Investigating the Physical Activity Behaviour and Exercise Capacity of Pediatric Cardiomyopathy Patients

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A thesis submitted to the Faculty of Graduate and Postdoctoral Studies

In conformity with the partial fulfillment requirements for

the Master of Science degree in Human Kinetics

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Ottawa, Ontario, Canada

(August, 2018)

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General Thesis Abstract

Background: Physically active lifestyles are important for health and quality of life across all stages of development. Exercise interventions have recently been incorporated as an effective strategy for adult cardiomyopathy patients, but have yet to be examined in children with cardiomyopathy. The overall goal of this pilot study was to provide preliminary data on whether there is a need to develop exercise interventions among children with cardiomyopathy. This study sought to characterize the moderate-to-vigorous physical activity (MVPA) level, submaximal exercise capacity and physical activity barriers among children with cardiomyopathy.

Methods: This study employed a mixed-methods approach. Children were eligible if they were between the ages of 5 to 17 years, had a medical diagnosis of cardiomyopathy (i.e. hypertrophic, dilated, or cancer induced), atrial septal defect, or had been identified as carrying a genetic risk for cardiomyopathy. Participants were excluded if they had physical activity contraindications, had a non-cardiac medical condition or disability known to influence physical activity, or if they underwent cardiac surgery within the preceding 6 months. MVPA was assessed using 7-day omni-directional accelerometry. Submaximal exercise capacity was determined by intermittent treadmill protocol targeting 40% to 80% of predicted maximum heart rate. Physical activity barriers were identified through semi-structured interviews, which were audio-recorded and transcribed verbatim for thematic analysis using Braun & Clark's approach.

Results: Pediatric cardiomyopathy patients (n=5) were compared to children who are genotype-positive but phenotype-negative for cardiomyopathy (n=5), children with simple congenital heart defects (CHD, n=8) and published data for Canadian children (n=1,300). Daily MVPA (48.2 ± 19.0 minutes) was variable but did not differ significantly between groups (η^2=0.025, p=0.82) or from published data on Canadian children ($t(17)$ = -1.52 p=0.15). Submaximal exercise testing

revealed that children with cardiomyopathy may be able to participate in activities at moderate intensities (i.e. 4.5 ± 3.1 METs) at 150 beats per minute (bpm). Children with cardiomyopathy reported primarily disease-centred barriers to participation, including physical activity restriction and physical influences from the disease which were not reported by children who carry a genetic risk for cardiomyopathy.

Conclusion: These novel data within this population group suggest that pediatric cardiomyopathy patients may have sufficient submaximal exercise capacity to participate in moderate physical activity, despite reporting disease centered barriers to physical activity. A diagnosis of cardiomyopathy may not preclude these children from achieving a healthy, active lifestyle, but their current level of participation is less than recommended for optimal health and cardiac function.

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List of Abbreviations

ASD	Atrial septal defect
A-V O_2	Arterial venous oxygen difference
bpm	Beats per minute
CAO_2	Arterial oxygen concentration
CCM	Chemotherapy-induced cardiomyopathy
CVO_2	Venous oxygen concentration
CHD	Congenital heart disease
CHEO	Children's Hospital of Eastern Ontario
cm	Centimeter
CPET	Cardiopulmonary exercise test
CSEP	Canadian Society for Exercise Physiology
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
G+P-	Genotype-positive phenotype-negative
HCM	Hypertrophic cardiomyopathy
HR	Heart rate
HR_{max}	Maximum heart rate
kg	Kilogram
LV	Left ventricle
MET	Metabolic equivalent
mph	Miles per hour
MVPA	Moderate to vigorous physical activity
PA	Physical activity
RCT	Randomized controlled trial
RMR	Resting metabolic rate
RPE	Ratings of perceived exertion
SD	Standard deviation
SV	Stroke volume
U.S.	United States
$\dot{V}O_2$	Rate of oxygen consumption
$\dot{V}O_2peak$	Rate of peak oxygen consumption

Acknowledgements

I would first like to express my sincerest gratitude towards my supervisors Dr. Patricia Longmuir, Research Scientist at the Healthy Active Living and Obesity (HALO) Research Group of the Children's Hospital of Eastern Ontario Research Institute and Dr. Kristi Adamo, Professor at the Faculty of Health Sciences at the School of Human Kinetics, for agreeing to be my thesis supervisors. I have learned so much from the both of you and I am forever grateful for the opportunities you have given me to pursue research. For that, I am greatly appreciative for the both of you! I would also like to extend my gratitude to my thesis committee members, Dr. Glen Kenny and Dr. Francois Gravelle for their feedback and comments that improved the quality of my research. To the School of Human Kinetics at the University of Ottawa and the Ontario Trillium Foundation and Cardiac Health Foundation of Canada, thank you so much for the financial support and allowing me to pursue this very niche area of research.

In the Cardiology clinic, I would like to acknowledge and thank the cardiologists, Dr. Gardin, Dr. Lougheed and Dr. Lee, for your assistance during recruitment. To Denise Melo, thank you so much for your assistance during the exercise tests and for your patience with scheduling participants. To all the nurses and receptionists, you were all a great help during recruitment and testing.

To the families, I would also like to acknowledge the participants and their families. Thank you so much for taking the time out of your busy schedules to come to CHEO and do an exercise test. Without your commitment to research, none of this would have been possible.

I am also very thankful for my colleagues at HALO who have helped me in a small way or another throughout my experience at HALO, whether it was helping me pilot my exercise testing protocol or testing my accelerometers. To my colleague and good friend, Tyler Kung, thank you

for your assistance during my exercise testing. I am glad we became close friends during our couple of years at HALO. To my good friends Darrin Wijeyaratnam, Michael Del Bel, Kaamel Hafizi, Jay Schooley, Sara Kramers and all the STOH boys, thank you so much for all the help and support, amazing times and memories. I look forward to collaborating and having more fun with you all one day! To, Clara Moore, for your everlasting support and friendship, enthusiasm on a daily basis, and for constantly being my testing "guinea pig", I can't thank you enough. I owe you more Suzie-Q donuts than you might think! I cannot end these acknowledgements without speaking about my amazing family. To my parents, Marc and Helene Moncion, and my sister Line Burke, thank you all for always believing in me during my undergraduate degree, varsity football (Go Gee Gees) and graduate endeavours. I wouldn't be who I am today if it wasn't for you guys. I love you very much!

Part 1: Introduction

Cardiomyopathy is a disease that causes the myocardium to become weak and ineffective, reducing the heart's ability to pump blood through the body (Maron et al., 2002). Ultimately, a reduction of cardiac output impacts the performance of activities of daily living and physical activity (PA) due to inadequate oxygen delivery to exercise muscles. Most children with cardiomyopathy are diagnosed with either dilated cardiomyopathy (DCM) or hypertrophic cardiomyopathy (HCM). HCM is characterized by left-ventricular hypertrophy and diastolic dysfunction, while DCM is distinguished by dilation of the ventricles and systolic dysfunction (Lipshultz et al., 2013a). Both diagnoses are associated with abnormal cardiac structure, function and ultimately a greater risk of morbidity and mortality later on in life (Somarriba, Extein & Miller, 2008; Wilkinson et al., 2010). Though, pediatric cardiomyopathy patients often are absent the comorbidities, such atherosclerosis, hypertension, renal dysfunction, or diabetes that are typically found in adults with cardiomyopathy (Lee et al., 2017). With advancements in genetic testing, identification of inherited forms of cardiomyopathy is increasing (Maron, Yeates & Semsarian., 2011; Semsarian, Ingles, Maron and Maron, 2015). Relatives of individuals with inherited cardiomyopathy are offered genetic testing, and as a result there is an increasing population of children who are known to have a genetic predisposition to HCM, which will be referred to herein as genotype-positive–phenotype-negative (G+P-). There is also a growing incidence of cardiomyopathy as a complication of surviving childhood cancer treatment (Armenian et al., 2015). The cardiotoxic nature of chemotherapy agents put these children at risk for ventricular dilation (Lipshultz et al., 2013a; Okada et al., 2012) and are otherwise known as having cancer-induced cardiomyopathy (CCM).

Historically, PA was discouraged among cardiomyopathy patients in order to reduce cardiac workload and preserve cardiac function, with the ultimate goal of reducing the risk of sudden cardiac death (Mitchell, Maron & Epstein., 1984; Maron & Mitchell., 1994; Maron et al., 2004 Maron & Zipes., 2005; Maron et al., 2015). According to the World Health Organization (WHO), "insufficient physical activity (PA) is one of the leading risk factors for death worldwide and is a key risk factor for non-communicable diseases such as cardiovascular diseases, cancer and diabetes" (WHO, 2018). Thus, individuals with cardiomyopathy who were advised against physical activity would be expected to have an increased risk for the negative health outcomes (i.e. obesity and cardiovascular morbidities) associated with sedentary lifestyles (Reineck et al., 2013; Somarriba et al., 2008).

In adults with cardiomyopathy, this restriction of PA has resulted in disease-focused barriers (i.e. I was advised not exercise, I might get injured or damage my health etc.) and detrimental effects associated with inactivity, including but not limited to a lower health-related quality of life, decreased psychological well-being and increased risk for obesity (Ingles et al., 2013; Olivotto et al., 2013; Reineck et al., 2013; Sweeting et al., 2016). Exercise restriction and purposeful reduction of PA after diagnosis has resulted in anxiety toward exercise, further impacting the emotional and psychological well-being of individuals with HCM (Reineck et al., 2013). To mitigate these negative health outcomes, exercise rehabilitation programs for adults with cardiomyopathy have been shown to improve endothelial and cardiac function, exercise capacity and quality of life (Klempfner et al., 2015; Saberi et al., 2017; Sweeting et al., 2016; Thrush & Vogel, 2018).

There is a paucity of information regarding the PA patterns, submaximal aerobic exercise capacity, and barriers to PA for children with cardiomyopathy. This information is needed by

clinicians to support their efforts to promote PA among pediatric cardiomyopathy patients. Furthermore, exercise and PA data could provide valuable insight for clinicians as they strive to mitigate uncertainty about whether certain activities are appropriate (Christian, Somerville, Taylor, & Atallah., 2016). In the absence of objective data, researchers have hypothesized that clinicians might be overly conservative when advising patients with cardiomyopathy about exercise (Reineck et al., 2013). It is expected that parents and other adults responsible for these children (e.g., teachers), or the children themselves, may naturally err on the side of caution by restricting their PA participation. As a result, these children might be in a physical inactivity cycle as a result of being diagnosed with pediatric cardiomyopathy and may not be achieving the well-known benefits of PA (Figure 1.1).

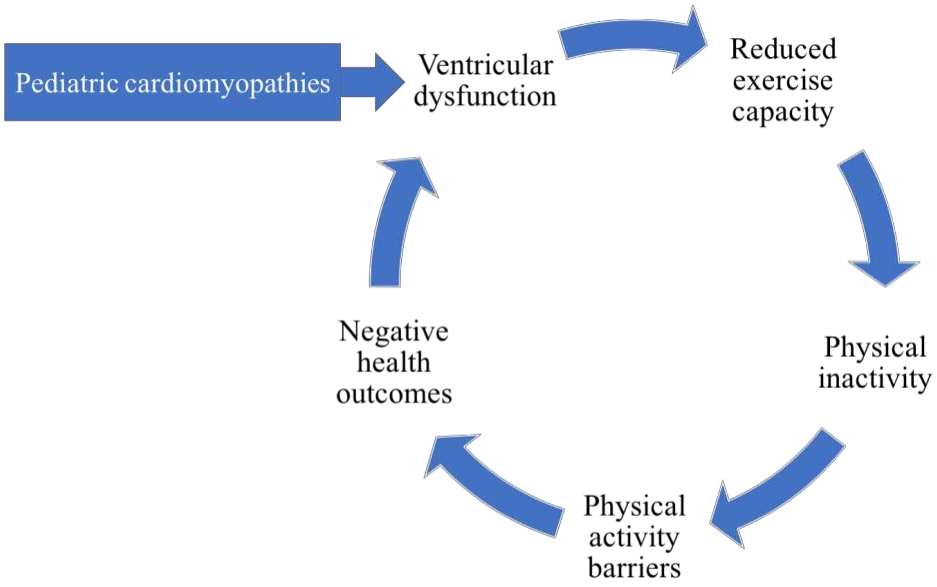

Figure 1.1 The potential physical inactivity cycle as a result of being diagnosed with pediatric cardiomyopathy

1.1 Rationale and Statement of the Problem

Research studies have shown that adults with cardiomyopathy have comorbidities that are known to impact myocardial function (Lee et al., 2017), live physically inactive lifestyles, have

disease focused barriers (Reineck et al., 2013; Sweeting et al., 2016), and a reduced functional capacity (Frenneaux et al., 1989; Jones et al., 1998; Lele et al., 1995; Somarriba et al., 2008). Importantly, these foundational research studies have enabled exercise rehabilitation programs to improve the cardiovascular health of adults with cardiomyopathy (Klempfner et al., 2015; Saberi et al., 2017; Sweeting et al., 2016; Thrush & Vogel, 2018). Although, the adult literature can provide initial insight regarding the cardiovascular health, potential PA levels, barriers and functional capacity among pediatric cardiomyopathy patients, additional research is warranted given that, compared to adults, children: 1) don't typically have confounding comorbidities that impact myocardial function (Lee et al., 2017); 2) demonstrate different PA patterns; and 3) identify different barriers to PA.

Therefore, it is important to describe the MVPA levels, submaximal exercise capacities and PA barriers of children with children with or at risk for cardiomyopathy to determine whether they have the functional capacity to perform PA and if negative health behaviours occur or develop in childhood. Similar to healthy children (Colley et al., 2017) and children with CHD (Banks, McCrindle, Russell & Longmuir, 2013; Banks et al., 2017; Dean et al., 2014; McCrindle et al., 2007; Voss et al., 2017), it is expected that the majority of children with cardiomyopathy do not meet PA guidelines. While their levels of inactivity might be similar, it is possible that different and more specific support may be needed for children with cardiomyopathy given that perceived contraindications or concerns with PA may differ. It is expected that a healthy active lifestyle is crucial for improving functional capacity, quality of life, and decreasing the likelihood of further cardiac risk factors and confounding comorbidities in children with cardiomyopathy. This research will enhance our understanding of which children require support in achieving an active lifestyle, what barriers need to be addressed, and whether they have the functional capacity for physically

active lifestyles. These preliminary data could help determine whether future interventions are needed to improve the health of children with cardiomyopathy. Below are the specific research objectives for this dissertation.

1.2 Research Objectives

1.2.1 Primary objectives:

1. To objectively measure the daily MVPA levels of children with cardiomyopathy using accelerometry.
2. To characterize the submaximal aerobic exercise capacity, defined as the $\dot{V}O_2$ required at a heart rate of 150 bpm, of children with cardiomyopathy.
3. To determine whether there is a relationship between submaximal aerobic exercise capacity and daily time spent in MVPA among children with cardiomyopathy.
4. To describe the PA barriers reported by children with cardiomyopathy (i.e. HCM, DCM, and CCM) and children who are G+P-.

1.3 Research Hypotheses:

1. Children with cardiomyopathy will not attain the 60 minutes of MVPA per day recommended in the Canadian Society for Exercise Physiology (CSEP) 24-hour movement guidelines.
2. Children with cardiomyopathy (i.e. HCM, DCM, or CCM) will have a lower submaximal aerobic exercise capacity in comparison to children who have a genetic risk for cardiomyopathy (i.e., are gene positive but currently without disease (phenotype negative); denoted as G+P-) or children with simple CHD.
3. Submaximal aerobic exercise capacity will be positively correlated with daily time spent in MVPA among children with and without cardiomyopathy.

4. Children with cardiomyopathy will report disease centered barriers to PA in addition to the common PA barriers that other children face.

Part 2: Literature Review

2.1 Classifications of Cardiomyopathy

Pediatric cardiomyopathies are diseases of various functional classifications, disease severities and etiologies with a reported annual incidence of 1.1 to 1.5 per 100,000 people (Lee et al., 2017). The causes are generally idiopathic in nature, but also include genetic predisposition and toxic exposure (Thrush & Vogel, 2018). For the purpose of this dissertation, the focus will be on the pediatric forms of cardiomyopathy (referred to as HCM, DCM, or CCM) and on children who are at risk for cardiomyopathy but do not currently have the disease (G+P-).

2.1.1 Hypertrophic cardiomyopathy (HCM)

HCM is a genetic heart disorder that accounts for 42% of childhood cardiomyopathy (Lipshultz et al., 2003). HCM is a heterogeneous group of myocardial disorders caused by greater than 1,000 mutations in more than 13 genes encoding proteins within and associated with cardiac sarcomeres (Maron et al., 2011). The common pathophysiology of HCM includes thickening of the left ventricular (LV) wall without dilation of the LV itself resulting in impairment in cardiac output. This impairment is often caused by the septal wall physically obstructing LV outflow (Lipshultz et al., 2013b). The HCM phenotype is typically obstructive, where the LV wall is thickened and physically obstructs the LV outflow (Lipshultz et al., 2013b). HCM is considered the most frequent cause of sudden cardiac death in the young as well as among competitive athletes (Maron et al., 2011; Loar et al., 2015).

2.1.2 Dilated cardiomyopathy (DCM)

DCM is a rare and extremely debilitating cardiomyopathy that is characterized by progressive LV dilation and systolic dysfunction (Lipshultz et al., 2013b). Other hallmark characteristics of DCM include, thinning of the interventricular septum, thinning of the posterior wall of the LV, as well as myocardial fibrosis. These characteristics stem from changes at the molecular, cellular and interstitial levels which result in the death of cardiomyocytes and collagen fibers (Lipshultz et al., 2013b). The causes of DCM are extremely diverse and are often considered idiopathic in nature (Lipshultz et al., 2013b).

2.1.3 Chemotherapy-induced cardiomyopathy (CCM)

Cardiomyopathy can also be a consequence of surviving childhood cancer. Due to the nature of chemotherapy agents, which are designed to interfere with rapidly dividing cancerous cells, they can cause serious adverse effects on the cardiac muscle, normal tissues and cellular processes (Lipshultz et al., 2013a). These chemotherapeutic agents may also cause acute and/or long-term adverse effects by directly compromising myocardial function and the cardiovascular system. In pediatric populations, anthracyclines (i.e. doxorubicin) are frequently used to treat the most common forms of cancer in children (Lipshultz et al., 2013a). Anthracycline cardiomyopathy is often characterized by changes in cardiomyocyte morphology and growth due to radiation-induced cardiac damage. This cardiomyocyte morphology is responsible for the initial onset of diastolic dysfunction and a later onset of systolic dysfunction and heart failure (Lipshultz et al., 2013a). As a result, childhood cancer survivors who have received anthracycline chemotherapy are at increased risk for cardiomyopathy, specifically DCM, and other adverse cardiovascular effects (Okada et al., 2012).

Table 2.1 Key characteristics of the different types of cardiomyopathy.

Type	Characteristics
HCM	LV hypertrophy associated with non-dilated ventricular chambers and diastolic dysfunction[1].
DCM	LV dilation that reduces contractility resulting in systolic dysfunction[1].
CCM	LV dilation, systolic and diastolic dysfunction. Caused by chemotherapy agents[1].

HCM: hypertrophic cardiomyopathy. DCM, dilated cardiomyopathy. CCM: chemotherapy induced cardiomyopathy. [1](Lipshultz et al., 2013a)

2.2 Genetic Risk for Hypertrophic Cardiomyopathy

With recent advancements in technology and genetic testing, a new subset of potential HCM patients has been identified. This new subgroup is defined as "genotype-positive–phenotype-negative" (G+P-) for HCM. G+P- patients carry mutations in genes encoding for proteins of the cardiac sarcomere that are associated with HCM (Semsarian et al., 2015). However, these patients are currently healthy and asymptomatic with no evidence of LV hypertrophy (Maron et al., 2011).

2.3 PA Participation

2.3.1 Which activities are permitted for individuals with cardiomyopathy?

Healthcare professionals caring for individuals with cardiomyopathy can refer to two expert consensus documents that outline recreational PA guidelines for individuals with cardiomyopathy (Maron et al., 2004; Pelliccia et al., 2006). These guidelines restrict individuals with HCM from participating in most high intensity recreational PA. These recommendations were developed with the perspective that vigorous physical activity may result in greater susceptibility to sudden cardiac death in individuals with heart disease (Maron et al., 2004). In addition, some moderate PA may be restricted given the effect of exercise on a specific patient with cardiomyopathy. Specifically, the cardiovascular response is dependent the duration, intensity, dynamic and static components of the activity, environmental conditions, hydration and the use of medications (Maron et al., 2004). For example, body building in considered a moderate intensity activity, but given

the intense isometric exertion, it is strictly prohibited among individuals with cardiomyopathy (Maron et al., 2004).

The European guidelines by Pelliccia et al. (2006) outline various types of sport and exercise that are " not recommended", "allowed on an individual basis" or "permitted". In contrast, the American guidelines from Maron et al. (2004) combine a subjective rating scale with estimates of the required energy expenditure (METs) during the activity (Maron et al., 2004). The Maron et al. (2004) guidelines rank various recreational activities based on the energy cost (in METs) of the activity, where high intensity activities are considered >6 METs, moderate activities 4 to 6 METs and low <3 METs (Maron et al., 2004). The activities are then graded on a relative scale, from 0 to 5 (0-1, not advised/discouraged; 4-5, probably permitted) (Maron et al., 2004). This ranking system allows clinicians the flexibility to determine individualized eligibility for a patient with cardiomyopathy. Most low intensity sports are permitted (i.e. bowling, and golf etc.) and most moderate sports are probably permitted (i.e. tennis, biking, hiking etc.). Most high intensity sports are strongly discouraged (i.e. basketball, ice hockey, soccer, etc.), with the exception of downhill and cross-country skiing given that these activities could be performed in moderation and at a leisurely pace (Maron et al., 2004).

The European guidelines (Pelliccia et al., 2006) differ in that they allow different types of activities (i.e. moderate intensity weightlifting, cross country skiing etc.) that are restricted in the American guidelines. Although these guidelines can be a useful tool for clinicians, research suggests that PA restrictions must be individualized given that the physiological effect of exercise varies based on several individual factors including phenotype, type of activity (i.e. static or dynamic), duration (i.e. continuous or intermittent), guidelines referred to, and physicians' own level of activity (Christian et al., 2016; Maron et al., 2004). Research has shown that Canadian

healthcare providers only partially implement PA guidelines, by either over or under restricting PA and competitive sports for children with various cardiovascular conditions (Roston et al., 2013). However, recreational sports are less commonly restricted for children with inherited arrhythmogenic conditions, such as HCM, regardless of clinical symptoms (Christian et al., 2016).

2.3.2 Youth compendium of physical activities can be a valuable tool for clinicians

The Youth Compendium of Physical Activities is a helpful document that provides estimates of energy costs in metabolic equivalents (METs) for 196 physical activities using data from only children and youth (Butte et al., 2017). One MET is defined as "the amount of oxygen consumed at rest, sitting quietly in a chair" (Jetté, Sidney & Blümchen, 1990). Children have a higher resting metabolic rate (RMR) due to differences in age, body mass and other characteristics (Ridley & Olds, 2008). The value of one MET for a child is defined by a child-specific RMR (Ridley & Olds, 2008) or predicted RMR using the Schofield equation (Schofield, 1985). The energy cost of an activity can be calculated by dividing the relative oxygen cost of the activity (ml O_2/kg/min) by a child-specific or estimated RMR. Therefore, utilizing the specific PA recommendations for children with cardiomyopathy outlined in section 2.3.1 and the Youth Compendium of PA's (Butte et al., 2017) in conjunction with objectively determined PA thresholds could provide clinicians a valuable indication of which activity intensities can be recommended for children with cardiomyopathy.

2.3.3 PA participation in adults with cardiomyopathy

Adults with HCM self-report reduced physically active as compared to their healthy counterparts (Reineck et al., 2013; Sweeting et al., 2016). For example, in Australia, 55% of adults with HCM (n=198) reported being physically inactive (Sweeting et al., 2016). They showed that the inactivity suggested by these self-reports corroborates with objectively measured PA levels,

where only 8 out of 63 adults with HCM (12%) achieved the 150 minutes of PA recommended on a weekly basis (Sweeting et al., 2016). Although individuals with cardiomyopathy are often perceived to be restricted in physical activity and less physically fit, their levels of inactivity are fairly similar to that of the general adult population (Colley et al., 2011; Sweeting et al., 2016). Research has shown that adults with HCM spend less time participating in PA, and self-report a lower exercise capacity and purposeful reductions in PA after diagnosis. Furthermore, it has been reported that physician-imposed exercise restrictions can have a negative impact on the emotional well-being of individuals with HCM (Reineck et al., 2013).

2.3.4 Expected PA participation in children with cardiomyopathy

A significant number of children with cardiomyopathy are surviving into adulthood, making it an important chronic illness for both pediatric and adult healthcare professionals to understand (Lipshultz et al., 2013a). Currently, the PA behaviours of children with cardiomyopathy are unknown. Given that adults with cardiomyopathy report being physically inactive, resulting in detrimental effects on their health and well-being, we would posit that children with cardiomyopathy would be similarly impacted. However, children are not miniature adults in terms of their physiology or exercise behavior; therefore, the PA behaviour findings from adults with cardiomyopathy (Reineck et al., 2013) may not be directly applicable to children with cardiomyopathy.

2.4 Exercise Capacity

2.4.1 How does cardiomyopathy influence the physiological response to exercise?

Although objective measurements can quantify the amount and intensity of PA, they do not indicate an individual's capacity to engage in PA. Reduced exercise capacity, related to both sub-optimal cardiac and pulmonary functionality, has been reported for adult patients with various

classifications of cardiomyopathy (Frenneaux et al., 1989; Jones et al., 1998; Lele et al., 1995; Somarriba et al., 2008). Dyspnea has been reported as an important factor that can limit exercise capacity, presumably due to increased ventilation due to inadequate oxygen delivery to skeletal muscle (Frenneaux et al., 1989). In addition, a thickened septal wall may also physically obstruct or limit left ventricular outflow (Lipshultz et al., 2013b) decreasing stroke volume (Lele et al., 1995). Maximal oxygen consumption is moderately impaired in adults with HCM and cardiac output is reduced due to limited left ventricular diastolic filling (Frenneaux et al., 1989; Lele et al., 1995). The relationship between maximal oxygen consumption and cardiac output can be explained using the Fick principle. The Fick principle states that oxygen uptake of exercising muscle is the product of oxygen delivery by cardiac output and the arterial-venous oxygen difference (Takken et al., 2009). In adults with cardiomyopathy, a reduction of cardiac output can be a limiting factor that impedes the amount of oxygen delivery to exercising muscles. As exercise intensity increases, individuals with cardiomyopathy will need to compensate with a greater heart and ventilation rate to account for a limited stroke volume and oxygen delivery to exercising muscles. Unfortunately, these adaptations cannot be maintained at all exercise levels, especially for activities above ventilatory and anaerobic threshold.

In adults, these findings have provided researchers with a foundation for the development of exercise interventions suitable for adults with cardiomyopathy, which have been shown to be safe and effective at improving functional capacity (Klempfner et al., 2015; Saberi et al., 2018). The changes in cardiac structure and function resulting either from hypertrophy or dilatation subsequent to cardiomyopathy could be similar regardless of the age of the patient. Thus, it can be hypothesized that children with cardiomyopathy will have similar physiological limitations during exercise as those observed among adults with cardiomyopathy (i.e. reduced cardiac output).

Although research indicates that adults with cardiomyopathy live physically inactive lifestyles, physical activity recommendations and levels of participation differ between children and adults. Therefore, research is required to indicate whether children with cardiomyopathy have the functional capacity to engage in moderate-to-vigorous PA or if an exercise training intervention is required.

2.4.2 Estimated exercise capacity in pediatric cardiomyopathy patients

Few studies have conducted exercise testing in pediatric cardiomyopathy patients. Two studies examined the role of cardiopulmonary exercise testing, via cycle ergometer, as a prognostic tool for children with DCM. Both studies found that lower exercise capacity, heart rate (HR), blood pressure response, peak HR, and peak oxygen consumption ($\dot{V}O_{2peak}$) were all associated with adverse outcomes and an increased risk for death or heart transplant (Chen et al., 2017; Giardini, Genton, Andrews, Derrick, and Burch, 2011). Research is required to investigate the submaximal aerobic exercise capacities of children with cardiomyopathies because knowledge of the cardiovascular response at similar intensities in day-to-day activities is clinically very important (McManus & Leung, 2000). Given that the expert consensus guidelines outlined in section 2.2.1 provide recommendations that are based on METs, submaximal exercise testing outcomes like rate of oxygen consumption ($\dot{V}O_2$) could provide clinicians with valuable information for ascertaining which types of PA intensities are recommended for a specific individual with cardiomyopathy.

2.5 PA Barriers

While objective methods such as exercise testing and accelerometry may capture exercise capacity and PA patterns respectively, these assessments provide no information about the feasibility of an active lifestyle. Understanding the barriers to PA may help to explain why children are physically inactive. Perceived barriers can be defined as an individual's judgment of how

personal, social, environmental and economic obstacles can hinder their ability to participate in PA (Zabinksi, Saelens, Stein, Hayden-Wade and Wilfley, 2003). Important barriers that can impede PA participation in youth include, lack of time and support, low motivation for PA, and negative attitudes toward PA (Gunnell, Brunet, Wing and Belanger, 2015). Understanding and identifying specific PA barriers can aid the design of more effective interventions (Sallis, Prochaska and Taylor, 2000) to help induce behavioural changes supporting the adoption of physically active lifestyles in children. Given that adults with cardiomyopathy report unique barriers to PA, examining the PA barriers of children with cardiomyopathy is an important first step to understand the feasibility of PA participation for these children.

2.5.1 PA barriers in pediatric oncology patients

The Children's Oncology Group (2008), recommends that children should participate in MVPA for at least 60 minutes per day for at least 5 days a week. Pediatric oncology patients are at high risk for physical inactivity during or after chemotherapy treatment, increasing their risk for chronic conditions including obesity, type-2 diabetes and cardiovascular disease (Yelton and Forbis, 2016). Historically, aerobic and strength training have been recommended for pediatric oncology patients, although certain strength training exercises (i.e. bench press) have been discouraged to preserve their cardiac function (Okada, Meeske, Menteer and Freyer, 2012). Given the intensive and invasive treatments often endured by childhood cancer patients, it is not surprising that a high proportion of childhood cancer patients do not meet PA guidelines (Zhang et al., 2012).

Barriers to PA in pediatric oncology patients during and after treatment are well documented. In fact, a recent systematic review of barriers to PA in pediatric oncology patients indicated that chemotherapy treatment, and its associated side-effects (e.g., fatigue andinfection),

are major barriers to PA (Yelton and Forbis 2016). Childhood cancer survivors have reported barriers including, worries about injury and inexperience with exercise (Arroyave et al., 2008). Preference to participate in more sedentary activities such as watching television or reading was also frequently reported as reasons why childhood cancer survivors don't participate in adequate PA (Arroyave et al., 2008). Psychological barriers, including a lack of energy are also a commonly reported barrier among oncology patients after treatment. Organizational barriers, including lack of time, sports equipment, weather and lack of space for physical activities also had a negative influence on PA participation (Arroyave et al., 2008; Yelton and Forbis, 2016). Whether the barriers to PA are similar among the subset of pediatric oncology patients who have developed cardiomyopathy has not been investigated.

2.5.2 PA barriers in pediatric CHD patients

Barriers to PA have been investigated among youth with CHD. Children with CHD report low levels of self-efficacy and perceived confidence for PA, two important factors that may explain their low daily PA participation (Moola, McCrindle and Longmuir, 2009). Social and environmental barriers also play an important role at impeding PA participation for youth with CHD. Specifically, parental overprotection, lack of access to safe and enjoyable PA programs, and exclusion by teachers and peers in physical education are prominent barriers that impede PA participation (Moola, Faulkner, Kirsh, and Killburn 2008). The identification of these PA barriers is a critical first step in designing specific PA interventions to address and support the specific PA needs of children with CHD. Therefore, given that there are similarities in the clinical care of children with CHD and cardiomyopathy, it is hypothesized that additional barriers may also exist among pediatric cardiomyopathy patients. The identification of PA barriers among these patients will help determine whether specific interventions are required.

2.5.3 PA barriers in adults with cardiomyopathy

Two studies have examined PA barriers among adults with cardiomyopathy (Reineck et al., 2013; Sweeting et al., 2016). The most commonly reported barriers included comorbidities preventing PA, pain interfering with PA participation, lack of time and the receipt of advice discouraging exercise (Sweeting et al., 2016). Adults with HCM also self-impose PA restrictions due to both perceived safety concerns and physical limitations to exercise (Reineck et al., 2013). Exercise restrictions had a negative effect on the emotional well-being of adults with HCM, resulting in emotional stress that exacerbated symptoms of HCM including dyspnea, chest pain, and syncope (Reineck et al., 2013).

2.5.4 Do children with cardiomyopathy have PA barriers?

It is expected that children with cardiomyopathy will report barriers to PA participation. Data from adults with cardiomyopathy suggest that low exercise capacity could prevent these children from consistently engaging in recreational PA with their friends and family. Physical inactivity in this population could also be attributed to the many previously outlined PA barriers that all children face, whether or not they have a chronic disease. It is expected that children with cardiomyopathy could face an additional set of barriers that may be unique to their disease, given that PA barriers and preconceived perceptions or concerns for PA have been reported among adults with cardiomyopathy (i.e. I've been advised not to exercise, Sweeting et al., 2016) and childhood cancer survivors (i.e. worried about injury, Arroyave et al., 2008). Ultimately, a multitude of factors within and outside of our control can contribute to physical inactivity. Any of these barriers, alone or in combination, may prevent children from having positive experiences during PA. Exploring PA barriers among this population of children could help determine: i) if these children face barriers to PA participation that are more numerous or different from the barriers that impact

children without cardiomyopathy, ii) which barriers have the most significant impact on PA participation, and iii) which barriers may be modifiable through an intervention.

Part 3: Article

Children with cardiomyopathy have inactive lifestyles despite the exercise capacity needed for moderate-intensity activity – a pilot study

Short title: Physical activity in pediatric cardiomyopathy patients

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Keywords: physical activity, health behaviours, exercise physiology, pediatric cardiomyopathy

Word count: 9364

3.1 Abstract

Adults with cardiomyopathy have limited functional capacity, live inactive lifestyles and report disease-focused barriers to physical activity (PA). As a result, PA and exercise interventions are now incorporated as an important management therapy for adult patients. Since children are more active than adults, engage in different forms of PA and identify different barriers to PA participation, this study sought to characterize daily PA, assess submaximal exercise capacity and identify barriers to PA among pediatric cardiomyopathy patients. Seven-day accelerometry assessed daily moderate-to-vigorous physical activity (MVPA). An intermittent treadmill protocol, targeting 40 to 80% of estimated maximum heart rate, used indirect calorimetry to measure submaximal exercise capacity, defined as the $\dot{V}O_2$ (ml/kg/min) achieved at 150 beats per minute (bpm). PA barriers were identified through semi-structured interviews. Pediatric cardiomyopathy patients (n=5, 2 females, 14.2 ± 2.7 years old) were compared to children who are genotype-positive but phenotype-negative (G+P-) for cardiomyopathy (n=5, 3 females, 9.2 ± 2.8 years old), children with simple congenital heart defects (CHD, n=8, 4 females, 9.4 ± 3.8 years old) and published data for Canadian children (n=1,300, Colley et al. 2017). Daily MVPA (minutes) was variable but did not differ ($p=0.83$, $\eta^2=0.03$) between the cardiomyopathy (46.7 ± 27.2), G+P- (52.7 ± 17.2) and simple CHD (45.7± 16.3) participants. Mean MVPA (48.2 min/day) of study participants did not differ ($t(17) = -1.518$, $p=0.15$) from the mean value for Canadian children (55 min/day). The proportion of study participants (28%) who achieved the recommended average of 60 minutes of MVPA/day did not differ from data for Canadian children (33%, $z=0.54$, $p=0.29$). Mean $\dot{V}O_2$ (ml/kg/min) at 150 bpm did not statistically differ ($p=0.91$, $\eta^2=0.015$) between the cardiomyopathy (n=4, 25.8 ± 10.2 ml/kg/min), G+P- (n=4, 24.1 ± 1.1 ml/kg/min) and CHD (n=7, 25.4 ± 4.8 ml/kg/min) groups. Participants achieved 4.5 ± 3.1 METs at 150 bpm, suggesting that

children with cardiomyopathy could participate in low-to-moderate intensity recreational activities and games. Children with cardiomyopathy reported disease centered barriers to PA, which were not reported by children (G+P-) who are currently healthy. These novel data suggest that a diagnosis of cardiomyopathy may not preclude these children from achieving a healthy, active lifestyle, but their current level of participation is less than recommended for optimal health.

3.2 Introduction

Physical activity (PA) is an important determinant of health for all children, since they inherently choose to move and engage in physically active play (Takken et al., 2011). Children between the ages of 5 and 17 should "accumulate at least 60 minutes per day of moderate to vigorous physical activity" (MVPA) (CSEP, 2018) as it is essential for the physical, psychosocial and cognitive health of all children (Janssen & LeBlanc, 2010). Although MVPA is encouraged in the general population, current expert consensus guidelines restrict individuals with hypertrophic cardiomyopathy (HCM) from participating in most high intensity, recreational physical activities (Maron et al., 2004).

In adults with cardiomyopathy, restricting PA has resulted in unique barriers to PA (i.e. I was advised not to exercise) and detrimental effects of inactivity, including a lower health-related quality of life, decreased psychological well-being and increased obesity (Ingles et al., 2013; Olivotto et al., 2013; Reineck et al., 2013; Sweeting et al., 2016). Furthermore, exercise restriction can lead to a purposeful reduction of PA after diagnosis that result in anxiety toward exercising and can further impact the emotional and psychological well-being of individuals with HCM (Reineck et al., 2013). To counteract these negative outcomes, exercise rehabilitation programs targeted to adults with cardiomyopathy have been developed. Such programs lead to improved cardiac function and exercise capacity and appear to be safe (Klempfner et al., 2015; Saberi et al.,

2017; Sweeting et al., 2016). However, parallel information regarding the PA behaviours, submaximal aerobic exercise capacity, and barriers to PA for children with cardiomyopathy has not been reported.

Clinicians have an important role in promoting PA among pediatric cardiomyopathy patients. They are required to mitigate uncertainty about whether certain activities are appropriate and must carefully weigh the risks and benefits of restricting PA participation (Christian et al., 2016). In the absence of objective data, it has been hypothesized by some that clinicians might be overly conservative when advising patients with cardiomyopathy about exercise (Reineck et al., 2013). It is also unknown whether parents, other adults responsible for the child (e.g., teachers), or the children themselves, naturally err on the side of caution by restricting the PA participation of children with cardiomyopathy. Understanding the PA behaviours, submaximal exercise capacities and perceived barriers to PA among children with cardiomyopathy will help determine whether intervention strategies are required and potential targets for optimizing intervention effects.

Therefore, the primary objectives of this study were threefold, 1) to objectively measure the daily physical activity (minutes of MVPA) of children with cardiomyopathy using accelerometry, 2) to characterize the submaximal aerobic exercise capacity, defined as the $\dot{V}O_2$ required at a heart rate of 150 bpm, of children with cardiomyopathy and 3) to explore the PA barriers reported by children with cardiomyopathy. We hypothesized that children with cardiomyopathy would not meet the 60 minutes of MVPA recommended per day and would have lower submaximal aerobic exercise capacity in comparison to the G+P- and simple CHD groups. Lastly, we hypothesized that children with cardiomyopathy would report unique barriers to PA in comparison to the G+P- group.

3.3 Methodology

This cross-sectional study followed a convergent parallel mixed methodology design, in which qualitative and quantitative data were collected in parallel, analyzed separately and then merged to form preliminary conclusions about the PA behaviours of children with cardiomyopathy. This study was approved by the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board (REB #17/189x) and the University of Ottawa Research Ethics Board (Ethics file: H-04-18-461). All participants and their parents gave written informed assent and/or consent to participate.

3.3.1 Participants

All pediatric cardiomyopathy patients from CHEO were screened for study eligibility. Children were included in the study if they were between the age of 5 and 17 years old and met one of the following inclusion criteria: a) a medical diagnosis of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or chemotherapy-induced cardiomyopathy (CCM), b) identified as carrying a genetic risk for cardiomyopathy without current evidence of disease, otherwise known as genotype-positive phenotype negative for HCM (G+P-), or c) children with a repaired atrial septal defect (ASD) or ASD not requiring repair. Children with an ASD ("simple CHD" group) were enrolled as a reference population of children. They have a cardiac diagnosis and are followed in a cardiac clinic but would be expected to have "normal" exercise capacity and physical activity behaviour. Participants were excluded if they had PA contraindications preventing study participation as determined by the treating cardiologist, had a syndrome, non-cardiac medical condition or disability known to influence PA or motor skill development (e.g. cerebral palsy, Down syndrome) or if they underwent cardiac surgery or catheterization intervention within the preceding 6 months. Participant eligibility was determined via medical

chart review and confirmed with the responsible cardiologist. Recruitment and data collection occurred between March 2018 and July 2018.

3.3.2 Accelerometry

Participants were asked to wear an Actical Z-series accelerometer (Philips Respironics) above the right iliac crest at the mid-axillary line for all waking hours for 7 consecutive days (Trost, Pate, Freedson, Sallis, & Taylor., 2000). A PA log enabled participants to report periods of accelerometer removal (i.e. sleep times) and the physical activities performed each day. Accelerometer data were recorded in 15-second epochs, and established cut points (Puyau, Adolph, Vohra, Zakeri & Butte., 2004) were used to calculate daily MVPA. Accelerometry data were considered valid and included in the analysis if participants wore the Actical for at least 3 weekdays and 1 weekend day (Trost et al., 2000), with at least 10 hours of Actical wear time each day (Colley and Tremblay, 2011b). To account for participant wear time variability, Actical data were transformed to get average MVPA for valid weekdays and weekend days. The time spent in MVPA per day was then calculated using the following equation:

$$Daily\ MVPA = \frac{(5\ days \times Average\ MVPA\ week\ day) + (2\ days \times Average\ MVPA\ weekend\ day)}{7\ days};$$

Equation 1.

3.3.3 Submaximal exercise capacity test

Prior to the test, body mass (kg) and height (cm) were measured. Each participant was equipped with a standard 10-lead electrocardiogram (ECG, CASE 8000; GE Medical Systems, Milwaukee, Wisconsin), blood pressure cuff (FlexiPort re-usable blood pressure cuff; Welch Allyn, Skaneateles Falls, New York) and a fitted rubber mouthpiece for breath-by-breath analysis of metabolic variables. The fitted rubber mouthpiece was connected to a VMAX Encore Metabolic Cart (Sensormedic, San Diego, California) for indirect measures of oxygen consumption. Standard

volume and gas calibration procedures were completed prior to each testing period. Firstly, the flow sensor was zeroed. The flow sensor was then calibrated by completing two room-air purges using the 3L syringe and one inspiratory and one expiratory stroke for each recommended target range (i.e. 0 to 0.6, 0.9 to 1.6, 2.4 to 5.5, and 7.0 to 12.0 litres/second). Lastly, calibration was verified by performing 5 full inspiratory and expiratory strokes (i.e. at 0.5, 1.5, 3.0, 8.0 and 12.0 litres/second). After volume calibration, gasses were calibrated using compressed gas containing a mix of O_2 and CO_2 and by connecting the sample line to the calibration fitting on the VMAX. Baseline measurements of heart rate (HR), blood pressure, metabolic variables (i.e. oxygen consumption ($\dot{V}O_2$), and respiratory exchange ratio (RER)) were measured while the participant was seated comfortably for 10 minutes or until RER stabilized between 0.67 and 1.00 (Rhodes, Tikkanen and Jenkins, 2010).

All participants then completed a submaximal cardiopulmonary exercise test following an intermittent treadmill protocol. Participants performed a warm-up stage (6% grade at 1.0 mph) to familiarize themselves with walking on the treadmill while wearing the monitoring equipment. Following the warm-up stage, participants completed a minimum of three 5-minute bouts of exercise with the workload designed to achieve 40%, 60%, and 80% of their estimated maximum heart rate (HR_{max}). HR_{max} was estimated using the calculation of $HR_{max} = 208 – 0.7$ (age) (Mahon, Marjerrison, Lee, Woodruff, & Hanna., 2010; Tanaka, Monahan, & Seals., 2001) and target heart rates were estimated using the Karvonen equation (Karvonen & Vuorimaa, 1988). However, it is recognized that these estimation equations are validated among healthy children, but may not be valid for children with changes to cardiac structure and function due to cardiomyopathy. There was a rest period between each exercise stage that continued until the participant's HR returned to within 10% of the resting value. Standard 10-lead ECG, blood pressure, and breath-by-breath

analysis of metabolic variables were monitored during each stage of the protocol. Ratings of perceived exertion (RPE) on a 1-10 Borg Scale (Borg, 1982) were collected at the end of each exercise stage. After the completion of the last exercise bout, participants completed a 2-minute cool down, where the treadmill speed and incline were gradually decreased to the initial warm up speed.

3.3.4 Semi-structured interviews

A phenomenological approach was used to explore participants' perceived barriers to PA. Given that PA barriers have previously been reported among pediatric congenital heart disease patients (Moola, Fusco & Kirsch, 2011), only participants with cardiomyopathy (n=5) or at risk for cardiomyopathy (G+P-) (n=5) were interviewed. Parents were given the opportunity to accompany their children during the interviews. Data were collected using semi-structured interviews and analyzed using a thematic inductive approach (Braun and Clark, 2006; Braun, Clarke, & Weate, 2016). The semi-structured interview guide consisted of a series of open-ended questions (Appendix I), created by the authors, to provide participants an opportunity to discuss and elaborate on their perceived barriers towards PA. Questions asked about participants' PA interests and reasons for inactivity. The lead author conducted all 10 interviews, either before or after the submaximal exercise test in a private room in CHEO's Cardiology Clinic. All interviews were audio recorded and then transcribed verbatim for analysis.

3.3.5 Data Analyses

Daily time spent in MVPA (minutes) was defined as the cut point at 1600 counts per minute (Puyau, Adolph Vohra, Zakeri and Butte, 2004) via 7-day accelerometer monitoring and was calculated using Equation 1. Submaximal aerobic exercise capacity was defined as the rate of oxygen consumed ($\dot{V}O_2$) when exercising at a heart rate of 150 bpm. It was assessed by intermittent

submaximal exercise testing and calculated by extrapolating or interpolating the HR-$\dot{V}O_2$ linear relationship to a standardized value of 150 bpm. Oxygen consumption data were not available for two participants (1 male G+P-; 1 female ASD) who refused to wear the $\dot{V}O_2$ monitoring equipment during the exercise test and one CCM participant (female) whose medical status changed prior to the scheduled testing date such that she could complete the interview and MVPA measurements but was no longer eligible to complete the submaximal exercise protocol. The MET cost at 150 bpm was calculated for each participant by dividing the mean $\dot{V}O_2$ required at a heart rate of 150 bpm by the participants resting metabolic rate (RMR). RMR was estimated for each participant using the Schofield equations (Schofield, Schofield and James., 1985) for boys and girls respectively:

$$Boys: RMR = [(0.082 \times \mathbf{weight\ (kg)}\ ] + [0.545 \times (height\ (cm))/100] + 1.736 \quad ; \text{ Equation 2.}$$

$$Girls: RMR = [(0.071 \times \mathbf{weight\ (kg)}\ ] + [0.677 \times (height\ (cm))/100] + 1.554 \quad ; \text{ Equation 3.}$$

Descriptive statistics (mean ± SD), ANOVAs (*F*-statistic) and eta-squared effect sizes (η^2, small = 0.01, moderate = 0.06 and large = 0.14, Cohen, 1988), were used to examine outcome variables by study group. *T*-tests and Cohen's *d* effect sizes (small = 0.2, moderate = 0.5 and large = 0.8, Cohen, 1988) were computed to determine significant differences between two means. Z-score calculations were used to determine the differences between two proportions. A Pearson product-moment correlation was calculated to determine the relationship between estimated mean $\dot{V}O_2$ achieved at 150 bpm and daily time spent in MVPA. Two age groups, 5 to 11 years old and 12 to 17 years old, were used to compare study daily MVPA data to reference daily MVPA data for Canadian children (Colley et al., 2017). All quantitative analyses were conducted using SPSS version 23.0.

An inductive thematic analysis of the interview data was completed by the lead author, according to the six steps described by Braun and Clark (2006) and Braun, Clarke and Weate (2016). Data familiarization occurred as the data were transcribed verbatim, and through reading and re-reading the transcripts. Codes were then identified across each data set, with the data from one participant analyzed at a time. Once all interviews had been coded, themes were developed by ordering and refining the identified codes into lower-level and higher-level themes. Finally, the themes were named and defined, and the most relevant quotations were chosen to exemplify each theme. NVivo 12 was used to assist in the coding and management of the qualitative data.

3.4 Results

3.4.1 Sample characteristics

A total of 18 participants (50% female, age range 5-17 years, with a mean age of 10.7 ± 3.8 years old) were enrolled in the study. All enrolled patients had complete MVPA data and were included in the analyses. Age differed significantly between groups ($F(2,17) = 4.069$, $p=0.04$). Cardiomyopathy patients were significantly older (14.2 ± 2.7 years) in comparison to the simple CHD group (9.4 ± 3.7 years) and the G+P- group (9.2 ± 2.7 years). There were no statistically significant differences in sex ($F(2,17) = 0.170$, $p=0.85$, $\eta^2 =0.02$), height ($F(2,17) = 0.604$, $p=0.56$, $\eta^2 =0.07$), or weight ($F(2,17) = 0.904$, $p=0.43$, $\eta^2 =0.11$) between study groups, although moderate effect sizes suggest a heterogeneous sample, such that the participants with cardiomyopathy tended to be taller and heavier (Table 3.8.1).

One participant with HCM and another with DCM were restricted from competitive sports participation. Another participant with HCM had a prosthetic leg. Non-cardiac conditions, present in 6 participants (33.3%, n=4 cardiomyopathy, n=1 simple CHD, n=1 G+P-), included respiratory conditions (n=2), digestive conditions (n=2), cancer (n=1) and attention deficit hyperactivity

disorder (n=1). Prescription medication use was reported in these 6 patients, including the use of respiratory (n=2), gastrointestinal (n=2), beta-blocker (n=1), ACE-inhibitor (n=1), anxiety (n=1), thyroid (n=1) and attention deficit hyperactivity disorder (n=1) medications.

In total, 45 potential participants were identified and initially assessed for eligibility of whom 40 were deemed eligible. Twenty-two participants were subsequently excluded from study participation (Figure 3.8.1), leaving a total of 18 study participants. Individuals who did not participate in the study did not differ by age ($t(17) = -0.316$, $p=0.76$) compared to those who enrolled. There was a trend towards a higher proportion of females among those who did not participate (72.7%, n=16) compared to those who enrolled (50%, n=9) in the study ($z=1.43$, $p = 0.07$).

3.4.2 Accelerometry

Study participants performed 48.2 ± 19.0 minutes of MVPA per day. Daily MVPA was not significantly different ($F(2,17) = 0.189$, $p=0.83$, $\eta^2 =0.03$) between the cardiomyopathy (46.7 ± 27.2 minutes), G+P- (52.7 ± 17.2 minutes) and simple CHD (45.7± 16.3 minutes) groups. Daily MVPA did not differ by sex ($t(16) = 0.22$, $p=0.83$, Cohen's $d = 0.11$). Participants aged 5 to 11 years-old (n=9) accumulated 52.2 ± 14.6 minutes of daily MVPA, while participants aged 12 to 17 years (n=9) performed 44.2 ± 22.8 minutes per day. This difference was not statistically significant ($t(16) = 0.878$, $p=0.39$), but the small effect size (Cohen's $d=0.41$) suggests that older participants may be less active. The MVPA/day of participants aged 5 to 11 group (52.2 ± 14.5 min/day, $t(8) = -2.02$, $p=0.077$) was not significantly different from the 62 min/day reported for Canadian children aged 5 to 11 years old (Colley et al., 2017). Similarly, the MVPA/day of participants age 12-17 years old was not significantly different (44.3 ± 22.8 min/day, $t(8) = -0.493$, $p=0.63$) than the 48 min/day reported for Canadian children aged 12 to 17 years old (Colley et al.,

2017). Overall, the mean MVPA per day (48.2 ± 19.0 min/day) among study participants was not significantly different ($t(17) = -1.518$, $p=0.15$) from the 55 min/day reported for Canadian children (Colley et al., 2017). The mean MVPA per day among the cardiomyopathy group (47.6 ± 27.2 min/day, $t(4) = -0.61$, $p=0.57$), G+P- group (52.7 ± 17.2 min/day, $t(4) = -0.296$, $p=0.78$) and the simple CHD group (45.7 ± 16.3 min/day $t(7) = -1.60$, $p=0.15$) did not differ significantly to the 55/min reported for Canadian children (Colley et al., 2017). Twenty eight percent of the children in this study achieved the recommended average of 60 minutes of MVPA per day. This proportion was not significantly different ($z=0.54$, p=0.29) from the 33% of Canadian children who achieve this standard.

3.4.3 Submaximal aerobic exercise capacity

Submaximal aerobic exercise capacity, defined as the rate of oxygen consumed ($\dot{V}O_2$) when exercising at a heart rate of 150 bpm, was measured among 15 study participants. There were no statistically significant differences between groups for RMR or measures of submaximal aerobic exercise, including $\dot{V}O_2$ achieved at 150 bpm, HR, $\dot{V}O_2$/kg and RER at each stage (Table 3.8.2). $\dot{V}O_2$ at 150 bpm (n=15) was not significantly different between study groups (Table 3.8.2, $F(2,14) = 0.91$, $p=0.091$, $\eta^2 =0.015$). The estimated MET required to work at a heart rate of 150 bpm did not differ significantly between study groups ($F(2,14) = 0.29$, $p=0.76$, $\eta^2=0.046$). Children with cardiomyopathy achieved on average 4.5 ± 3.1 METs at 150 bpm. There was a small, non-significant correlation ($r = 0.11$, n = 15, $p= 0.69$) between submaximal aerobic capacity and daily MVPA, with the $\dot{V}O_2$ required at 150 bpm being lower as daily-time spent in MVPA increased.

3.4.4 Physical activity barriers

Ten participants (n=5 cardiomyopathy and n=5 G+P-) and two parents participated in a semi-structured interview. The interviews lasted between 10 and 33 minutes (Mean=14.5 ± 7.9 minutes). All interviews were transcribed verbatim resulting in 35 pages of transcripts. The main themes identified were "*influences of the disease*" and "*psychosocial influences*" (Figure 3.8.2).

3.4.4.1 Influences of the disease

Participants with cardiomyopathy and their parents often described restriction of physical activity participation. One participant with HCM who was restricted from participating in competitive level sports said "*My mom doesn't let me do certain things… she always makes me bring the defibrillator around [when I am playing away from home with my friends], HCM 7".* Another instance where parental restriction was found to be a barrier to PA was when a family member also has cardiomyopathy. *"His dad also has HCM and so when the whole family is planning an activity, we choose safer sports, but it is more restricted than it usually is with just him, HCM Parent 1".* When HCM Parent 2 was asked whether the child with HCM would be allowed to participate in sports with their friends, he responded *"I would allow it but his mom wouldn't let him because of the fear that many, many things can go wrong."*

Participants with cardiomyopathy also described teacher restrictions as a source of discouragement for participating in PA. *"For school, we needed to complete a 5km run… it was worth 10% of my mark depending on the times that we got on the run. I was advised to try and pick something else to do, DCM 9".* PA restriction was consistent among HCM participants, *"well my teachers encourage me to not be active, HCM 7"* and *"my teacher last year said I couldn't play soccer because of physical reasons... I haven't played soccer at school ever since, HCM 11".* Similarly, one participant expressed that her gym classes were exempted.

> *"I got all my gyms exempted because the teachers couldn't adapt gym to me. They recommended that I sit down because I couldn't run a 5km run. I understand that it is extremely unrealistic. I have tried before, like I've ran a 2km but I stopped halfway because I couldn't continue anymore. So, I guess, not being able to adapt the activities to me".*
>
> CCM 22

Most participants in the cardiomyopathy group reported being out of breath as a common barrier to participation when asked what makes it difficult for them to do PA. *"Um… I find I get short of breath very easily, so much that I feel that like, sometimes I walk up the stairs and I feel like I need to stop walking, CCM 22"* or *"I get tired pretty quick sometimes and I am out of breath, so I stop, DCM 10".* HCM parent 1 also described that their child gets tired quickly during PA *"there are times where we go for bike rides and sometimes he just can't make it home… because he is just too tired, HCM parent 1".* Participants also recognized the limitations imposed by their physical abilities.

> *"I used to play soccer and I would love to play volleyball but it just doesn't seem reachable for me from a physical perspective… I was playing volleyball with my friend and she was trying to show me the basics and I was like this is impossible for me".*
>
> CCM 22

3.4.4.2 Psychosocial influences

Participants with G+P- often described their parents and family as being inactive, that they prefer to choose sedentary activities or their parents are too busy to do activities with them. When asked about the type of activities they do with their families, multiple G+P- participants reiterated similar ideas *"at home we play board games… We watch movies together. When we have nothing to do, we are just sitting there on the couch to read and watch something, G+P- 8".* This G+P-

participant also expressed interest in trying out new activities instead of sedentary activities, *"I've never tried snowboarding, I feel like that would be fun. My family doesn't do skiing and stuff, G+P- 8".* Several participants indicated a lack of time together *"Sometimes they have work to do and they are really busy and stuff, G+P- 1".* One G+P- participant mentioned that it's hard for his parents to be active with him because he views his parents as incapable of being physically active. *"Yes, my mom can't run and my dad… he probably can't run either. Well my mom can run, she just doesn't like it… and well my dad works all week-days, G+P- 6".* Similarly, *"No... my mom can't she has fibromyalgia so she can't really and my dad is really busy, he leaves at 7am and comes back at 630, G+P- 5".* There was one participant who reported being active with his family, *"I like to jump on my trampoline with everyone, G+P- 2".*

Participants also commented about the impact that their peers have on their PA participation. Some participants with cardiomyopathy indicated that their friends were not very active, often citing a lack of time and interest in PA, that makes it difficult for them to participate in PA. "*My friends aren't very active… we don't have much time to be active, DCM 9".* They also indicated that their peers were sometimes too rough or competitive during active play. *"I don't like playing soccer at school because sometimes kids are a bit rough, so I play three squares with my friend, HCM 11".*

Among the G+P- group, lack of motivation or limited self-efficacy were identified as barriers to PA. Specifically, *"Sometimes I don't have enough energy at the end of the day… I would rather play video games than go outside, I like to play a lot of card games on my tablet, G+P- 6". S*imilarly, a G+P- participant was describing how she had to stop participating in gymnastics, *"my parents wanted me to go on a competitive team, but I wasn't ready to move up to competitive, so I decided to stop altogether G+P- 1".* Another G+P- participant, who played

football, stated that being in better physical shape would make it easier for him to participate in more PA.

> *"Probably be in better shape, like that's really the only thing… Because I am not the skinniest, fastest or strongest, but being in better shape would still help me… My friends are really big risk takers, like they do hip-hop and gymnastics. They'll do backflips and wheelies on their bikes and I'll just watch and bike around. I can't do that stuff, I am not physically capable to do those things".*
>
> G+P- 5

3.5 Discussion

Children with cardiomyopathy or who carry a genetic risk for cardiomyopathy (G+P-) participate in similar amounts of MVPA each week as children with simple CHD or reference data from Canadian children (Colley et al., 2017). They also have similar capacity for submaximal exercise at a standardized heart rate of 150 bpm, suggesting that children with cardiomyopathy may have the ability to perform PA at a level similar to other children seen in a cardiac clinic, despite PA restrictions and their perception of disease-centred barriers to physical activity participation. Given the very small number of participants in this study, our results must be considered preliminary. Given the small and moderate effect sizes found among MVPA and submaximal exercise capacity outcomes, and that age differed significantly between study groups, future multi-site research is required to elucidate our results with a more representative sample.

3.5.1 How active are children with cardiomyopathy in comparison to other children?

The present study found no statistically significant differences in daily MVPA between children with cardiomyopathy, G+P-, simple CHD or data for Canadian children (Colley et al., 2017). Previous studies have demonstrated that children with CHD are significantly less active

than their healthypeers (Massin, Hovels-Gurich, Gerard, Seghaya, 2006; McCrindle et al., 2007). The small effect size for lower amounts of MVPA in the simple CHD and cardiomyopathy groups suggests that a larger study of children with cardiomyopathy may find that they are also less active than their peers. The lack of significant difference in MVPA between groups of cardiac patients agrees with previous studies that demonstrated MVPA/week did not differ based on CHD diagnosis (Banks et al., 2017) or severity (Voss et al., 2017). The mean MVPA/day achieved in the present study (48.2 minutes/day) is also similar to previous reports (49 minutes/day) among children with mild, moderate, or severe CHD or who have undergone cardiac transplant (Voss et al., 2017). Although our sample is small, the results obtained align with the existing literature and suggest that children with cardiomyopathy may have levels of MVPA similar to other pediatric cardiac patients.

The high proportion of children with cardiac disease who do not meet the recommended guideline for daily physical activity (72.3%) is of concern, and indicates that most of these children are at risk for the negative health outcomes associated with inactivity. Physical inactivity creates a situation that may worsen someone's state of health. As health declines, it typically leads to a further reduction in physical activity and thus a detrimental cycle of inactivity. Inactivity is associated with adverse co-morbidities and serious cardiovascular effects, leading to an increased mortality in the general population (Reineck et al., 2013). Of particular concern is the fact that such negative health outcomes may be magnified in patients who already have the burden of cardiovascular disease. These children may have abnormal hemodynamic adaptations to exercise, such as reduced stroke volume and ventricular dysfunction (Rhodes, Tikkanen and Jenkins, 2010). Reduced cardiac output will result in higher heart rates or a greater arterial-venous oxygen difference in order to ensure that there is adequate oxygen delivery to the working muscles. Since

heart rate and oxygen extraction are ultimately limited, children with cardiomyopathy may not be able to sustain endurance exercise and vigorous workloads, where health benefits and improvements in cardiorespiratory fitness are typically achieved (Takken et al., 2011). In adults with cardiomyopathy, inactivity has been associated with atherosclerosis, hypertension, and diabetes mellitus; conditions which are confounding variables that can severely impact myocardial function (Lee et al., 2017).

Data for Canadian adults indicates that only 15% achieve the 150 minutes of PA recommended on a weekly basis (Colley et al., 2011a). Similar levels of physical inactivity (12% meeting the guidelines) have been reported among adults living with cardiomyopathy (Sweeting et al., 2016). Reineck and colleagues (2013) reported that adults with cardiomyopathy perform on average 2.1 hours of moderate of PA per week. These results suggest that adults with cardiomyopathy have inactive lifestyles in a pattern similar to healthy adults. Given the similarity in PA participation among our study participants and healthy Canadian children (Colley et al., 2017), our data suggest that children with cardiomyopathy may be just as likely as healthy children to move into a "cycle of inactivity" as they get older.

3.5.2 Do children with cardiomyopathy have sufficient exercise capacity for PA?

Maximal exercise testing has demonstrated reduced exercise capacity, specifically a reduced $\dot{V}O_{2peak}$, in adult patients with various classifications of cardiomyopathy (Frenneaux et al., 1989; Jones et al., 1998; Lele et al., 1995; Sharma et al., 2000; Somarriba et al., 2008). The reduced exercise capacity is often caused by the thickened septal wall that physically obstructs or limits LV outflow (Lipshultz et al., 2013b). In DCM patients, LV dilation and thinning of the interventricular septum can result in contractility deficits (Lipshultz et al., 2013b). Hypertrophic/dilated ventricles cause a reduction in cardiac output and inadequate oxygen delivery

to skeletal muscle during bouts of high intensity exercise resulting in exercise intolerance (Lele et al., 1995). We examined submaximal exercise capacity among children with cardiomyopathy, hypothesizing that it would provide a more appropriate measure of whether the child had the cardiopulmonary function relevant to a physically active lifestyle (McManus and Leung, 2000). At submaximal exercise intensities, a lower submaximal $\dot{V}O_2$peak or HR for a given workload is indicative of greater physical fitness (Thompson, Gordon, Pescatello, 2010). The present study also found that submaximal aerobic exercise capacity (i.e. $\dot{V}O_2$ at 150 bpm) was similar among study groups. This finding suggests that a limited cardiac output may not have a drastic impact on oxygen consumption at moderate intensities among children with cardiomyopathy.

Our participants with cardiomyopathy achieved, on average, an estimated 4.5 ± 3.1 METs at a heart rate of 150 beats/min. Since moderate PA is defined as 3-6 METs (Dencker and Anderson, 2011; Maron et al., 2004) or activities producing a heart rate of 140-160 bpm (Allor and Pivarnik, 2000), children with cardiomyopathy may have the capacity to perform a variety of sports and physical activity that are of moderate intensity. Moderate intensity activities, including but not limited to hiking, swimming, doubles tennis, free play (i.e. Frisbee, catch) (Butte et al., 2017), could be performed. Unfortunately, the current study was limited to 5 minutes of activity at a moderate workload and this may be insufficient to understand whether an individual with cardiomyopathy can sustain a moderate level of PA in the community.

Current expert consensus guidelines restrict individuals with HCM from participating in most high intensity recreational PA (Maron et al., 2004). Results from this study suggest that, on average, children with cardiomyopathy could participate in moderate intensity PA which is in line with the current recommendations (Maron et al., 2004; Pelliccia et al., 2005). If children with cardiomyopathy undergo routine submaximal exercise testing, their capacity for sustained aerobic

activity (<60-70% of maximum) can be determined. Clinicians can utilize knowledge of a patient's submaximal exercise performance to reassure patients and their families about the patients' ability to be physically active (Longmuir et al., 2013). Specifically, comparing the patient's capacity for exercise to the activity intensities specified in the Youth Compendium of Physical Activities (Butte et al., 2017) could potentially provide children with cardiomyopathy and their families with more specific information about appropriate types of physical activity. This could prove valuable by encouraging children with cardiomyopathy to focus on activities that are recommended, rather than activities that are restricted as has been reported among adults with HCM (Sweeting et al., 2016).

A small correlation between submaximal exercise capacity and daily MVPA was found, with the $\dot{V}O_2$ achieved at 150 bpm decreasing as daily-time spent in MVPA increased. In the general population, it is often assumed that PA and fitness are strongly related (Rowland, 2017). However, a systematic review suggests that most studies in children and adolescents have shown no significant relationship between PA and aerobic fitness, while a few have shown modest correlations similar to what was observed in this study (Morrow & Freedson, 1994). In children with CHD, studies examining the relationship between PA and exercise capacity have also shown conflicting results. Among children with repaired CHD (i.e. ASD, transposition of the great arteries, tetralogy of Fallot and Fontan), greater MVPA levels were associated with a greater predicted peak $\dot{V}O_2$ (Banks et al., 2017), while other research in Fontan and CHD populations has suggested that PA level is not be related to exercise capacity (Arvidsson et al., 2009; McCrindle et al., 2007). It is important to note that these studies have measured maximal and peak $\dot{V}O_2$ rather than submaximal exercise capacity. One study among Fontan patients found that MVPA was not associated with submaximal $\dot{V}O_2$ z-score (Banks et al., 2013). In line with previous findings in

healthy children, submaximal exercise capacity does not appear to be a reliable indicator for MVPA for children with cardiomyopathy. Additional research with a larger sample size is required to confirm these findings

3.5.3 What are the barriers to PA for children with cardiomyopathy?

Study participants reported various PA barriers including parental and teacher restriction, fear of injury, shortness of breath and lack of self-efficacy for PA. These findings align with previous research among children with CHD, who often report low levels of self-efficacy and perceived confidence for PA (Moola, Faulkner, Kirsh and Kilburn, 2008; Moola, McCrindle and Longmuir, 2009; Voss et al., 2017). Parental overprotection and exclusion by teachers in physical education class are also prominent barriers that may impede PA participation for children with CHD (Moola, Faulkner, Kirsh and Kilburn, 2008). Interventions that target barriers to participation in physical education class should be evaluated, given the physical, psychological, and social health benefits of increased PA during school hours (Smedegaard, Christiansen, Lund-Cramer, Bredahl and Skovgaard, 2016).

The barriers described by children with cardiomyopathy often focused on consequences as a result of their disease. They reported overprotection by parents and teachers, fear or injury, and physical limitations such as shortness of breath. These barriers are consistent with the barriers reported by adults with HCM, such as “I was advised not to exercise”, “I might get injured or damage my health”, “pain interferes with my exercise” and “my health isn’t good enough” (Sweeting et al., 2016). These disease-focused barriers were not reported among our G+P- participants, who focused primarily on barriers such as having an inactive family, a lack of time and low motivation for PA. The barriers described by our G+P- participants are more consistent with data on the barriers to PA among healthy youth (Allinson, Dwyer and Makin, 1999; Gunnell,

Brunet, Wing and Belanger, 2015). Together these results suggest that children with cardiomyopathy and their families identify barriers unique to their medical condition, and may benefit from targeted PA interventions in addition to more general supports for an active lifestyle.

3.5.4 Does age have an influence on MVPA, submaximal exercise capacity and PA barriers?

Given that age differed significantly between study groups, such that cardiomyopathy patients were significantly older, it is important to consider the influence of age on the study results. Research has shown that MVPA participation decreases as age increases. Specifically, among Canadian children, 6- to 11-year-olds accumulate more MVPA per day (62 minutes) than 12- to 17-year-olds (48 minutes, Colley et al., 2017). In the present study, a small effect size (Cohen's d=0.41) demonstrated that participants aged 5 to 11 years-old accumulated more minutes of daily MVPA (52.2 ± 14.6), in comparison to participants aged 12 to 17 years (44.2 ± 22.8). This trend can be seen in the older cardiomyopathy group (14.2 ± 2.7 years), where participants achieved on average 47.6 ± 27.2 minutes of daily MVPA. The activity of the older cardiomyopathy patients is consistent with the 48 minutes of daily MVPA reported among participants aged 12-17 (Colley et al., 2017). The younger CHD (9.4 ± 3.8 years old) and G+P- (9.2 ± 2.8 years old) groups achieved much lower daily MVPA than the reported 62 minutes per day for children 6- to 11-year- olds (Colley et al., 2017), though this finding was not significantly different. These results suggest that the difference in age between groups might be an important factor that could explain the lower MVPA participation among the cardiomyopathy group. Similarly, normative values for children with innocent heart murmurs suggest that oxygen uptake at a given workload decreases with age (Cumming, Everatt, Hastman, 1978). This may suggest that the cardiomyopathy patients were more comparable to the simple CHD group in terms of submaximal exercise capacity. However,

a larger sample size consisting of age-matched groups would be needed in order to more accurately understand differences between cardiomyopathy, simple CHD and G+P- patients.

Age may also be a factor in how participants perceive PA barriers. Children commonly report a lack of interest, a lack of time and environmental barriers such as bad weather or no equipment as barriers that impede PA (Zabinski, Saelens, Stein, Hayden-Wade, Wilfley, 2003). These barriers are also commonly reported among adolescents (Gunnell, Brunet, Wing & Bélanger, 2015). In addition, adolescents often report a lack of enjoyment and negative attitudes as barriers that impact their PA participation (Allison, Dwyer, & Makin 1999; Gunnell, Brunet, Wing & Bélanger, 2015). As children age, social support and peer influences become increasingly more important for PA participation (Bungum and Vincent, 1997). This idea was seen in the older cardiomyopathy group, where having inactive friends was seen as a common psychosocial barrier to PA. In the younger G+P- group, commonly reported barriers included a low motivation, lack of self-efficacy, a lack of time and a preference to pursue other activities (i.e. reading, videogames). These barriers seem to be consistent with previously reported research among younger children (Zabinski, Saelens, Stein, Hayden-Wade, Wilfley, 2003). Taken together, these results suggest that the significant age difference between study groups could have had an influence on the study outcomes.

3.5.5 Strengths and limitations

Exercise recommendations for children with cardiac diagnoses are often extrapolated from the results of a maximal cardiopulmonary exercise test (Takken et al., 2011). A strength of the present study was the use of an intermittent submaximal exercise protocol to indirectly measure the submaximal exercise capacity relevant to a child's every dayactivities (McManus and Leung, 2000). PA barriers were identified using semi-structured interviews, rather than quantitative

surveys. This methodology provided participants with the opportunity to discuss and elaborate on their thoughts and perspectives relating to PA. The mixed-methods approach, which combined quantitative examinations of MVPA and submaximal exercise capacity with the qualitative exploration of PA barriers, provided a holistic perspective of the PA behaviours of children with cardiomyopathy.

The following limitations should be considered when interpreting these study findings. The small sample size limits our ability to generalize or make definitive conclusions. All eligible symptomatic cardiomyopathy (n=9) and G+P- (n=9) patients from a single institution were contacted to participate in this study. However, only half of those patients (n=5 cardiomyopathy, n=5 G+P-) agreed to participate within the brief period available for data collection, and there was a tendency for more female patients to decline participation. The cardiomyopathy patients were older than the simple CHD and G+P- participants. Since physical activity typically declines with increasing age and activity levels were similar across all study groups, the cardiomyopathy participants who volunteered for this study were possibly more active than those who declined participation. During submaximal exercise testing, children were allowed to hold onto the guard rails, which could have reduced the metabolic cost of the work (Gumming et al., 1974). RMR was estimated for study participants using the Schofield equation, and therefore the accuracy of the predicted RMR would impact the calculation of METs performed.

3.6 Conclusion

Despite reporting disease-centered PA barriers, the children with cardiomyopathy in this study may have sufficient submaximal exercise capacity to participate in moderate-intensity activity and active play with peers, potentially enabling the health benefits of an active lifestyle. In addition, healthcare professionals, parents and others caring for children with cardiomyopathy

should continue to encourage these children to participate in 60 minutes of moderate PA per day to achieve the physical and mental health benefits of PA. All study participants had physical activity levels similar to those reported for healthy peers, although the lack of statistically significant effects may be due to the small sample size. This pilot study offers preliminary data on the physical activity and exercise capacity of children with or at risk for cardiomyopathy from a single institution. A larger multi-site trial is recommended to examine the physical activity capacity of a more representative sample of these patients.

3.7 Acknowledgements

The support of participating families and contributions of the cardiology clinic staff, specifically, Denise Melo and Tyler Kung for assistance during exercise study assessments, your help is greatly appreciated. The Ontario Trillium Foundation (Grant number: SD99638) funded this study. Kevin Moncion was supported by the University of Ottawa and the Ontario Trillium Foundation.

3.8 Tables and Figures

Table 3.8.1. Descriptive characteristics of study participants.

Characteristics	
N	18
Cardiomyopathy	5 (HCM=2; DCM=2; CCM=1)
Age*	14.2 ± 2.7 years*
Female	2
Height (cm)*	150.4 ± 27.6*
Weight (kg)*	48.9 ± 21.8*
Documented PA restrictions	2
Simple CHD	8 (Repaired ASD=4, ASD not treated=4)
Age*	9.4 ± 3.8*
Female	4
Height (cm)*	130.1 ± 41.0*
Weight (kg)*	34.5 ± 18.0*
Documented PA restrictions	0
G+P-	5
Age*	9.2 ± 2.8*
Female	3
Height (cm)*	138.4 ± 15.6*
Weight (kg)*	39.9 ± 17.3*
Documented PA restrictions	0

*Data on age, height and weight are presented as mean ± standard deviation.
Abbreviations: HCM=hypertrophic cardiomyopathy; DCM=dilated cardiomyopathy; CCM=chemotherapy-induced cardiomyopathy; PA=physical activity; CHD=congenital heart disease; ASD=atrial septal defect; G+P-=genotype-positive phenotype-negative for genetic cardiomyopathy.

Figure 3.8.1 Participant flow chart

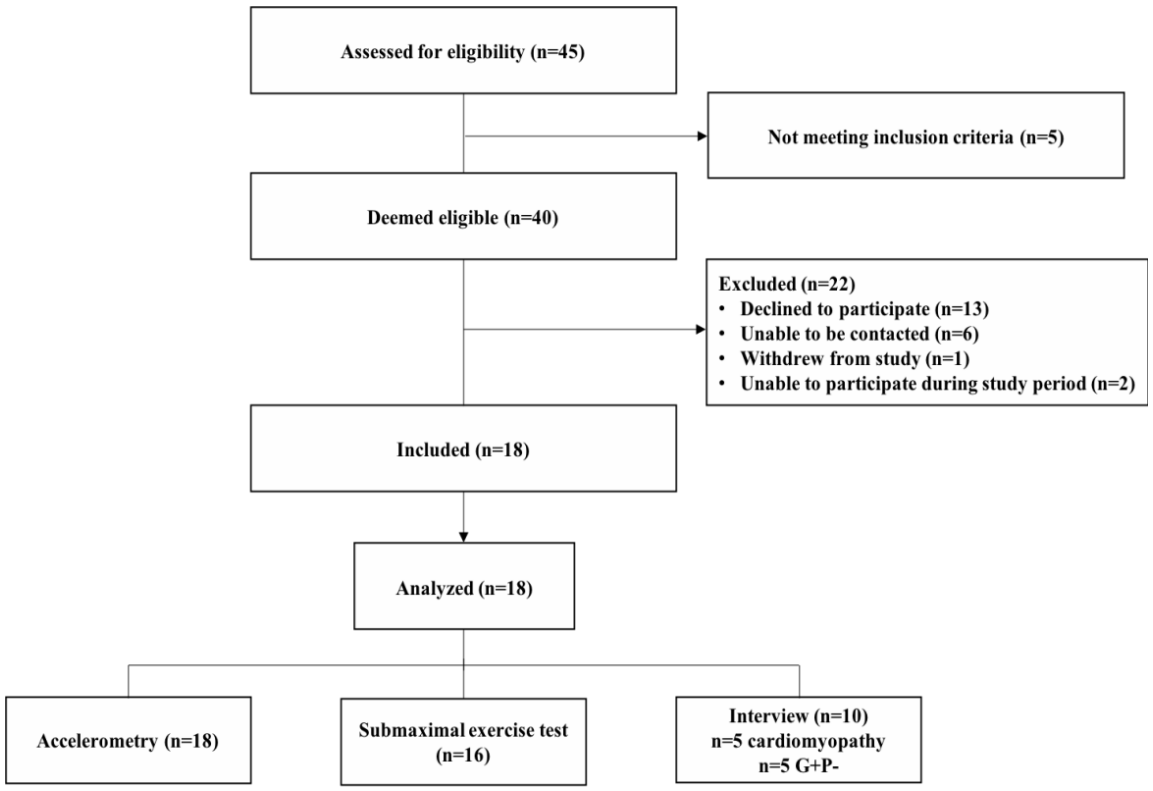
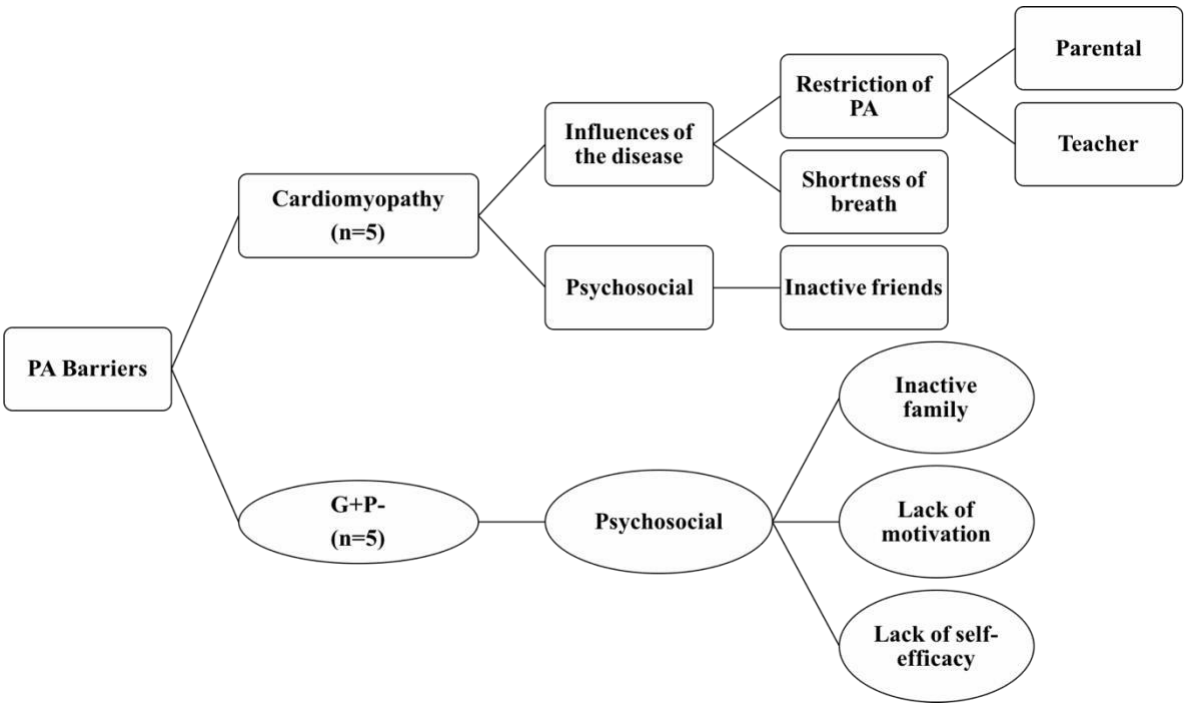


Table 3.8.2 Submaximal aerobic exercise capacity measures and physical activity by study group.

Variable	n	Cardiomyopathy	n	CHD	n	G+P-	η^2	*p*
Stage 1								
HR	4	120.4 ± 16.2[a]	8	119.8 ± 10.9 [a]	4	132.4 ± 9.3 [b]	0.19	.25
$\dot{V}O_2$/kg/min	4	16.2 ± 4.1 [a]	7	15.8 ± 3.7 [a]	4	19.3 ± 2.4 [b]	0.18	.31
RER	4	0.92 ± 0.6	7	0.91 ± 0.9	4	0.91 ± 0.06	0.003	.98
Stage 2								
HR	4	136.1 ± 14.8 [a]	8	130.3 ± 11.8 [b]	4	143.8 ± 8.6 [c]	0.21	.22
$\dot{V}O_2$/kg/min	4	21.1 ± 5.0	7	20.1 ± 3.5	4	22.5 ± 2.6	0.081	.60
RER	4	0.95 ± 0.03	7	0.94 ± 0.07	4	0.94 ± 0.04	0.006	.96
Stage 3								
HR	4	154.8 ± 23.8[a]	8	147.8 ± 19.8[b]	4	164.1 ± 11.4[c]	0.13	.41
$\dot{V}O_2$/kg/min	4	27.2 ± 9.5	7	25.5 ± 6.2	4	27.6 ± 2.7	0.025	.86
RER	4	1.00 ± 0.05	7	1.00 ± 0.08	4	1.00 ± 0.06	0.001	.99
Stage 4								
HR	1	147.5[a]	4	164.9 ± 17.2[b]	1	161.5[b]	0.21	.69
$\dot{V}O_2$/kg/min	1	38.5	3	32.0 ± 4.3	1	27.6	0.62	.38
RER	1	1.00	3	1.08 ± 0.07	1	1.00	0.35	.65
Peak Values								
HR	4	161.8 ± 20.3[a]	7	166.6 ± 21.9[b]	4	177.2 ± 11.3[c]	0.10	.52
$\dot{V}O_2$/kg/min	4	30.2 ± 12.4	7	31.6 ± 7.2	4	30.9 ± 4.6	0.007	.96
RER	4	1.02 ± 0.03	7	1.06 ± 0.09	4	1.07 ± 0.04	0.10	.53
Estimated Values								
$\dot{V}O_2$ 150 bpm	4	25.8 ± 10.2	7	25.4 ± 4.8	4	24.1 ± 1.1	0.015	.91
RMR	4	6.6 ± 1.8[a]	7	5.2 ± 1.5[b]	4	5.9 ± 1.5[c]	0.14	.41
METs 150 bpm	4	4.5 ± 3.1	7	5.2 ± 1.7	4	4.3 ± 0.9	0.046	.76
MVPA/week	5	333.3 ± 190.2	8	320.2 ± 114.1	5	368.9 ± 120.4	0.025	.82
MVPA/day	5	47.6 ± 27.2	8	45.7 ± 16.3	5	52.7 ± 17.2	0.025	.82

Data have been presented as mean ± standard deviation where appropriate. Superscript letters indicate where the groups differed for moderate and large effect sizes. Abbreviations: RMR=resting metabolic rate; HR=heart rate; $\dot{V}O_2$/kg/min=oxygen consumption per kilogram per minute; $\dot{V}O_2$ 150 bpm=oxygen consumption at a heart rate of 150 beats/min; RER=respiratory exchange ratio; MVPA/week=moderate to vigorous physical activity per week in minutes; MVPA/day=moderate to vigorous physical activity per day in minutes. MET= metabolic equivalent group

Figure 3.8.2 Physical activity barriers by study group



Data have been presented as keywords among themes developed during the thematic analysis for both study groups. The cardiomyopathy group includes 2 participants with HCM, 2 participants with DCM and 1 participant with CCM. Abbreviation: G+P-, genotype-positive phenotype-negative.

3.9 List of Abbreviations

ASD	Atrial septal defect
bpm	Beats per minute
CCM	Chemotherapy-induced cardiomyopathy
CHD	Congenital heart disease
CHEO	Children's Hospital of Eastern Ontario
cm	Centimetre
CSEP	Canadian Society for Exercise Physiology
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
G+P-	Genotype-positive phenotype-negative
HCM	Hypertrophic cardiomyopathy
HR	Heart rate
kg	Kilogram
METs	Metabolic equivalents
MVPA	Moderate to vigorous physical activity
PA	Physical activity
RER	Respiratory exchange ratio
RMR	Resting metabolic rate
RPE	Ratings of perceived exertion
SD	Standard deviation
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2\ peak}$	Peak oxygen consumption

3.10 Declarations

Ethics approval and consent to participate
Obtained from the Children's Hospital of Eastern Ontario Research Ethics Board (REB study #17/189x) and the University of Ottawa (H-04-18-461)

Competing interests
The authors declared no conflicts of interest.

Funding
This study was funded by the Ontario Trillium Foundation (SD99638).

Author's Contribution
AUTHORS' STATEMENT
KM – Conceptualization, methodology, analysis, writing – manuscript writing, review and editing
JL – Analysis, writing – review and editing
LG – Analysis, writing – review and editing
KA – Methodology, analysis, writing – review and editing
PEL – Conceptualization, methodology, analysis, writing – manuscript writing, review and editing

CONFLICT OF INTEREST
None.

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3.12 Appendix I

Interview guide

1. What do you like to do in your free time?
    - For example, I like to play sports with my friends, like hockey and basketball, but sometimes I also like to relax and watch tv.
    - What do you like to do when you get home from school?
    - What do you like to do on the weekends?

2. How often do you do physical activity? (for young children, do you do things that make you breathe harder):
    - Are you active (walking, riding your bike, swimming, playing in the park, etc.) at home? Everyday? Sometimes?
    - Are you active at school or daycare? Everyday? Sometimes?
    - Do you play sports or games? Everyday? Sometimes?
    - Elsewhere?

3. Are there any things that make it difficult for you to do physical activity?
    - Is it difficult because you don't have the equipment?
    - Maybe you don't have anyone to be active with?
    - Or don't know how what activities your allowed to do?
    - Is it difficult when the activity is too expensive?

4. What would make it easier for you to do more physical activity?
    - Is it easier if you have friends to be active with?
    - Do your parents or teachers encourage you be active?

5. Are there any activities that you see others doing that you would like to do?
    - Why don't you do those activities?
    - In gym class? Or at recess?
    - Is it because you don't know how to do those activities?

6. Does anything prevent you from participating in physical activity?
    - Does your doctor help you be active?
    - Do you have time after school?
    - Is it because you would rather do other things?
    - Not enough energy?

7. Is there an activity that you've always wanted to try but haven't? For example, I have always wanted to learn how to downhill ski.
    - Are there any activities/sports you see on TV that you would like to try?
    - Are there any activities/sports that your siblings/friends do that you would like to try?
    - Why not? Why haven't you tried this activity?

8. What types of activities do you like to do with your friends?
    - What do you do with your friends when they come over?
    - What do you do when you go to your friend's house?
    - What makes it hard for your friends to be active with you?
    - Do they have a lot of homework?
    - Are they busy with sports teams or lessons?

9. What types of activities do you do with your family?
    - What do you do at your house?
    - What do you do outside?
    - Do you parents play with you? Or do they usually just relax with you?

10. What makes it hard for your parents to be active with you?
    - Do they have to work a lot?
    - Are they busy with sports teams or lessons?

Part 4: Global Discussion

4.1 Summary of Key Findings

The goal of the present thesis was to investigate whether children with cardiomyopathy require support for an active lifestyle, if they face barriers to PA, and whether they have the functional capacity for physically active lifestyles. In order to provide a preliminary direction for future research, the following research questions were addressed: 1) how physically active are children with cardiomyopathy? 2) Do children with cardiomyopathy have the exercise capacity to participate in PA? Lastly 3) are children with cardiomyopathy faced with disease-centered PA barriers? Children in this study did not have significantly lower MVPA than children with simple CHD, children who are G+P- or data for Canadian children (Colley et al., 2017). Although, a larger sample size would allow for more robust analyses to test these statistical hypotheses. On average, most of the study participants had sufficient submaximal exercise capacity to perform moderate PA (i.e. 3 to 6 METs. Children with cardiomyopathy, in comparison to children who are G+P-, reported disease-specific barriers that could hinder PA participation in some individuals. These results suggest that: 1) perceived barriers may not be sufficient to reduce PA compared to peers, 2) it can be speculated that health risks of an inactive lifestyle are important because inactivity is below the recommended level, 3) children with cardiomyopathy may have the capacity to participate in moderate PA, however it remains unknown how long these children can sustain this level of intensity.

4.2 What are the Limitations in the Present Study?

In light of the findings, it is important to discuss the limitations and potential biases that might have influenced the results in the present study. To begin, the largest limitation to the present

study is the small sample size. The present study suggest that on average, children with cardiomyopathy do not differ significantly between study groups in terms of MVPA and submaximal exercise outcomes. Although small to moderate effect sizes demonstrate mean differences between study groups, a larger sample size is required to display statistically significant differences between MVPA and submaximal outcomes (i.e. HR, $\dot{V}O_2$, and RER) by study groups. In terms of methodological limitations, the indirect measurement of submaximal exercise capacity is a limitation, given that it only provides a limited perspective regarding the submaximal exercise capacity of study participants.

In terms of potential biases, of those assessed for eligibility (*n*=45, Figure 3.8.1), 11% (*n*=5), were deemed ineligible to participate by their responsible cardiologist. Reasons for ineligibility included having a syndrome known to impact motor skill development (*n*=1 HCM), recent cardiac catherization (*n*=1 G+P-), residing in a different country (*n*=1 CCM), patient discharged to an adult institution (*n*=1 HCM) and eligibility not approved by the responsible cardiologist (*n*=1 ASD). At the Children's Hospital of Eastern Ontario, only nine participants (n= 9 out of 12) were deemed eligible to participate and only 5 were able to participate in the current study. Therefore, the small sample size limits the generalizability of the study findings.

For those deemed eligible for study participation (*n*=40), 55% (n=22) were excluded from study participation. Thirty-three percent declined study participation (n=13 out of 22). Common reasons for declining study participation included having a parent that was unwilling or unable to provide transportation to the study location (*n*=5) and the child not being interested in participating in PA research (*n*=3). The latter could have also resulted in volunteer bias, where there could be a systematic difference between individuals who volunteered to be part of the study and then those

from the population who did not. Given the rarity of these conditions (i.e. cardiomyopathy and G+P-), this bias could be noteworthy. Other reasons for exclusion included, unable to be contacted (n=6/22), unable to participate during study period (n=2), and withdrawal from study participation (n=1).

The collection of qualitative data in the present study could have been prone to ascertainment bias. Such bias could have occurred during the semi-structured interviews, and could have originated from the principle investigator or the participants (Sedgwick, 2015). In terms of the investigators, assessment bias could have taken place given that the lead author conducted all 10 interviews, and that interview guide was created by the authors to specifically explore the barriers to PA. In terms of the response bias of participants, having the presence of a parent in the room during some interviews may have limited the full scope of participant responses. During data collection, it was originally planned to have all participants conduct the submaximal exercise test prior to the PA barriers interview, however due to extraneous circumstances (i.e. scheduling conflicts and emergency exercise stress-tests) not all interviews took place before the exercise test. Unfortunately, this information was not systematically captured in the present study. It could be speculated that participants who completed the submaximal testing prior to the interview felt more confident and therefore could have reported less PA barriers. In contrast, some children might have been nervous or scared to participate in the exercise test, which could influence the participant's responses during the interviews. Future research should investigate whether this in itself could have resulted in response bias.

4.3 Future Research Directions

Given this research was a pilot study; there are many ways to extend the findings of this research. Firstly, it would be beneficial to build on this study with a larger multi-site project so that the findings could be more generalizable to the population of children with cardiomyopathy. A larger sample size would also allow for more robust statistical and qualitative analyses. Further, a longer study period would allow for one to consider seasonality differences. Given that the study data collection occurred primarily in the spring and summer, it would be important to conduct a year-round study to determine the environmental impacts (i.e. hot or cold environments) on PA and exercise capacity in children with cardiomyopathy. Finally, the present study found that children with cardiomyopathy can safely exercise at moderate intensities. Future research should examine whether these patients have the capacity to sustain moderate exercise in order to engage in an exercise training program. Potential outcomes of exercise training would be hypothesized to include an improvement in exercise capacity ($\dot{V}O_2$) or METs achieved, MVPA or cardiac dimensions.

4.4 Conclusion

The study results provide preliminary but novel information for clinicians and families caring for children with cardiomyopathy, suggesting that despite disease-centered PA barriers, children with cardiomyopathy have sufficient submaximal exercise capacity to participate in moderate-intensity activity and active play with peers. Encouraging these children to adopt and maintain a physically active lifestyle would enable the physical and mental health benefits of an active lifestyle. Given that adults with cardiomyopathy live physically inactive lifestyles and suffer from comorbidities that impact cardiac function, it is important for children with cardiomyopathy

to develop strong PA habits during childhood as it could have positive implications for their physical and psychosocial health over the short and long term.

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