

Autonomic Cardiovascular Regulation in Children  
with Hypoplastic Left Heart Syndrome  
and the Fontan Circulation

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By  
Stephanie Fusnik

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## ABSTRACT

**Background:** Hypoplastic left heart syndrome (HLHS) is a congenital heart disease phenotype where the left side of the heart is severely underdeveloped and cannot support systemic circulation. Children with HLHS undergo the Fontan operation, where the caval veins are attached to the pulmonary artery, and the right ventricle pumps blood through the aorta. Children with HLHS with Fontan circulation (HLHS-FC) have a reduced exercise tolerance and suffer from autonomic dysfunction. Understanding the role of autonomic dysfunction by studying the exercise pressor reflex through the stimulation of mechano- and metaboreceptors could provide further insight on potential mechanisms contributing to exercise intolerance. We hypothesized that children with HLHS-FC would have an augmented exercise pressor response resulting in increased sympathetic stimulation through mechano- and metaboreflex (handgrip) and metaboreflex only (post-exercise circulatory occlusion, PECO) as defined by change in mean arterial pressure (MAP) versus healthy controls (CTL). **Methods and Results:** Nine HLHS-FC (f=3, m=6; 13±4 y) and 9 CTL (f=3, m=6; 13±3 y) rested supine for 10 minutes to assess heart rate variability (HRV) and resting physiologic parameters, then performed 2 minutes of 40% maximal voluntary contraction isometric handgrip exercise, followed by 3 minutes of PECO on the exercised arm. Continuous blood pressure, heart rate (HR), ventilation, and forearm blood flow (FBF) of the contralateral limb were measured throughout the protocol. Children with HLHS-FC had lower resting heart rate variability (HRV) values of standard deviation of normal R-R intervals (31.9±32.4 vs. 70.4±24.0;  $P = 0.011$ ), root mean square of successive R-R interval differences (31.9±32.3 vs. 70.3±24.0;  $P = 0.011$ ), percentage of consecutive normal R-R intervals that differ by more than 50ms (19.8±28.2 vs. 44.7±18.8;  $P = 0.043$ ), low frequency power percentage (21.8±5.4 vs. 35.7±10.4;  $P = 0.003$ ), high frequency power percentage (31.5±15.4 vs. 46.8±9.7;  $P < 0.023$ ) than CTL. Mean arterial pressure (MAP) increased significantly less during handgrip (5±5mmHg vs 16±10mmHg;  $P < 0.001$ ) and PECO (4±5mmHg vs 14±9mmHg  $P = 0.002$ ) in HLHS-FC than CTL. There was a blunted exercise HR response in HLHS-FC compared to CTL (6±7 bpm vs. 24±8 bpm;  $P < 0.001$ ). Ventilation was lower in HLHS-FC than CTL during handgrip (0.32±1.15 L/min vs 3.36±3.94 L/min;  $P = 0.003$ ). In HLHS-FC FBF increased substantially during PECO when compared to rest (0 mL/min/m<sup>2</sup> vs 19.8±32.6 mL/min/m<sup>2</sup>;  $P = 0.012$ ) and handgrip (2.9±16.7 mL/min/m<sup>2</sup> vs 19.8±32.6 mL/min/m<sup>2</sup>;  $P = 0.036$ ). **Conclusion:** Children with HLHS-FC suffer from

autonomic dysfunction, with a sympathovagal balance favouring the sympathetic nervous system, and contrary to our hypothesis, have a blunted exercise pressor reflex response to increased sympathetic stimulation. The exercise pressor reflex may play a key role in the exercise intolerance encountered by children with HLHS-FC.

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## CHAPTER ONE

### 1.1 Introduction

Congenital heart disease (CHD) is classified as lesions present at birth that affect the structure and function of the heart (9), and is the world's leading birth defect (2, 10, 41). There is a wide range of severity in CHD, based on the size, location and other associated defects that come with each type of CHD. Approximately 1 in every 100 children in North America are born with CHD (2, 9, 10, 41). In 2010 it was estimated that there were approximately 2.4 million people living with CHD in the United States (2, 10, 41) and 257,000 in Canada (2, 9, 41). Approximately 85-90% of patients born with CHD in the past 20 years are expected to survive until the age of 18 (2, 9), but fewer than 50% of individuals born with severe CHD survive to this same age (2). Consequently, this improvement in survival rate has contributed to a continually growing population of young adults who will require life-long cardiac care related to their CHD (9). Some CHD phenotypes have been linked to genetic disorders, maternal conditions and environmental factors; however risk factors for the majority of CHD phenotypes are unknown (2). Most individuals with CHD require surgical intervention to survive with 55% of all CHD surgeries performed in newborns or infants, and 38% of corrective surgeries on children between one and 18 years of age (2). Unfortunately, 50% of individuals with CHD require two or more surgeries, and surgical intervention may not necessarily be curative (2). Individuals with CHD typically have comorbidities related to their cardiac condition that include, in part, exercise intolerance and/or restrictions, irregular heart rhythms, valve dysfunction and pulmonary hypertension (2). These health problems increase the risk of heart failure, stroke, thrombosis, myocardial infarction, and premature/sudden death (2, 10). The cost burden related to CHD on the health care system in the United States in 2009 for individuals with CHD under the age of 18 was approximately \$1.5 billion, and \$280 million for adults (2) and \$121.1 million in Canada for CHD related hospitalizations in 2013 (26).

There are much fewer resources allocated for the care of adults with CHD when compared to patients with other cardiac problems such as myocardial infarctions or heart failure (10). This results in longer wait times for clinical visits, and surgical interventions for individuals with CHD (10). Of all the adults with CHD in Canada, 77% are considered "lost in the system", suggesting that only 23% are actually followed by a physician on a semi-annual basis (10). Of all cardiologists in Canada, only 1.8% have received formal training in managing patients with CHD (10). An emerging issue related to CHD treatment is the

unanticipated need for transferring health records of CHD patients from pediatric to adult care providers, which further contributes to inadequate patient care for many individuals with CHD (10). The health care disparities for those with CHD characterize an extremely underfunded and under-researched area when compared to other areas of cardiac disease care and research.

## **1.2 Hypoplastic Left Heart Syndrome and Surgical Correction**

Hypoplastic left heart syndrome (HLHS) is a CHD phenotype where the left side of the heart is severely underdeveloped and cannot support systemic circulation (5). Systemic perfusion is decreased and without surgery, results in hypoxemia, acidosis and shock (4). The cause of the HLHS malformation is not fully understood (4). There are three surgeries a child must undergo in order to have a functional univentricular heart (4, 5). The first stage of palliation is known as the Norwood operation, which is performed at birth (4, 5). This surgery consists of creating a new aortic root and arch, disconnecting the pulmonary trunk from the pulmonary circulation and incorporating it into the systemic outflow tract (4, 5). A modified (Blalock-Taussig) shunt of approximately 3-4 mm in diameter is constructed in order to deliver blood to the lungs (4, 5). The shunting is performed in order to facilitate right ventricle ejection directly to the systemic circulation (4, 5). After this surgery the right ventricle is volume overloaded (approximately 250-350% of normal for body surface area) (18). This leads to overgrowth and eccentric hypertrophy of the ventricle, which can lead to dilation and pump dysfunction (18). At approximately 6-8 months of age the infant will undergo the second stage of palliation, the bi-directional Glenn operation (4, 5, 18). This procedure consists of anastomosis of the superior caval vein to the right pulmonary artery, and removal of the systemic-to-pulmonary arterial shunt (4, 5, 18). After this second phase of palliation the volume load of the ventricle is decreased to approximately 90% of normal for body surface area (18). Lastly, the Fontan operation is performed anywhere between 18 months and 4 years of age (4, 5). This final stage of palliation involves routing the inferior caval venous blood through a conduit placed in the wall of the right atrium, into the pulmonary arteries, or through an extracardiac conduit (4, 5). This completes the total cavopulmonary connection (4, 5). The Fontan procedure further decreases volume load of the ventricle to approximately 50-80% of normal for body surface area (18). Therefore, through the process of palliation the right ventricle goes from overloaded and overstretched, to overgrown and deprived, which results in systolic and diastolic dysfunction (18). Despite advances in medical technology and operation methods, individuals with HLHS with Fontan

circulation (HLHS-FC) continue to have the highest mortality of all CHD phenotypes (4, 5) due to some of the physiological downfalls that the Fontan circulation creates. One underlying factor that may influence mortality is a disruption in the normal functioning of the autonomic system, which can adversely affect cardiovascular regulation at rest and during exercise (13, 24, 33).

### **1.3 Fontan Circulation in HLHS**

Patients with the Fontan circulation can develop a variety of problems that include, in part, decreased exercise capacity, ventricular systolic and diastolic dysfunction, dysrhythmias, and cyanosis, all of which contribute to early mortality (18). There are 5 CHD phenotypes that can be palliated using the Fontan circulation, including HLHS. Individuals with Fontan circulation often suffer from venous congestion, low cardiac output, a large thick hypocontractile ventricle, and autonomic dysfunction (18).

In the Fontan circulation, unlike a biventricular heart, there is no pump to propel blood flow into the pulmonary arteries (Figure 1.1). The systemic veins are directly connected to the pulmonary arteries, and thus deoxygenated blood is passively transported to the lungs. The capillary beds pool blood into neighboring capillary beds, which significantly decreases output, due to the non-pulsatile flow. The pulmonary resistance created in this circulation decreases venous return through the pulmonary vascular bed (17, 18), potentially thickening the alveolar capillary membrane (27). A thicker alveolar capillary membrane leads to decreased diffusing capacity leading to decreased blood oxygenation (27). The increased pulmonary resistance also results in further congestion upstream and limits blood flow downstream, creating a “bottleneck-type” phenomenon (17, 18), which severely limits the performance of the whole circulatory system. The majority of the physiological and clinical conditions in those with Fontan circulation are due to the increased venous congestion and decreased cardiac output, caused by the increased pulmonary resistance (18).

In the Fontan circulation, the resistance within the capillary beds is the main contributing factor to low cardiac output (18). The blood flow through this system is determined by resistance within the capillary beds and the pressure on either side of the capillary bed. The pressure prior to the capillary bed is the systemic and pulmonary veins, and the pressure after the capillary bed is the ventricular filling pressure. However, the body can only tolerate a small range in ventricular filling pressure as well as in the systemic veins up to 20 mmHg (18). The inability to tolerate and change these pressures then leaves the main the determinant of cardiac output as the passive pooling created by the Fontan

circulation (18). The ventricle can provide enough driving force for the systemic circulation but is unable to compensate for the restriction that the Fontan circulation creates (18). The ventricle is incapable of pulling blood into the heart, as the amount of suction necessary is not physiologically possible (17, 18). The right ventricle is therefore no longer in control of cardiac output and cannot relieve any of the congestion in the systemic veins. Chronically the ventricle will dilate as a consequence of decreased flow, and the increased end-diastolic pressure, thus contributing to the worsening systemic venous congestion, and further decreasing output (17, 18). The Fontan circulation results in chronic blood volume deprivation of less than 70% of the preload expected for the size of the ventricle and leads to the development of the phenomenon termed ‘disuse hypofunction’ (18). Disuse hypofunction occurs from chronically low preload, which induces cardiac remodeling and dilation, and reduces ventricular compliance that subsequently increases filling pressure, all of which further reduces cardiac output (18). Although the ventricular diastolic suction is not the primary factor that reduces blood flow through the capillaries, over time ventricular function declines and thus goes from having a minimal role to becoming a major contributor of the declining Fontan circulation (15, 18).

The Fontan circulation also creates an abnormal environment for the pulmonary vascular bed. There is decreased blood flow, desaturation, increased collateral flow, mixing of superior and inferior caval flows, no pulsatile flow, endothelial dysfunction, and an absence of periods of high flow and high pressure with vessel recruitment which would normally occur during times of physical exertion (18). The chronic low flow conditions created by the Fontan circulation results in global vasoconstriction in order to maintain perfusion, through the stimulation of the sympathetic nervous system (SNS), which increases pulmonary vascular pressure immensely (18, 30). Therefore, the passive pooling of blood from capillary beds and the high pulmonary vascular resistance severely limits cardiac output, which in turn limits exercise capacity in individuals with the Fontan circulation.

#### **1.4 Exercise Intolerance in CHD Patients with Fontan Circulation**

Exercise intolerance is the single best independent predictor of mortality (21, 29), thus improving exercise tolerance of individuals with CHD should be a priority for improving quality of life and mitigating further disease risk. Successfully improving both quality of life and exercise capacity of individuals with CHD will help relieve some of the economic burden this population creates on the health care system as they age. The CHD phenotypes with one of the lowest levels of peak oxygen consumption and significant chronotropic incompetence

are those who have had the Fontan operation (14, 20, 23), such as those born with HLHS. Zajac and colleagues (45) determined that children with the Fontan circulation had significantly reduced peak  $\text{VO}_2$ , anaerobic threshold, peak minute ventilation (VE) and peak heart rate (HR) compared to healthy controls, as well as an increased physiological dead space to tidal volume ratio at peak exercise. Diller and colleagues (14) found that adults with Fontan circulation had a peak oxygen consumption of 20.9 mL/kg/min, and an extremely blunted exercise HR of 140 bpm at peak exercise. Larsson et al. (25) had findings similar to Zajac (45) in that lung volumes, maximal expiratory flows, diffusion capacity, and maximal oxygen uptake were significantly lower than predicted values in adults, mean of 25 years, with the Fontan circulation. Kempny and colleagues (23) also reported similar results where adults with Fontan circulation, with an mean of 20 years of age, had a peak  $\text{VO}_2$  of 59% of predicted values (mean peak  $\text{VO}_2$  of 22.8 mL/kg/min). These data illustrate that individuals who have undergone the Fontan operation have one of the lowest exercise capacities among all CHD phenotypes. Giardini and colleagues (20) and Ohuchi (35) are the only to have characterized individuals with HLHS-FC from those with hypoplastic right heart syndrome to date. Both reports concluded that individuals with HLHS-FC had significantly lower peak  $\text{VO}_2$  compared to those with hypoplastic right heart syndrome (56% vs 64% of predicted peak  $\text{VO}_2$ , respectively) and that the decline in peak  $\text{VO}_2$  was greater at rate of approximately 3.7% of predicted values per year in HLHS-FC compared to 1.7% for those with hypoplastic right heart syndrome (20). These prior data suggest that individuals with the Fontan circulation have poor exercise tolerance and consequently are at increased risk for poor health outcomes (15, 29, 31, 32, 40)

#### *1.4.1 Pulmonary Vascular Resistance*

The physiological limitations created by the Fontan circuit become quite evident during exercise. For example, healthy adults are able to increase pulmonary blood flow greatly during peak exercise, where as individuals with Fontan circulation demonstrate a marginal increase if at all (17–19). Normally a reduction in pulmonary vascular resistance is accomplished through vasodilation and increased right ventricular work (18). The increased work of the right ventricle (subpulmonary ventricle) accelerates blood flow into the pulmonary vessels as well as aids in the increase of systolic pressures (18). Without a subpulmonary ventricle in the Fontan circulation, it is not possible to increase and accelerate blood flow to the pulmonary vessels (14, 18). Blood flow is further limited by the Fontan circulation because it has limited or even absent vascular reactivity and recruitment of vessels

(14, 18). Normally the number and cross-sectional area of capillaries are increased upwards of 100% during exercise with pulsatile flow (22). The recruitment and dilation of capillaries leads to a 30% reduction in pulmonary vascular resistance, this however is not present in Fontan circulation (22). Consequently, there is lower blood flow through the pulmonary bed than normal, due to increased pulmonary vascular resistance. Pulmonary vascular resistance increases due to a lack of recruitment and dilation of capillaries, which confers a lesser preload and therefore less output through an impaired Frank-Starling mechanism.

#### *1.4.2 Preload and Afterload*

Preload of the heart has a large effect on cardiac output, which greatly determines exercise capacity. The lack of the subpulmonary pump, and the bottleneck-like physiology created by the passive capillary pooling, largely decreases the preload reserve (22, 30, 31). Stroke volume can therefore not increase without an increase in end-diastolic volume, and an increase in HR will only increase cardiac output a modest amount (30). Without a subpulmonary ventricle, the right ventricle is not able to generate adequate suction to pull blood through the capillaries in order to increase preload, which largely limits exercise capacity. Afterload is the force against which the heart must contract against in order to eject blood, and is determined by arterial blood pressure and vascular tone. Afterload is higher both at rest and exercise in the Fontan circulation compared to healthy controls. This is due to the need to maintain perfusion pressure, which is decreased due to the decrease in cardiac output. The perfusion pressure is maintained through the increase of sympathetic nerve activity (SNA) (30). The greater afterload is thus a consequence of reduced cardiac output, rather than the cause (22, 30). Although the ventricular afterload is not considered a limiting factor for exercise capacity, it may result in the heart having to generate greater work against the higher-pressure system. Because of the increase in filling pressures, poor ventricular filling and chronic exposure to high pressures can stimulate cardiac remodeling, subsequently leading to dilation and reduced compliance of the ventricle (17, 18) and the progression of heart failure.

#### *1.4.3 Heart Rate and Oxygen Uptake*

Heart rate and  $\text{VO}_2$  during peak exercise has been found to be significantly lower in individuals with the Fontan circulation than healthy controls (40). This is because  $\text{VO}_2$  is dependent on increasing cardiac output during exercise, and it is well known that cardiac output is decreased in these individuals (30). However, at any given cardiac output, individuals with the Fontan circulation will have a significantly higher relative  $\text{VO}_2$  than



healthy controls, which indicates some compensatory augmented use of O<sub>2</sub> in working muscle (30). The decreased preload created by the Fontan circulation, due to the lack of a subpulmonary ventricle, decreases stroke volume and peak cardiac output (30, 31). The blunted exercise stroke volume is normally compensated for, in part, by the quick increase in HR; however, in HLHS-FC the HR response is blunted and does not adequately compensate for the needed increase in cardiac output for the exercise demand (30, 31). An increased HR at peak exercise may not improve exercise capacity in individuals with the Fontan, including those with HLHS-FC, as is seen in individuals with a biventricular heart (30). Impaired ventricular diastolic function, along with the decreased preload, likely impairs diastolic filling of the ventricle at increased HR (30). At increased HR there is a reduction in diastolic filling time that could potentially decrease stroke volume in a heart with diastolic dysfunction, which could contribute to a reduced exercise capacity. Therefore a further increase in HR would not promote an increase in stroke volume or ejection fraction, and thus would not increase exercise capacity (30).

#### *1.4.4 Role of Perfusion Pressure During Exercise*

The low cardiac output is problematic during exercise as the body requires adequate pressure for perfusion (to ensure enough blood travels to the lungs and becomes oxygenated) as well as to provide blood and oxygen to the exercising muscles in order to meet metabolic demands. In healthy individuals, the level of blood pressure is maintained through the arterial baroreflex mechanism. The baroreceptors are located in the aortic arch and carotid bodies, and detect changes in blood pressure through mechanical distortion. During exercise the baroreflex mechanism resets to function at a higher pressure level (30, 36). At moderate and high intensities of exercise the muscle mechano- and metaboreflex function to vasoconstrict vessels in order to maintain perfusion pressure (discussed in section 1.6) (6). However, in the Fontan circulation the muscle metaboreflex is involved in achieving the proper perfusion pressure both at rest and mild exercise intensities (30). This is due to the severely impaired cardiac autonomic nervous activity, especially the diminished vagal activity (30). Greater reliance on the metaboreflex at rest and mild exercise intensities may cause global vasoconstriction, which further limits blood flow to metabolically active tissues during exercise. An additional mechanism in the Fontan circulation that maintains or increases perfusion pressure is the respiratory pump, which may also serve to augment cardiac venous return during mild exercise (30).

#### *1.4.5 Ventilation*

Individuals with the Fontan circulation have a greater minute VE at any given submaximal exercise intensity than healthy controls (7, 30, 45). Minute VE will typically increase rapidly during exercise in individuals with the Fontan circulation and this could be attributed to an increase in dead space VE due to a mismatch between alveolar VE and perfusion that is potentially secondary to the lack of a subpulmonary ventricle (30). The perfusion is the blood flow from the heart to the lungs and into the capillaries where oxygen and nutrient exchange occur, whereas the alveolar VE is the process of drawing air into the lungs. The low cardiac output in this circulation results in lower production of carbon dioxide and lower  $\text{VO}_2$  during exercise (30). The imbalance between alveolar VE and perfusion occurs because the pooling from capillary bed to capillary bed is too slow, and thus when the air reaches the alveoli it can not undergo oxygen extraction due to the lack of blood flow in the capillary beds from breath to breath. The imbalance between VE and perfusion leads to a lower partial arterial pressure of carbon dioxide, and the body attempts to compensate for this is through excessive VE (30). This mismatch influences exercise capacity because the exercising muscles are unable to get adequate levels of oxygen to keep up with demands for exercise, and can result in hypoxia, faintness, shortness of breath, muscular fatigue or confusion, which can be common in individuals with the Fontan circulation. This lack of oxygen can also increase reliance on the lactic anaerobic system, resulting in the accumulation of lactic acid, which further limits exercise capacity.

### **1.5 Autonomic Dysfunction in CHD**

Autonomic dysfunction is a common feature of CHD (13, 24, 33, 34, 36), and may contribute to exercise intolerance secondary to the underlying cardiac defect. Autonomic dysfunction occurs when there is an imbalance between the SNS and the parasympathetic nervous system (PNS). The sympathovagal balance is sympathetic dominant because of a reduction in vagus nerve tone (of the PNS), and results in three HR characteristics: a higher resting HR, blunted increase in HR during exercise, and slower HR recovery to baseline following exercise (14, 34). The blunted exercise HR is characteristic of chronotropic incompetence (14). These three HR features are common in patients with cardiovascular disease and CHD and are all associated with a decrease in exercise tolerance (15, 23), increased mortality (14, 23) and impaired autonomic function (34). Chronic high levels of sympathetic activity (SNA) results in global vasoconstriction at rest and during exercise, which increases total vascular peripheral resistance and thus blood pressure. This in turn, results in the heart having to contract against a higher afterload in order to eject blood from

the ventricle. If SNA remains chronically elevated the heart will undergo remodelling (42). The ventricle becomes enlarged due to increased filling pressures, and high afterload. Unfortunately, the heart will eventually become dilated, and reach a size where it is no longer efficient at pumping and the amount of blood left in the chamber after contraction (end systolic volume) begins to increase. This will further passively stretch the ventricle and further decrease heart pump function. This sustained sympathetic hyperactivity and increased blood pressure will then eventually lead to heart failure, to which there is no cure and the only option is a heart transplant (37, 42).

Heart rate variability (HRV) is a noninvasive technique for assessing autonomic control of the heart. HRV provides both time domain measures, and frequency domain measures. The three commonly interpreted frequency domain measures are low frequency (LF) (0.04-0.15 Hz) and high frequency (HF) (0.15-0.4 Hz) ranges, and a balance ratio between the two (LF/HF). The LF may represent sympathetic activity while the HF represents parasympathetic activity. Healthy individuals will have a lower LF/HF ratio, while those with autonomic dysfunction such as CHD and heart failure tend to have a higher LF/HF ratio, suggesting a more sympathetically dominant sympathovagal balance.

Both adults and children with the Fontan circulation have reduced resting HRV (8, 12, 13, 38). Lower HRV frequency and time domains are not only associated with a sympathetic dominant nervous system but are associated with an increased mortality, and hospitalization risk (43, 44). Dahlqvist et al. (12) found that children with the Fontan circulation with univentricular hearts had a significantly reduced LF and HF domains at rest than healthy controls. Studies conducted by both Butera et al. (8) and Rydberg et al. (38) measured HRV using 24-hour Holter monitoring and were consistent with those of Dahlqvist. However, the sub-group analysis of Rydberg et al. (38) on children below the age of 10 and above the age of 10 revealed that HRV progressively decreased over time, as there were greater differences compared to controls in the older age group, than controls in the younger age groups. Davos and colleagues (13) measured HRV in 8 male adults with the Fontan circulation and also found that LF and HF signals were significantly reduced when compared to healthy controls, implying a sympathovagal balance favouring the SNS. Although studies are lacking, there is some evidence of autonomic dysfunction in individuals with the Fontan circulation in that they are sympathetic dominant, and that there is a potential aging effect. These prior reports are limited for the following reasons: First they do not separate HLHS-FC from other CHD that are palliated with the Fontan circulation. Therefore they lack homogeneity in their

Fontan group, even though these various Fontan phenotypes may be physiologically different from one another. Secondly there is a need for studies with larger samples sizes, and be prospective in nature to provide more in depth knowledge about the autonomic dysfunction in various types of CHD that have the Fontan circulation to further understand its effect on exercise capacity and help guide future therapies.

### **1.6 The Exercise Pressor Reflex and its Possible Role for Exercise Intolerance in HLHS**

The exercise pressor reflex, which is made up of the mechano- and metaboreflex, can function as a mechanism for autonomic dysfunction, and demonstrate how it is exaggerated in individuals with CHD. The muscle mechano- and metaboreflex are muscle-based signaling mechanisms that stimulate the SNS, which results in increased HR, myocardial contractility, blood pressure and vasoconstriction (6, 16, 36). The vasoconstriction of vessels helps redirect blood flow to areas of the body that need it the most (36), such as the exercising muscles. Nitric oxide is released as a response to the shear stress of blood against the blood vessel wall at the muscle from the increased blood flow (36). Thus, nitric oxide induces vasodilation in muscle beds (16, 36), further redirecting blood flow to metabolically active tissues. This can be tested using handgrip exercise, which stimulates both the mechano- and metaboreflex, followed by post exercise circulatory occlusion (PECO) to isolate the stimulated metaboreflex only. In individuals who suffer from autonomic dysfunction, such as those with heart failure, the muscle metaboreflex is exaggerated (11, 28), and because of similarities in autonomic dysfunction between heart failure and HLHS-FC, may also be the case for children with HLHS-FC.

During exercise, the exercise pressor reflex is activated by the muscle mechanoreflex and muscle metaboreflex thus increasing sympathetic activity. The mechanoreflex is comprised of type III afferent neurons that are stimulated by the physical distortion of the mechanoreceptors during muscle contraction. The metaboreflex is activated as follows: First, metabolites that are produced as a by-product during muscle contraction stimulate the metabolically sensitive type III and IV muscle afferent fibres in skeletal muscle (1, 16). The stimulation signals the SNS to increase activity resulting in vasoconstriction of the vessels that feed oxygen and blood to the exercising muscles (16). Endothelial dysfunction in sympathetically dominant individuals causes the vessels feeding O<sub>2</sub> and blood to the exercising muscles to constrict rather than dilate during exercise. This is because the vessels are unable to override the sympathetic stimulation through the release of nitric oxide from the shear stress stimulation of the blood against the vessel walls. Normally the shear stress causes

nitric oxide to be released locally, inducing vasodilation, but sympathetic hyperactivity is so strong in those with autonomic dysfunction that it overrides the vasodilatory effects of the nitric oxide (39). The exaggeration of this sympathetic response has obvious implications on exercise tolerance (16), because vasoconstriction results in decreased blood flow to metabolically active tissues. With less blood available to the exercising muscles, there is less oxygen available, which results in higher muscle and blood lactate accumulation (3). Lactate accumulates due to a greater reliance on carbohydrate metabolism and/or reduced lactate removal (3). The muscle cells become too acidic as lactate levels increase and the body can no longer work at that intensity, thus limiting exercise capacity.

The mechanisms that govern the decreased exercise tolerance in individuals with the Fontan circulation are not well understood. Further investigation of the autonomic dysfunction and potential influence that the muscle metaboreflex has on exercise tolerance in HLHS-FC is important. The muscle metaboreflex influences vasoconstriction and vasodilation, which thus influences mean arterial pressure response during exercise. This is important to further examine given that an exaggerated muscle metaboreflex response can exasperate blood pressure and exercise tolerance, which increase risk for adverse cardiac events. Homogeneity of individuals in the Fontan group is also important in further research as previous findings have found differences in exercise tolerance and maintenance of exercise ability, thus individuals with different pre-Fontan lesions may be physiologically different. Therefore, therapies for individuals with the Fontan circulation may have to be specific to the type of congenital pre-Fontan lesion.

### **1.7 Purpose, Outcomes, and Hypotheses**

The majority of clinical physiology research completed in children with CHD has been retrospective in nature, with small sample sizes, and lacks homogeneity of participants, specifically those with the Fontan circulation. Individuals with the Fontan circulation can include those with tricuspid atresia, pulmonary atresia with hypoplastic right heart syndrome, double inlet left ventricle, double outlet right ventricle, and HLHS. It is unknown if the physiology between various pre-Fontan CHD lesions that are palliated using the Fontan operation differ.

#### *1.7.1 Purpose*

The purpose of this study was to determine the cardiovascular response to SNS activation subsequent to activation of the exercise pressor reflex from activation of the

mechano- and metaboreceptors (handgrip exercise) and metaboreceptors only (PECO) in children with HLHS-FC compared to healthy controls (CTL).

#### *1.7.2 Primary Hypothesis*

We hypothesized that children with HLHS-FC will have an augmented mean arterial blood pressure (MAP) response during handgrip exercise, which will remain elevated above rest during isolation of the muscle metaboreflex during PECO.

#### *1.7.3 Secondary Hypotheses*

We hypothesized that children with HLHS-FC will have a blunted HR during handgrip exercise, and return towards baseline levels during PECO. We hypothesized that forearm blood flow (FBF) would be reduced, and systemic vascular resistance (SVR) would be greater in HLHS-FC, compared to CTL during handgrip and PECO. We hypothesized that VE, and respiratory rate ( $f$ ) would be greater, and tidal volume (TV) would lower in HLHS-FC than CTL during handgrip and PECO.

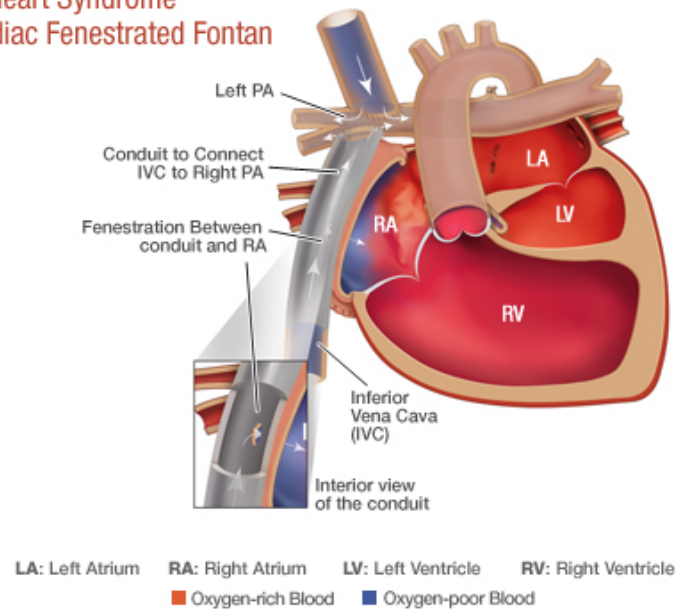
#### *1.7.4 Primary Outcome*

The primary outcome was the change in MAP from rest to handgrip and PECO.

#### *1.7.5 Secondary Outcomes*

Secondary outcomes were the change in HR, FBF, SVR, VE, TV, and  $f$  from rest to handgrip and PECO.

Hypoplastic Left Heart Syndrome  
Stage III Extracardiac Fenestrated Fontan



**Figure 1.1** Fontan circulation. The superior and inferior vena cava become connected to the pulmonary arteries. Blood by-passes the heart, through the pulmonary artery, to the lungs, and out through the pulmonary vein. The blood goes through the pulmonary vein goes into the left and right atrium, to the right ventricle and finally out through the aorta. Retrieved from: Children's Hospital of Philadelphia <http://www.hearts-of-hope.org/congenital-heart-disease/hlhs-treatment/stage-3-fontan/>

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## CHAPTER TWO

### 2.1 Introduction

Children with Fontan circulation have a reduced exercise tolerance, this may be secondary to autonomic dysfunction (15, 21, 24, 26, 30). There are a number of pre-Fontan congenital heart disease phenotypes that are palliated using the Fontan operation, such as hypoplastic left heart syndrome (HLHS). Children with HLHS lack a functional left ventricle and are characterized as one of the congenital heart disease phenotypes with the lowest exercise tolerance (8, 9, 11, 14, 16, 20, 30). Given that exercise intolerance is the single best predictor of mortality (13, 18), improving exercise tolerance and quality of life in this population should be a priority. However, the mechanisms underlying the severe exercise intolerance in HLHS with Fontan circulation (HLHS-FC) are not well understood.

Our understanding of determinants of exercise intolerance in Fontan patients is limited by prior studies not accounting for the various Fontan phenotypes. Notably, children with HLHS-FC have lower peak  $\text{VO}_2$  (56% predicted) than children with a hypoplastic right ventricle (64% predicted), and peak  $\text{VO}_2$  tends to decline at a faster rate in HLHS-FC (3.7%/year) compared to hypoplastic right heart syndrome patients (1.7%/year) (11). This prior work strongly suggests that the unfavorable physiologic changes that determine peak  $\text{VO}_2$  in HLHS-FC are more significant than other pre-Fontan etiologies.

One mechanism that may have an important role in the exercise intolerance observed in HLHS-FC could be related to the exercise pressor reflex. The exercise pressor reflex is modulated by mechano- and metaboreflexes that are activated during exercise to increase sympathetic activity. The mechanoreflex is stimulated by distortion of the mechanoreceptors during muscle contraction and the metaboreflex is stimulated by metabolic by-products produced during muscle contraction. The subsequent increase in sympathetic activity contributes to vasoconstriction and an exaggerated blood pressure response in individuals with autonomic dysfunction, which is characteristic of heart failure (1, 27, 29) and CHD patients (6, 15, 23). An exaggerated blood pressure response can adversely affect exercise tolerance due to vasoconstriction and reduced blood flow to exercising muscles. The exercise pressor reflex has not been studied in children with HLHS-FC, and therefore its contributing role to exercise intolerance observed in these children remains unknown.

The purpose of this study was to determine the cardiovascular response to sympathetic stimulation during exercise that engages mechano- and metaboreceptors (handgrip exercise) and metaboreceptors only (post-exercise circulatory occlusion, PECO) in

children with HLHS-FC versus healthy controls (CTL). The primary hypothesis was that mean arterial pressure (MAP) would be augmented and blood flow reduced as a consequence of an exaggerated exercise pressor reflex in children with HLHS-FC versus CTL.

## **2.2 Methods**

### *2.2.1 Participants*

A total of 18 participants were recruited for this study; 9 with HLHS-FC and 9 healthy controls (CTL) matched for sex and age. Inclusion criteria for HLHS-FC was to have undergone the Fontan procedure, be between the ages of 8-18 at the time of testing, be able to perform handgrip exercise for two minutes and follow verbal commands related to the experimental procedures. Participants with HLHS-FC were recruited through the Pediatric Cardiology Department at the Royal University Hospital in Saskatoon, Saskatchewan. A pediatric cardiologist screened patients and identified 10 individuals who met our inclusion criteria. These families were contacted and 9 agreed to participate. Individuals in the CTL group were recruited through word of mouth and social media. Inclusion criteria for the CTL group included being free from cardiovascular and respiratory disease, ability to perform 2 minutes of isometric handgrip exercise, and able to follow verbal commands related to the experimental procedures. Parents and/or legal guardians of child participants provided written consent (Appendix A and B) and children participants provided written assent (Appendix C and D). This study was approved by the University of Saskatchewan Research Ethics Board (Appendix E).

### *2.2.2 Testing Protocol*

Participants laid supine on a bed throughout the entirety of the test in a temperature controlled dimly light room. Participants were then instrumented with a finger blood pressure cuff and 3 lead ECG. Following a 10-minute resting period, a 5-minute HRV recording session was performed. Following, maximal handgrip strength was determined by having participants squeeze a handgrip dynamometer (MLT004/ST, ADInstruments, Bella Vista, NSW, Australia) with maximal effort three times with a 1-minute rest period between trials. Using the average of the three maximal trials, 40% maximum handgrip voluntary contraction (MVC) was calculated and used for subsequent testing. Participants then had a brief familiarization period where they practiced a continuous handgrip exercise test using a visual target of 40% MVC. Participants were then instrumented with a facemask that was connected to a pneumotach for the purpose of collecting ventilation data. On the left arm we determined probe placement for the duplex vascular ultrasound in order to measure FBF from the

brachial artery throughout the protocol. The probe was fastened into place using a custom probe holder. Once instrumented, the experimental protocol began with recording the participant at rest for 3 minutes, followed by 2 minutes of 40% MVC, and 3 minutes of post exercise circulatory occlusion (PECO). Five seconds before the 40% MVC stage was completed, a blood pressure cuff was inflated on the exercising arm at 50 mmHg above resting systolic blood pressure (circulatory occlusion) for 3 minutes. Protocol representative data highlighting handgrip exercise, PECO and blood pressure is shown in Figure 2.1.

### 2.2.3 Heart Rate Variability (HRV) and Heart Rate (HR)

Datum were recorded and integrated using a Powerlab data acquisition system and analysed using LabChart 8 software (Powerlab 16/30; ADInstruments). Continuous HR was measured using a 3-lead ECG in a lead II configuration. HRV analysis was performed on a 5-minute ECG recording sampled at 1000 Hz, and time domain and frequency domain data was calculated. Time domain HRV parameters included the standard deviation of normal R-R intervals (SDRR), the root mean square of successive R-R interval differences (RMSRR), and the percentage of consecutive normal R-R intervals that differ by more than 50ms (pNN50%). Power spectral HRV analyses included low frequency (LF) power (0.04 – 0.15 Hz), high frequency (HF) power (0.15 – 0.45 Hz), and the LF/HF ratio.

### 2.2.4 Mean Arterial Pressure (MAP)

Continuous mean arterial pressure was recorded using finger photoplethysmography (Finopress Midi, Amsterdam, The Netherlands) on the left hand. Resting blood pressure was measured using an automated blood pressure cuff (WelchAllyn, Skaneateles Fall, United States) for the purpose of calibrating our blood pressure readings using LabChart 8 (Units Conversion function) at time of automated measurement.

### 2.2.5 Forearm Blood Flow (FBF)

Continuous blood flow was measured from the left brachial artery (non-exercising limb) using duplex ultrasound (Logiq e, Wauwatosa) with a 12L-RS linear probe (5.0-13.0 MHz). Diameter and pulsed wave blood velocity data was measured from 10 consecutive beats on the ultrasound machine. Blood flow was calculated as  $\pi \times (D/2)^2 \times V_{\text{mean}} \times 60$ , where  $V_{\text{mean}}$  was mean blood velocity (cm/s) and  $D$  was arterial diameter (cm). Blood flow was then scaled to body surface area (BSA; Mosteller's method (17)) to account for differences in body size within and between HLHS-FC and CTL groups.

### 2.2.6 Systemic Vascular Resistance (SVR)

Systemic vascular resistance was calculated as the ratio between MAP and FBF.

### 2.2.7 Ventilation

Continuous flow was recorded breath-by-breath with a heated pneumotach (3830 series; Hans Rudolph, Shawnee) and flow was calibrated using a known volume to obtain VE, TV and *f*.

### 2.2.8 Data Analysis

Resting, handgrip and PECO data for HR, VE, TV, *f*, and MAP were analyzed as average values over 30 seconds. Resting, handgrip and PECO data for FBF and SVR were analyzed as average values over 10 beats within each 30-s window. To account for individual differences in physiologic responses that inherently contribute to increased group variance that subsequently masks physiological differences between groups, values during handgrip and PECO were subtracted from the respective baseline value for each participant (7, 10, 12). Baseline values were subsequently modified to a reference value of zero and were included in the analysis in order to facilitate addressing the study hypothesis. Data was analyzed with a 2 × 3 repeated measures ANOVA (group: HLHS-FC, CTL × condition: rest, handgrip, PECO) in SPSS (v24.0, Chicago, IL, USA) and Tukey post-hoc tests (SigmaPlot v13.0, Systat Software Inc. San Jose, CA, USA). If the assumption of sphericity was violated, degrees of freedom were adjusted using the Greenhouse-Geisser correction. If the assumption of homogeneity of variance was violated, between group analyses were performed with the Mann-Whitney U Rank Sum test. Data are reported as mean ± SD change from resting values ( $\Delta$ ). Demographic data, HRV data, and baseline physiologic characteristics were analyzed using unpaired *t*-tests. Significance for all testing was determined when  $P < 0.05$ . Appendix F details degrees of freedom, Greenhouse-Geisser corrected degrees of freedom, *F*-values, and specific non-parametric testing when used.

## 2.3 Results

### 2.3.1 Demographics

Age and BMI were not different between HLHS-FC and CTL groups (Table 2.1). Although there was no statistical difference the children with HLHS-FC tended to be smaller in stature, weight, and BMI. All CTL reported being regularly physically active (defined as 60+ min ×  $\geq 3$  days/week), where as all HLHS-FC reported being physically inactive. All children with HLHS-FC all took a daily dose of aspirin. We were satisfied with MVC effort levels during this protocol and individual participant MVC values are reported in Appendix G.

### 2.3.2 Heart Rate Variability

Children with HLHS-FC had lower SDRR, RMSSD ( $31.9\pm 32.3$  vs.  $70.3\pm 24.0$ ;  $P = 0.011$ ), pRR50% ( $19.8\pm 28.2$  vs.  $44.7\pm 18.8$ ;  $P = 0.043$ ), LF% ( $21.8\pm 5.4$  vs.  $35.7\pm 10.4$ ;  $P = 0.003$ ) and HF% ( $31.5\pm 15.4$  vs.  $46.8\pm 9.7$ ;  $P < 0.023$ ) than the CTL (Table 2.2). There was no difference in LF/HF ratio between groups ( $0.83\pm 0.40$  vs.  $0.82\pm 0.39$ ;  $P > 0.05$ ).

### 2.3.3 Baseline Physiologic Characteristics

Resting MAP, HR, FBF and VE did not differ between groups at rest (Table 2.3). Participants in the HLHS-FC group had a lower TV ( $0.59\pm 0.23$  vs.  $0.92\pm 0.18$ ;  $P = 0.005$ ), and higher  $f$  ( $22\pm 4$  vs  $17\pm 4$ ;  $P = 0.01$ ) and SVR ( $2.61\pm 1.6$  vs.  $1.13\pm 0.56$ ;  $P = 0.018$ ) than the CTL group.

### 2.3.4 Mean Arterial Pressure

Children with HLHS-FC had a lower change in MAP from rest to handgrip ( $5\pm 5$  mmHg vs.  $16\pm 10$  mmHg;  $P < 0.001$ ) and rest to PECO ( $4\pm 5$  mmHg vs.  $14\pm 9$  mmHg;  $P = 0.002$ ) than CTL (Figure 2.2). The increase in MAP was significant in CTL from rest to handgrip ( $16\pm 10$  mmHg;  $P < 0.001$ ) and from rest to PECO ( $14\pm 9$  mmHg;  $P < 0.001$ ), but not in HLHS-FC.

### 2.3.5 Heart Rate

Children with HLHS-FC had a lower change in HR from rest to handgrip ( $6\pm 7$  bpm vs.  $24\pm 8$  bpm;  $P < 0.001$ ) compared to CTL (Figure 2.3). The increase in HR was significant from rest to handgrip ( $24\pm 8$  bpm;  $P < 0.001$ ) and decreased significantly from handgrip to PECO ( $24\pm 8$  bpm vs  $4\pm 7$ ;  $P < 0.001$ ) in CTL.

### 2.3.6 Forearm Blood Flow

There was no difference in FBF between groups (Figure 2.4).

### 2.3.7 Systemic Vascular Resistance

Children with HLHS-FC had a significantly lower SVR during PECO than during handgrip ( $0.29\pm 0.67$  mmHg/ml/min vs  $-0.38\pm 0.65$  mmHg/ml/min;  $P = 0.001$ ) There was no difference in SVR between groups (Figure 2.5).

### 2.3.8 Respiratory Measures

VE was lower during handgrip in HLHS-FC than CTL ( $0.32\pm 1.15$  L/min vs  $3.36\pm 3.94$  L/min;  $P = 0.047$ ) (Figure 2.6). In CTL, VE increased during handgrip from rest ( $3.36\pm 3.94$  L/min;  $P < 0.001$ ) decreased significantly from handgrip to PECO ( $3.36\pm 3.94$  vs  $1.24\pm 2.59$ ;  $P = 0.025$ ). The change in TV was lower in HLHS-FC during handgrip than CTL ( $-0.01\pm 0.04$  ml vs  $0.17\pm 0.18$  ml;  $P = 0.024$ ) (Figure 2.7). In CTL, TV increased from rest to



handgrip ( $0.17 \pm 0.18$  ml;  $P = 0.002$ ) and decreased from handgrip to PECO ( $0.17 \pm 0.18$  ml vs  $0 \pm 0.10$ ;  $P = 0.003$ ), but not in HLHS-FC. There was no difference in  $f$  between groups (Figure 2.8).

## 2.4 Discussion

The major novel finding of this study is that, contrary to our hypothesis, MAP was lower during handgrip and PECO in HLHS-FC compared with CTL. During exercise, MAP normally increases and following circulatory occlusion MAP is expected to remain elevated due to sympathetic stimulation through isolation of the muscle metaboreflex (observed in CTL; Figure 2.2). HLHS-FC participants compared to CTL had a severely blunted MAP response to handgrip where we observed a negligible increase in MAP. When followed by circulatory occlusion, MAP remained elevated as expected but the magnitude of this response was also blunted. Our observation of an overall lower MAP during both mechano- and metaboreflexes suggests that the exercise pressor reflex is blunted in children with HLHS-FC. To our knowledge, this is the first study to characterize the exercise pressor reflex in children who have undergone the Fontan operation due exclusively to HLHS-FC.

### 2.4.1 Mechanisms Underlying a Blunted Exercise Pressor Reflex in HLHS-FC

Our data show that there was no difference in MAP at baseline between HLHS-FC and CTL. However, participants in the HLHS-FC group had a markedly reduced MAP response to both handgrip exercise and isolated muscle metaboreflex sympathetic stimulation than CTL. Prior research characterizing the blood pressure response to exercise in patients with the Fontan circulation is lacking. There has only been one study to date that employed handgrip exercise and circulatory occlusion to determine the muscle metaboreflex in both children and adults with Fontan circulation (4). A limitation of this previous work was the inclusion of a small sample ( $n = 6$ ), none of whom had an univentricular right heart (4). Brassard et al. (4) reported that only diastolic blood pressure differed between Fontan patients and CTL, where Fontan patients had a significantly higher diastolic blood pressure response to circulatory occlusion. Ohuchi (21, 22) found resting and peak exercise systolic blood pressures to be lower in patients with Fontan circulation than CTL. The lower blood pressure response to exercise is problematic as MAP has a role in maintaining proper perfusion pressure. In healthy individuals, parasympathetic withdrawal at exercise onset is responsible, in part, for increasing cardiac output to achieve proper perfusion and MAP. As exercise continues, mechano- and metaboreflexes from the contracting muscles and vasoconstrictive mechanisms provide additional sympathetic stimulation to further increase

MAP to necessary levels to maintain proper perfusion (20). The metaboreflex, when stimulated, is responsible, in part, for increasing or maintaining blood pressure to redistribute blood flow and blood volume through the vasoconstriction of non-active tissues. The increase in blood flow and blood volume through active muscle beds will decrease vascular resistance substantially. Elevated levels of blood pressure and metabolic by-product accumulation further trigger sympathetic activation. In the current investigation, our data suggests there is an impaired MAP response to exercise in children with HLHS-FC and therefore implicates abnormal function in one of these regulating systems. Patients with Fontan circulation tend to display less vagal tone at rest as suggested by our observation of a reduction in time domain HRV and alterations in the HRV frequency domain, which is consistent with several prior reports (5, 6, 24, 25). Results from our study support previous findings of significantly reduced HRV, however the previous studies looked at multiple Fontan phenotypes, making the participant group heterogeneous. Our study is the first to assess HRV in a very homogeneous group of children with HLHS-FC. This study further supplements the evidence of autonomic dysfunction in these individuals, which is of importance as it influences heart rate kinetics which is an independent predictor of cardiac events in adults with cardiovascular disease and various types of CHD (25). Cumulatively, hemodynamic abnormalities and autonomic dysfunction may adversely influence the ability of HLHS-FC participants to regulate MAP during exercise.

#### *2.4.2 Heart Rate*

Baseline measures of HR were similar between groups. Conflicting reports exist about whether resting HR is higher (4, 21, 22), similar (20, 25), or lower (15) in individuals with the Fontan circulation than CTL. It is important to note that the previous studies were conducted on heterogeneous groups of children with the Fontan circulation, and did not separate the different Fontan phenotypes.

During handgrip, the increase in HR was significantly lower in HLHS-FC than CTL. Changes in HR were significantly higher in CTL during handgrip when compared to rest and PECO. This observation supports prior and well documented findings of a blunted exercise HR in Fontan patients (4, 20–22, 25, 28). Two studies conducted by Ohuchi et al. (20, 25) reported an exaggerate rate of increase in HR at exercise onset, but an overall blunted HR response to exercise. The author suggested the rapid increase in HR occurred in an attempt to compensate for a lack of increase in stroke volume, and the blunted response could potentially be due to intrinsic sinus node dysfunction following cardiac surgery, as it is

associated with exercise-related HR dynamics (20, 25). Ohuchi et al. (22, 25) also reported measures of high sympathetic nerve activity (characteristic of patients with the Fontan circulation), and this may contribute to the blunted HR increase with exercise and is what contributes the most to low peak exercise HR. This is important to note as the change in HR from baseline to exercise is a predictor of future cardiac events, as the exercise HR reflects global cardiac autonomic dysfunction, and is an independent predictor in adult patients with ischemic heart disease and various CHD (25). Our findings of a blunted HR during handgrip and PECO provide further insight into exercise intolerance mechanisms.

#### *2.4.3 Forearm Blood Flow Responses to Handgrip and PECO*

We hypothesized the HLHS-FC group to have an exaggerated increase in SVR and decrease in FBF. We observed that FBF was similar between groups at rest and did not differ during handgrip and PECO between groups. However, we observed a trend in HLHS-FC with a FBF increase during PECO compared to rest and handgrip. One possible explanation for our observation of increased FBF during PECO could be secondary to the blunted exercise pressor reflex as evidenced the low MAP and HR responses during handgrip and PECO (for MAP only). Because HLHS-FC demonstrated a blunted HR during handgrip, it may follow that contractility, although not measured, may have compensated to facilitate cardiac output during handgrip. Subsequently, during PECO, ventricular contractility may have remained elevated thereby working to maintain an elevated cardiac output. An increased cardiac output coupled with hyporesponsive blood vessels to sympathetic activity, as evidenced by the low MAP response during PECO, may have facilitated a reduction in resistance during PECO and could lead to an increase in FBF. It is important to note that our observation is limited by not having simultaneously assessed cardiac output during the protocol, and FBF did not have a significant interaction.

Participants with HLHS-FC had significantly higher SVR at baseline than CTL, but the change in SVR during handgrip and PECO did not differ between groups. However, the change in SVR was significantly higher during handgrip than PECO in HLHS-FC, which could result in a decreased trend observed in FBF. Although further investigation is needed, we believe that because the exercise pressor response is blunted, there is a hypotensive response to sympathetic activity, which results in some vasodilation and thus a reduced SVR and increased FBF.

#### *2.4.4 Respiratory Responses to Handgrip and PECO*

There was no difference at baseline for VE between groups, but contrary to previous findings (19, 20), CTL had significantly higher increase in VE during handgrip than HLHS-FC. Studies conducted by Ohuchi et al. (19, 20) demonstrated that VE at any given intensity was higher in Fontan patients than CTL. They attributed enhanced VE to be secondary to one of two things; increased dead space due to a mismatch between ventilation and perfusion or reduced lung compliance from pulmonary congestion as is seen in heart failure patients (19, 20). Shafer et al. (28) did not find differences in VE between Fontan patients and healthy controls during cycle ergometer graded exercise tests. In that study, patients could potentially already be working near maximum contractility when cycling and therefore an increase in intrathoracic pressure during inspiration would not further increase cardiac output (28). Key differences between prior work and the present investigation include our experiment employing supine small muscle isometric handgrip exercise compared to cycle ergometry or treadmill testing that employs a large muscle mass (3, 19, 30).

The change in VE was significantly higher in CTL during handgrip compared to rest and PECO, which is consistent with previous reports in healthy individuals (2). It is anticipated that VE will increase during exercise, as the body needs to compensate for an increase in oxygen demand from the working muscles; this however did not occur in HLHS-FC.

Our data show that children with HLHS-FC had significantly lower baseline TV, and lower change in TV during handgrip than CTL, which is similar to previous studies (20). This finding suggests that there may be a potential increase in dead space created from the ventilation – perfusion mismatching that occurs during exercise in HLHS-FC (20).

As expected, the CTL change in TV was significantly higher during handgrip when compared to rest and PECO. During exercise, when there is an increased demand for O<sub>2</sub>, VE and TV increase to accommodate this demand. During exercise carbon dioxide production is increased, and an increase in TV allows for the removal of that carbon dioxide through exhalation.

Baseline data for  $f$  was significantly higher in HLHS-FC than CTL. When considering our VE and TV findings, it is not surprising that  $f$  at rest was higher in HLHS-FC. Since VE was similar at rest and TV was reduced,  $f$  would have to be increased in order to compensate for a lower TV, in order to maintain a similar VE to CTL. Our findings support previous studies in that there was no difference between or within groups during the experimental protocol (20).

## **2.5 Conclusion**

The present study demonstrated for the first time in a homogeneous group of children with HLHS-FC and the Fontan circulation that these children have a blunted exercise pressor reflex as defined by a reduced change in MAP and HR during handgrip exercise and reduced MAP during PECO compared to CTL. The blunted exercise pressor reflex in HLHS-FC was accompanied by an abnormal decrease in SVR from handgrip to PECO and a blunted ventilation response to HG and PECO. Cumulatively, our findings provide a possible mechanistic basis for the observed exercise intolerance in children with HLHS-FC.

**Table 2.1:** Participant demographics

	CTL	HLHS-FC
Age, yrs	13 ± 3	13 ± 4
Sex (f:m)	3:6	3:6
Height (cm)	161 ± 17	148 ± 17
Weight (kg)	55 ± 22	40 ± 18
BMI (kg/m <sup>2</sup> )	20 ± 5	18 ± 5
BSA (m <sup>2</sup> )	1.5 ± 0.4	1.2 ± 0.4

Values are mean ± SD. BSA, body surface area. CTL, controls; HLHS-FC, hypoplastic left heart syndrome with Fontan circulation

**Table 2.2:** Heart rate variability

	CTL	HLHS-FC	<i>P</i> -value
SDRR	75 ± 24	32 ± 32	0.011
RMSSD	70 ± 24	32 ± 32	0.011
pNN50%	45 ± 19	20 ± 28	0.043
LF%	36 ± 10	22 ± 5	0.003
HF%	47 ± 10	32 ± 16	0.023
LF/HF	0.82 ± 0.39	0.83 ± 0.40	0.941

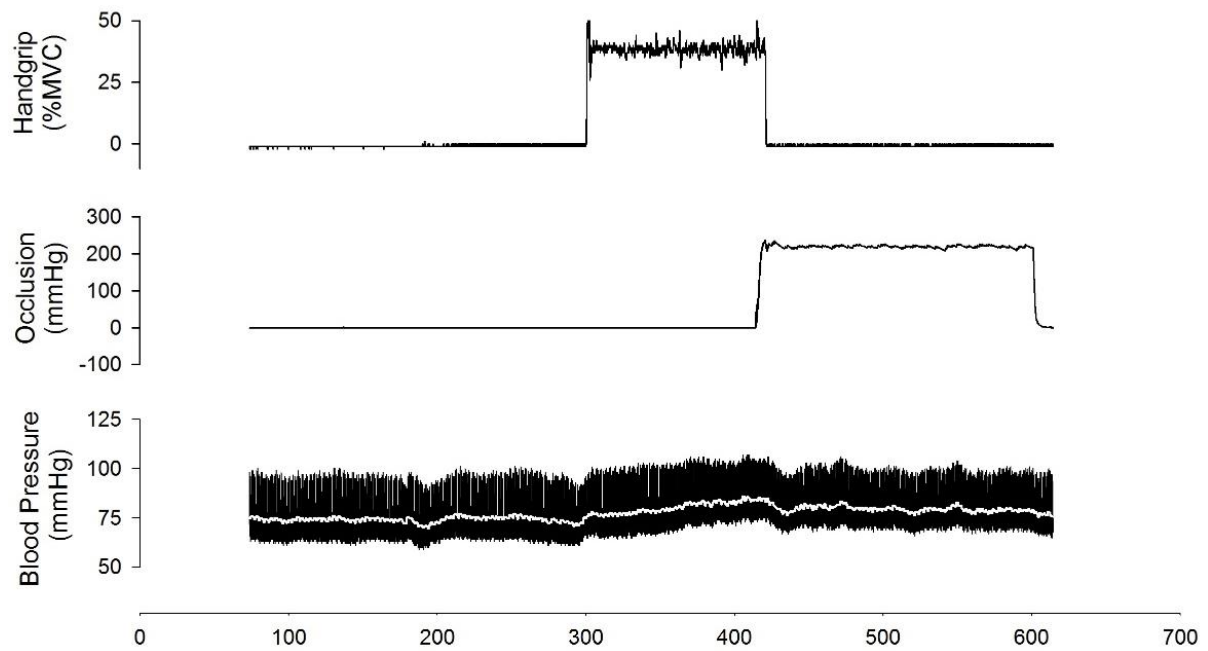
Values are mean ± SD. SDRR, standard deviation of normal R-R intervals; RMSSD, root mean square of successive R-R interval differences; pNN50%, percentage of consecutive normal R-R intervals that differ by more than 50 ms; LF, low frequency power; HF, high frequency power; LF/HF, low frequency to high frequency ratio; CTL, controls; HLHS-FC, hypoplastic left heart syndrome with Fontan circulation.

**Table 2.3:** Baseline physiologic characteristics

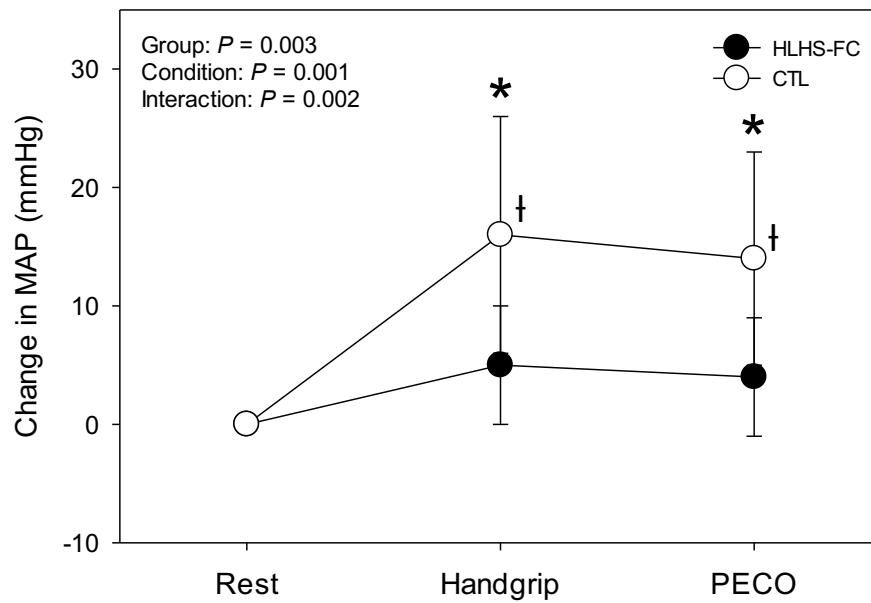
	CTL	HLHS-FC	<i>P</i> -value
MAP (mmHg)	75 ± 10	78 ± 10	0.401
HR (beats/min)	69 ± 9	75 ± 6	0.096
FBF (ml/min/m <sup>2</sup> )	41.3 ± 38.0	62.1 ± 46.0	0.312
SVR(mmHg/ml/min)	1.13 ± 0.56	2.61 ± 1.6	0.018
VE (L/min)	14.9 ± 3	12.4 ± 3.8	0.141
TV (L)	0.92 ± 0.18	0.59 ± 0.23	0.005
<i>f</i> (breaths/min)	17 ± 4	22 ± 4	0.010

Values are mean ± SD. MAP, mean arterial pressure; HR, heart rate; FBF, forearm blood flow; SVR, systemic vascular resistance; VE, ventilation; TV, tidal volume; *f*, respiratory rate; CTL, controls; HLHS-FC, hypoplastic left heart syndrome with Fontan circulation.

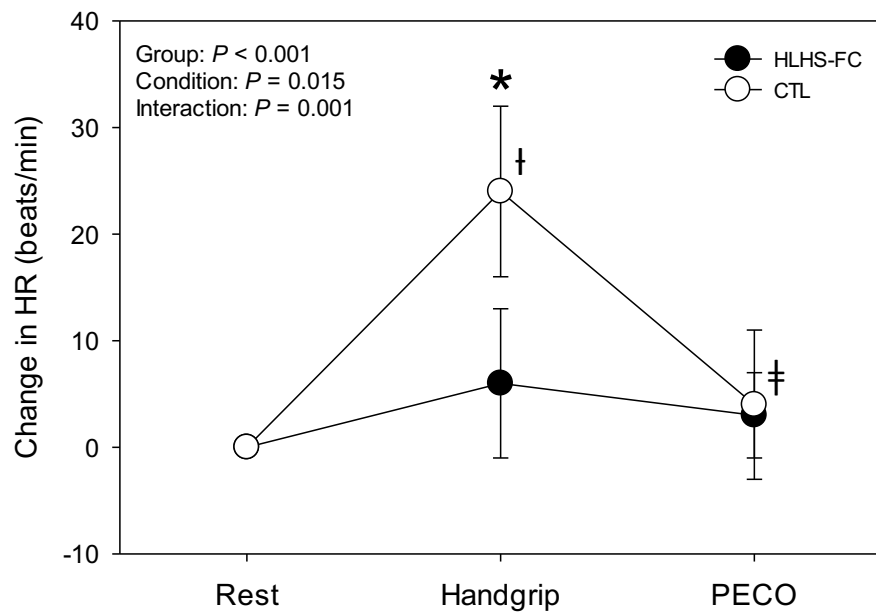




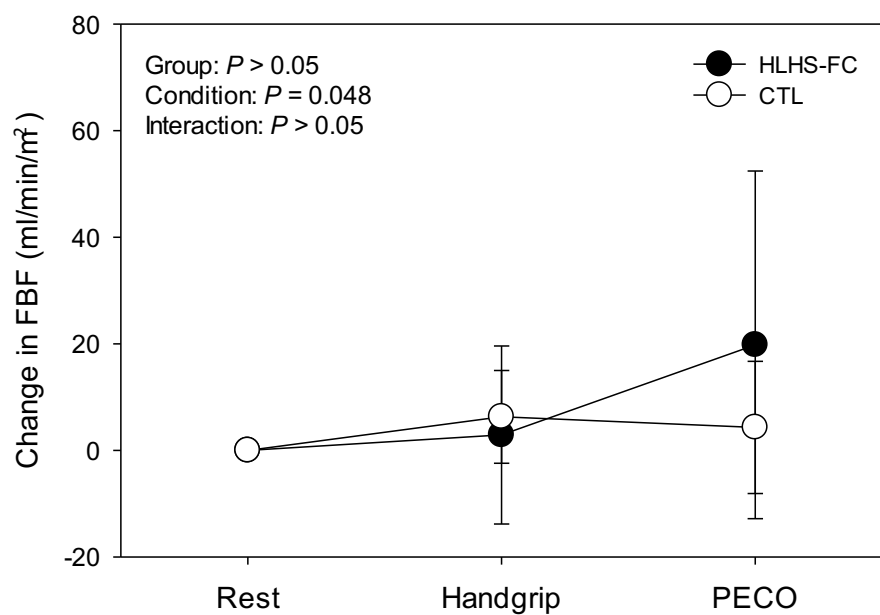
**Figure 2.1:** Representative data. Representative data from a participant in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group. Blood pressure was measured throughout the protocol (bottom panel), with mean arterial pressure (MAP) in white. First three minutes was resting data, followed by two minutes of handgrip isometric exercise at 40% maximum voluntary contraction (MVC) as seen in the top panel. Fifteen seconds before handgrip exercise was complete a blood pressure cuff was inflated to 50 mmHg above resting systolic values for three minutes (middle panel).



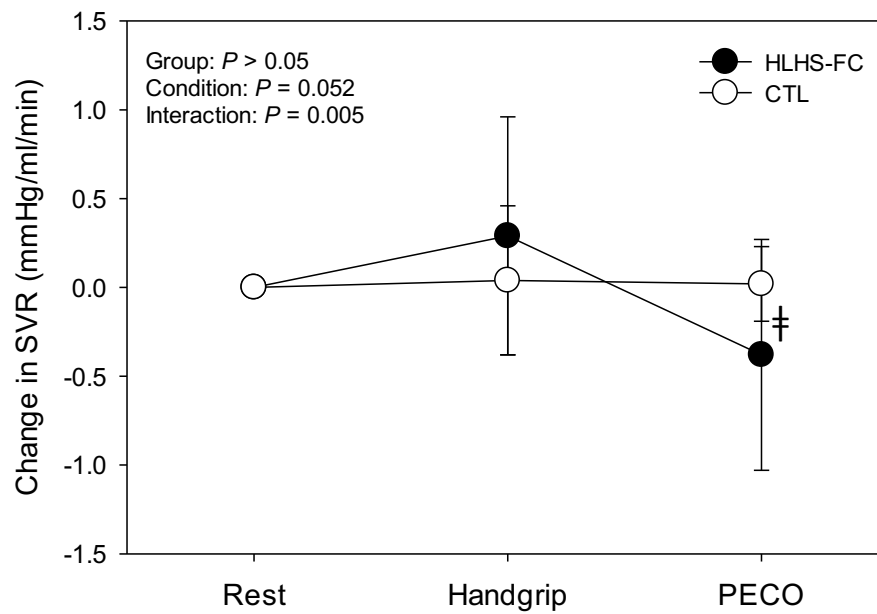
**Figure 2.2:** Change in mean arterial pressure (MAP). Change in MAP in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). \*Significantly different between groups ( $P < 0.01$ ); †Significantly different from rest within group ( $P < 0.001$ ). Values are means  $\pm$  SD.



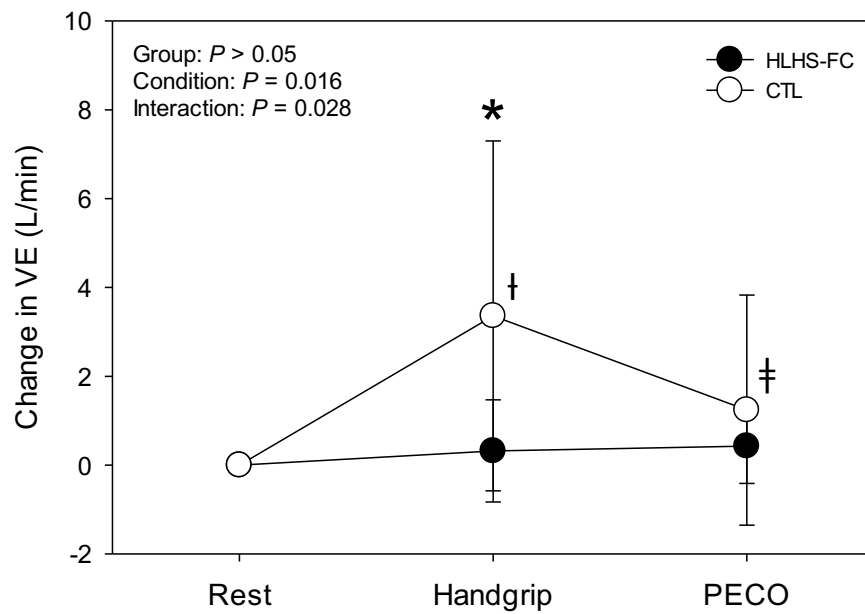
**Figure 2.3:** Change in heart rate (HR). Change in HR in hypoplastic left heart syndrome with Fontan circulation group (HLHS-FC) and control group (CTL) from rest during handgrip and post-exercise circulatory occlusion (PECO). \*Significantly different between groups ( $P=0.001$ ); ‡Significantly different from handgrip within CTL group ( $P<0.001$ ). †Significantly different from rest within CTL group ( $P<0.001$ ). Values are means  $\pm$  SD.



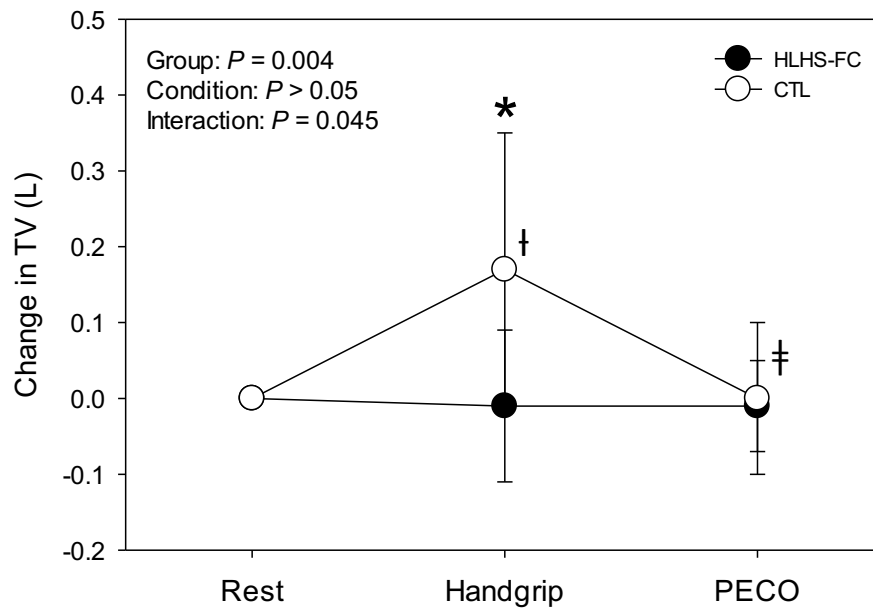
**Figure 2.4:** Change in forearm blood flow (FBF). Change in FBF in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). Values are means  $\pm$  SD.



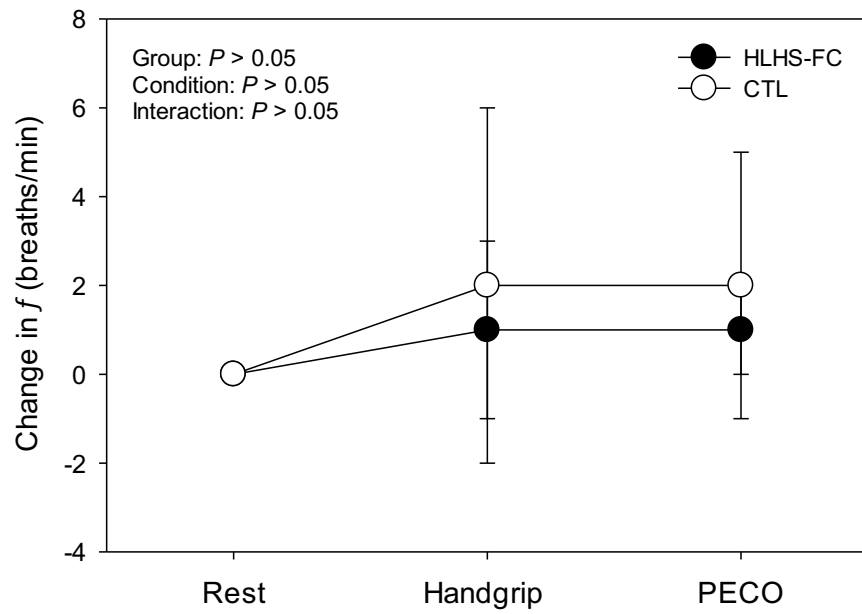
**Figure 2.5:** Change in systemic vascular resistance (SVR). Change in SVR in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). ‡Significantly different from handgrip within HLHS-FC group ( $P=0.001$ ). Values are means  $\pm$  SD.



**Figure 2.6:** Change in ventilation (VE). Change in ventilation in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). \*Significantly different between groups ( $P=0.047$ ). ‡Significantly different from handgrip within group ( $P=0.025$ ). †Significantly different from rest within group ( $P<0.001$ ). Values are means  $\pm$  SD.



**Figure 2.7:** Change in tidal volume (TV). Change in tidal volume in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). \*Significantly different between groups ( $P=0.024$ ). ‡Significantly different from handgrip within group ( $P=0.003$ ). †Significantly different from rest within group ( $P<0.001$ ). Values are means  $\pm$  SD.



**Figure 2.8:** Change in respiratory rate ( $f$ ). Change in  $f$  in hypoplastic left heart syndrome with Fontan circulation (HLHS-FC) group and control (CTL) group from rest during handgrip and post-exercise circulatory occlusion (PECO). Values are means  $\pm$  SD.



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## CHAPTER THREE

### 3.1 Discussion

The present study demonstrated for the first time, in a homogeneous sample of children with hypoplastic left heart syndrome (HLHS) and the Fontan circulation (HLHS-FC), a blunted exercise pressor reflex as defined by a lower change in mean arterial pressure (MAP) and heart rate (HR) during handgrip exercise and lower MAP during post-exercise circulatory occlusion (PECO) compared to controls (CTL). The exercise pressor response may play a key role in the autonomic dysfunction encountered by children with HLHS-FC. Our findings further support that children with HLHS-FC have reduced resting heart rate variability (HRV) and thus have a relatively sympathetic predominant sympathovagal balance. However, contrary to our hypothesis, MAP was blunted during handgrip and PECO, rather than augmented. In addition, our finding of a blunted HR response during handgrip exercise compared to CTL is consistent with prior reports (2, 25, 26, 29, 35, 37). We also observed an abnormal trend in FBF and a concomitant decrease in SVR in during PECO in children with HLHS-FC compared to CTL. Children with HLHS-FC demonstrated a decreased ventilation (VE) and tidal volume (TV) response to exercise. Cumulatively, our study illustrates that the autonomic dysfunction in children with HLHS-FC may affect the exercise pressor reflex. Based on several key similarities between children with HLHS-FC and adults with heart failure (HF, detailed below), we hypothesized that our experimental protocol (handgrip exercise and PECO) would adversely exacerbated MAP.

#### *3.1.1 Cardiovascular Similarities between Heart Failure (HF) and Fontan Patients*

We hypothesized that children with HLHS would have an exaggerated metaboreflex response and thus an exaggerated increase in MAP as is seen in HF patients (6, 7, 19), based on similarities in pathophysiology between both patient groups such as reduced  $VO_2$ , exercise HR, HRV, cardiac output, ejection fraction and high central venous pressure.

First and foremost, both individuals with the Fontan circulation and HF patients have reduced exercise tolerance objectively measured by  $VO_2$ . Kempny et al. (20) compared CHD phenotypes and found that individuals with the Fontan circulation had one of the lowest peak percent predicted  $VO_2$  values (59% predicted). Giardini et al. (16) compared predicted percent peak  $VO_2$  values and found children with HLHS ranged from 46-66% of predicted scores, which was lower than children with hypoplastic right heart syndrome who ranged from 53-75% of predicted scores. Shafer et al. (35) found that healthy children had a 50% higher increase in  $VO_2$  during submaximal exercise than children with the Fontan circulation.

Results from three studies originating from the same lab (26, 27, 29) consistently found that children with the Fontan circulation had significantly reduced peak  $\text{VO}_2$  ranging from 18-28 ml/kg/min. Patients with HF have significantly reduced exercise capacity with  $\text{VO}_2$  peak of 50% of healthy control values (21–23, 31, 36).

Children with the Fontan circulation and HF patients both have a blunted HR response to exercise. Shafter et al (35) found that exercise HR in children with the Fontan circulation was reduced by approximately 25%. Ohuchi found similar findings in four studies (26–29) where HR during exercise was significantly reduced in Fontan patients. Similarly, HF patients also suffer from chronotropic incompetence (3, 22).

Both patients with HF and HLHS-FC have a reduced resting HRV, suggesting marked changes in sympathovagal balance favoring relative sympathetic predominance at rest. Dahlqvist et al. (8) found that children with the Fontan circulation have significantly reduced LF and HF spectral signals at rest. Butera (4) and Rydberg (33) both determined HRV with 24-hour Holter monitoring in Fontan children and observed the same reduction in HRV as Dahlqvist (8). Davos and colleagues (10) measured HRV in adults with the Fontan circulation and also described similar findings of decreased HRV. Reduced resting HRV is also a typical characteristic of HF patients. Ponikowski et al. (31) and Bilchick et al. (1) not only found that HRV spectral domains were reduced in HF patients, but that these reductions also independently predicted mortality and sudden death. Both HLHS-FC and HF patients have unfavorable changes in HRV and are at increased risk for adverse cardiac events and mortality.

Reduced cardiac output and low ejection fraction are also characteristic of both Fontan and HF patients. Ohuchi et al. (27–29) assessed cardiac output and ejection fraction in Fontan patients and observed both to be significantly reduced when compared to controls at rest, but cardiac output and ejection fraction were not determined during exercise. Shafer et al. (35) also found cardiac output to be reduced at rest and during submaximal cycle ergometry exercise in children with the Fontan circulation compared to healthy controls. It appears that on average Fontan patients have an ejection fraction ranging from 50-80% of normal values when indexed for body surface area (11, 15, 28). Cardiac output during exercise in healthy individuals increases substantially, whereas Fontan patients increase only about 50% of that of controls (13–15, 34). Patients with HF may achieve less than 50% of maximal cardiac output than that achieved by healthy controls during exercise (3, 30), and cardiac output is also decreased at rest. Ejection fractions in HF are also markedly reduced

compared to healthy controls during rest and exercise at approximately 25% of control values (5).

Lastly, both HF and HLHS-FC demonstrate characteristically high central venous pressures, which results in the heart having a higher ventricular filling pressure in an attempt to increase ventricular diastolic filling. In three studies conducted by Ohuchi and colleagues (26, 27, 29) the authors reported central venous pressure at rest to be significantly higher in Fontan patients (5-15 mmHg) than in healthy controls (2-8 mmHg); this is also true for heart failure patients (24). This is worrisome as high central venous pressures are associated with increased risk for mortality (9).

### *3.1.2 Factors Influencing Mean Arterial Pressure*

Considering the above characteristic pathophysiological similarities between HF and HLHS-FC we hypothesized the exercise pressor reflex in children with HLHS-FC would be exaggerated during exercise, similar to patients with HF. This however was not the case and children with HLHS-FC demonstrated a blunted exercise pressor reflex as evidenced by a lower MAP during handgrip and PECO.

The arterial baroreflex is one mechanism that influences blood pressure regulation during exercise by controlling HR, contractility and SVR. An alteration in the baroreflex in HLHS-FC may help explain the blunted MAP response observed during handgrip exercise and PECO. Specifically, the baroreflex detects changes in blood pressure through baroreceptors, which are activated when stretched or deformed in the walls of the carotid sinuses and the aortic arch (32). When the baroreceptors are activated there is a decrease in sympathetic activity and increase in parasympathetic activity which in turn results in a decrease in cardiac contractility and SVR in order to decrease blood pressure (12, 32). During exercise, the baroreflex continues to regulate blood pressure by resetting around the exercise-induced elevated blood pressure to work at a new, higher “baseline” blood pressure (called the “set point”). However, when baroreflex sensitivity is reduced, as has been reported in individuals with the Fontan circulation (27, 28), a greater change in blood pressure is required in order to elicit an concomitant increase in sympathetic activity and increase HR and SVR. The reported decreased baroreceptor sensitivity in HLHS may be secondary to stiffening of the aortic and carotid sinus walls, subsequently conferring a greater pressure requirement for baroreceptor distortion or from a lack of unloading of the cardiopulmonary baroreceptors (12).

The cardiopulmonary baroreceptors are also mechanically sensitive receptors but are located in the heart, lungs, and great veins. Unloading of the cardiopulmonary baroreceptors caused by a decrease in central venous pressure improves arterial baroreceptor sensitivity and aids in the resetting of that reflex (12). The augmented central venous pressure in individuals with the Fontan circulation may continually load the cardiopulmonary baroreceptors during exercise, thus preventing the arterial baroreflex from resetting in order to function at a higher blood pressure level. Previous work has shown that baroreflex sensitivity is reduced in individuals with the Fontan circulation (27, 28), however this was not a feasible outcome in our study. We did attempt to measure baroreflex sensitivity from resting HR and systolic blood pressure data using the sequence method. However, this method requires the detection of spontaneous changes in blood pressure in three or more cardiac cycles accompanied with a change in HR in the same direction (positive or negative). The slope of the regression line between systolic blood pressure and R-R interval changes is used as an index of arterial baroreflex sensitivity. After performing the baroreflex sensitivity analysis, we found adequate sequences on only three HLHS-FC and six CTL. We were therefore unable to properly analyze and interpret the role of baroreflex sensitivity on blood pressure regulation in the present study.

Another major determinant of MAP is cardiac output, which has been shown to be reduced in children with the Fontan circulation (13–15, 28, 35). However, the cause for the low cardiac output is due primarily to the lack of a subpulmonary ventricle in the Fontan circulation (13–15), whereas a diastolic dysfunction and cardiac remodeling are responsible for a reduction in cardiac output in HF (5, 18, 22). In individuals with the Fontan circulation there is a blunted increase in stroke volume during exercise because central venous pressure is substantially high (27). The high venous pressure results in less blood flow to the heart and therefore the volume of blood pumped per beat can only increase slightly with an increase in contractility (26), thus resulting in a reduced cardiac output and MAP.

Heart rate is severely blunted during exercise in HLHS-FC, which reduces cardiac output and thus exercise tolerance. The blunted HR has been suggested to be a consequence of the autonomic dysfunction that characterizes this patient group (29). An interesting observation in our HLHS-FC study group was that although the participants demonstrated a blunted exercise pressor reflex, they were still able to complete the handgrip exercise task. Prior reports involving large muscle mass exercise in HLHS-FC have demonstrated a blunted low HR (26, 29, 35), and presumably blunted cardiac output. In the current study, however,

children with HLHS-FC were able to complete the handgrip exercise task, suggesting that perhaps there was a potential peripheral adaptation at the muscle that facilitated the exercise. An adaptation such as increased capillarization despite physical inactivity could cause children with HLHS-FC to be more efficient at extracting O<sub>2</sub> at the muscle. Greater oxygen extraction may compensate for poor cardiac output and could be one possible adaptive mechanism related secondary to exercise intolerance. Indeed, patients with HF classically demonstrate an often higher arterial-venous O<sub>2</sub> content difference at peak exercise compared to health controls (17). However, cardiac output was not directly measured in this study.

### **3.2 Clinical Relevance**

The findings from the current study have characterized novel mechanisms that, in part, may contribute to the previously reported exercise intolerance in children with HLHS-FC. Investigation of the determinants of exercise intolerance in children with HLHS-FC will aid in providing more specific and appropriate evidence-based exercise and rehabilitation guidelines that are currently lacking for HLHS-FC. Once key exercise determinants are established for individuals with HLHS-FC, then prospective exercise intervention studies can be conducted to examine the efficacy of targeted exercise therapies ameliorating exercise intolerance, thereby improving quality of life and conferring reduced mortality risk in this poorly understood population.

### **3.3 Limitations**

There were a number of limitations with the present study. The size of our sample could be perceived as a limitation, however we believe ours to be the only experiment of this kind performed on only children with HLHS. Because of limitation of prior work not differentiating pre-Fontan lesion, having an extremely homogenous group was a priority (16). Another limitation of our study was that vascular diameters were determined manually from duplex vascular ultrasound, and thus are prone to bias and variability. It is difficult to directly compare our investigation to other previous studies as ours employed supine isometric handgrip (small muscle mass) exercise, whereas previous studies used graded exercise tests on a cycle ergometer or treadmill, and did not utilize a PECO protocol (25, 27, 29, 35). However, by using handgrip exercise we were able to have a controlled experimental design that enabled specific determination of the possible exercise pressor reflex role on exercise tolerance.

### **3.4 Future Suggestions**



Future studies should compare children with HLHS-FC to CTL using a larger muscle mass to confirm if findings during exercise and PECO are similar to the smaller muscle mass experimental model used in the study. Assessing stroke volume, cardiac output and baroreflex sensitivity would provide a more complete picture as to the cardiovascular regulation in children with HLHS during exercise and PECO. Lastly, determining FBF in the exercising limb would provide a more physiologic representation of blood flow regulation where sympathetic vascular control is countered with local metabolic vasodilatory stimuli.

### **3.5 Conclusion**

The present study demonstrates for the first time in a homogenous group of children with HLHS and the Fontan circulation that the exercise pressor reflex is blunted, as evidenced by a reduced change in MAP and HR during handgrip and reduced MAP during PECO when compared to CTL. The blunted exercise pressor reflex was accompanied by a blunted VE response during handgrip and PECO. Cumulatively, our findings provide insight for a mechanistic basis for exercise intolerance observed in children with HLHS-FC and may help guide future studies, as well as exercise and therapy guidelines in this population.

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**APPENDIX A: HLHS-FC Consent Form**



## PARTICIPANT INFORMATION AND PARENTAL CONSENT FORM

### *A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS – Children’s Healthy Heart Camp in Saskatchewan*

**PRINCIPAL INVESTIGATOR:**

Dr. Marta Erlandson, College of Kinesiology  
Email: [marta.erlandson@usask.ca](mailto:marta.erlandson@usask.ca)  
Phone: 306-966-1071

**CO-PRINCIPAL INVESTIGATORS:**

Dr. Corey Tomczak, College of Kinesiology  
Email: [corey.tomczak@usask.ca](mailto:corey.tomczak@usask.ca)  
Phone: 306-966-1066

Dr. Kristi Wright, University of Regina  
Email: [Kristi.wright@uregina.ca](mailto:Kristi.wright@uregina.ca)  
Phone: 306-585-4772

**CO-INVESTIGATOR:**

Dr. Ashok Kakadekar, Pediatric Cardiology  
Email: [a.kakadekar@usask.ca](mailto:a.kakadekar@usask.ca)

Study funded by: Children’s Hospital Foundation of Saskatchewan

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**INTRODUCTION**

Your child is invited to participate in this study because he/she is between the ages of 7-15 and has a clinical diagnosis of a congenital heart defect. This study is looking at the physical and mental health of children with congenital heart defects compared to children without congenital heart defects. The study is also examining a 1-week summer camp style physical activity, heart health and psychological health intervention for children with congenital heart defects.

Your child’s participation is voluntary. It is up to him/her and you to decide whether or not he/she wishes to take part. If your child wishes to participate, you will be asked to sign this form. If he/she does decide to take part in this study, he/she is still free to withdraw at any time and without giving any reasons for the decision.

If your child does not wish to participate in the study, it will not affect his/her medical care in any way. Pediatric cardiologists and clinic staff will not know whether your child chooses to participate or not.

Please take time to read the following information carefully. You can ask the researcher to explain any words or information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

**WHO IS CONDUCTING THE STUDY?**

The study is led by Dr. Marta Erlandson, a faculty member in the College of Kinesiology at the University of Saskatchewan. This research is funded by the Children’s Hospital Foundation of Saskatchewan. Neither the University nor any of the investigators will receive any direct financial benefit for conducting this study.

### **WHY IS THIS STUDY BEING DONE?**

Congenital heart defects are the world's leading type of birth defect. Children with congenital heart defects have higher rates of physical inactivity and obesity compared to healthy peers. This may mean that children with congenital heart defects are more likely to have chronic conditions such as heart disease and poor bone health (osteoporosis) later in life. It has also been found that children with congenital heart defects have high levels of anxiety around physical activity participation. While we know that children with congenital heart defects have higher rates of obesity little is known about their muscle, bone and heart health. This study will look at important aspects of the physical and mental health of children with congenital heart defects.

Past research has highlighted the need for programming for children with congenital heart defects that involves healthy lifestyle counseling and physical activity participation. Parents of children with congenital heart defects have reported having minimal resources for knowing how to establish safe levels of physical activity for their children. Currently, there is no such program in Saskatchewan or Canada to help parents and children with congenital heart defects. This study will be the first step in developing a physical activity, heart health and psychological health program for children with congenital heart defects and their families.

### **WHO CAN PARTICIPATE IN THE STUDY?**

Your child is eligible to participate in this study if he/she is aged 7-15 years and has been cleared to participate by the pediatric cardiology team at the Royal University Hospital (RUH). Your child is not eligible if he/she: (1) had cardiac surgery in the last six months; (2) has cyanotic congenital heart disease; (3) has significant valve disease; (4) has any physical condition limiting physical activity; and/or (5) is unable to complete all the questionnaires.

### **WHAT DOES THE STUDY INVOLVE?**

The study involves two or three parts.

Part 1 involves a single visit to the Physical Activity Complex (PAC) at the University of Saskatchewan in June, July or August. This visit will take approximately four hours. During this visit, your child will be asked to complete a form with his/her personal information (such as name, telephone number, and date of birth) and will also be asked to complete, with your assistance if needed, questionnaires about his/her general health history, physical activity and psychological well-being (health related anxiety questionnaires). We will measure the following:

- Your child's height, sitting height, weight, waist circumference, and limb length.
- Your child's body composition using DXA (dual energy x-ray absorptiometry). DXA is a scan that is done while your child lies on his/her back on what looks like a padded x-ray table. We will measure his/her total body, hip and spine. The scan assesses total body bone, muscle and fat tissues. The scans take approximately 10 minutes and will expose your child to a minimal amount of radiation (less than 5 $\mu$ SV).
- Your child's bone shape and strength using a peripheral quantitative computed tomography (pQCT) scan of his/her non-dominant arm and lower leg (each scan takes about 2 minutes). For these scans your child will sit on a padded chair with his/her arm or leg resting on a support. All tests are painless and non-invasive. pQCT is a form of x-ray and therefore does emit a small amount of radiation. The total radiation for all measurements (DXA and pQCT) is less than 4 $\mu$ SV; this is comparable to the amount of background radiation a person receives in two days from naturally-occurring sources in Saskatchewan. For reference a cross-country flight could expose a person to about 30 $\mu$ SV of radiation (<http://www.hc-sc.gc.ca/hc-ps/ed-ud/respond/nuclea/measurements-mesures-eng.php>). All scans will be administered by trained and certified personnel.
- Your child's heart health using the following seven tests:



1. Three small stickers connected with a wire to our computer will be attached to your child's shoulders and stomach. The information from the stickers will tell us about the activity of your child's heart. The stickers are gentle on the skin and are the same ones that the hospital uses when it measures your child's heart activity. We will measure your child's heart activity while he/she lies on his/her back for ten minutes. This test does not cause any discomfort and there are no health risks associated with it.
2. The health of your child's blood vessels will be measured using a special machine at the same time as the first test. The machine uses a special pen that is placed on the skin to give a picture of your child's blood pressure. Your child will need to lie still for about 5 minutes. This test does not cause any discomfort and there are no health risks associated with it.
3. Your child's nerves and blood vessels will be tested by having your child squeeze a hand gripper for two minutes. After this we will inflate a blood pressure cuff and will keep it inflated for two to three minutes. While the cuff is inflated we will monitor your child's blood pressure. The handgrip test will be repeated without inflating a blood pressure cuff. During both handgrip tests we will measure blood pressure. This test can cause a slight tingling sensation in the arm from the blood pressure cuff. The sensation goes away when the cuff pressure is released.
4. Your child's fitness will be tested with a low-intensity walk test to see how far he/she can walk in 6 minutes. Your child will walk at his/her own speed back and forth in a hallway for 6 minutes. We will measure your child's heart rate and blood pressure before and after the walk test. The walk test is safe for those with heart problems because it is of low intensity and your child chooses how fast or slow he/she walks. We will closely monitor your child during the walk test.
5. Your child's fitness will also be tested using a stationary exercise bike while they breathe through a special mouthpiece that measures how much oxygen they use during exercise. This test will take 5 to 10 minutes. We will measure your child's blood pressure and monitor their breathing and heart activity. This test is also safe for those with heart problems in whom their condition is stable. As an extra precaution, a pediatric resident will monitor this test. This test will take a total of 30 minutes.
6. Your child's heart structure and function will be assessed using cardiac ultrasound. This assessment will entail your child lying restfully on their side for 30 minutes. During this time, Dr. Timothy Bradley (Pediatric Cardiologist) will use a special ultrasound machine to take pictures of your child's heart. The assessment will entail performing a series of images by placing a probe in different positions over your child's chest. This assessment is very safe, low risk, is entirely non-invasive, and places no stress on your child. This test will take a total of 30 minutes.
7. Your child's blood vessel function will also be measured using vascular ultrasound. This assessment will be performed while your child is doing the handgrip exercise test described in #3 above. The assessment will entail placing a probe over your child's arm. This assessment is very safe, low risk, is entirely non-invasive, and places no stress on your child. This test will not add any time to your child's session.

After the visit to the University, your child will be asked to wear an accelerometer for 7 consecutive days. An accelerometer is a type of motion sensor that measures your child's physical activity. It is a small device that will be worn around your child's waist on an elastic belt. He/she will be asked to put it on first thing in the morning and wear it all day except when bathing, swimming or playing contact sports. During your visit at the University, you will be provided with an addressed and stamped envelope to return the accelerometer after the seven days of wear.

Part 2 of the study involves a week long summer day-camp. This portion of the study will take place at the College of Kinesiology, University of Saskatchewan from August 10-14<sup>th</sup>, 2015. The program will run from 9am-5pm and will consist of three parts: (1) physical activity promotion and

participation; (2) heart health and health behavior; and (3) psychological well-being. Your child will be grouped based on age: younger (7-12) and older (13-15) and take part in activities that are age-appropriate. The physical activity portion will be of low to moderate intensity and comply with established international recommendations for children with congenital heart defects. Example activities include: swimming and ball and racquet sports. Your child will wear an accelerometer for the week long camp to assess the amount of physical activity. Your child will also engage in sessions on healthy eating, heart health, and how to detect his/her physical limitations (heart health and health behavior part). The psychological wellbeing part will focus on teaching your child healthy psychosocial coping mechanisms with a special emphasis on understanding and coping with anxiety related to physical activity participation. The program will incorporate many important health aspects but will do so in a fun, summer camp style of programming. During the Camp we will also assess your child's physical literacy; their ability to run, jump, throw and catch and have you fill out a questionnaire about your perceptions of their ability to move confidently. To assess your and your child's satisfaction with the program we will ask both of you to fill out a short questionnaire when you pick your child up on the last day. After the week long program your child will be mailed an accelerometer to once again wear for seven consecutive days along with an addressed and stamped envelope to return it after the seven days.

Part 3 of this study will include a small sample of parents and children so you may or may not be invited to participate in a focus group held at the Social Science Research Lab at the University of Saskatchewan in late August or early September. The focus group will look at satisfaction with the camp, what participants liked and would like to see changed in future programming.

If you consent, we may take photographs of your child during the study that would be used only for research and/or teaching presentations. These photographs would be de-identified so your child's face would not be recognizable.

### **WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**

There may be no direct benefit to your child from participating in this study. Your child will get to participate in the week long program aimed to teach your child how to detect his/her physical limitations with regard to physical activity and provide him/her with the tools cope with health related physical activity anxiety and hopefully empower him/her to be more physically active. It is hoped that the information gained from this study can be used in the future to create a sustainable program for children with congenital heart defects.

### **ARE THERE POSSIBLE RISKS AND DISCOMFORTS?**

The risks of participating are minimal. The fitness test on a stationary bike will assess your child's exercise capacity. During this test, your child may feel a few minutes of physical fatigue that comes with exercise. They also may experience some leg soreness as a consequence of this test, but this should disappear within 2 days. This stationary bike test is safe and the intensity of how hard your child exercises is determined by your child. As an extra precaution, a pediatric resident will supervise the stationary bike test. As stated above, the bone measures (DXA and pQCT) will expose your child to a minimal amount of radiation. These tests are very low risk; the total radiation dose for each study visit is less than half of that of a standard chest x-ray. As with any physical activity there is the potential of physical injury or discomfort. Your child may experience sore muscles after the six minute walk test. If your child experiences soreness it will not last very long. We have taken every precaution to ensure all physical activity during the camp will be safe for your child and a pediatric resident will be at the weeklong camp in the unlikely event that medical attention is needed.

### **WHAT HAPPENS IF I DECIDE TO WITHDRAW?**

Your child's participation in this research is voluntary. He/she may withdraw from this study at any time. You do not have to provide a reason. Your child's relationship with the department of pediatric cardiology will not be affected and pediatric cardiologists and clinic staff will not be informed.

If your child chooses to enter the study and then decides to withdraw later, all data collected about him/her during his/her enrolment will be retained for analysis.

**WHAT WILL THE STUDY COST ME?**

You will not be charged for any research-related procedures and your child will not be paid for participating in this study. Your parking costs at the University for the Part 1 visit will be covered.

**WHAT HAPPENS IF SOMETHING GOES WRONG?**

In the unlikely event that your child is injured while participating in this research, appropriate medical care will be provided at no cost to you. By signing this document, you and your child do not waive any of your legal rights.

**WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?**

Your child's confidentiality will be respected. No information that discloses your child's identity will be released or published without your specific consent to the disclosure. The information collected in this study will be stored in the locked office of the PI, Dr. Marta Erlandson. The results of this study may be presented in a scientific meeting or published, but your child's identity will not be disclosed. If you consent we may use de-identified photographs of your child for the purpose of research and/or teaching presentations.

**WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?**

If you have any questions or desire further information about this study before or during participation, you can contact Marta Erlandson by phone at 306-966-1071 or by email at [marta.erlandson@usask.ca](mailto:marta.erlandson@usask.ca).

If you have any concerns about your child's rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975(out of town calls 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.



***A Pilot Health Intervention Study of Children with Congenital Heart Defect: CHAMPS – Children’s Healthy Heart Camp in Saskatchewan***

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I understand that my child is free to withdraw from this study at any time for any reason.
- I have been informed that there is no guarantee that this study will provide any benefits to my child.
- I give permission to the use and disclosure of my child’s de-identified information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my or my child’s legal rights.
- I understand I will be given a signed copy of this consent form.

I agree to allow de-identified photographs of my child to be used for research and/or teaching presentations:

- Yes
- No

I agree to allow my child to participate in this study:

Printed name of person providing consent: \_\_\_\_\_

Signature of Consenting Parent: \_\_\_\_\_ Date \_\_\_\_\_

Printed name of person obtaining consent: \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

**APPENDIX B: CTL Consent Form**



## PARTICIPANT INFORMATION AND PARENTAL CONSENT FORM

### *A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS – Children’s Healthy Heart Camp in Saskatchewan*

#### **PRINCIPAL INVESTIGATOR:**

Dr. Marta Erlandson, College of Kinesiology  
Email: marta.erlandson@usask.ca  
Phone: 306-966-1071

#### **CO-PRINCIPAL INVESTIGATORS:**

Dr. Corey Tomczak, College of Kinesiology  
Email: corey.tomczak@usask.ca  
Phone: 306-966-1066

Dr. Kristi Wright, University of Regina  
Email: Kristi.wright@uregina.ca  
306-585-4772

#### **CO-INVESTIGATOR:**

Dr. Ashok Kakadekar, Pediatric Cardiology  
Email: a.kakadekar@usask.ca

Study funded by: Children’s Hospital Foundation of Saskatchewan

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#### **INTRODUCTION**

Your child is being invited to participate in this study because he/she is between the ages of 7-15 and is a healthy child with no history of heart problems. This study is looking at the physical and mental health of children with congenital heart defects compared to healthy children.

Your child’s participation is voluntary. It is up to him/her and you to decide whether or not he/she wishes to take part. If your child wishes to participate, you will be asked to sign this form. If he/she does decide to take part in this study, he/she is still free to withdraw at any time and without giving any reasons for the decision.

Please take time to read the following information carefully. You can ask the researcher to explain any words or information that you do not clearly understand. You may ask as many questions as you need. Please feel free to discuss this with your family, friends or family physician before you decide.

#### **WHO IS CONDUCTING THE STUDY?**

The study is led by Dr. Marta Erlandson, a faculty member in the College of Kinesiology at the University of Saskatchewan. This research is funded by the Children’s Hospital Foundation of Saskatchewan. Neither the University nor any of the investigators will receive any direct financial benefit for conducting this study.

#### **WHY IS THIS STUDY BEING DONE?**

Congenital heart defects are the world’s leading type of birth defect. Children with congenital heart defects have higher rates of physical inactivity and obesity compared to healthy peers. This may mean that children with congenital heart defects are more likely to have chronic conditions such as heart disease and poor bone health (osteoporosis) later in life. It has also been found that children with congenital heart defects have high levels of anxiety around physical activity participation. While

we know that children with congenital heart defects have higher rates of obesity little is known about their muscle, bone and heart health. This study will look at important aspects of the physical and mental health of children with congenital heart defects compared to healthy peers.

### **WHO CAN PARTICIPATE IN THE STUDY?**

Your child is eligible to participate in this study if he/she is aged 7-15 years and of good health. Your child is not eligible if he/she has any type of heart issues or other health condition that affects his/her ability to perform physical activity.

### **WHAT DOES THE STUDY INVOLVE?**

If your child decides to participate in the study it will involve a single visit to the Physical Activity Complex (PAC) at the University of Saskatchewan. The visit will take approximately four hours. Your child will be requested to complete a form with his/her personal information (such as name, telephone number, and date of birth) and will also be asked to complete, with your assistance if needed, questionnaires regarding his/her general health history, physical activity and psychological well-being (health related anxiety questionnaires). We will measure the following:

1. Your child's height, sitting height, weight, waist circumference, and limb length.
2. Your child's body composition using DXA (dual energy x-ray absorptiometry). DXA is a scan that is done while your child lies on his/her back on what looks like a padded x-ray table. We will measure his/her total body, hip and spine. The scan assesses total body bone, muscle and fat tissues. The scans take approximately 10 minutes and will expose your child to a minimal amount of radiation (less than 5 $\mu$ SV).
3. Your child's bone shape and strength using a peripheral quantitative computed tomography (pQCT) scan of his/her non-dominant forearm and lower leg (each scan takes about 2 minutes). For these scans your child will sit on a padded chair with his/her arm or leg resting on a support. All tests are painless and non-invasive. pQCT is a form of x-ray and therefore does emit a small amount of radiation. The total radiation for all measurements (DXA and pQCT) is less than 4 $\mu$ SV this is comparable to the amount of background radiation a person receives in two days from naturally-occurring sources in Saskatchewan. For reference a cross-country flight could expose a person to about 30 $\mu$ SV of radiation (<http://www.hc-sc.gc.ca/hc-ps/ed-ud/respond/nuclea/measurements-mesures-eng.php>). All scans will be administered by trained and certified personnel.
4. Your child's heart health using the seven following tests:
  - A) Three small stickers will be attached to your child's shoulders and stomach. The stickers are connected with a wire to our computer and will tell us about your child's heartbeat. The stickers are gentle on the skin. They are the same stickers that the hospital uses when it measures heart activity. The stickers are thrown away after we are done the measure. With the stickers we will measure your child's heart activity while he/she lies on his/her back for ten minutes. This test does not cause any discomfort and there are no health risks associated with this test.
  - B) The second test will measure your child's blood vessels. This will be done using a special machine at the same time as the first test. The machine uses a special pen that is placed on the skin to give a picture of your child's blood pressure. The test will tell us about the health of the blood vessels and requires your child to lie still for about 5 minutes. This test does not cause any discomfort and there are no health risks associated with it.
  - C) The third test will measure how your child's nerves and blood vessels work. This will be done by having your child squeeze a hand gripper for two minutes. After this we will inflate a blood pressure cuff and will keep it inflated for two to three minutes. While the cuff is inflated we will monitor your child's blood pressure. The handgrip test will be repeated without inflating a blood pressure cuff. During both handgrip tests we will measure blood pressure. This test can cause a slight tingling sensation in the arm from the blood pressure cuff. The sensation goes away when the cuff pressure is released.

D) Your child's fitness will be tested with a low-intensity walk test. We want to know how far your child can walk in 6 minutes. Your child will walk at his/her own speed back and forth in a hallway for 6 minutes. We will measure your child's heart rate and blood pressure before and after the walk test. The walk test is safe for most individuals because it is of low intensity and your child chooses how fast or slow he/she walks. We will closely monitor your child during the walk test and he/she will choose how fast or slow he/she walks.

E) Your child's fitness will also be testing using a stationary exercise bike while they breathe through a special mouthpiece that measures how much oxygen they use during exercise. This test will take 5 to 10 minutes. We will measure your child's blood pressure and monitor their breathing and heart activity. This test is also safe for the general population. This test will take a total of 30 minutes.

F) Your child's heart structure and function will be assessed using cardiac ultrasound. This assessment will entail your child lying restfully on their side for 30 minutes. During this time, Dr. Timothy Bradley (Pediatric Cardiologist) will use a special ultrasound machine to take pictures of your child's heart. The assessment will entail performing a series of images by placing a probe in different positions over your child's chest. This assessment is very safe, low risk, is entirely non-invasive, and places no stress on your child. This test will take a total of 30 minutes.

G) Your child's blood vessel function will also be measured using vascular ultrasound. This assessment will be performed while your child is doing the handgrip exercise test described in #3 above. The assessment will entail placing a probe over your child's arm. This assessment is very safe, low risk, is entirely non-invasive, and places no stress on your child. This test will not add any time to your child's session.

After the visit to the University, your child will also be asked to wear an accelerometer for 7 consecutive days. An accelerometer is a type of motion sensor that measures your child's physical activity. It is a small device that will be worn around your child's waist on an elastic belt. He/she will be asked to put it on first thing in the morning and wear it all day except when bathing, swimming or playing contact sports. During your visit at the University you will be provided with an addressed and stamped envelope to return the accelerometer after the seven days of wear.

#### **WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**

There may be no direct benefit to your child from participating in this study. It is hoped that the information gained from this study will positively affect the health of children with congenital heart defects and contribute to the development of a program to promote physical activity and healthy lifestyle counseling for this population.

#### **ARE THERE POSSIBLE RISKS AND DISCOMFORTS?**

The risks of participating are the minimal. The fitness test on a stationary bike will assess your child's exercise capacity. During this test, your child may feel a few minutes of physical fatigue that comes with exercise. They also may experience some leg soreness as a consequence of this test, but this should disappear within 2 days. This stationary bike test is safe and the intensity of how hard your child exercises is determined by your child. As stated above the bone measures (DXA and pQCT) will expose your child to a minimal amount of radiation. The tests are very low risk; the total radiation dose for the study is less than half of that of a standard chest x-ray. As with any physical activity there is a slight risk that your child may experience sore muscles after the six minute walk test. If your child experiences soreness it will not last very long.

#### **WHAT HAPPENS IF I DECIDE TO WITHDRAW?**



Your child's participation in this research is voluntary. He/she may withdraw from this study at any time. You do not have to provide a reason.

If your child chooses to enter the study and then decides to withdraw later, all data collected about him/her during his/her enrolment will be retained for analysis.

**WHAT WILL THE STUDY COST ME?**

You will not be charged for any research-related procedures and your child will not be paid for participating in this study. Your parking costs at the University will be covered.

**WHAT HAPPENS IF SOMETHING GOES WRONG?**

In the unlikely event that your child is injured while participating in this research, appropriate medical care will be provided at no cost to you. By signing this document, you and your child do not waive any of your legal rights.

**WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?**

Your child's confidentiality will be respected. No information that discloses your child's identity will be released or published without your specific consent to the disclosure. The results of this study may be presented in a scientific meeting or published, but your child's identity will not be disclosed.

**WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?**

If you have any questions or desire further information about this study before or during participation, you can contact Marta Erlandson by phone at 306-966-1071 or by email at [marta.erlandson@usask.ca](mailto:marta.erlandson@usask.ca).

If you have any concerns about your child's rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Research Ethics Board, at 306-966-2975(out of town calls 1-888-966-2975). The Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Research Ethics Board.



***A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS – Children’s Healthy Heart Camp in Saskatchewan***

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I understand that my child is free to withdraw from this study at any time for any reason.
- I have been informed that there is no guarantee that this study will provide any benefits to my child.
- I give permission to the use and disclosure of my child’s de-identified information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my or my child’s legal rights.
- I understand I will be given a signed copy of this consent form.

I agree to allow my child to participate in this study:

Printed name of person providing consent: \_\_\_\_\_

Signature of Consenting Parent: \_\_\_\_\_ Date \_\_\_\_\_

Printed name of person obtaining consent: \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

**APPENDIX C: HLHS-FC Assent Form**



## PARTICIPANT INFORMATION AND ASSENT FORM

### *A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS – Children’s Healthy Heart Camp in Saskatchewan*

#### **Researchers:**

Dr. Marta Erlandson, College of Kinesiology  
Email: marta.erlandson@usask.ca  
Phone: 306-966-1071

Dr. Kristi Wright, University of Regina  
Email: Kristi.wright@uregina.ca  
Phone: 306-585-4772

Dr. Corey Tomczak, College of Kinesiology  
Email: corey.tomczak@usask.ca  
Phone: 306-966-1066

Dr. Ashok Kakadekar, Pediatric Cardiology  
Email: a.kakadekar@usask.ca

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#### **Introduction**

This form may use words you do not understand. Please ask the person explaining the study to explain any words or information that you do not clearly understand.

You are being asked to take part in a research study because when you were born your heart didn’t work exactly as it was supposed to. The study will help us find out more about your muscle, bone and heart health. It will also help us learn how you feel about participating in physical activity.

A research study is something like a science project in school. The people who are doing this study want to learn something new about children who are born with heart problems like the one you have and how you feel about physical activity and exercise. When the study is over, they will see what kinds of activities are the best for you to participate in. At the end of the study the researchers want you to feel more comfortable and confident in participating in different physical activities at school and with your friends.

#### **What happens in this Study?**

The study will be done at the College of Kinesiology on the University Campus. You will come to the university two times. The first time you come the researchers will ask you to fill in some questionnaires which your parents can help you with if you would like. The researchers will then measure how tall you are, how much you weigh and how long your lower arm and leg are. The researchers will measure your bones using two special imaging machines. One of the machines will take a picture of your whole body while you lay on a bed and the other one will take a picture of your arm and leg bones. The researchers will also measure your heart and the veins and arteries that carry your blood around your body and to your heart using four different tests. For the first test they will put stickers on your shoulders and stomach while you lay on a bed. The stickers will read what your heart is doing, you will not feel anything. For the second test you will have to lie still while the researcher measures your blood vessels with a special pen. Again you will not feel anything while they take this measurement. For the third test, you will squeeze your hand on a special machine for two minutes while the researcher measures your blood pressure. The researcher will also take a picture of your blood vessels. For the fourth test you will be asked to walk at whatever speed you would like for 6 minutes. For the fifth test you will be asked to pedal on a bike your

breathing is measured. For the last test you will be asked to lie still while a researcher takes pictures of your heart. After finishing these activities the researchers will give you a small device (motion sensor) that you will wear on your hip for seven days.

For the second part of the study you will come back to the College of Kinesiology for a week in August. This part of the study will be similar to summer camp. Each day you will participate in different physical activities like swimming and playing in the gym. You will also learn skills to help you feel more comfortable about participating in physical activity as well as healthy eating and heart health.

You will be asked to wear the small motion sensor on your hip for seven days again after the camp has finished.

If you agree the researchers may also take pictures of you while are you participating in the study. The pictures would be used only for research or teaching presentations and your face would be blacked out so no one would be able to recognize you.

You do not have to agree to be in this study.

**Withdrawal from Study**

You do not have to be in this study and you can stop being in this study at any time. If you say yes now, but change your mind later, you can say no and that will be okay. If you decide not to participate, no one will be upset or disappointed.

**ASSENT**

**I have read this paper or have had it read to me. I understand what I have to do in this study and I agree to take part in it.**

\_\_\_\_\_  
Child's Name (Print)

\_\_\_\_\_  
Child's Signature

\_\_\_\_\_  
Date

It is okay for the researchers to take my picture

\_\_\_\_\_

---

**Check which applies (to be completed by person administering assent):**

- The subject is capable of reading and understanding the assent form and has signed above as documentation of assent to take part in this study.
- The subject is not capable of reading the assent form, however, the information was explained verbally to the subject who has verbally given assent to take part in this study.

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Name of Person Administering Assent (Print)

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Signature of Person Administering Assent

---

Date

**APPENDIX D: CTL Assent Form**



## PARTICIPANT INFORMATION AND ASSENT FORM

### *A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS – Children's Healthy Heart Camp in Saskatchewan*

#### **Researchers:**

Dr. Marta Erlandson, College of Kinesiology  
Email: marta.erlandson@usask.ca  
Phone: 306-966-1071

Dr. Kristi Wright, University of Regina  
Email: Kristi.wright@uregina.ca  
Phone: 306-585-4772

Dr. Corey Tomczak, College of Kinesiology  
Email: corey.tomczak@usask.ca  
Phone: 306-966-1066

Dr. Ashok Kakadekar, Pediatric Cardiology  
Email: a.kakadekar@usask.ca

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#### **Introduction**

This form may use words you do not understand. Please ask the person explaining the study to explain any words or information that you do not clearly understand.

You are being asked to take part in a research study because you are a healthy person. The study will help us find out more about your muscle, bone and heart health.

A research study is something like a science project in school. The people who are doing this study want to learn something new about children who are born with heart problems. When the study is over, they will see how muscle, bone and heart health is different in children with heart problems compared to healthy children.

#### **What happens in this Study?**

The study will be done at the College of Kinesiology on the University Campus. When you come in the researchers will ask you to fill in some questionnaires which your parents can help you with if you would like. The researchers will then measure how tall you are, how much you weigh and how long your lower arm and leg are. The researchers will measure your bones using two special imaging machines. One of the machines will take a picture of your whole body while you lay on a bed and the other one will take a picture of your arm and leg bones. The researchers will also measure your heart and the veins and arteries that carry your blood around your body and to your heart using four different tests. For the first test they will put stickers on your shoulders and stomach while you lay on a bed. The stickers will read what your heart is doing, you will not feel anything. For the second test you will have to lie still while the researcher measures your blood vessels with a special pen. Again you will not feel anything while they take the measurement. For the third test, you will squeeze your hand on a special machine for two minutes while the researchers measure your blood pressure. The researcher will also take pictures of your blood vessels. For the fourth test you will be asked to walk at whatever speed you would like for 6 minutes. For the fifth test you will be asked to pedal on a bike your breathing is measured. For the last test you will be asked to lie still while a researcher takes pictures of your heart. After finishing these activities the researchers will give you a small device (motion sensor) that you will wear on your hip for seven days.



You do not have to agree to be in this study.

**Withdrawal from Study**

You do not have to be in this study and you can stop being in this study at any time. If you say yes now, but change your mind later, you can say no and that will be okay. If you decide not to participate, no one will be upset or disappointed.

**ASSENT**

**I have read this paper or have had it read to me. I understand what I have to do in this study and I agree to take part in it.**

\_\_\_\_\_  
Child's Name (Print)

\_\_\_\_\_  
Child's Signature

\_\_\_\_\_  
Date

**Check which applies (to be completed by person administering assent):**

- The subject is capable of reading and understanding the assent form and has signed above as documentation of assent to take part in this study.
- The subject is not capable of reading the assent form, however, the information was explained verbally to the subject who has verbally given assent to take part in this study.

\_\_\_\_\_  
Name of Person Administering Assent (Print)

\_\_\_\_\_  
Signature of Person Administering Assent

\_\_\_\_\_  
Date

**APPENDIX E: Research Ethics Board Approval Certificate**

# Certificate of Approval Study Amendment

PRINCIPAL INVESTIGATOR  
Marta ErlandsonDEPARTMENT  
KinesiologyBio #  
15-148INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT  
College of Kinesiology  
University of Saskatchewan  
Saskatoon SK S7N 5B2STUDENT RESEARCHER(S)  
Guillaume Leclair, Shonah RunallsFUNDER(S)  
CHILDREN'S HOSPITAL FOUNDATIONTITLE  
A Pilot Health Intervention Study of Children with Congenital Heart Defects: CHAMPS - Children's Healthy Heart Camp in SaskatchewanAPPROVAL OF  
REB Amendment Summary  
Participant Information and Parental Consent Form (v.5 September 2016)  
Participant Information and Parental Consent Form - Control Group (v.5 September 2016)  
Participant Information and Assent Form (v.5 September 2016)  
Participant Information and Assent Form- Control Group (v.5 September 2016)APPROVED ON  
22-Sep-2016CURRENT EXPIRY DATE  
06-Jun-2017Delegated Review  Full Board Meeting IRB 1 FWA Registration #00001471  IRB 2 FWA Registration #00008358  Not Applicable **CERTIFICATION**

The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

**FIRST TIME REVIEW AND CONTINUING APPROVAL**

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit <http://research.usask.ca/for-researchers/ethics/index.php>.

PRINCIPAL INVESTIGATOR  
Marta Erlandson

- 2 -  
DEPARTMENT  
Kinesiology

Bio #  
15-148

**REB ATTESTATION**

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board has been approved by the Minister of Health, Province of Saskatchewan, to serve as a Research Ethics Board (REB) for research studies involving human participants under section 29 of The Health Information Protection Act (HIPA).



Gordon McKay, PhD., Chair  
University of Saskatchewan  
Biomedical Research Ethics Board

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Please send all correspondence to:

Research Ethics Office  
University of Saskatchewan  
Box 5000 RPO University  
1607-110 Gymnasium Place  
Saskatoon SK S7N 4J8

## **APPENDIX F: Enhanced Statistical Details**

**MAP:**

2×3 Repeated Measures ANOVA. Greenhouse-Geisser correction used for condition because assumption of sphericity was violated.

$$\text{Group: } F(1,8) = 17.339, P = 0.003$$

$$\text{Condition: } F_{GG}(1.136, 9.092) = 22.900, P = 0.001$$

$$\text{Interaction: } F(2,16) = 9.146, P = 0.002$$

**HR:**

2×3 Repeated Measures ANOVA.

$$\text{Group: } F(1,8) = 4.002, P < 0.001$$

$$\text{Condition: } F(2, 16) = 63.611, P = 0.015$$

$$\text{Interaction: } F(2,16) = 12.204, P = 0.001$$

**FBF:**

2×3 Repeated Measures ANOVA. Greenhouse-Geisser correction used for condition and interaction because assumption of sphericity was violated.

$$\text{Group: } F(1,7) = 0.146, P = 0.473$$

$$\text{Condition: } F_{GG}(1.141, 7.985) = 5.232, P = 0.048$$

$$\text{Interaction: } F_{GG}(1.141, 7.985) = 2.146, P = 0.182$$

**SVR:**

2×3 Repeated Measures ANOVA.

$$\text{Group: } F(1,7) = 0.146, P = 0.714$$

$$\text{Condition: } F(2,14) = 3.687, P = 0.052$$

$$\text{Interaction: } F(2,14) = 7.968, P = 0.005$$

**VE:**

2×3 Repeated Measures ANOVA. Mann-Whitney U Rank Sum Test used for handgrip and PECO because assumption of homogeneity of variance was violated.

$$\text{Group: } F(1,8) = 4.002, P = 0.08$$

$$\text{Condition: } F(2,16) = 5.461, P = 0.016$$

$$\text{Interaction: } F(2,16) = 4.507, P = 0.028$$

$$\text{Handgrip: } U = 18, P = 0.047$$

$$\text{PECO: } U = 29, P = 0.310$$

**TV:**

2×3 Repeated Measures ANOVA. Greenhouse-Geisser correction used for condition and interaction because assumption of sphericity was violated. Mann-Whitney U Rank Sum Test

used for handgrip and PECO because assumption of homogeneity of variance was violated.

Group:  $F(1,8) = 16.629, P = 0.004$

Condition:  $F_{GG}(1.253, 10.025) = 4.154, P = 0.062$

Interaction:  $F_{GG}(1.166, 9.331) = 5.098, P = 0.045$

Handgrip:  $U = 15, P = 0.024$

PECO:  $U = 33, P = 0.508$

*f*:

2×3 Repeated Measures ANOVA.

Group:  $F(1,8) = 0.382, P = 0.554$

Condition:  $F(2,16) = 2.136, P = 0.151$

Interaction:  $F(2,16) = 0.119, P = 0.888$

## **APPENDIX G: Participant MVC Values**



HLHS-FC		CTL	
Participant	MVC (N)	Participant	MVC (N)
1	117	10	355
2	102	11	141
3	236	12	161
4	99	13	234
5	77	14	345
6	279	15	125
7	64	16	262
8	229	17	263
9	103	18	451
Mean	145*	Mean	260
SD	80	SD	109

\* $P = 0.022$  by unpaired  $t$ -test.