3 employed randomized study design¹⁸. Eighteen patients with repaired Tetralogy of Fallot (ToF) participated in a 12 week moderate intensity aerobic exercise program resulting in a 2 mL/kg/min increase in peak VO₂¹⁹. CHD patients with systemic right ventricles participating in a 10-week home based training program increased peak VO₂ by 3 mL/kg/min without adverse events²⁰. Neither of these studies evaluated the effect of exercise training on cardiac structure or function. Resistance exercise training in 11 Fontan patients resulted in approximately 3.5 mL/kg/min increase in peak VO₂²¹. However not all studies have demonstrated improved VO₂ with exercise training. In a recently published mixed population of ToF and Fontan patients which was likely underpowered, 12 weeks of exercise training resulted in a more modest increase in peak VO₂ of 1.7 mL/kg/min, not significantly increased from untrained controls²². None of the studies simultaneously compared different training modalities or assessed whether exercise training resulted in sustained improvement in physical activity levels, limitations that we plan to address in the proposed study.

A major barrier to prescribing exercise in patients with CHD is the lack of evidence derived from randomized controlled trials supporting the use of a specific training modality (i.e. resistance versus aerobic), training intensity, or duration of training. Furthermore uncertainty about the safety of exercise training in CHD with residual severe valve regurgitation or ventricular dysfunction, and concern about propensity for arrhythmias has limited widespread availability of cardiac rehabilitation opportunities for CHD patients.

Interval training (IT) has a superior effect on exercise capacity. IT is a training method utilized for decades by athletes to improve performance. IT involves exercise at higher intensities through repeated bouts at intensities greater than 85% of peak HR or 90% of peak VO₂, interspersed by periods of active or passive rest. Exercise performed in this manner allows the individual to exercise closer to their peak VO₂ than would otherwise be possible if a similar effort were to be done continuously. IT results in greater cardiovascular stress and promotes greater training adaptation resulting in superior effects on exercise capacity²³.

Interval training in acquired heart disease. A growing body of literature supports the notion that higher intensity aerobic exercise appears to be superior to moderate continuous exercise training (MCT) in individuals with acquired heart disease. IT in stable coronary artery disease²⁴, post MI²⁵ and in patients with stable severe LV systolic dysfunction^{26, 27} consistently improves exercise capacity to a greater magnitude than MCT^{28, 29}. An increase in peak VO₂ of 2 – 4 mL/kg/min can be expected with IT compared to MCT^{28, 29}. IT is associated with reduced ventilatory demand and relative perceived effort³⁰ suggesting that it may be a more tolerated training modality. Although studies to date have been underpowered for mortality, training at higher intensity appears to be safe³¹. Data from observational studies suggests that more vigorous exercise is associated with beneficial effects on mortality^{32, 33}.

Significance. In summary, exercise capacity is reduced in CHD for a variety of physiologic, anatomic and behavioral issues that are unique from acquired heart disease patients. Reduced exercise capacity is prognostically significant, and impacts on adult weight and cardiovascular risk factors. Data on exercise training in CHD is limited. There is an urgent need to identify the optimal training method that is tolerable and results in the greatest adherence and increase in exercise capacity. IT appears promising for cardiac patients, but its role remains to be elucidated in CHD.

RESEARCH PLAN

Hypotheses

Primary

- Exercise training in patients with CHD will result in improved peak VO₂ compared to controls.
- IT will have a superior effect on peak VO₂ compared to MCT

Secondary

- Exercise training will not be associated with adverse clinical events
- Exercise training will be associated with significant cardiac adaptation (decreased right ventricular end-diastolic volume and increased right ventricular ejection fraction)

- Exercise training will improve quality of life (QoL)
- Exercise training will lead to a sustained increase in physical activity levels

Trial design. Single center randomized trial in accordance with CONSORT guidelines³⁴. Patients will be randomly allocated to one of three arms: IT exercise, MCT exercise or usual care (no exercise training).

Planned trial interventions.

Baseline characteristics. Subjects' anthropometric measurements, exercise capacity measured by cardiopulmonary exercise stress testing (CPET) and peak power output (PPO) in Watts on bicycle ergometer will be evaluated. Quality of life will be assessed with the Short Form 12 (SF-12), Satisfaction with Life Survey, NYHA class, TAAQOL and LAS questionnaires. Cardiac MRI scanning or echocardiography will be performed for assessment of right ventricular volumes and function. Baseline physical activity will be documented with accelerometers worn for 4 consecutive days.

Exercise training. A 12-week training regime consisting of 3 sessions per week will occur in the Jim Pattison Center for Cardiac Rehabilitation. PPO will be known by the exercise physiologist from the baseline CPET. IT will include a warm up and cool down period of 5 minutes each at 30% PPO, and 5 intervals of 4 minutes (5x4 min) of intense aerobic activity at 90-100% PPO. The intervals will be interspersed with 4 periods of 3 minutes of activity at 30-60% of PPO. MCT will include a warm up and cool down period of 5 minutes each at 30% PPO, with 30-40 min of aerobic activity on bicycle or treadmill equipment at 60% of PPO. The MCT group's sessions will be adjusted in length to approximate the energy expenditure of the IT group. All training sessions will be supervised by a graduate student in exercise physiology to assess relative perceived effort and tolerability and to ensure appropriate PPO is achieved for each exercise arm. Adherence of at least 66% or 24 exercise sessions over 12 weeks will be accepted. In addition, subjects will be requested to continue usual activities, even if this includes exercise.

In a study that employed IT in patients with systemic right ventricles, a similar 5x4 minute IT regimen was used²⁰, hence we feel proposed IT regimen is feasible. However that study used home-based exercise with heart rate targets so it is uncertain if IT was rigorously performed, and there was no MCT arm for comparison. Our study will overcome those limitations.

Usual care. Subjects in the usual care arm will not be given specific advice about exercise. Subjects may continue usual activities, even if this includes exercise.

Measurement of outcomes at follow-up. After the 12-week training period, anthropometric measurements, CPET, cardiac MRI and/or echocardiography and QoL will be reassessed. Physical activity will be reassessed 6 months after randomization with accelerometers worn for 4 consecutive days and patients will complete QoL surveys at that time-point.

Group allocation. Subjects will be randomized by clusters defined by week of attendance in the cardiology clinic. As week (not study subject) is the unit of randomization, this is a cluster randomization design. This method of randomization: 1) prevents two subjects in the same waiting room being allocated to different groups, with subjects in the usual care group potentially preferring to be in an exercise group; and 2) facilitates scheduling of study staff, who will be available at short notice to describe the intervention during "IT weeks" and "MCT weeks". A given cardiologist's patients will be allocated to usual care or intervention arms equally, preventing potential bias by cardiologist co-intervention through exercise recommendations. We anticipate enrolment of 1 subject per week, i.e. cluster size will be ≤ 4 . In order to determine which weeks are "intervention weeks" vs. "usual care weeks", a biostatistician will prepare the randomization sequence. Permuted blocks of 3, 6, and 9 will be used to ensure a similar number of weeks are randomized to "IT", "MCT" and "usual care."

Protecting against sources of bias. Subjects and their caregivers, including exercise physiologist and cardiologist will be aware of group allocation as blinding is not feasible. However the primary outcome is objectively measured by CPET. Adjudication of MRIs will be done by an observer unaware of the group allocation.

Inclusion/exclusion criteria: medically stable patients aged 16 or greater with congenital heart disease (CHD). Exclusion criteria will be uncorrected cyanotic CHD (SpO₂ ≤ 85%), severe outflow tract obstruction (peak Doppler gradient >50 mmHg) and sustained arrhythmia.

Outcome measures:

Primary outcome: The primary outcome is change in peak VO₂ from baseline to 12 weeks post enrolment.

Secondary outcomes:

1. Adverse events. High intensity exercise has the potential to transiently increase the risk of arrhythmias and myocardial infarction in susceptible persons. In a large cohort of patients with coronary artery disease, IT was associated with increased cardiovascular event rates compared to MCT, although events rates were very low (1/23,000 hours of interval training)³¹. CHD patients with ToF are at small but increased risk of ventricular tachycardia and sudden cardiac death¹³. To date IT has not been utilized in ToF patients so monitoring for safety will be an important secondary outcome. Adverse events are defined as cardiac arrest, myocardial infarction, sustained ventricular or supraventricular arrhythmias or heart failure occurring during training or within one hour afterward. The exercise specialist will complete a case report form immediately following each exercise session to document the presence/absence of these events. In addition death and cardiac related hospitalization occurring anytime during the study observation period will be recorded.

2. Cardiac adaptation. Exercise training results in adaptive changes both centrally (cardiac) and peripherally (improved muscle metabolism and more efficient oxygen extraction) which affect VO₂. Assessment of cardiac adaptation is an important corollary to exercise capacity in cardiac rehabilitation research, and understanding the cardiac adaptations that occur with exercise training in CHD will enhance insights gained from this study. Very limited data is available on the effect of exercise training on cardiac structure and function in CHD patients¹⁸. One study found no adverse cardiac changes in ToF and Fontan patients after MCT exercise²². IT has been shown to produce reverse remodeling in patients with ischemic cardiomyopathy, with improvements in left ventricular end-diastolic volume and ejection fraction²⁸. However IT in patients with severe valvular regurgitation, such as those with ToF and pulmonary regurgitation, has not been assessed. Theoretically greater cardiovascular stress could worsen regurgitant fraction and result in ventricular dilation so assessment of right ventricular volume and function is important to establish the safety of exercise training in CHD.

Cardiac MRI will be used to assess RV volumes and ejection fraction (EF) at baseline. Pulmonary regurgitation fraction, left ventricular volumes and EF will also be assessed. MRI is the reference standard for RV imaging³⁵ in patients with ToF and pulmonary regurgitation. Baseline and follow-up scans will be performed within 4 weeks of starting and completing the intervention respectively. In those with pacemakers or contraindication to MRI, echocardiography will be used to assess right ventricular volume and function.

As a *substudy*, we plan to use the Ventripoint echocardiographic fusion system³⁶ to simultaneously assess RV volumes in order to explore feasibility of this novel echocardiographic technique compared to the gold standard of MRI. Two-dimensional echocardiography (echo) images will be acquired with standard ultrasound equipment connected to a specialized console and used with a magnetic field generator, located underneath the patient bed (Ventripoint Diagnostics Ltd, Seattle, WA). The magnetic field localizing system tracks the transducer movements and position relative to the magnetic field transmitter located under the examination bed. The position and orientation of the receiver and thus the plane of the 2D picture can be computed and placed within the volume created by the magnetic transmitter. Images of the RV are obtained in multiple views. Echo images and magnetic field data are linked to derive a 3D model of the RV. An echo using the Ventripoint system will be obtained immediately after MRI imaging in a subset of patients to calculate intraobserver, interobserver, and intertechnique variability.

3. Quality of life. Studies of the effects of exercise training on QoL have produced variable results, with some finding no impact^{20, 37} whereas others find improved quality of life³⁸. Impact on QoL may depend on the type of exercise training regimen, as IT has a greater effect on QoL than MCT²³. The SF-12, which has been utilized in CHD patients^{38, 39}, will be used as brief, reliable measure of overall health. It is a shorter version of the Short-Form-36, a multipurpose health survey with 36 questions. The SF-12 contains 12 items from the SF-36 and reproduces the SF-36 with a 90% accuracy⁴⁰. Published age and gender-matched population norms are

available. The Satisfaction With Life Scale (SWLS) measures global life satisfaction and has high internal and temporal consistency⁴¹. Our group has experience with this tool, which has also been utilized by others^{38, 39} to assess QoL in CHD. In addition the LAS measures the subjects global quality of life on a visual scale. The TAAQOL questionnaire was developed as a specific tool for symptom assessment in congenital heart patients. NYHA class will also be assessed. Study subjects will complete questionnaires during study visits or be sent a link by email to complete the questionnaires on-line at baseline, 3 months (after exercise training intervention) and 6 months after randomization.

4. Physical activity levels. Whereas physical activity questionnaires lack sensitivity and are inaccurate, accelerometers provide accurate physical activity information⁴². We propose to use the SenseWear arm bands to describe baseline physical activity levels and to assess long-term changes in physical activity 6 months after randomization. Data will be acquired for 4 days at each time-point and change from baseline compared between exercise training groups and usual care. There is evidence that IT, because of its greater tolerability and lower perceived exertion, results in greater long term improvement in physical activity than MCT²³. Upon receipt of the follow-up accelerometer data, all study subjects will receive the fitbit® Zip fitness monitor^{43, 44, 45} as acknowledgement of their time and commitment to the study.

As a *substudy*, we will evaluate the relationship between exercise capacity (VO_{2peak}) and daily time spent in moderate-to-vigorous PA (MVPA ≥ 3.0 METs) in patients with ToF or ToF-like physiology compared to healthy age and gender matched controls. This substudy has already been completed.

Proposed sample size. Canadian quality assurance indicators for cardiac rehabilitation programs suggest that exercise training should result in at least 0.5 MET increase in exercise capacity⁴⁶. Using a standard conversion factor of 1MET=3.5 mL/kg/min, this translates into a peak VO_2 change of approximately 2 mL/kg/min. Exercise studies in CHD patients have documented changes in peak VO_2 ranging from 2 to 3.5 mL/kg/min, depending on the patient population and exercise regime¹⁹⁻²¹. Exercise studies in heart failure patients have documented changes in peak VO_2 of 2-4 mL/kg/min for IT compared to MCT^{28, 29}. Taking these ranges into consideration, we consider the minimum clinically important difference (MCID) in peak VO_2 to be 3 mL/kg/min. With an improvement in peak VO_2 between usual care and MCT as well as between MCT and IT of 3 mL/kg/min, SD 2.5, a sample size of 17 per group will be required assuming 10% attrition, 90% power and a 2-sided alpha of 0.05. Hence we propose to enroll 17 patients in each arm (usual care, MCT exercise and IT exercise) for a total of 51 patients.

| Minimum clinically important difference between groups | Control group VO_2 mL/kg/min | MCT effect mL/kg/min | IT effect mL/kg/min | Sample size per group (80% Power) | Sample size per group (90% Power) |
|---|--------------------------------|----------------------|---------------------|-----------------------------------|-----------------------------------|
| Comparing two groups at a time (two sample t-test) | | | | | |
| 3 mL/kg/min | 22 | 25 | - | 12 | 17 |
| | 22 | - | 28 | 3 | 4 |
| | | 25 | 28 | 12 | 17 |

Recruitment. Subjects aged 16 and 17 will be recruited from the pediatric cardiology clinic at the Stollery Children's Hospital by a study research coordinator, provided in-kind by Dr. Mackie's research team. Adult subjects will be recruited from the NAACH Clinic which is staffed by three cardiologists and two nurses who collaborate closely which will facilitate enrollment. CHD patients are searchable by diagnosis through the Western Canadian Children's Network database.

We would like to request a waiver of consent for screening purposes using both eClinician and Connectcare. We currently have ethics approval to pre screen eClinician and paper printed lists, to determine potential eligibility. We have found that with Connect Care implementation, there are not always printed lists available, and if there are they often don't include the information that we used to gather from them to determine eligibility (main criteria being age and diagnosis). Therefore, we would like to request for a waiver of consent in order to pre screen

using Connect Care to determine eligibility, prior to the patient being approached by an AHS staff to ask for permission to be approached for research by our team.

We will also invite patients to participate by notices on patient websites and letters of invitation mailed to patients meeting inclusion criteria.

Healthy age and gender matched controls will be recruited via word-of-mouth and posters throughout the University of Alberta. Patients interested in participating will complete consent forms, quality of life surveys and scheduled baseline measurements. Our healthy participants will be age and gender matched and screened for health issues as determined by Physical Activity Readiness Questionnaire (PAR-Q).

Proposed analysis. Intention-to-treat analyses will be used and all statistical tests will be two-sided. Analyses will be performed by an experience biostatistician affiliated with Dr. Mackie's group using SAS software. Baseline characteristics of the control (usual care) and exercise groups will be summarized using descriptive statistics (e.g., means, medians, standard deviations [SDs], frequencies, proportions). The primary outcome of change in peak VO₂ from baseline will be assessed with linear mixed models with random effects to evaluate the intervention effect at 3 months. To account for the cluster allocation and longitudinal nature of the trial, both effects of weeks (clusters) and those of individual participants will be considered random. Each participant has two measurements: at baseline (enrolment) and 3 months. We will adjust for the baseline peak VO₂. Secondary outcomes: We will assess differences in mean scores of each secondary outcome at 3 months and/or 6 months, where applicable, by treatment group by using general linear mixed models that take both the cluster randomization and longitudinal nature of the data into account. Treatment group differences in mean change scores (e.g., 3 months vs. baseline) will also be assessed in the same modeling framework with different parameterizations.

Data management. Dr. Mackie's research group will oversee quantitative data management using REDCap™ software. REDCap™ allows on-line completion of questionnaires by subjects, and password-protected data entry by study staff for all case report forms.

Threats to internal validity.

Co-intervention. Subjects randomized to the usual care arm will be encouraged to maintain their normal activities and not embark on a new program of exercise training. This is similar to other trials of exercise training, where increased exercise in the usual care/non-training arm has not precluded demonstrating an effect of the exercise training intervention.

Drop-out/attrition. Previous studies of exercise training in CHD patients had drop-out rates between 3-15%^{20, 22}. Hence our sample size has been adjusted with an anticipated attrition rate of 10%.

Limitations. Subjects in the study will be those consenting because they are physically well enough to exercise and motivated to participate, which has the potential to create a select patient group. Data on baseline characteristics of those eligible for the study who decline to participate will be collected to determine if our study subject population is representative. Data derived from our study will be applicable to ToF but may not be extrapolated to other CHD conditions, with different hemodynamic concerns.

Ethical considerations. While cardiac rehabilitation is available to ToF patients after valve replacement surgery, exercise training is not routinely offered to stable patients with severe pulmonary regurgitation. Thus randomization to usual care is acceptable. Data will be stored in locked filing cabinets and password-protected desktop computers. Approval will be obtained from the University of Alberta Health Research Ethics Board.

KNOWLEDGE TRANSLATION

Knowledge translation (KT) will be integrated with end-user groups from the time of funding. We will develop research evidence that can be applied to clinical practice, health policy, and health service delivery to optimize cardiac rehabilitation and outcomes for adolescents and adults with CHD. Groups to be incorporated include:

1. The Canadian Congenital Heart Alliance which represents adults living with CHD
2. Health-care providers, including nurses, pediatric and adult congenital cardiologists, psychologists, and organizations such as the Canadian Adult Congenital Heart Network, and the Canadian Nurses Association.
3. Health care administrators and policy development personnel at the local and provincial levels.

We will form an Advisory Council that will meet quarterly by teleconference. Members of the council will include two adults with CHD, representatives from nursing, cardiology and allied health from the NAACH program, senior University of Alberta Hospital administration (Dr. Dylan Taylor, who is also an adult CHD cardiologist), and a policy expert from Alberta Health Services. KT strategies will include easy-to-read lay summaries, meeting with administrators to advocate for access to rehabilitation programs for CHD patients, stories in patient organization newsletters, presentations at national and international meetings, and manuscript publication.

EXPECTED OUTCOMES AND FUTURE DIRECTIONS

We anticipate that exercise training for CHD patients will produce significant improvements in peak VO₂ compared to usual care. We anticipate IT will have a greater effect than MCT, which will be mediated by favorable effects on cardiac structure and function. We expect that IT will lead to sustained changes in quality of life and physical activity. The proposed research program is novel in its exploration of IT in congenital heart disease and comprehensive in its evaluation of cardiac structure, QoL and long-term activity levels. Should this research program be funded, it will position the Jim Pattison Center to be Canadian leader in cardiac rehabilitation for CHD patients.

Currently there is little data to guide exercise prescription CHD, and this study will help practitioners prescribe a specific exercise modality and intensity to benefit their patients. Ultimately it is expected study results will lead to optimized training protocols, enhanced local expertise and increased confidence in utilization of cardiac rehabilitation for CHD.

Knowledge and experience gained in the moderately complex CHD patients will serve as groundwork to developing protocols in more complex patient groups, such as single ventricle survivors (Fontan). Next steps would also include evaluating the role of resistance training alone or in combination with aerobic exercise in CHD patients.

An additional anticipated outcome is proving the feasibility and validating the reproducibility of 3D echocardiographic reconstruction (Ventripoint system) to assess RV volumes. This will build local expertise and may permit substitution of costly MRI imaging with echocardiography in future studies of CHD patients.

BUDGET

The anticipated duration of this study is two years to allow sufficient time for enrollment and follow-up. Funding for a graduate student is necessary for data collection, data entry, study coordination and performance of exercise testing and exercise training. This individual will come from an exercise physiology/kinesiology background and will ensure that patients in the IT arm achieve the necessary PPO during interval training to ensure the integrity of the intervention. Reimbursement of parking expenses will be necessary because of the frequency of visits in the two intervention arms. With 36 exercise sessions and 2 additional study visits for baseline and follow-up assessments, patients would incur \$285 in parking expenses. Given the demographics of these young adult patients, we feel this would be a significant barrier to enrollment without reimbursement. Transit passes will be offered as an alternative to patients not requiring parking reimbursement.

The research team will provide in-kind support in the form of a research coordinator (0.2 FTE) who is funded by the Women and Children's Health Research Institute (PI Dr. Mackie). In addition, a University Hospital Foundation grant will be used to purchase the Ventripoint echocardiographic system (Dr. Windram, \$60,000).

BUDGET

| | | Price per unit | Cost |
|---------------------------|----------------------------------|----------------|---------------------|
| Total Patients | Graduate student | \$24,000.00 | \$48,000.00 |
| 51 | CHD Fellow (0.25 x \$60,000) | \$15,000.00 | \$30,000.00 |
| Exercise arm | CPET (2 studies per patient) | \$200.00 | \$10,200.00 |
| 34 | | | |
| Duration of Study (years) | | | |
| 2 | MRI (2 scans per patient) | \$1,000.00 | \$51,000.00 |
| | Accelerometers | \$60.00 | \$3,060.00 |
| | Parking-baseline, 3 month visits | \$15.00 | \$765.00 |
| | Parking-for 36 exercise sessions | \$270.00 | \$9,180.00 |
| | Total cost | | \$152,205.00 |

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