

**Submaximal Exercise Capacity is Associated with Moderate-to-Vigorous Physical Activity
in Children with Complex Congenital Heart Disease**

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Abstract

Background: Children with complex congenital heart disease (CHD) are exposed to cyanosis from birth until their surgical repair and are often not expected to participate in physical activities to the same extent as healthy peers because of a limited maximal exercise capacity ($\dot{V}O_{2\max}$). Despite limitations in $\dot{V}O_{2\max}$, these children may still have the capacity to perform most daily physical activity because it requires only a submaximal effort. The purpose of this research was to examine the relationships between submaximal exercise capacity, daily physical activity and cyanosis exposure, in children with complex CHD.

Methods: Children with a single functioning ventricle (Fontan), tetralogy of Fallot or transposition of the great arteries, 10 to 17 years old were deemed eligible. The Bruce treadmill protocol with breath-by-breath analysis of oxygen consumption was used to assess submaximal exercise capacity. Five measures of submaximal exercise capacity were evaluated: energy consumption ($\dot{V}O_2$) at the ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 beats per minute (bpm), metabolic equivalents (METs) at ventilatory threshold, METs at 130bpm and heart rate at stage 1 of the Bruce protocol. Moderate-to vigorous physical activity (MVPA) was measured (Actical accelerometer with 15 second epochs) for 7 consecutive days. Exposure to cyanosis was calculated by subtracting the child's date of birth from the date of surgical repair.

Results: Participants were children with a Fontan single ventricle (n=5), tetralogy of Fallot (n=4) or transposition of the great arteries (n=7). Daily physical activity was positively associated with $\dot{V}O_2$ at ventilatory threshold ($r = 0.78$, $n = 16$, $p = < 0.01$) and $\dot{V}O_2$ at a heart rate of 130 bpm ($r = 0.61$, $n = 16$, $p = 0.01$). Children who did more than 60 minutes of physical activity per day (n=4) achieved significantly higher energy expenditure before reaching ventilatory threshold, (95% CI of the difference [8.23, 24.85], $t(14) = 4.27$, $p = < 0.01$) and at a heart rate of 130 bpm

(95% CI of the difference [1.61, 14.33], $t(14) = 2.69$, $p = 0.02$). Lastly, $\dot{V}O_2$ at ventilatory threshold was negatively associated with days spent in cyanosis ($r = .55$, $n = 16$, $p = 0.03$),

Conclusion: Higher $\dot{V}O_2$ at ventilatory threshold and $\dot{V}O_2$ at a heart rate of 130 bpm was associated with more daily minutes spent in moderate-to-vigorous physical activity. These results suggest that children who meet the recommended 60 minutes of MVPA would have a higher submaximal exercise capacity ($\dot{V}O_2$ at ventilatory threshold or a heart rate of 130 bpm), than children who did not meet the MVPA guidelines. Lastly, children who were exposed to cyanosis for a longer period of time had a lower submaximal $\dot{V}O_2$ at ventilatory threshold, than children who were exposed to cyanosis for a shorter period of time.

List of Abbreviations and Acronyms

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
bpm	Beats Per Minute
CEP	Certified Exercise Physiologist
CHD	Congenital Heart Disease
CHEO	Children's Hospital of Eastern Ontario
cm	Centimeters
CSEP	Canadian Society of Exercise Physiology
ECG	Electrocardiogram
HALO	Healthy Active Living and Obesity
HR	Heart Rate
kg	Kilogram
METs	Metabolic Equivalents
mph	Miles per hour
MVPA	Moderate-to-Vigorous Physical Activity
ON	Ontario
PA	Physical Activity
PA _{CO2}	Partial Pressure of Arterial Carbon Dioxide
RER	Respiratory Exchange Ratio
RMR	Resting Metabolic Rate
RPE	Rating of Perceived Exertion
SD	Standard Deviation
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
VO ₂	Oxygen Consumption
VO _{2max}	Maximal Oxygen Consumption
VO _{2peak}	Peak Oxygen Consumption
VT	Ventilatory Threshold
VSD	Ventricle Septal Defect

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Part 1: Introduction

Congenital heart disease (CHD) is diagnosed in 1.3% (13/1000) of children, typically in their first year of life (Marelli et al., 2014). The focus for this thesis will be the examination of children with complex CHD. Decades ago, the majority of affected children would not survive into adulthood (Klausen et al., 2015) because of the inadequate methods of treating CHD. With improvements in clinical care, the life expectancy of patients with CHD has greatly increased (Moons, Bovijn, & Budts, 2010). Care has improved to the extent where the proportion of children with complex CHD has increased by 19% in Canada, since 2010 (Marelli et al., 2014). With improved survival, it is increasingly important for children and adults with complex CHD to be physically active to improve or maintain their health and quality of life (Longmuir et al., 2013).

Although the importance of physical activity (PA) is recognized, children born with complex CHD are often not expected to participate in physically active play with peers to the same extent as healthy children. The rationale for these reduced expectations is based on research that indicating that children with complex CHD have limited capacity for maximal exercise (Banks, McCrindle, Russell, & Longmuir, 2013; Brassard et al., 2006; Glaser et al., 2004; McCrindle et al., 2007; Takken et al., 2007). Currently, children with complex CHD often receive counselling and advice that is focused on prescribing physical activity based on the children's maximal exercise capacity. It is possible that these children are told that their performance may be limited in comparison to healthy children (Takken et al., 2007) if the result of a maximal exercise test indicated they have a reduced maximal capacity. If the child receives information regarding a reduced exercise capacity, they may be dissuaded them from engaging, or they could adjust their expectations for participating in active play, sports, and exercise with

their healthy peers. Although maximal exercise tests can evaluate aerobic capacity at the limit of physical capacity, such testing may not be directly relevant to childhood play with peers because most daily physical activity is performed using a submaximal effort.

While submaximal exercise capacity is most relevant to participation in active play, there are limited research data regarding the submaximal exercise capacity of children born with complex CHD. Knowledge of this relationship could potentially provide clinicians with an indicator of whether each patient can engage in physical activity with their peers.

Children born with complex CHD are also exposed to cyanosis, which depending on the type of CHD may occur for several days up until two to three years (Bailliard & Anderson, 2009; Brassard et al., 2006; Martins & Castela, 2008). Although a history of prolonged exposure to cyanosis may further reduce expectations for the child's exercise capacity, it is possible that early exposure to cyanosis may have a physiological benefit on submaximal exercise capacity. Hypothetically, if the prolonged hypoxic state resulted in an increased ability to extract oxygen from the blood or an increased capacity to transport oxygen within the blood, it would offer a potential explanation for the few reports of normal or enhanced exercise capacity at submaximal workloads among children with complex CHD (Banks et al., 2013). However, there are limited data and research on the potential benefits or physiological change that may occur in these patients who are exposed to cyanosis.

1.1 Research Goal and Objectives

Based on the above, the goal of this research was to more thoroughly examine the submaximal exercise capacity of children born with complex CHD, and to examine the relationships between exercise capacity, daily physical activity and cyanosis exposure among these children. Specifically, this research addressed the following objectives:

Primary Objective:

1. To determine whether there was a relationship between moderate to vigorous physical activity among children with complex CHD and their submaximal exercise capacity, defined as the $\dot{V}O_2$ at ventilatory threshold.
 - a. It was hypothesized that children with a higher submaximal $\dot{V}O_2$ at ventilatory threshold would perform more daily moderate to vigorous physical activity.

Secondary Objectives:

2. To evaluate whether the measurement of submaximal exercise capacity could be a reliable clinical indicator of the daily PA of children with complex CHD.
 - a. It was hypothesized that children who met the recommended 60 minutes of moderate-to-vigorous physical activity per day would have a higher submaximal energy utilization than children who do not meet the recommended physical activity guidelines.
3. To evaluate whether exposure to cyanosis during infancy and early childhood is associated with submaximal exercise capacity.
 - a. It was hypothesized that children who were cyanotic for the longest period would utilize less oxygen to perform submaximal exercise than children who were cyanotic for a shorter duration of time.

Part 2: Literature Review

2.1 Classification of Complex Congenital Heart Disease

Congenital heart disease (CHD) describes a range of birth defects affecting the anatomy of the heart (O'Brien & Marshall, 2014). For this thesis, the focus will be children with three diagnoses categorized as complex CHD: i) Univentricular heart – repaired by Fontan circulation, ii) Tetralogy of Fallot – repaired with a bi-ventricular repair, iii) Transposition of the Great Arteries – repaired by arterial switch. (Figure 1)

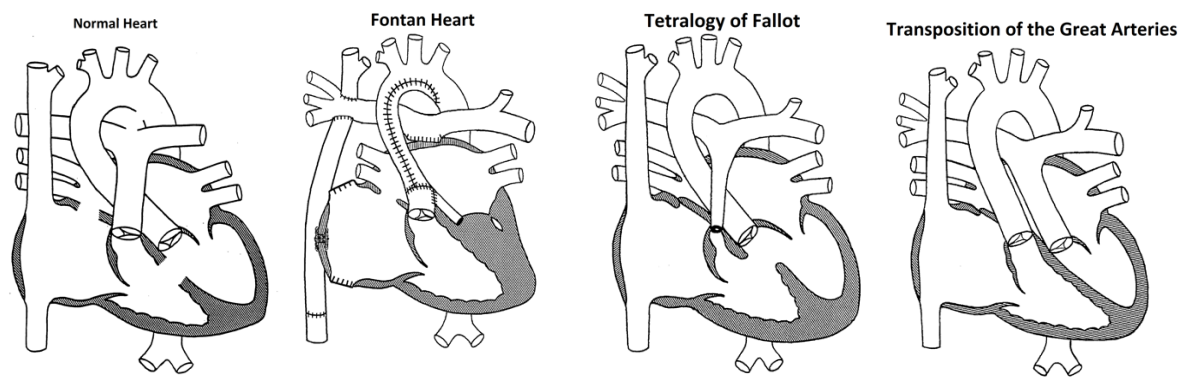


Figure 1. From left to right, the pictures illustrate: 1. A normal heart, 2. A univentricular – Fontan heart, 3. A tetralogy of Fallot heart and 4. A transposition of the great arteries heart. All images were retrieved from (Mullins & Mayer, 1988): “All rights reserved. This book is protected by copyright. No part of it, except brief excerpts for review, may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without permission from the publisher” (Mullins & Mayer, 1988).

2.1.1 Univentricular Heart - Repaired by Fontan Circulation

A univentricular heart is a birth defect that results in one single functioning ventricle. The single ventricle presents several physiological issues including the mixing of oxygen saturated and desaturated blood (Brassard et al., 2006), and the one ventricle pumping blood to both the body and lungs (Gewillig, 2005). This process is inefficient, which results in ventricular overload, a lack of oxygenated blood at rest and during exercise and reduced cardiac output (Gewillig, 2005).

Children born with one single functioning ventricle undergo a three-stage operation (Gewillig, 2005; Nayak & Booker, 2008), referred to as the Fontan procedure for repair (de Leval, 2005; Gewillig, 2005; Goldberg & Paridon, 2014). The first stage of the Fontan procedure is to surgically place a small systemic-pulmonary shunt that allows for additional oxygenation of the blood before it gets delivered to the tissues (Nayak & Booker, 2008). After 2 to 6 months from birth, the second stage (Glenn shunt) can be performed (Nayak & Booker, 2008), which connects the superior vena cava and the pulmonary artery (Fredenburg, Johnson, & Cohen, 2011; Gewillig, 2005; Nayak & Booker, 2008). After 1 to 5 years of age (Gewillig, 2005; Nayak & Booker, 2008), the Fontan procedure can be performed, which attaches the inferior vena cava to the pulmonary artery (Nayak & Booker, 2008). Thus, the three stages are necessary to relieve exposure to the cyanotic state (Gewillig, 2005; Nayak & Booker, 2008) as illustrated in Figure 1. The survival rate into adulthood following the Fontan operation is approximately 80% to 95% (Driscoll, 2007), thus indicating that this operation is successful. Most children live normal lives, attending school and performing low to moderate intensity activities (Gewillig, 2005). Unfortunately, the majority of patients with a Fontan heart will experience a progressive decline in their functional capacity as they reach adulthood (Gewillig, 2005).

2.1.2 Tetralogy of Fallot – Bi-Ventricular Repair

Tetralogy of Fallot (TOF) is a heart defect that results in a limited flow of blood being able to reach the lungs for oxygenation (O'Brien & Marshall, 2014). TOF is a defect combining four related abnormalities (Table 1).

Table 1

The four abnormalities of TOF and their descriptions.

Abnormality/Pathophysiology	Description
1. “Right ventricular outflow tract obstruction (O’Brien & Marshall, 2014)”.	Narrowed pulmonary valve, which causes a decrease in blood flow to the lungs (O’Brien & Marshall, 2014).
2. “Ventricular septal defect (O’Brien & Marshall, 2014)”.	A hole between ventricles, causing mixing of oxygenated and deoxygenated blood (O’Brien & Marshall, 2014). Causes cyanosis.
3. “Overriding of the aorta (O’Brien & Marshall, 2014)”.	The aorta is positioned above the VSD, causing the blood from the right and left ventricle to flow into the aorta and get pushed outwards towards the body (O’Brien & Marshall, 2014).
4. “Hypertrophy of the right ventricle (O’Brien & Marshall, 2014)”.	The right ventricle is bigger than normal because of the increased resistance (O’Brien & Marshall, 2014) to work against.

Note. This information was stated from O’Brien & Marshall, (2014, p.e26).

Most patients with TOF will have their abnormalities repaired by 3 to 6 months of age (O’Brien & Marshall, 2014). One deciding factor for the timing of the surgery is the prevalence of hypercyanotic spells (Tet spells) (O’Brien & Marshall, 2014; Sharkey & Sharma, 2012). Tet spells are episodes where there is a dramatic decrease in the level of oxygen in the blood (Sharkey & Sharma, 2012) resulting from reduced blood flow to the lungs (Bailliard & Anderson, 2009). Tet spells can be triggered when a baby is crying or feeding (O’Brien & Marshall, 2014) because these two tasks can influence an infant’s breathing pattern. Open heart surgery can reduce the abnormalities, improve long-term survival (85% survival rate) and reduce morbidity (Bailliard & Anderson, 2009; O’Brien & Marshall, 2014; Sharkey & Sharma, 2012). The majority of children with TOF are expected to be similar to healthy children in growth, and development as well as the ability to participate in regular daily PA; however many will continue

to have limited exercise capacity and symptoms of decreased heart function (O'Brien & Marshall, 2014).

2.1.3 Transposition of the Great Arteries – Repaired by Arterial Switch

Transposition of the Great Arteries (TGA) is characterised by the aorta being attached to the right ventricle and the pulmonary artery being attached to the left ventricle (see Figure 1) (Martins & Castela, 2008). In normal hearts, there is a continuous flow of blood from the body to the right atrium, then to the lungs for oxygenation and back to the left ventricle for distribution to the body through the aorta. The normal blood flow circuit is not the case for TGA where the anatomical malformation results in two independent closed circuits (Martins & Castela, 2008). The systemic blood flow stays on the right side of the heart, while the pulmonary blood flow stays on the left side of the heart (Martins & Castela, 2008).

In the neonatal stage (Karamlou, 2014; Martins & Castela, 2008; Villafañe et al., 2014; Warnes, 2006), the arterial switch operation is performed to detach the great vessels from the heart and then reattach them in the correct anatomical position. The surgical operation is successful, with a survival rate into adulthood of 90% (Martins & Castela, 2008). However, patients are required to undergo long-term follow-up to monitor potential declines in ventricular function or exercise capacity (Warnes, 2006).

2.2 Exercise Capacity in Children with Complex CHD

Exercise testing is essential to determine the functional limitations of children with complex CHD (Takken et al., 2009; Takken et al., 2007). Exercise tests can provide valuable information about the physiological responses of muscles and organ systems (heart, lungs, skeletal) to different exercise intensities (Takken et al., 2009). An exercise test that measures the maximum rate of oxygen consumed ($\dot{V}O_{2\max}$), through calorimetry, is typically known as the

gold standard (Poole & Jones, 2017). It is however important to distinguish the difference between a $\dot{V}O_{2\max}$ and $\dot{V}O_{2\text{peak}}$. A true $\dot{V}O_{2\max}$ represents the maximal physiological capacity that the body is capable of utilizing under intense exercise. It can be directly determined when there is a plateau in $\dot{V}O_2$ as intensity increases; which is then verified with a supramaximal test at ~110% of work rate (Poole & Jones, 2017). An exercise test that culminates in a measurement of $\dot{V}O_{2\text{peak}}$ may be perceived as a maximal voluntary effort. It is then classified as a peak exercise test because the maximal capacity of the body has not been identified as there is no plateau in $\dot{V}O_2$. However, it is important to note that there is a level of individual variability when it comes to achieving a true $\dot{V}O_{2\max}$. This is highly dependent on the individual's motivational state to push themselves to the point where they are not physically able to continue. It is well known that children with a single functioning ventricle have a lower $\dot{V}O_{2\text{peak}}$ than healthy children (Brassard et al., 2006; McCrindle et al., 2007). Children with TOF and TGA also have a reduced $\dot{V}O_{2\text{peak}}$, but not to the same extent as children with a single functioning ventricle (Banks et al., 2017; Koning & Osch-gevers, 2008; Mahle, McBride, & Paridon, 2002). In children with complex CHD, these limitations are due to different underlying factors that influence their performance.

2.2.1 Factors Influencing the Exercise Capacity of Children with CHD

For this thesis proposal, exercise capacity will be defined as the amount of oxygen consumed ($\dot{V}O_2$, measured in $\text{mL/kg}\cdot\text{min}^{-1}$) at each workload during a progressive exercise test. The factors that influence exercise capacity in children with complex CHD are summarized below, in Table 2.

Table 2

Factors that potentially influence exercise capacity in children with CHD.

Heart Condition	Factors Influencing Exercise Capacity
1. Univentricular Heart	i. Passive blood flow to the lungs, decreasing pre-load (Bassareo et al., 2014) ii. Decreased cardiac output and peak blood pressure (Takken et al., 2007) iii. Chronotropic intolerance (Bassareo et al., 2014; Takken et al., 2007) (heart rate does not increase with increased intensity)
2. Tetralogy of Fallot	Bassareo and colleagues (2014) stated that these factors may influence exercise capacity: i. “Residual right ventricular outflow tract obstruction” (Bassareo et al., 2014, p.2; O’Brien & Marshall, 2014) ii. “Residual pulmonary insufficiency” (Bassareo et al., 2014, p.2; O’Brien & Marshall, 2014) iii. “Impaired biventricular function” iv. “Pulmonary regurgitation (O’Brien & Marshall, 2014) (leaky pulmonary valve, controls blood from heart to the lungs) (Bassareo et al., 2014, p.2)”
3. Transposition of the Great Arteries	i. Chronotropic incompetence (Giardini et al., 2009) (heart rate does not increase with increased intensity).

Note. This table describes the factors that influence exercise capacity among the 3 different heart conditions. This information was retrieved from Takken and colleagues (2007), Bassareo and colleagues (2014), O’Brien and Marshall (2014) and Giardini and colleagues (2009).

2.2.2 Oxygen Consumption ($\dot{V}O_2$) of Pediatric Complex CHD patients.

Research indicates that the pediatric complex CHD cohort has a significantly decreased peak energy expenditure ($\dot{V}O_{2peak}$) when compared to healthy controls (Bassareo et al., 2014; Durongpisitkul et al., 1997; Mazurek et al., 2016). Children with a univentricular heart have demonstrated an average $\dot{V}O_{2peak}$ of 24 to 27 mL/kg*min⁻¹, which represents 50% to 60% of predicted $\dot{V}O_{2peak}$ values for their respective age and sex norms (Cordina et al., 2013; Driscoll et al., 1986; Goldberg, Avitabile, McBride, & Paridon, 2013; Hebert et al., 2014; Opocher et al., 2005; Takken et al., 2007). By comparison, children with TOF possess a slightly better $\dot{V}O_{2peak}$, with an average of 34.5 to 39.7 mL/kg*min⁻¹ (Mahle et al., 2002; Mazurek et al., 2016), which is

indicative of 85% to 90% of predicted values. Lastly, children with TGA are shown to perform the best of the three complex CHD groups, with an average $\dot{V}O_{2\text{peak}}$ of 36.9 to 41.4 mL/kg*min⁻¹ (Mazurek et al., 2016; van Beek et al., 2010) which represents 90% of predicted values for their respective age and sex. Therefore, at maximal intensities, children with a single ventricular heart are shown to significantly underperform, when compared to both children with TOF and TGA.

2.2.3 Physiological Responses to Exercise in Children with and without Complex CHD

During progressive exercise, physiological changes are required to transport oxygen and nutrients, while also removing metabolic by-products from the working muscle (Takken, Bongers, van Brussel, Haapala, & Hulzebos, 2017). Examples of these physiological responses include the increase in cardiac output, or an increase in systemic and a decrease in diastolic blood pressure. These physiological responses occur in both healthy children and children with complex CHD, but the maximum variability observed is influenced by the physiological limit that each child can achieve.

Systolic blood pressure is representative of the amount of pressure in the arteries during a heart contraction, and diastolic blood pressure is the amount of pressure when the heart relaxes (after a contraction). In both healthy and children with complex CHD, systolic blood pressure increases and diastolic blood pressure decreases or remains relatively the same, with increasing exercise intensity. Cardiac output is a function of heart rate and stroke volume. During progressive exercise below about 50% of $\dot{V}O_{2\text{max}}$, stroke volume is the primary cause for the increase in cardiac output. At higher workloads, cardiac output increases mainly due to an increase in heart rate (Takken, Bongers, van Brussel, Haapala, & Hulzebos, 2017). Healthy children have a normal physiological response in both stroke volume and heart rate, but children with complex CHD typically have a lower heart rate and stroke volume response to progressive

exercise (Takken et al., 2012; Takken et al., 2007). Specifically, children with a single functioning ventricle or tetralogy of Fallot typically have a smaller increase in systolic blood pressure because of their decreased cardiac output (Takken et al., 2012, 2007). Conversely, children with transposition of the great arteries have a similar heart rate and blood pressure response to exercise, compared to healthy children (Hövels-Gürich et al., 2003). Therefore, children with a single functioning ventricle and tetralogy of Fallot have similar, but limited, physiological responses to progressive exercise as children with transposition of the great arteries and healthy children.

Another physiological factor to consider in children with complex CHD is their oxygen saturation levels. This is important because low oxygen saturation levels would indicate that there is an insufficient amount of oxygen to be delivered to the cells, tissues and organs. Theoretically, post-surgical intervention, children with complex CHD should have normal or near normal oxygen saturation. However, children with a single functioning ventricle are known to have slightly lower oxygen saturation at rest, which may further decrease during exercise in comparison to healthy children (Takken et al., 2007). Meanwhile, children with tetralogy of Fallot typically have normal oxygen saturation at rest and have a slight decrease during exercise (Mahle et al., 2002). Lastly, children with transposition of the great arteries are expected to have normal oxygen saturation, comparable to healthy children. Decreasing oxygen saturation levels with increases in progressive exercise (particularly in children with a single functioning ventricle) would have an influence on the readily available oxygen to be transported to exercising muscles as intensity increases.

2.3 Daily Physical Activity in Children with Complex CHD

2.3.1 PA Guidelines and Physical Inactivity

Physical activity (PA) guidelines describe the amount and types of physical activity that are required for optimal health benefits (Canadian Society for Exercise Physiology, 2017). Current Canadian PA guidelines (2017) state that “children between 5 to 17 years of age should accumulate at least 60 minutes of moderate to vigorous physical activity (MVPA) per day” (Canadian Society for Exercise Physiology, 2017, p.2). Despite readily available PA guidelines, most Canadian children spend a large proportion of their time sedentary (Fedewa & Ahn, 2011) and have increased risks for obesity, cardiovascular disease, high blood pressure and diabetes (Biddle, Gorely, & Stensel, 2004; Fedewa & Ahn, 2011). Sedentary lifestyles are of particular concern for children with complex CHD who are at greater risk of developing those health-related illnesses (Caplan, & Allen, 2011). With their increased risk of developing comorbidities, it is important that children with complex CHD engage in regular PA, yet research indicates these children are at greater risk for inactivity than the general population (Stone et al., 2015; Voss, Duncombe, Dean, de Souza, & Harris, 2017).

2.3.2 PA Guidelines and Promotion in Children with Complex CHD

It has been recommended that children with complex CHD monitor their exercise intensity with the “talk test” (Longmuir et al., 2013). The talk test provides a general rule that if the children are unable to hold a conversation while performing activities, then their intensity is too high. This method is a valuable self-regulating technique that allows children with complex CHD to perform a multitude of PA activities, when individualized PA guidelines are not readily available.

Children with complex CHD also have access to competitive sport specific guidelines that can assist their choice of PA activity, based on recommended levels of intensity (Mitchell, Haskell, Snell, & Van Camp, 2005; Van Hare et al., 2015). Van Hare and colleagues (2015) published recommendations for children with CHD who wish to engage in competitive sports (Van Hare et al., 2015), based on the reference table by Mitchell, Haskell, Snell, and Van Camp (2005). Their recommendations and guidelines are based on a combination of clinical assessment, ECG, exercise test and echocardiography (Van Hare et al., 2015). Children with single ventricle (Fontan) are recommended to stay between low static; low dynamic to moderate static; moderate dynamic activities (Van Hare et al., 2015). Children with TOF are limited to low static; low dynamic to moderate-high static; moderate dynamic (Van Hare et al., 2015). Lastly, children with TGA can perform low static; low dynamic to all competitive sports (high static; high dynamic) (Van Hare et al., 2015). Examples of activities that are recommended for children a single ventricle (Fontan), TOF or TGA can be found in the classification of sports table (Figure 2).

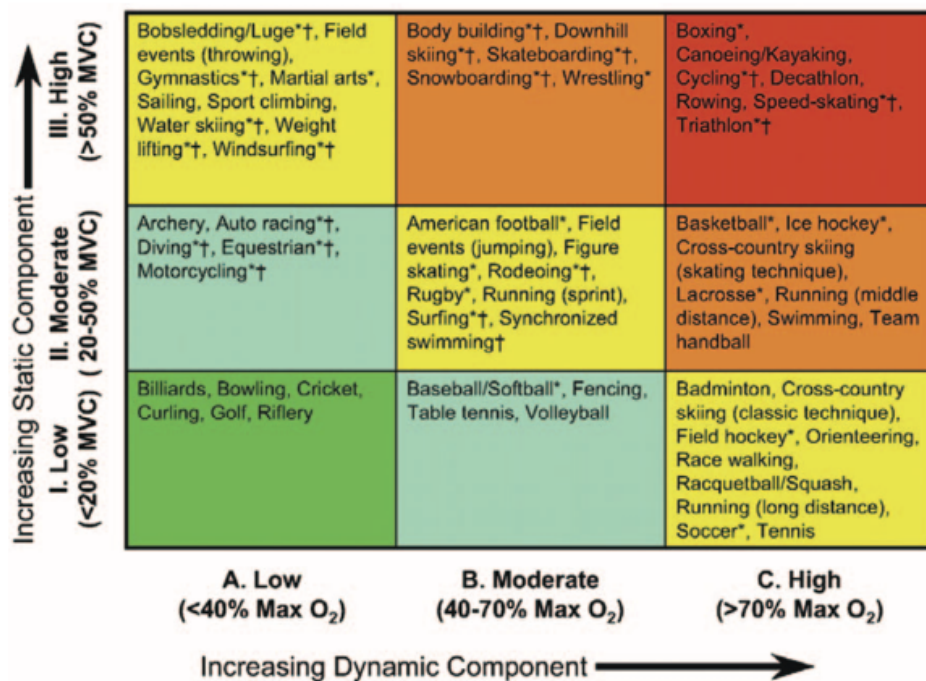


Figure 2. The degree of peak dynamic effort is expressed on the x-axis, while the peak static effort is expressed on the y-axis. Longmuir and colleagues (2013) described that “the colour green represents the lowest cardiovascular demand; blue, low moderate; yellow, moderate; orange, high moderate; and red, the highest” (p.2153). Reprinted from Mitchell and colleagues (2005).

It is recommended that children with CHD consult with their own clinician’s / health care providers (e.g., cardiologist) to obtain personal PA guidelines. Unfortunately, clinicians and healthcare providers express that they lack the knowledge or competency to appropriately promote and prescribe PA recommendations (Ackerman, Falsetti, Lewis, Hawkins, & Heinschel, 2011; Bull & Milton, 2011; Lin, O’Connor, Whitlock, & Beil, 2010). With a lack of in-depth knowledge related to PA, healthcare providers most commonly recommend physical activity based on the child’s performance during a maximal exercise test. Prescribing PA based on a child’s $\dot{V}O_{2peak}$ may not be entirely accurate because daily PA is typically performed at

submaximal intensities. Therefore, if healthcare providers were provided with submaximal $\dot{V}O_2$ data, they may be better able to set appropriate PA recommendations for children with CHD.

2.3.3 PA Participation in Children with CHD

Objective measures of PA and sedentary behaviour among most children with CHD indicate they do not meet the current PA guidelines of 60 minutes of MVPA per day (Ray, Green, & Henry, 2011; Voss et al., 2017). Ray and colleagues (2014), reported: “that 57% of children (n=84) did not engage in MVPA, and 74% of children reported no participation in vigorous PA” (Ray et al., 2011, p. 605). This finding indicates that the majority (roughly 60%) of children spend their time primarily in light PA (Ray et al., 2011). Voss and colleagues (2017) reported similar findings “that the median MVPA was 43 mins/day, with only 8% of the 90 children with complex CHD meeting the PA guidelines of 60 minutes of MVPA at least six days a week” (Voss et al., 2017, p.1). The 8% of children with complex CHD reported to meet the PA guidelines is similar to the 7% of healthy children meeting the MVPA guidelines (Colley et al., 2017). Although the proportion of children meeting the MVPA guidelines are similar between healthy children and children with complex CHD, there are notable differences between the average minutes spent in MVPA per day. Research indicates that healthy children average 55 minutes of MVPA per day (Colley et al., 2017), while children with complex CHD average 43 minutes of MVPA per day (Voss et al., 2017). While data from objective measurements of daily PA levels in children with complex CHD are available (Ray et al., 2011; Voss et al., 2017), it is unknown whether their low levels of daily PA are associated with limited $\dot{V}O_2$ at submaximal exercise intensities. As previously mentioned, a few examples of physiological responses that influence $\dot{V}O_2$ during progressive exercise are increases in heart rate and stroke volume (Takken et al., 2012; Takken et al., 2017). At 40 to 60% of maximal intensity, the primary response to

exercise will be an increase in stroke volume. In exercise conditions above 40 to 60% of maximal intensity, an increase in heart rate is required to sustain cardiac output demands (Takken et al., 2017). Therefore, heart rate and stroke volume are important factors to consider when assessing $\dot{V}O_2$ at submaximal intensities.

2.3.4 Capacity for Daily PA in Complex CHD

Reduced peak exercise capacity (in comparison to expected age and sex) does not mean that children with complex CHD should not engage in physical activity. Current research has indicated that children with complex CHD can safely participate in an exercise training program (Harkel & Takken, 2010; Rhodes, Tikkanen, & Jenkins, 2010; Takken et al., 2009). Children who regularly engage in PA or an exercise training program are found to have an improvement in aerobic capacity, as measured by a cardiopulmonary exercise test (Harkel & Takken, 2010; Rhodes et al., 2010; Takken et al., 2009). Children with a single ventricular heart also appear to be better responsive to perform submaximal exercise because their blood pressure is relatively well-maintained (Bassareo et al., 2014). Banks and colleagues (2013) found that children with a univentricular heart (repaired by Fontan) performed better at submaximal workloads compared to published data for healthy children. Banks and colleague's (2013) participants had a lower heart rate and $\dot{V}O_2$ response, suggesting that these children may be more efficient at performing submaximal exercise. While maximal exercise testing may provide insight on cardiac function with maximal effort, these assessments provide relatively little context of whether children with complex CHD have the submaximal capacity to withstand more common forms of active play.

2.4 Relationship Between $\dot{V}O_2$ and PA in Healthy Children

Dencker and Andersen (2011) reviewed studies examining the relationship between daily PA levels and $\dot{V}O_{2peak}$, in young children and adolescents. Their review included a total of 6116

children, and results illustrate that there is a relationship between daily PA (measured with an accelerometer) and $\dot{V}O_{2\text{peak}}$ (Dencker & Andersen, 2011). This group found that the relationship was weak – to – moderate ($r = 0.10$ to 0.45) in children between the ages of 10 and 19 years.

2.4.1 Relationship between $\dot{V}O_2$ and Energy Requirements for different PA in Healthy Children

In healthy children, research indicates that there is a relationship between energy requirements (measured in $\dot{V}O_2$) and different types of PA (Ainsworth et al., 2011; Butte et al., 2017). Recently, Butte and colleagues (2017) developed a youth compendium to distinguish between different energy costs (expressed in METs) for different physical activities done by children. The youth compendium differs from a previous adult compendium (Ainsworth et al., 2011) because it takes into account a calculation for a resting $\dot{V}O_2$, as opposed to a pre-set value. For example, children 6 years of age have a basal metabolic rate (BMR) of approximately $6.5 \text{ mL/kg}\cdot\text{min}^{-1}$, which differs from the $3.5 \text{ mL/kg}\cdot\text{min}^{-1}$ of resting $\dot{V}O_2$ used in adults (Ainsworth et al., 2011; Butte et al., 2017). Instead of the constant value used for adults, Butte and colleagues (2017) suggest using a BMR calculation that is indicative of the child's age and sex (encompassing body mass). Notably, most physical activities described in the compendium are performed at submaximal intensities.

However, the relationship between submaximal $\dot{V}O_2$ and PA is not well established in children with complex CHD. Perhaps, children with complex CHD and healthy children may have a similar trend with regards to submaximal $\dot{V}O_2$.

2.5 Cyanosis in Children with Complex CHD

In children with complex CHD, central and/or peripheral cyanosis originates from their heart defect. Physiologically, cyanosis is caused by high levels of deoxygenated hemoglobin circulating within the blood (McMullen & Patrick, 2013) and a limited amount of oxygen

reaching the tissues. Physically, cyanosis leads to peripheral discolouration (blue-like colour) of the skin. Theoretically, there may be some physiological benefits from the days spent in a cyanotic state, in children with complex CHD. The cyanotic state would potentially force the body to respond to prevent complete deprivation of O₂ to the tissues and allow for homeostasis of O₂ levels. Such change could theoretically include an improved ability to extract oxygen from the periphery. Once the cyanotic state is relieved (through surgical repair), it is possible that children would maintain these physiological changes, leading to an enhanced ability to perform daily PA and sub-maximal exercise.

The physiological changes described above may be similar to that of high altitude training. Children with complex CHD are born with their cyanotic state. The altered blood flow pathways result in reduced oxygen saturation levels at birth, whereas, high altitude environments cause a decreased partial pressure of oxygen due to a drop in barometric pressure (Luks, Stout, & Swenson, 2010). Nonetheless, the result is that both a cyanotic state and a decreased partial pressure of oxygen would lead to decreased alveolar oxygenation. When the body is exposed to a reduced oxygen environment, the body acclimatizes through physiological alterations including increased hematocrit, red blood cell (RBC) mass, oxidative enzyme activity (citrate synthase) and mitochondrial and capillary density (Millet, Roels, Schmitt, Woorons, & Richalet, 2010). Although similar physiological responses may occur in children with complex CHD, it is unknown to what extent or how long these theoretical physiological changes may last.

It is also important to note the impact of oxygen desaturation during exercise. As previously mentioned, some children with complex CHD experience a decrease in oxygen saturation with progressive exercise. If a child with complex CHD (after their surgical repair) were to exercise to the point of intermittent desaturation, it could hypothetically result in a

similar effect as that of intermittent hypoxic training (high altitude training at sea level) (Millet et al., 2010). Perhaps the intermittent desaturation during exercise in children with complex CHD would allow them to maintain the theoretical physiological responses to the cyanosis exposure experienced before surgical repair.

2.6 Significance

As previously outlined, children born with complex CHD are not expected to perform as much active play as their healthy peers because of a reduced maximal exercise capacity. Although maximal exercise capacity is reduced, most daily physical activity is performed using a submaximal rather than maximal effort. Therefore, this research focused on enhancing the limited research regarding submaximal exercise capacity in children with complex CHD. As mentioned above, the goal of this research was to examine the submaximal exercise capacity, daily physical activity and cyanosis exposure among children born with complex CHD. The present study provides valuable information about the relationship between submaximal exercise capacity and daily physical activity, about the relationship between submaximal exercise capacity and cyanosis exposure, and whether submaximal exercise capacity can be used as a reliable clinical indicator of daily moderate-to-vigorous physical activity. These findings may provide valuable information to healthcare providers to better enable them to set appropriate PA recommendations for children with complex CHD.

Part 3: Article

**Submaximal Exercise Capacity is Associated with Moderate-to-Vigorous Physical Activity
in Children with Complex Congenital Heart Disease**

Short title: Submaximal Exercise and Physical Activity in Children with Congenital Heart
Disease

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3.1 Abstract

Purpose: This study examined the relationships between submaximal exercise capacity, moderate-to-vigorous physical activity (MVPA) and history of cyanosis. The purpose was to better characterize the capacity of children with complex congenital heart disease for a physically active lifestyle because the influence of submaximal exercise capacity on MVPA is unknown within this cohort. **Methods:** This cross-sectional study recruited five Fontan, four tetralogy of Fallot and seven transposition of the great arteries patients (44%, female), 10-17 years of age (mean = 14 ± 2.4). Study assessments included: exercise testing (Bruce protocol on the treadmill), accelerometry (7 days of consecutive Actical wear time) and medical record reviews (to determine the amount of days spent in cyanosis). Five measures of submaximal exercise capacity were evaluated (to compare different submaximal intensities): energy consumption ($\dot{V}O_2$) at the ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 beats per minute (bpm), metabolic equivalents (METs) at ventilatory threshold, METs at 130 bpm and heart rate at stage 1 of the Bruce protocol. **Results:** Daily physical activity was positively associated with $\dot{V}O_2$ at ventilatory threshold ($r = 0.78$, $n = 16$, $p = < 0.01$) and $\dot{V}O_2$ at a heart rate of 130bpm ($r = 0.61$, $n = 16$, $p = 0.01$). Children who did more than 60 minutes of physical activity per day ($n=4$) achieved significantly higher energy expenditure ($\dot{V}O_2$) before reaching their ventilatory threshold (95% CI of the difference [8.23, 24.85], $t(14) = 4.27$, $p = < 0.01$) and at a heart rate of 130 bpm (95% CI of the difference [1.61, 14.33], $t(14) = 2.69$, $p = 0.02$). Lastly, $\dot{V}O_2$ at ventilatory threshold was negatively associated with days spent in cyanosis ($r = .55$, $n = 16$, $p = 0.03$). **Conclusions:** Children with a higher $\dot{V}O_2$ at ventilatory threshold and at a heart rate of 130 bpm performed more MVPA, suggesting that submaximal $\dot{V}O_2$ may be a useful clinical

indicator of daily physical activity. Higher $\dot{V}O_2$ at ventilatory threshold was associated with fewer days spent in cyanosis.

Key words: VENTILATORY THRESHOLD, OXYGEN CONSUMPTION, CYANOSIS, FONTAN, TETRALOGY OF FALLOT, TRANSPOSITION OF THE GREAT ARTERIES

3.2 Introduction

Children born with complex congenital heart disease (CHD) are often not expected to participate in physically active play with peers to the same extent as healthy children. The rationale for these reduced expectations is based on research that indicates children with CHD often have limited maximal exercise capacity (Banks et al., 2013; Brassard et al., 2006; Glaser et al., 2004; McCrindle et al., 2007; Takken et al., 2007). However, there is conflicting research about the relationship between exercise capacity and daily physical activity, in children with CHD. Previous research has indicated that exercise capacity is associated with daily physical activity among children with CHD (Banks et al., 2017; Müller, Hess, & Hager, 2012), but also that daily physical activity is not associated with peak exercise capacity among children with a single functioning ventricle (McCrindle et al., 2007). However, the moderate-to-vigorous physical activity associated with health benefits requires only 60% to 80% of a maximal effort (Takken et al., 2012). Therefore, perhaps it is more suitable to analyze daily physical activity with intensities that only require 60-80% effort, as opposed to peak intensities.

In paediatric cardiac clinics, exercise capacity is assessed using a maximal cardiopulmonary exercise testing protocol, but the broad spectrum of data provided by such testing remains underutilized in clinical practice (Williams, Saynor, Tomlinson, & Barker, 2014). For example, submaximal exercise capacity can be assessed through the physiological responses to initial stages of exercise or the analysis of ventilatory threshold (Rhodes et al., 2010; T. Takken et al., 2009). Since most daily physical activity is performed using a submaximal effort, such measures of submaximal exercise capacity may be more relevant than maximal exercise performance to assess participation in daily PA. Currently, there are limited research data

regarding the submaximal exercise capacity of children born with complex CHD (Banks et al., 2013; Müller et al., 2013; Paridon et al., 2008).

Children born with complex CHD are exposed to cyanosis, which depending on the type of CHD may occur for only 1 or 2 days, or it may last until two to three years of age (Bailliard & Anderson, 2009; Brassard et al., 2006; Martins & Castela, 2008). Although a history of prolonged exposure to cyanosis may further reduce expectations for the child's exercise capacity, it is possible that early exposure to cyanosis may have a physiological benefit on submaximal exercise capacity. Theoretically, a prolonged cyanotic state may result in an increased ability to extract oxygen from the blood or increased capacity to transport oxygen within the blood. Such changes would offer a potential explanation for the few reports of normal or enhanced exercise capacity at submaximal workloads among children with complex CHD (Banks et al., 2013; Paridon et al., 2008)

The purpose of this study was to assess the submaximal exercise capacity of children born with complex CHD and its relationship with daily physical activity and cyanosis exposure. The primary objective was to determine the relationship between daily moderate-to-vigorous physical activity and submaximal exercise capacity, defined as oxygen consumption ($\dot{V}O_2$) at the ventilatory threshold, with a positive association being hypothesized. The secondary objectives were to evaluate whether: (a) submaximal exercise capacity could be a reliable clinical indicator of the daily physical activity of children with complex CHD, and (b) if children who are exposed to cyanosis during infancy and early childhood could perform submaximal exercise with a lower level of oxygen consumption. It was hypothesized that: (a) children who met the 60 minutes of moderate-to-vigorous physical activity guidelines would have a higher relative submaximal

oxygen consumption, and (b) children who were cyanotic for the longest period of time would have a greater ability to utilize anaerobic energy sources.

3.3 Methodology

3.3.1 Study Design

A cross-sectional study design was used to evaluate daily physical activity, submaximal exercise capacity and history of cyanosis among children with complex CHD. The study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board (CHEOREB# 18/62X) and the University of Ottawa Research Ethics Board (Ethics File Number: H-08-18-978). Written consent and/or assent to participate was obtained from all participants and their parents/guardians.

3.3.2 Participants

All patients followed in our institution with a single ventricle (with Fontan repair), tetralogy of Fallot (with a biventricular repair) and transposition of the great arteries (with arterial switch repair) were identified via medical chart review and then study eligibility was confirmed by the responsible cardiologist. The inclusion criteria were: i) the child had one of the three diagnoses of complex CHD, ii) male or female between the ages of 10 and 17 years old, and iii) approval from the responsible cardiologist that the child could be approached for study participation and did not have any medical contraindications to completing the study protocol. Children who had been instructed to rest as needed or who were restricted from competitive and/or contact sports were included in the study because these restrictions should not limit the performance of light, moderate or vigorous physical activity. Participants were excluded if: i) they had a medical condition(s) or disability that would impact their ability to perform physical activity and/or the study protocol (i.e., cerebral palsy, Down syndrome), ii) they were taking

digoxin or other medication that may limit the increase in heart rate during exercise, iii) they had surgery or a catheter intervention in the previous 6 months, or iv) they required any restriction of non-contact light, moderate and/or vigorous activity. Figure 1 demonstrates the participant flow chart.

3.3.3 Pre-exercise Testing Guidelines and Equipment Calibration

All exercise tests were performed in the cardiac clinic exercise testing laboratory. A certified exercise physiologist (TK) conducted each exercise test, in conjunction with an ECG technician. Pre-exercise testing instructions asked participants to refrain from: i) eating for at least 2 hours, ii) caffeinated beverages for 2 hours, iii) alcoholic beverages for at least 6 hours, iv) smoking for 2 hours and v) performing strenuous exercise for 6 hours before the testing. Children were also instructed to take any medication as prescribed. Before the test, each participant had their height (cm) and body mass (kg) measured. Each participant was equipped with a standard 12-lead ECG (CASE 8000; GE Medical Systems, Milwaukee, Wisconsin), headgear to hold a fitted mouthpiece (for breath-by-breath assessment of aerobic capacity), nose clip and blood pressure cuff. Indirect calorimetry was measured using a Vmax Encore Metabolic Cart (Sensormedic, San Diego, California). Gas and volume calibrations were completed as per manufacturer recommendations.

3.3.4 Submaximal Exercise Capacity Test

Baseline measurements of oxygen consumption ($\dot{V}O_2$), respiratory exchange ratio, blood pressure and heart rate were taken for 10 minutes while the participant was seated to ensure a resting heart rate of under 100 bpm, no ECG complications and the child was acclimatized to breathing with the mouth piece ($RER < 0.85$). To promote exercise equipment familiarization and confirm a quality ECG tracing during exercise, participants were asked to perform a 2-minute

warm-up stage (6% grade at 1.5mph). After the warm-up stage, all participants then completed the Bruce protocol until voluntary or symptomatic exhaustion. Although the Bruce protocol is a maximal exercise testing protocol, each stage of the Bruce protocol provides data regarding submaximal exercise capacity. After completion of the Bruce protocol (testing), all participants completed a 2-minute cool down at the same grade and speed as the initial warm-up stage. Heart rate (bpm), breath-by breath measures of oxygen consumption and a standard 12-lead ECG were continually monitored through the warm-up, testing protocol and cool-down. Blood pressure and rating of perceived exertion (RPE) were collected during the last minute of each stage of the Bruce protocol. The 0-10 Borg Scale (Borg, 1990) was chosen instead of the 6-20 scale for simplicity of children being able to understand level estimation (0 = rest and 10 = maximal).

3.3.5 Daily Physical Activity Measurement with Actical Accelerometers

Participants were provided with an omnidirectional Actical Z-series accelerometer (Philips Respironics, Murrysville, Pennsylvania) to measure their daily physical activity. Participants were asked to wear the accelerometer at the right iliac crest along the mid-axillary line of the body for 7 consecutive days. The participants were also asked to manually log the time they woke up, bed time, the type of physical activities performed that day and whether or not the accelerometer was worn all day. Accelerometers were pre-set to record data in 15-second epochs.

3.3.6 History of Cyanosis

Days of cyanosis exposure was calculated by subtracting the child's date of birth from the date the child was relieved of cyanosis. The day the child was relieved of cyanosis and date of birth were confirmed through medical record reviews. The length of time since the child was

relieved of cyanosis was calculated as the child's current age minus the date the child was relieved of cyanosis.

3.4 Data Management

3.4.1 Outcome Measures

The primary outcome measure was submaximal oxygen consumption ($\dot{V}O_2$) at the ventilatory threshold, which standardized the submaximal exercise workload across all participants. Ventilatory threshold was defined as the point when $\dot{V}CO_2$ increased at a faster rate than ventilation (VE). $\dot{V}O_2$ at a heart rate of 130 beats per minute (bpm), metabolic equivalents at ventilatory threshold, metabolic equivalents at a heart rate of 130 bpm and heart rate at stage 1 in the Bruce protocol were used as secondary submaximal measures. A heart rate of 130 bpm was chosen because physiologically each study group should be able to achieve that level of intensity. The heart rate at 130 bpm was also chosen to represent a lower submaximal intensity. Metabolic equivalents at ventilatory threshold and a heart rate of 130 bpm were calculated by dividing the child's submaximal $\dot{V}O_2$ by the child's resting metabolic rate ($\dot{V}O_2$). The heart rate in stage 1 of the Bruce protocol was determined through averaging the heart rate during the final minute of the stage.

Valid days of accelerometer data were defined as having a minimum wear time of 10 hours per day for at least four of seven days (three weekdays and one weekend) (Barreira et al., 2015). The counts were classified as light or moderate-to-vigorous intensity based on the established Actical accelerometer cut-points for this age group (Puyau, Adolph, Vohra, Zakeri, & Butte, 2004). Moderate-to-vigorous physical activity was defined as the minutes per day of accelerometer data that exceeded 375 counts per 15-second epoch (Puyau et al., 2004). The daily physical activity data were calculated using the following equation: Moderate-to-vigorous

physical activity = [(Five days x average moderate-to-vigorous physical activity for the weekday) + (two days x average moderate-to-vigorous physical activity for the weekend)] / by seven days. It is important to note that the minutes of moderate-to-vigorous physical activity is the sum of all minutes spent in moderate-to-vigorous physical activity per day, but there is no requirement that the minutes be performed in a continuous bout.

3.4.2 Sample Size Calculation

It was estimated that a sample size of 6 to 8 participants per group would be necessary to provide 80% power, $\alpha = 0.05$, to detect a difference between single ventricle patients and the TOF and TGA patient groups in measures of peak exercise. With the lack of published submaximal exercise capacity data, the sample size calculation was based on studies that assessed peak exercise capacity (Mahle et al., 2002; Mazurek et al., 2016; Paridon et al., 2008; van Beek et al., 2010).

3.4.3 Data Analyses

Descriptive statistics (mean $\pm$ 1 SD; frequency tabulations) were used to characterize the study participants. Alpha was set to 0.05 for all analyses.

Relationship between moderate-to-vigorous physical activity and submaximal exercise capacity

A Pearson correlation assessed the association between submaximal exercise capacity, as measured by (1) $\dot{V}O_2$ at ventilatory threshold (VT), 2) $\dot{V}O_2$ at a heart rate of 130 bpm, 3) metabolic equivalents (METs) at VT, 4) METs at a heart rate of 130 bpm, or 5) heart rate response at stage 1 of the Bruce protocol), and moderate-to-vigorous physical activity. The strength of the correlation was defined as: small: $0.1 < r < 0.3$, moderate: $0.3 < r < 0.5$, strong: $r > 0.5$ (Cohen, 1988). A Shapiro-Wilk's test was used to assess whether both variables were normally distributed.

The rationale for having five different measures of submaximal exercise capacity ($\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 bpm, METs at ventilatory threshold, METs at 130 bpm and heart rate at stage 1) were the following: a) $\dot{V}O_2$ at ventilatory threshold is representative of the peak exercise that can be performed using aerobic energy sources as it is the point where the respiratory exchange ratio begins to exceed 1.0 (the peak of aerobic metabolism), b) $\dot{V}O_2$ at a heart rate of 130 bpm was chosen as a work rate representative of aerobic exercise that could be sustained for a period of time c) METs at ventilatory threshold and d) METs at 130 bpm were chosen to incorporate the amount of oxygen consumption above resting values, e) heart rate at stage 1 of the Bruce protocol was chosen because this stage is low to moderate intensity and will provide a representation of a submaximal effort.

Submaximal exercise capacity as a clinically useful indicator of daily physical activity

Five variables were evaluated as potential clinical indicators of the child's daily physical activity: 1) submaximal $\dot{V}O_2$ at ventilatory threshold, 2) $\dot{V}O_2$ at a heart rate of 130 bpm, 3) Metabolic equivalents at ventilatory threshold, 4) Metabolic equivalents at a heart rate of 130bpm, or 5) heart rate at stage 1 of the Bruce protocol. Independent t-tests compared the results for each variable between children that did and did not meet the moderate-to-vigorous physical activity guideline of 60 minutes per day (Canadian Society for Exercise Physiology, 2017).

The relationship between submaximal exercise capacity and exposure to cyanosis

The correlations between the five measures of submaximal exercise capacity [(1) $\dot{V}O_2$ at ventilatory threshold (VT), 2) $\dot{V}O_2$ at a heart rate of 130 bpm, 3) metabolic equivalents (METs) at VT, 4) METs at a heart rate of 130 bpm or, 5) heart rate at Bruce stage 1] and days spent in

cyanosis were assessed. The correlation between moderate-to-vigorous physical activity and days spent in cyanosis was also assessed.

3.5 Results

3.5.1 Participant Characteristics and Mean Resting Energy Expenditure

The study participants ($n = 16$) are described in Table 1. All enrolled participants had complete exercise and moderate-to-vigorous physical activity data, and were included in the analyses. As expected based on study design, there were statistically significant differences between groups in days spent in cyanosis ($F(2, 13) = 32.94, p < 0.001, \eta^2 = 0.84$) and the length of time since alleviation from cyanosis ($F(2, 13) = 4.99, p = 0.03, \eta^2 = 0.43$). There were no statistically significant between-group differences in sex ($F(2, 13) = 2.62, p = 0.11, \eta^2 = 0.29$), age ($F(2, 13) = 0.58, p = 0.57, \eta^2 = 0.08$), height ($F(2, 13) = 0.23, p = 0.80, \eta^2 = 0.03$) or body mass ($F(2, 13) = 0.94, p = 0.42, \eta^2 = 0.13$). The mean respiratory exchange ratio (RER) values that occurred at the time of the submaximal measures were: $\dot{V}O_2$ ventilatory threshold ≥ 1.0 , $\dot{V}O_2$ at a heart rate of 130 bpm 0.89 ± 0.09 and at stage 1 of the Bruce protocol 0.87 ± 0.07 .

One participant (Fontan) had a horse-shoe shaped lung. Ten participants (Fontan = 5, TOF = 4, TGA = 1) were taking one or multiple of the following prescription medications: fluoxetine HCL ($n=1$), acetylsalicylic acid ($n=5$), levetiracetam ($n=1$), lamotrigine ($n=1$), lorazepam ($n=1$), lisdexamfetamine ($n=2$), risperidone ($n=1$), levothyroxine ($n=1$), calcitriol ($n=1$), polyethylene ($n=1$), salbutamol sulfate ($n=1$), calcipotriol-betamethasone ($n=1$).

3.5.2 Submaximal Exercise Capacity, Resting Energy Expenditure and Daily Physical Activity by Diagnostic Group

Table 2 summarizes the resting energy consumption, submaximal exercise variables and moderate-to-vigorous physical activity by study group. Submaximal exercise capacity, but not MVPA or resting energy expenditure, differed by group.

3.5.3 Relationship between moderate-to-vigorous physical activity and submaximal exercise capacity

There was a strong positive relationship between $\dot{V}O_2$ at ventilatory threshold ($r = 0.78$, $n = 16$, $p = < 0.01$), $\dot{V}O_2$ at a heart rate of 130 bpm ($r = 0.61$, $n = 16$, $p = 0.01$) and METs at ventilatory threshold ($r = 0.52$, $n = 16$, $p = 0.04$) and moderate-to-vigorous physical activity. Figure 2 demonstrates the association between mean time spent in moderate-to-vigorous physical activity and a) $\dot{V}O_2$ at ventilatory threshold, and b) $\dot{V}O_2$ at a heart rate of 130 bpm. There was no significant association between METs at a heart rate of 130 bpm ($r = 0.19$, $n = 16$, $p = 0.47$) or heart rate at stage 1 ($r = 0.35$, $n = 16$, $p = 0.19$) and moderate-to-vigorous physical activity.

3.5.4 Submaximal exercise capacity as a clinically useful indicator of daily physical activity

Study participants performed 44.7 ± 24.6 minutes of moderate-to-vigorous physical activity per day. Study participants who met the physical activity guideline of 60 minutes of moderate-to-vigorous physical activity per day ($n=4$) could perform more submaximal exercise than children who did not meet the physical activity guidelines ($n=12$), regardless of whether their submaximal exercise capacity was measured at their ventilatory threshold (mean $\dot{V}O_2$ at VT = 41.8 ± 11.8 mlO₂/kg/min vs 25.3 ± 4.4 mlO₂/kg/min; 95% CI of the difference [8.23, 24.85], $t(14) = 4.27$, $p = < 0.01$), a heart rate of 130 bpm (mean $\dot{V}O_2$ = 29.4 ± 6.2 mlO₂/kg/min vs 21.4 ± 4.8 mlO₂/kg/min; 95% CI of the difference [1.61, 14.33], $t(14) = 2.69$, $p = 0.02$) or relative to

their resting energy requirements (METs) at their ventilatory threshold (mean METs = 7.5 ± 1.3 vs 5.9 ± 1.4 ; 95% CI of the difference [0.00, 3.33], $t(14) = 2.15$, $p = 0.05$). Figure 3 demonstrates the difference in $\dot{V}O_2$ at ventilatory threshold and $\dot{V}O_2$ at a heart rate of 130 bpm for children who met and did not meet the moderate-to-vigorous physical activity guidelines. Lastly, study participants that did or did not meet the physical activity guidelines did not differ in metabolic equivalent tasks (METs) at a heart rate of 130 bpm (mean METs = 5.4 ± 1.1 versus 4.9 ± 1.2 ; 95% CI of the difference [-0.99, 1.92], $t(14) = 0.68$, $p = 0.51$) or in the heart rate achieved during stage 1 of the Bruce protocol (mean heart rate = 102.0 ± 13.5 versus 117.8 ± 19.7 ; 95% CI of the difference [-38.71, 7.21], $t(14) = -1.47$, $p = 0.16$).

3.5.5 *Relationship between submaximal exercise capacity and exposure to cyanosis*

In a univariate analysis, higher $\dot{V}O_2$ at ventilatory threshold ($r = 0.55$, $n = 16$, $p = 0.03$), and higher METs at VT ($r = 0.59$, $n = 16$, $p = 0.02$) were associated with fewer days spent in a cyanotic state. $\dot{V}O_2$ at a heart rate of 130 bpm ($r = 0.47$, $n = 16$, $p = 0.07$), METs at a heart rate of 130 bpm ($r = 0.40$, $n = 16$, $p = 0.12$), heart rate at stage 1 of the Bruce protocol ($r = 0.24$, $n = 16$, $p = 0.16$) and moderate-to-vigorous physical activity ($r = 0.39$, $n = 16$, $p = 0.14$) were not related to days spent in cyanosis.

3.6 Discussion

Previous studies have reported a limited maximal exercise capacity within our cohort (Goldberg et al., 2013; Mahle et al., 2002; Mazurek et al., 2016; McCrindle et al., 2007). Among our study participants, children with a single functioning ventricle are known to have the lowest maximal exercise capacity (~70%) relative to healthy peers (Takken et al., 2012). However, it has been suggested that despite limitations in maximal exercise capacity, children with complex CHD should have sufficient submaximal exercise capacity to perform the recommended 60

minutes of moderate-to-vigorous physical activity per day (Takken et al., 2012). The results of this study suggest a positive association between moderate-to-vigorous physical activity and a) $\dot{V}O_2$ at ventilatory threshold, b) $\dot{V}O_2$ at a heart rate of 130 bpm, or c) METs at ventilatory threshold. Despite central limitations of the heart, our study demonstrated that children with complex CHD are capable of meeting the recommended physical activity guidelines (transposition of the great arteries = 3, Fontan = 1). Moreover, children who met the 60 minutes of moderate-to-vigorous physical activity per day had a higher submaximal exercise capacity than children who did not meet the physical activity guidelines. Lastly, the study results suggest an association between days spent in cyanosis and a) $\dot{V}O_2$ at ventilatory threshold, or b) METs at ventilatory threshold.

3.6.1 Association Between Submaximal Exercise Capacity and Daily Physical Activity

Previous studies reported that children with a single functioning ventricle (Paridon et al., 2008), tetralogy of Fallot and transposition of the great arteries often have a reduced ventilatory threshold, compared to healthy children (Amedro et al., 2017; Moalla et al., 2008; Rhodes et al., 2010). Ventilatory threshold is the transitioning point between aerobic and anaerobic metabolism. Activities below ventilatory threshold primarily rely on aerobic metabolism; the point where the partial pressure of arterial carbon dioxide ($PaCO_2$) remains relatively constant (Wasserman, K., Beaver, W.L. and Whipp, 1990). Activities above the ventilatory threshold are considered to be primarily reliant on anaerobic metabolism; the point where $PaCO_2$ increases, lowering blood pH and increasing blood lactate production (Wasserman, Beaver, and Whipp, 1990). If the ventilatory threshold is reduced, a child will transition to anaerobic energy stores earlier in physical activity exposure and therefore is presumed to have a more limited exercise capacity in comparison to a child with a higher ventilatory threshold. The mean values for

oxygen consumption at the ventilatory threshold obtained by subjects in our study were comparable to these previous reports suggesting that these children also have a reduced ventilatory threshold, in comparison to healthy children.

In examining the relationship between moderate-to-vigorous physical activity and submaximal exercise capacity in children with complex CHD, our study does not differ from previous work reporting a positive association between moderate-to-vigorous physical activity and peak exercise capacity among similar populations (Banks et al., 2017; Müller et al., 2012). This finding warrants further investigation of utilizing submaximal exercise capacity as the base for exercise and physical activity guideline recommendations. It is important to note that the results of both submaximal and peak efforts during an exercise test are reliant on voluntary efforts (i.e., motivation) of the participant. If a child is highly motivated to exercise, they are more likely to push themselves throughout the exercise test. Therefore, motivating children as they perform their exercise test is essential to distinguish true maximal and submaximal efforts (with analysis of RER). Although there is an association between submaximal exercise capacity and moderate-to-vigorous physical activity, it does not indicate the driving variable of the association. Therefore, children who have an increased exercise capacity may be able to be more active, or conversely, more active children may develop a higher exercise capacity.

When comparing the other measures of submaximal exercise capacity, our study results found no significant association between METs at 130 bpm and stage 1 of the Bruce protocol. As previously outlined, these measures are indicative of a lower submaximal intensity (whereas ventilatory threshold represents the peak of submaximal intensity). This null finding suggests that our study cohort had approximately similar $\dot{V}O_2$ at a heart rate at 130 bpm (once it is corrected for with resting $\dot{V}O_2$) and heart rates at stage 1 of the Bruce protocol. Therefore, at

lower submaximal intensities, our study participants exhibited similar performance, regardless of daily moderate-to-vigorous physical activity levels.

It is important to note that one child with a single functioning ventricle met the recommended 60 minutes of moderate-to-vigorous physical activity per day, but the child's ventilatory threshold was below the mean ventilatory threshold (25.2 versus 41.8 ± 11.79) $\text{mlO}_2/\text{kg}/\text{min}$ of the other children who met the recommended guidelines. Although it is only a single case, this finding may suggest that children with a single functioning ventricle may have a changed system of energy metabolism that enables them to sustain their physical activity anaerobically. A similar hypothesis of improved anaerobic energy metabolism was reported by Banks et al., (2013) who found an increase in submaximal exercise performance in children with a single functioning ventricle. These results suggest that children with a single ventricle may be able to perform activities for a longer period than would be suggested by traditional measures of ventilatory threshold. Future studies should evaluate the mechanisms through which these children are able to sustain activities for a prolonged period of time.

3.6.2 Achieving the Recommended Daily Physical Activity

Objectively measured moderate-to-vigorous physical activity indicated that, on average, the study participants did not meet the recommended guideline of 60 minutes of moderate-to-vigorous physical activity per day (Canadian Society for Exercise Physiology, 2017). Previous studies have demonstrated similar findings among children with CHD (McCrindle et al., 2007; Voss et al., 2017). The average daily minutes spent in moderate-to-vigorous physical activity of our study participants was similar to the results reported by Voss and colleagues (2017), 44.7 ± 24.6 minutes compared to 49 minutes, respectively. By contrast, McCrindle and colleagues (2007) reported that 38% of the children in their study achieved more than 60 minutes of

moderate-to-vigorous physical activity per day. In our study, 25% of participants met the 60-minute guideline, but this comparison needs to be taken with precaution considering our small sample size. The minutes spent in moderate-to-vigorous physical activity of our study participants (44.7 ± 24.6 minutes) differs from the 54 minutes per day reported for healthy children (“The participation report card on physical activity for children and youth,” 2018). As expected based on the results from previous studies (McCrindle et al., 2007; Voss et al., 2017), our study participants were less active than the healthy population.

Nevertheless, our results support our hypothesis that children with higher submaximal exercise capacity would perform more moderate-to-vigorous physical activity. Specifically, children who met the physical activity guidelines had a higher average $\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 bpm and METs at ventilatory threshold, when compared to children who did not meet the 60 minutes of moderate-to-vigorous physical activity per day. Our findings suggest that children who meet the physical activity guidelines would have a $\dot{V}O_2$ at ventilatory threshold above $30.0 \text{ ml/kg}\cdot\text{min}^{-1}$, a $\dot{V}O_2$ at 130 bpm above $23 \text{ ml/kg}\cdot\text{min}^{-1}$ or would achieve more than 6.0 METs at ventilatory threshold. Our study results also had null findings for METs at 130 bpm and heart rate at stage 1 of the Bruce protocol, suggesting that there are no differences at lower submaximal intensities between children who meet and do not meet the moderate-to-vigorous physical activity guidelines.

Not meeting the physical activity guidelines is concerning because these children are at greater risk of developing sedentary lifestyle-related illnesses (Caplan, & Allen, 2011; Stone et al., 2015). To our knowledge, clinicians primarily assess physical activity by asking their patients whether they are active and can keep up with their friends. Longmuir and colleagues (2013) recommended that physical activity should be assessed using valid and reliable self-report

questionnaires when objective measures are not feasible in the clinical setting. Although self-reported questionnaires may help provide a snapshot of children's physical activity, they typically have an increased risk of over or underestimating physical activity levels (Adamo, Prince, Tricco, Connor-Gorber, & Tremblay, 2009). Our preliminary findings suggest that $\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 bpm or METs at ventilatory threshold may be suitable for use as a clinical indicator of children's daily physical activity. An accurate method of assessing daily physical activity levels would assist clinicians to identify children requiring additional support to meet physical activity recommendations.

Even if ventilatory threshold is reduced, as occurred within our cohort, it does not necessarily mean that these children would have limited capacity for the daily physical activities recommended for optimal health. The mean METs at the ventilatory threshold achieved by our study participants (TGA: 7.4 ± 1.1 ; TOF: 5.9 ± 1.0 ; Fontan: 4.3 ± 1.8) indicate that they would have the ability to perform most (TGA, TOF) or at least some (Fontan) activities of moderate intensity using aerobic (i.e., longer lasting) energy sources. Knowledge of METs achieved before transitioning into anaerobic metabolism may assist clinicians in providing more specific activity recommendations to their patients based on data available in the youth compendium of physical activities (Butte and colleagues, 2017). For example, within our cohort, children with transposition of the great arteries have the capacity to perform active play (ball games: bouncing, kicking, dribbling – vigorous intensity, age 10+) which are reported to require 6.2 METs; our participants with tetralogy of Fallot can perform active play (basketball, Frisbee etc.), which require 5.8 METs; and our participants with a single functioning ventricle have the capacity for strength exercises (push-ups), which require 4.1 METs (Butte et al., 2017).

It is important to note that 3 out of 4 participants that met the physical activity guidelines were children with transposition of the great arteries. The other participant was a child with a single functioning ventricle, as previously mentioned. The 3 children with transposition of the great arteries had a mean $\dot{V}O_2$ at ventilatory threshold of $47.3 \pm 4.95 \text{ mL/kg}\cdot\text{min}^{-1}$ which differs from the child with the single functioning ventricle ($25.2 \text{ mL/kg}\cdot\text{min}^{-1}$). In comparison to healthy children, our 3 children with transposition of the great arteries had a higher $\dot{V}O_2$ at ventilatory threshold (range: (low end: 26.5 ± 4.7 for 17 to 18 year old to high end: 34.8 ± 6.6 for 9 to 10 year old) in comparison to healthy children (Reybrouck, Weymans, Stijns, Knops, & van der Hauwaert, 1985). This finding suggests that perhaps the children with transposition of the great arteries were biased toward the most active sector of the population.

3.6.3 Influence of Days Spent in Cyanosis on Ventilatory Threshold

Children with a single functioning ventricle, tetralogy of Fallot and transposition of the great arteries have their final surgical procedure at varying ages. Children with a single functioning ventricle have their repair at 1 to 5 years of age (Gewillig, 2005), tetralogy of Fallot from 4 to 6 months (Bailliard & Anderson, 2009; Sharkey & Sharma, 2012) and transposition of the great arteries at <30 days of age (Warnes, 2006). Within our participants, lower $\dot{V}O_2$ at ventilatory threshold and METs at ventilatory threshold were associated with increasing days spent in cyanosis. This finding is similar to that of Amedro et al., (2017) and Reybrouck et al., (1995), who found that children with a single functioning ventricle had the lowest $\dot{V}O_2$ at ventilatory threshold, when compared to other groups of healthy children or children with another congenital heart diagnosis (but did not relate their findings to cyanosis exposure). Amedro and colleague's (2017) participants had similar $\dot{V}O_2$ at ventilatory threshold in children with a single functioning ventricle (22.6 ± 5.8 versus 19.6 ± 7.2) and in children with tetralogy of

Fallot (25.5 ± 5.6 versus 24.1 ± 7.4), but slightly different in children with transposition of the great arteries (27.8 ± 6.5 versus 36.9 ± 10.2). A larger sample is needed to further investigate whether it is CHD diagnosis or days of cyanosis exposure that is more strongly related to $\dot{V}O_2$ at ventilatory threshold.

Despite the association between $\dot{V}O_2$ at ventilatory threshold ($RER \geq 1.0$) and days spent in cyanosis, our study found no association between $\dot{V}O_2$ at a heart rate of 130 bpm ($RER = 0.89 \pm 0.09$) or heart rate at stage 1 of the Bruce protocol ($RER = 0.87 \pm 0.07$) and days spent in cyanosis. Our results suggest that the association between cyanosis and submaximal exercise capacity is limited to the upper threshold of aerobic metabolism. Further research is required to investigate whether there are physiological benefits of cyanotic exposure for activities performed below the threshold of aerobic metabolism. If children exposed to a cyanotic state have an increased ability to extract oxygen or transport oxygen within the blood, those benefits would likely occur at intensities below an RER of 1.0 (i.e., before the aerobic energy systems are maximized).

3.6.4 Limitations

Not all eligible participants known to the cardiology clinic were able to be contacted. The vast majority of eligible participants could not be contacted about this study because contacting patients solely for research purposes was prohibited by the CHEO Research Ethics Board. All patients being contacted for clinical matters were approached to participate, but the majority of eligible participants did not have a visit scheduled to the cardiology clinic during the data collection timeframe. Therefore, the small sample size is the main limitation, making it difficult to draw definitive conclusions. Another limitation was that 3 out of 7 (43%) of the participants with transposition of the great arteries were representative of the active population because their

$\dot{V}O_2$ at ventilatory threshold was above that of healthy children, suggesting that perhaps the physical activity and exercise data may be lower in the population as a whole. Also, the generalizability of the study results are restricted to children between the ages of 10 to 17 years, with CHD defined as either a single functioning ventricle, tetralogy of Fallot or transposition of the great arteries.

3.7 Conclusions

Higher oxygen consumption ($\dot{V}O_2$) at ventilatory threshold or at a heart rate of 130 bpm and higher METs at ventilatory threshold was associated with more daily minutes spent in moderate-to-vigorous physical activity, within our complex CHD cohort. These results suggest that children who achieve a $\dot{V}O_2$ at ventilatory threshold above 30 ml/kg*min⁻¹, a $\dot{V}O_2$ at a heart rate of 130 bpm above 23 ml/kg*min⁻¹ or at least 6 METs at ventilatory threshold are likely to meet the recommended target of 60 minutes of moderate-to-vigorous activity daily or vice versa. Clinicians may be able to utilize the submaximal results of an exercise test, rather than the current practice of child/parent verbal self-report, as a more objective measure of whether these children are likely to be meeting the recommended physical activity guideline. It is important to note that verbal self-reports of physical activity are more feasible to achieve during an appointment, but the submaximal results of an exercise test may be a more accurate surrogate assessment of physical activity. They may be more accurate because this indirect method of assessment would rely on the child's physical performance, rather than their perception about their personal physical activity levels. However, there is a need to educate clinicians on how to use the submaximal data gathered during a clinical exercise test to adequately decipher whether these children are likely meeting the physical activity guidelines (Ackerman et al., 2011; Bull & Milton, 2011; Lin et al., 2010) Higher $\dot{V}O_2$ at ventilatory threshold and METs at ventilatory

threshold were associated with lower days spent in cyanosis but, cyanosis exposure was not related to submaximal exercise measures below the limit of aerobic energy systems (ventilatory threshold). Therefore, despite differences in CHD diagnoses, all children from this complex CHD cohort should be encouraged to become increasingly active to obtain the health benefits associated with an active lifestyle.

3.8 Acknowledgements

The support of participating families and contributions from the cardiology clinic staff members are greatly appreciated. Specifically, we greatly appreciate the contributions of Denise Melo and Patrick Laplante to patient scheduling and the monitoring of cardiac function during the exercise tests. The Children's Hospital of Eastern Ontario Research Institute's (CHEO-RI) Research Growth Award funded this study. Tyler Kung was supported by the CHEO-RI Research Growth Award and the University of Ottawa.

3.9 Author's Contributions

TK – Study design, data analysis, writing, review and editing

JB – Data Analysis

JL – Review and editing

KA – Study design, data analysis, writing, review and editing

PEL – Study design, data analysis, writing, review and editing

3.10 Conflicts of Interest

None.

3.11 Tables and figures

Table 1. Descriptive characteristics of participants (N=16).

Descriptive Characteristics					
	Fontan	TOF	TGA	p	η^2
N	5	4	7	-	-
Age	13.2 $\pm$ 1.92	15.0 $\pm$ 2.2	14.1 $\pm$ 3.0	0.57	0.08
Sex	3 Females (60%)	3 Females (75%)	1 Female (14%)	0.11	0.29
Height (cm)	153.8 $\pm$ 12.1	160.5 $\pm$ 7.9	160.4 $\pm$ 24.5	0.80	0.03
Body mass (kg)	53.2 $\pm$ 21.1	74.6 $\pm$ 17.8	56.6 $\pm$ 29.7	0.42	0.13
Days in cyanosis	1288 $\pm$ 497.5 ^{a,b}	228.25 $\pm$ 57.3 ^a	8.86 $\pm$ 3.5 ^b	<0.01	0.84
Days alleviated from cyanosis	3691.4 $\pm$ 862.6 ^c	5338.25 $\pm$ 825.5	5285.29 $\pm$ 1052.9 ^c	0.03	0.43

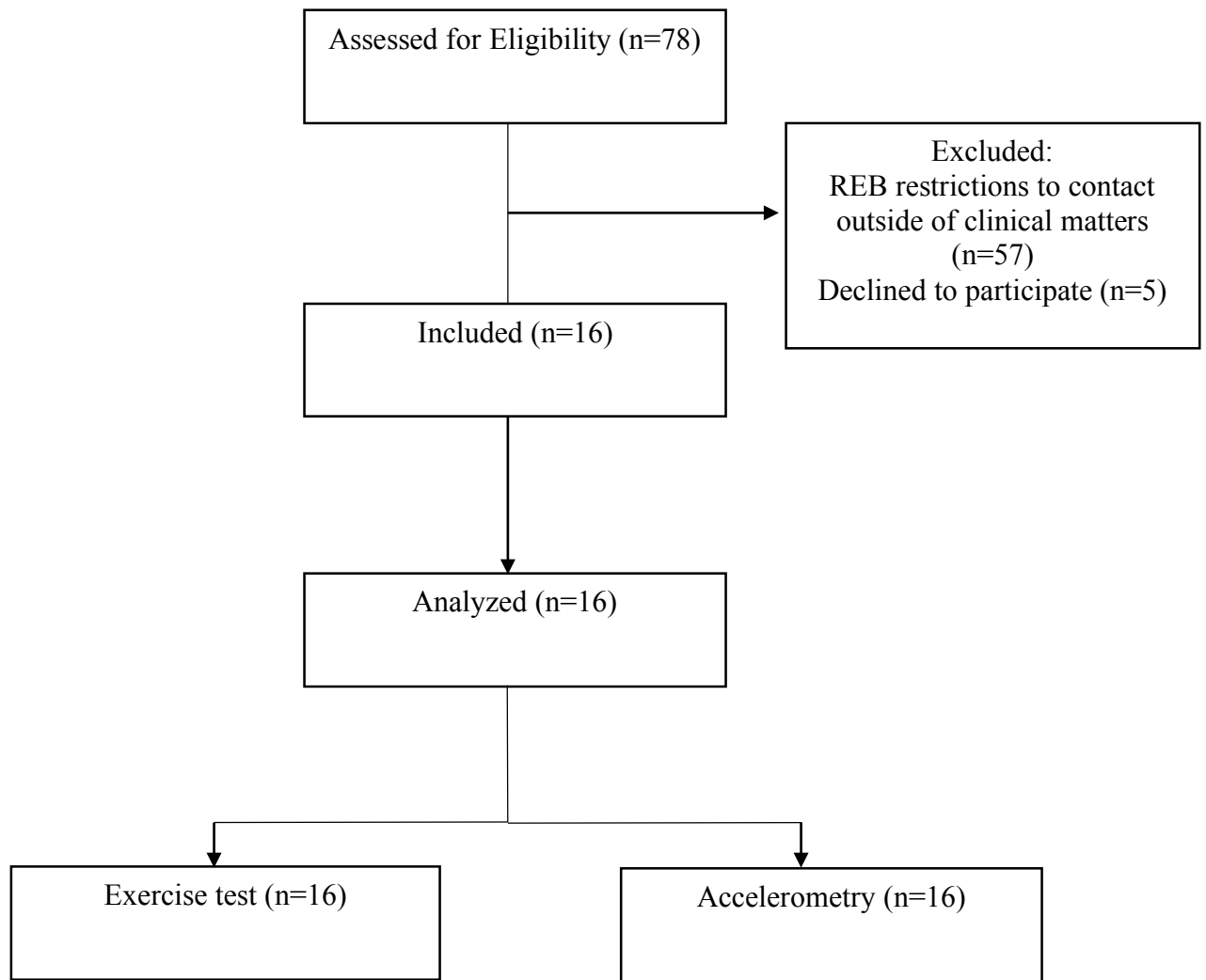
Note. The mean $\pm$ standard deviation, significance and effect size of descriptive characteristics by study group. Children with a Fontan procedure had significantly more days spent in cyanosis than children with tetralogy of Fallot and transposition of the great arteries^{a,b}. Children with a Fontan procedure also had significantly more days alleviated from cyanosis, than children with transposition of the great arteries^c.

Table 2. Submaximal exercise, resting and physical activity data by study groups (N=16).

	Fontan		TOF		TGA			
	<u>N</u>	<u>Mean ± SD</u>	<u>N</u>	<u>Mean ± SD</u>	<u>N</u>	<u>Mean ± SD</u>	<u>p</u>	<u>η²</u>
RMR	5	4.6 ± 0.7	4	4.2 ± 0.7	7	5.0 ± 1.1	0.33	0.16
$\dot{V}O_2$ at VT	5	19.6 ± 7.2 ^a	4	24.1 ± 2.4 ^b	7	36.9 ± 10.2 ^{a,b}	0.01	0.49
$\dot{V}O_2$ at 130bpm	5	20.9 ± 5.2	4	19.1 ± 5.1 ^c	7	27.6 ± 4.9 ^c	0.04	0.40
METs at VT	5	4.3 ± 1.8 ^d	4	5.9 ± 1.0	7	7.4 ± 1.1 ^d	0.01	0.46
METs at 130bpm	5	4.6 ± 0.9	4	4.7 ± 1.7	7	5.6 ± 0.9	0.28	0.18
HR after Stage 1	5	114.4 ± 20.4	4	126.5 ± 21.9	7	106.1 ± 15.3	0.25	0.19
MVPA	5	34.5 ± 16.6	4	29.4 ± 10.3	7	60.8 ± 27.0	0.06	0.36

Note. The number of participants, mean ± standard deviation and significance between groups of submaximal exercise testing, resting, and daily physical activity measures. List of abbreviations: TOF = Tetralogy of Fallot, TGA = Transposition of the great arteries, $\dot{V}O_2$ = Oxygen consumption, VT = Ventilatory threshold, bpm= Beats per minute, MVPA = Moderate-to-vigorous physical activity, METs = Metabolic equivalents, RMR = Resting metabolic rate. Children with transposition of the great arteries had a significantly higher $\dot{V}O_2$ at VT, than children with a Fontan procedure and tetralogy of Fallot^{a,b}. Children with transposition of the great arteries had a significantly higher $\dot{V}O_2$ at 130bpm, than children with tetralogy of Fallot^c. Children with transposition of the great arteries had significantly higher METs at VT, than children with a Fontan procedure^d.

Figure 1. Participant Flow Chart



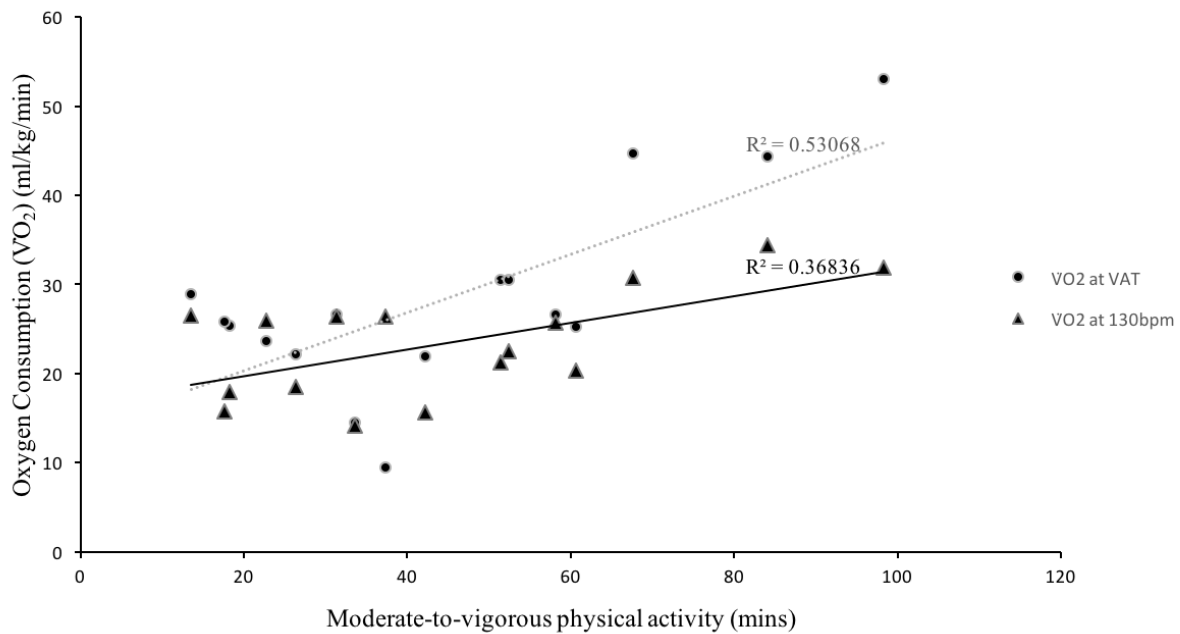


Figure 2 – The comparison between $\dot{V}O_2$ at ventilatory threshold (VT) and $\dot{V}O_2$ at a heart rate of 130 bpm ($\text{ml/kg} \cdot \text{min}^{-1}$), and the number of daily minutes spent in moderate-to-vigorous physical activity. The figure demonstrates a strong correlation between $\dot{V}O_2$ at VT ($R^2 = .53$) and a moderate correlation between $\dot{V}O_2$ at a heart rate of 130 bpm ($R^2 = .37$), and moderate-to-vigorous physical activity.

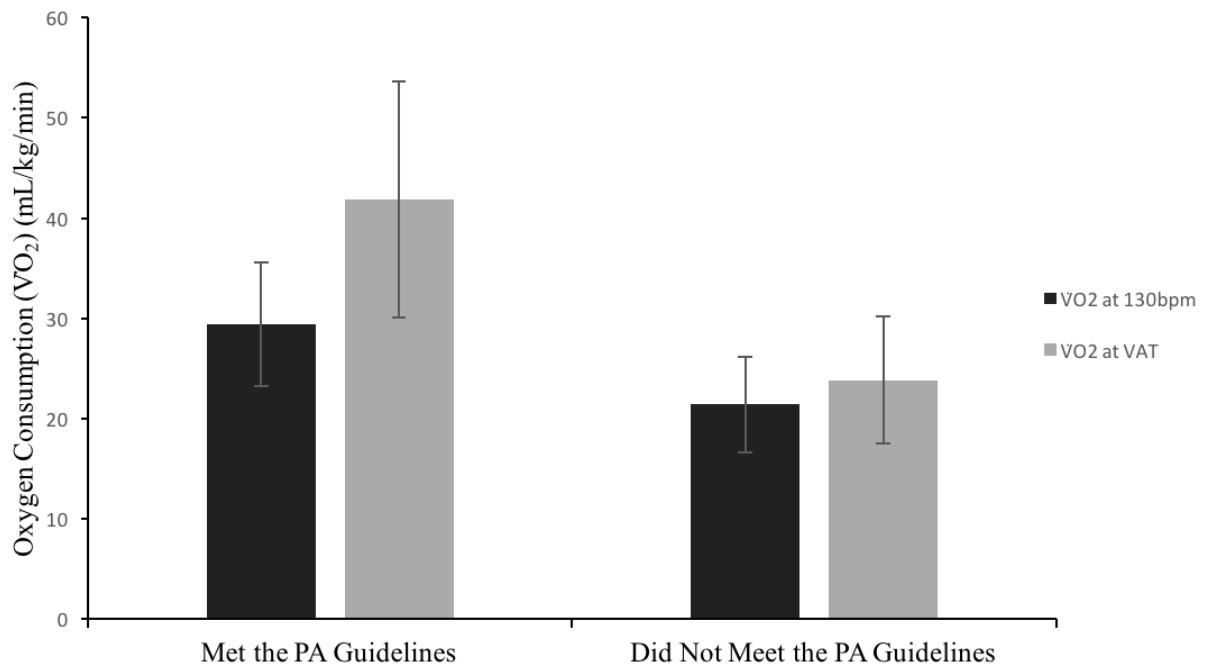


Figure 3 – Mean oxygen consumption ($\dot{V}O_2$) (mL/kg*min⁻¹) during submaximal exercise, at ventilatory threshold (VT) and a heart rate of 130 bpm, among children who did (n=4) and did not (n=12) meet the physical activity guideline of 60 minutes of moderate-to-vigorous physical activity per day.

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Part 4: Global Discussion

The goal of this research was to examine the submaximal exercise capacity of children born with a single functioning ventricle, tetralogy of Fallot or transposition of the great arteries. Specifically, we sought to examine the relationships between submaximal exercise capacity, daily physical activity, and cyanosis exposure.

4.1.1 Submaximal Exercise Capacity and Daily Physical Activity

As hypothesized, we observed an association between moderate-to-vigorous physical activity and submaximal exercise capacity (measured with $\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130bpm and METs at ventilatory threshold). To our knowledge, this was the first study to examine moderate-to-vigorous physical activity and submaximal exercise capacity in these clinical populations. Previous studies with a comparable population reported similar findings of an association between moderate-to-vigorous physical activity and peak exercise capacity (Banks et al., 2017; Müller et al., 2012). Our study focused on submaximal exercise capacity, but the association between exercise capacity and moderate-to-vigorous physical activity was similar.

It is important to note that one child with a single functioning ventricle and three children with transposition of the great arteries were able to attain the recommended 60 minutes of moderate-to-vigorous physical activity, but their ventilatory thresholds differed significantly (25.3 ± 4.4 ml/kg*min⁻¹ (single ventricle) versus 41.8 ± 11.79 ml/kg*min⁻¹). Given the difference in ventilatory threshold, the child with a single functioning ventricle who met the moderate-to-vigorous physical activity guidelines may have a changed energy system that enables higher physical activity levels. Future studies should evaluate the mechanisms through which these children can meet the recommended level of physical activity. For example, blood lactate

samples can be measured to determine how these children react to lactate accumulation in the blood during exercise.

4.1.2 Submaximal Exercise Capacity and Achieving the Recommended Guidelines

Currently, it is recommended that children perform 60 minutes of moderate-to-vigorous physical activity per day to achieve optimal health benefits (Canadian Society for Exercise Physiology, 2017). Our results provide preliminary data indicating that children who meet the moderate-to-vigorous physical activity guideline have a significantly higher $\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130 bpm and METs at ventilatory threshold, but not METs at a heart rate of 130 bpm. Our findings suggest that a $\dot{V}O_2$ at ventilatory threshold above 30 ml/kg*min⁻¹, a $\dot{V}O_2$ at 130 bpm above 23 ml/kg*min⁻¹ or more than 6.0 METs at ventilatory threshold would mean that these children are meeting the moderate-to-vigorous physical activity guidelines. These findings are potentially clinically relevant for the following reasons: 1) it provides clinicians with an alternative indirect method to assess daily physical activity and 2) results would assist cardiologists with exercise prescription, physical activity recommendations, a child's performance or assessed outcomes. Utilizing METs at ventilatory threshold as a guide to counsel children with CHD about their capacity to perform a variety of physical activities, based on data in the youth compendium by Butte and colleagues, (2017), should be investigated. Perhaps one might perform a cardiopulmonary exercise test to determine the child's ventilatory threshold and evaluate the child's performance on a variety of ergometers (with equivalent METs values).

4.1.3 Association Between Days Spent in Cyanosis and Ventilatory Threshold

Children with a single functioning ventricle, tetralogy of Fallot and transposition of the great arteries are all classified as a type of complex CHD. Despite similar CHD classification,

these children have varying days of cyanotic exposure from birth to their final surgical repair. As previously outlined, the length of cyanosis exposure varies greatly depending on the category of CHD. Children with a single functioning ventricle will be exposed for the longest period, followed by children with tetralogy of Fallot and then children with transposition of the great arteries. Our study found an association between a higher $\dot{V}O_2$ at ventilatory threshold and fewer days spent in cyanosis. This finding was expected because of previous research by Amedro and colleagues, (2017) and Reybrouck and colleagues, (1995), who found that children with a single functioning ventricle had the lowest $\dot{V}O_2$ at ventilatory threshold, when compared to healthy children or children with another congenital heart defect. This finding is similar to our study, but neither Amedro and colleagues, (2017) or Reybrouck and colleagues, (1995) took into consideration days spent in cyanosis. Our study took into consideration days spent in cyanosis to control for another variable that may have an influence on submaximal exercise capacity.

Our study results also found no association between $\dot{V}O_2$ at a heart rate of 130bpm ($RER = 0.89 \pm 0.09$) or heart rate at stage 1 of the Bruce protocol ($RER = 0.87 \pm 0.07$) and days spent in cyanosis. Considering ventilatory threshold occurred in our participants at an $RER \geq 1.0$, it suggests that ventilatory threshold was at the peak of aerobic metabolism (transitioning into primarily anaerobic metabolism). $\dot{V}O_2$ at a heart rate of 130bpm and heart rate at stage 1 of the Bruce protocol had an RER below the peak of aerobic metabolism ($RER = 0.89 \pm 0.09$ and $RER = 0.87 \pm 0.07$). Hypothetically, our participants may have experience physiological changes from days spent in cyanosis that impacted activities below an RER of 1.0. Future studies should investigate both central and peripheral mechanisms at submaximal intensities below the ventilatory threshold. One may conceivably test the influence of cardiac output and

arteriovenous oxygen difference on oxygen consumption at intensities below the ventilatory threshold.

4.1.4 Limitations

The main limitation of the present study was the small sample size. Not all eligible participants known to the cardiology clinic were able to be contacted because of Research Ethics Board restrictions. Participants were not permitted to be contacted outside of clinical matters, and the majority of eligible participants did not have a scheduled clinical visit. Although study results found significant relationships between submaximal exercise capacity, moderate-to-vigorous physical activity and using submaximal measures as a clinical indicator of daily physical activity, a larger sample size is required for definitive conclusions. Another limitation was that 43% of the children with transposition of the great arteries appear to be representative of a very active population. These children had a $\dot{V}O_2$ at ventilatory threshold well above that of healthy children, suggesting that the submaximal exercise capacity and moderate-to-vigorous physical activity levels reported in this study may not be representative of the population as a whole. Lastly, the generalizability of the study results is restricted to children between the ages of 10 to 17 years, with a single functioning ventricle, tetralogy of Fallot and transposition of the great arteries.

4.2 Conclusions

In conclusion, our study provides valuable clinical and physiological information about submaximal exercise capacity, moderate-to-vigorous physical activity and days spent in cyanosis in children with a single functioning ventricle, tetralogy of Fallot and transposition of the great arteries. Our findings indicate that higher $\dot{V}O_2$ at ventilatory threshold, $\dot{V}O_2$ at a heart rate of 130bpm and METs at ventilatory threshold are associated with more time spent in moderate-to-

vigorous physical activity. Preliminary results from this small sample suggest that children who achieve a $\dot{V}O_2$ at ventilatory threshold above $30 \text{ ml/kg}\cdot\text{min}^{-1}$, a $\dot{V}O_2$ at a heart rate of 130 bpm above $23 \text{ ml/kg}\cdot\text{min}^{-1}$ or at least 6 METs at ventilatory threshold are likely to meet the recommended target of 60 minutes of moderate-to-vigorous activity daily. Lastly, a higher $\dot{V}O_2$ at ventilatory threshold and METs at ventilatory threshold were associated with fewer days of exposure to cyanosis. Given that most daily physical activities are performed using a submaximal effort, these children should be encouraged to become increasingly active to obtain the health benefits associated with an active lifestyle.

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Part 6: Appendix I: CHEO's – Ethics Approval Documents

From: nanderson@cheo.on.ca
Sent: Friday, July 27, 2018 6:34 AM
To: Longmuir, Patricia
Cc: Kung, Tyler; Yaraskavitch, Jenna; Anderson, Natalie
Subject: ***Revised***REB Protocol No 18/62X - Final Approval - Delegated Review



CHEO Research Ethics Board Revised Approval - Delegated Review

Principal Investigator: Dr. Patricia Longmuir
REB Protocol No: 18/62X
Romeo File No: 20180241
Project Title: CHEOREB# 18/62X - The relationship between submaximal exercise capacity and physical activity behaviour in children with complex congenital heart disease
Primary Affiliation: HALO\HALO
Protocol Status: Active
Approval Date*: July 26, 2018
Approval Expiry Date:** July 15, 2019

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Other Document	Volunteer certificate	4/23/2018
Assent Form	REB Complex CHD - Assent Form - Cleaned version	7/25/2018
Consent Form	REB Complex CHD - Child Consent Form - Cleaned version	7/25/2018
Consent Form	REB Complex CHD - Parent Consent Form - Cleaned version	7/25/2018
Protocol	REB Complex CHD - Minimal Risk protocol - Cleaned version	7/25/2018
Other Document	Cardiology safety protocol.	4/23/2018

Recruitment Materials	REB Complex CHD - Recruitment Letter - Clean	7/15/2018
Recruitment Materials	REB Complex CHD - Letter from Chief of Pediatrics - Clean	7/15/2018
Recruitment Materials	Information sheet about the study	4/23/2018
Other Document	Actual Log Sheet	4/23/2018

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Your project was reviewed within the delegated stream, which is reserved for projects that involve no more than minimal risk to human participants.

Final approval is granted for the above noted study, with the understanding that the investigator agrees to comply with the following requirements:

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator is responsible for complying with all applicable guidelines and regulations regarding the ethical conduct of research with humans, as applicable to the research project.
3. Approval for studies that include an investigational device(s) is contingent upon the investigator securing an Investigational Testing Authorization notice from Health Canada.
4. Investigators must obtain annual renewal approval prior to the expiration date stated above.
5. The investigator must not implement any deviation from, or changes to, the protocol, consents or assents without the approval of the REB except where necessary to eliminate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review and approval.
6. The investigator must, prior to use, obtain approval from the Board for changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
7. Investigators must obtain approval from the Board of French version(s) of the consent/assent form(s), unless a waiver has been granted. An interpreter should be offered to participants as required or at the request of the participant throughout the course of research.
8. The investigator must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
9. Investigators must notify the REB of any study closures (closed to accrual, temporary, premature or permanent).
10. Investigators must submit a study closure event form at the conclusion of the study.

Should you have any questions or concerns, please do not hesitate to contact the Research Ethics Board Office at 613-737-7600 ext. 3350 or 2128.

Part 7: Appendix II: University of Ottawa – Ethics Approval Documents

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

24/08/2018
University of Ottawa
Office of Research Ethics and Integrity

Lettre d'approbation administrative | Letter of administrative approval

Numéro de dossier / Ethics File Number	H-08-18-978
Titre du projet / Project Title	The relationship between submaximal exercise capacity and physical activity behaviour in children with complex congenital heart disease
Type de projet / Project Type	Thèse de maîtrise / Master's thesis
CÉR primaire / Primary REB	CHEO / CHEO
Statut du projet / Project Status	Approuvé / Approved
Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)	24/08/2018
Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)	15/07/2019

Équipe de recherche / Research Team

Chercheur / Researcher	Affiliation	Role
Tyler KUNG	École des sciences de l'activité physique / School of Human Kinetics	Chercheur Principal / Principal Investigator
Patricia LONGMUIR	Département de pédiatrie / Department of Paediatrics	Superviseur / Supervisor
Kristi ADAMO	École des sciences de l'activité physique / School of Human Kinetics	Co-superviseur / Co-supervisor

Conditions spéciales ou commentaires / Special conditions or comments:

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Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

University of Ottawa

Office of Research Ethics and Integrity

L'Université d'Ottawa a signé une Entente, conforme aux exigences de la plus récente version de l'EPTC et tout autre règlement ou législation applicable, permettant au CÉR ci-haut nommé d'être désigné comme CÉR primaire pour les projets de recherche où

1) les activités principales de recherche sont menées sous l'autorité ou sous les auspices de l'établissement lié au CÉR primaire et

2) Une partie du projet est également réalisé sous l'autorité ou sous les auspices de l'Université d'Ottawa.

Cette lettre confirme que l'Université d'Ottawa a autorisé que le CÉR primaire soit le CÉR officiel pour l'évaluation et la supervision de ce projet de recherche. Ceci n'est pas une approbation éthique.

Afin de nous aider à garder votre dossier à jour, veuillez soumettre une copie de toutes demandes de modification, renouvellement d'approbation éthique etc. soumis à et approuvé par le CÉR primaire dès qu'elles sont disponibles.

Cette approbation administrative est valide pour la durée indiquée ci-haut et est sujette aux conditions énumérées dans la section intitulée « Conditions spéciales ou commentaires ».

The University of Ottawa has signed an Agreement, compliant with current TCPS guidelines and any other applicable guidelines or legislation regarding multisite review, allowing the REB named above to serve as Board of Record (BoR) for research projects where

1) the main research activities are conducted within the auspices or jurisdiction of the BoR's institution and

2) parts of the project are also conducted under the jurisdiction or auspices of the University of Ottawa.

This letter confirms that the University of Ottawa has authorized the REB named above to serve as Board of Record for the review and oversight of this research project. This is not an REB approval.

In order to help us keep your file up to date, please submit a copy of all amendment requests, project renewals or any other changes submitted to and approved by the BoR, as they become available.

Administrative approval is valid for the period indicated above and is subject to the conditions listed in the section entitled «Special conditions or comments».

Catherine PAQUET

Directeur / Director

Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences sociales et humanités / Social Sciences and Humanities Research Ethics Board**

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