The Relationship Between Aerobic Capacity and Moderate-to-Vigorous Physical Activity in Adult Tetralogy of Fallot.

by

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ABSTRACT

Background. Tetralogy of Fallot (ToF) patients have an aerobic capacity of ~ 50% of age-matched controls. This diminished aerobic capacity may partially be attributed to pulmonary regurgitation that limits augmentation of cardiac output during exercise. ToF patients have also been reported to be less physically active than their healthy peers, further diminishing their aerobic capacity. The extent to which low daily physical activity (PA) levels may contribute to the reduced peak oxygen uptake (VO_{2peak}) observed in ToF patients is not clear.

Purpose. To evaluate the relationship between aerobic capacity (VO_{2peak}) and daily time spent in moderate-to-vigorous PA (MVPA ≥ 3.0 METs) in patients with ToF (or ToF-like physiology), and to compare these findings with healthy age and gender matched controls.

Methods. Thirty-eight participants were included in the analyses. The ToF patients (n=19, 12 M:7 F; age 27 $\pm$ 7 years) were medically stable, with moderate or greater pulmonary regurgitation. The healthy controls (n=19) consisted of 12 males: 7 females and were of comparable age (28 $\pm$ 7 years) to the ToF participants. VO_{2peak} and submaximal cardiopulmonary exercise measures (e.g., ventilatory anaerobic threshold) were assessed using indirect calorimetry during a symptom-limited graded exercise test (SL-GXT). PA was assessed using multi-sensor accelerometer (SenseWear Mini Armband-SWA). PA participants were instructed to wear the SWA for a minimum of 4 consecutive days. Minute-by-minute data were then categorized into light PA (> 1.5 to < 3.0 METs) or MVPA (≥ 3.0 METs) and time spent in both categories were averaged over the recording period. Unpaired t-tests were used to compare the cardiopulmonary exercise measures and MVPA between the groups. Pearson correlations were used to determine the relationships between VO_{2peak} and submaximal cardiopulmonary measures with MVPA within both groups.

Results. VAT ($p = 0.156$), and VE/VCO_2 slope ($p = 0.187$) were comparable between the groups. The ToF group showed a lower VO_{2peak} ($p = 0.019$) and oxygen uptake efficiency slope (OUES) ($p = 0.018$) compared with

healthy controls. Healthy controls spent more time in MVPA (2.2 ± 1.2 hrs/day vs. 1.4 ± 0.8 hrs/day, p = 0.015). No correlation was found between daily time spent in MVPA and VO_{2peak} (r = 0.094, p = 0.720) in ToF patients, whereas a moderate positive correlation (r = 0.685, p = 0.001) was found in healthy controls. There were no relationships between MVPA and submaximal measures in ToF patients (VAT: r = 0.352, p = 0.166; OUES: r = 0.144, p = 0.582; VE/VCO_2 slope: r = - 0.200, p = 0.441). Conversely, strong correlations between MVPA and VAT (r = 0.912, p = 0.000) and OUES (r = 0.702, p = 0.001) were found in our healthy controls.

Conclusion. The ToF patients had a lower absolute aerobic capacity (L/min) compared to sedentary healthy controls. The ToF patients also spent less total daily time in MVPA. Present findings suggest that our ToF patients were achieving the daily recommended amount of PA, however further research is needed on the benefits of exceeding the recommended MVPA (≥ 30 min/day) on their aerobic capacity. The PA goal for ToF patients should be to decrease total sedentary time, while increasing PA and exercise participation should be encouraged.

Preface

This thesis is an original work by John Philip Willner. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “PhiT Study”, No. Pro00059680_AME5, January 9, 2017.

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LIST OF KEYWORDS and ABBREVIATIONS

CHD – congenital heart disease

ToF – tetralogy of Fallot

PA – physical activity

SWA – SenseWear Mini Armband

SL-GXT – symptom limited guided exercise test

VO_2 – oxygen uptake

VO_{2peak} - peak oxygen uptake

OUES – oxygen uptake efficiency slope

VAT – ventilatory anaerobic threshold

VE/VCO_2 – ventilatory equivalent for CO_2

MET – metabolic equivalent

RPE – rating of perceived exertion

EE – daily energy expenditure

Aerobic capacity

Sedentary

Volitional fatigue

DEFINITION OF TERMS

Physical Activity: Typically defined as "any bodily movement produced by skeletal muscles that requires energy expenditure and produces progressive health benefits."(1)

Exercise: Commonly described as planned physical activity. The resulting body movements are therefore typically structured and repetitive in nature and are performed with the express purpose of improving or maintaining health and fitness (1, 2).

Metabolic Equivalent: A metabolic equivalent (MET) is a means by which to represent the energy cost of physical activity as multiples of a resting metabolic rate. The advantage of using METs is that they provide a common descriptor of workload and intensity for most modalities and populations (3, 4).

Sedentary: Defined as "any waking behaviour characterized by energy expenditure ≤ 1.5 METs and in a sitting or reclined posture." (5) Yet operationally it may be defined as all behaviours with an energy cost ≤ 1.5 METs (2, 6).

Activities of daily living: Everyday tasks that are required for an individual to perform in order to live independently. They may be categorized as being either basic, those required for personal care (i.e., bathing, dressing, etc.), or instrumental, house hold tasks (i.e., cooking, cleaning, shopping, etc.) (7-10).

Aerobic capacity: The maximum physical exertion that an individual can sustain and is best characterised by maximum oxygen uptake (VO_{2max}) or VO_{2peak} (11, 12).

VO_{2max}: The maximum volume of oxygen consumed per unit time. It is the product of the maximal cardiac output (CO; L blood/min) and arterial-venous oxygen difference (avO_2 diff; mL O_2/L blood) and closely related to the functional capacity of the heart (13). VO_{2max} implies an individual's true physiologic limit has reached and a plateau in VO_2 may be observed (13).

VO_{2peak}: is used when leveling off of VO_2 does not occur or maximum performance appears limited by local muscular factors rather than central circulatory dynamics (13). This is often used to describe aerobic capacity in populations with chronic disease and health conditions (13).

Volitional fatigue: The voluntary limit beyond which a subject no longer desires to continue the prescribed protocol (14). This end point is highly dependent on the motivation of the subject, the influence of the person administering the protocol and established discontinuation criteria (14).

Ventilatory Anaerobic Threshold (VAT): The VAT reflects the point at which aerobic metabolism is substantially supplemented by anaerobic processes (15). The VAT is defined as the workload at which there is an increase in VE/VO_2 and no change in VE/VCO_2. The regression analysis of the VCO_2 and VO_2 slopes (the so called V-slope method) indicating the beginning of excess VCO_2 as a means of buffering excess $[H^+]$ is also used to determine the VAT (16).

Oxygen Uptake Efficiency Slope (OUES): The OUES is measured by plotting VO_2 versus $\log_{10}$ VE, resulting in a linear slope in which the steeper the slope or higher OUES value, the more efficient oxygen uptake is (17). A large OUES or steep slope depends on a substantial mass of working muscle, a vigorous and unimpaired blood flow to the muscles, efficient oxygen extraction and utilization of oxygen by the working muscles and the delayed appearance of lactate and lactic acidosis (18).

Ventilatory Equivalent for CO_2 (VE/VCO_2 slope): The ventilatory equivalent (for CO_2) is calculated from the slope of the line of VE/VCO_2. This slope is an indicator of ventilatory efficiency, and is thought to reflect pulmonary perfusion, ventilation/perfusion mismatch and ventilatory reflex sensitivity (19).

Chapter 1

INTRODUCTION

1.1 Problem Statement

Similar to many complex congenital heart diseases (CHD), tetralogy of Fallot (ToF) is typically diagnosed during fetal life. Fortunately, as a result of surgical interventions and improved medical management, approximately 85% of ToF patients now survive into adulthood, with most ToF patients functioning at New York Heart Association (NYHA) Class I or II (20, 21). Despite advances in surgical and medical interventions, residual lesions often remain, frequently leading to right ventricle overload which increases the patient's risk for heart failure and ventricular arrhythmias (20, 22, 23). Due to pulmonary valvotomy and reconstruction of the right ventricle outflow tract during primary repair of ToF, the dominant residual lesion in adult ToF patients is pulmonary regurgitation (20). Significant pulmonary regurgitation may limit augmentation of cardiac output during exercise. Indeed, severe pulmonary regurgitation is associated with a diminished aerobic capacity in adults with ToF (24).

It has been reported that ToF patients have an aerobic capacity roughly 50% of that reported in age-matched controls (24). A positive relationship between aerobic capacity (i.e., peak oxygen uptake [VO_{2peak}]) and time spent in moderate-to-vigorous physical activity (MVPA; ≥ 3.0 METs) has been reported in healthy adults (25) and post myocardial infarction patients (26). Although sparse, studies with ToF patients show that participation in structured physical activity (PA) programs may result in enhanced aerobic capacity and lower risk for morbidity and mortality (27-33). In fact, Dua et al., (29) found that a 10-week home-based walking program significantly increased VO_{2peak} in ToF patients while Therrien et al. (31) reported a 10% increase in aerobic capacity following a 3-month structured exercise program in adults with ToF. The improvement in aerobic capacity may be attributed to an increase in stroke volume, cardiac output, ventilatory threshold and a reduction in valvular regurgitation (27, 31). Although increased PA may improve aerobic capacity and decrease

the risk of morbidity and mortality for patients with ToF, to date existing research has focused almost exclusively on patients with repaired ToF participating in competitive sports or formal training regimes designed for healthy populations (27, 34-37).

There is little research on the association between aerobic capacity and daily PA in CHD patients however, CHD patients have been reported to be less physically active than their age matched healthy peers (33, 38-40). Therefore, the extent to which low daily PA levels may contribute to the reduced aerobic capacity observed in this patient population is unclear (41). Factors, such as physician and parental overprotection and lack of confidence and motivation may limit PA participation by patients with ToF (42-44). Indeed, patients with ToF also tend to report a decline in daily PA with increasing age, which in turn may increase their risk for morbidity and mortality (41, 45). Dulfer et al. (46) conducted a systematic review on the associations between VO_{2peak}, PA and psychosocial functioning in CHD patients and reported the association between aerobic capacity and objective PA measures were not consistent, however, a higher VO_{2peak} was associated with higher self-reported physical quality of life. Thus, while the health benefits of regular PA are well documented in many cardiac populations, there remains a need to further examine the effect of daily PA levels on the health and fitness of ToF patients.

1.2 Objective

This is a sub-study of the "Physical Activity in Tetralogy (PhiT) Study: A Randomized Trial of Interval Training Versus Moderate Continuous Training Versus Usual Activity". The purpose of this study was to evaluate the relationship between VO_{2peak} and daily time spent in moderate-to-vigorous PA (i.e., MVPA ≥ 3.0 METs) in patients with ToF or ToF-like physiology and to compare these findings with healthy age and gender matched controls. Further, this study evaluates the relationship between submaximal cardiopulmonary exercise measures (i.e., ventilatory anaerobic threshold [VAT], oxygen uptake efficiency slope [OUES], and VE/VCO_2 slope) and daily time spent in MVPA across the two groups.

1.3 Hypotheses

Primary Hypothesis: There will be a moderate positive correlation ($r > 0.4$) between VO_{2peak} and daily time spent in MVPA (≥ 3.0 METs) for the ToF patients, while the sedentary healthy age and gender matched controls will have a strong positive correlation ($r > 0.7$) between VO_{2peak} and daily time spent in MVPA (≥ 3.0 METs).

Secondary Hypotheses:

1) ToF patients will spend significantly less daily time in MVPA (≥ 3.0 METs) compared to sedentary healthy age and gender matched controls.
2) ToF patients will have a significantly ($p < 0.05$):
    a. Lower ventilatory anaerobic threshold (VAT) than sedentary healthy controls.
    b. Lower oxygen uptake efficiency slope (OUES) than sedentary healthy controls.
    c. Higher VE/VCO_2 slope when compared to sedentary healthy controls.
3) The OUES and VAT will have a moderate correlation ($r > 0.4$) with daily time spent in MVPA (≥ 3.0 METs) in sedentary healthy controls versus a weak correlation ($r < 0.399$) in ToF patients.
4) The VE/VCO_2 slope will have a moderate negative correlation with daily time spent in MVPA (≥ 3.0 METs) in sedentary healthy controls versus a weak negative correlation ($r < 0.399$) in ToF patients.

Chapter 2

LITERATURE REVIEW

2.1 Tetralogy of Fallot

Tetralogy of Fallot (ToF) accounts for 3-5% of all CHD births and, to date, the precise cause of ToF remains unknown (20). Patients with ToF have (i) a ventricular septal defect, (ii) an over-riding of the aorta, and (iii) right ventricular outflow tract obstruction which often leads to right ventricular hypertrophy (20). The ventricular septal defect is most often large and non-restrictive, ensuring right and left ventricular pressures are equal (20). Constriction of the right ventricular outflow tract causes directional and magnitude adaptations in blood flow and if obstruction of the right ventricular outflow tract is severe, it may cause low pulmonary blood flow and severe cyanosis (20, 47). Long-term hypoxemia contributes to myocardial degeneration and interstitial fibrosis, which have been implicated in myocardial dysfunction and ventricular arrhythmias (20). Long-term effects from residual lesions, mainly pulmonary regurgitation, may increase right ventricular end-diastolic volume and left-sided changes, which may cause reduced ventricular diastolic and systolic performance (32, 48).

A review by Van Arsdell et al., (49) found the optimal age for surgical repair of ToF is 3-6 months of age. Reparative surgery ideally closes the ventricular septal defect preserving right ventricular form and function with an unobstructed right ventricular outflow tract and pulmonic valve repair or replacement (20). Surgical palliation with systemic-to-pulmonary artery shunts, which effect the growth and development of the pulmonary arteries, are done in a minority of patients prior to complete repair to increase pulmonary blood flow by anastomosing a systemic artery to the pulmonary artery (21). Usually, complete repair involves patch closure of the ventricular septal defect with either transannular patching of the right ventricular outflow tract or creation of an right ventricle to pulmonary artery valve conduit (21). Recently, a shift to preserving the pulmonary valve has occurred, using subvalvar rather than transannular patches. This may keep adverse late effects of pulmonary incompetence to a minimum and retain the integrity of the right ventricular outflow tract

by avoiding late aneurysmal dilation (20, 48, 50). Significant pulmonary regurgitation resulting in right ventricle enlargement, dysfunction and/or arrhythmia are indications for pulmonary valve replacement (21). Surgery is usually completed with bioprosthetic valves, homograft or animal tissue, and occasionally mechanical or man-made synthetic valves (21).

For many, complete repair occurs without complications and the patient may be released from hospital within a week of surgery (20). However, early complications may include low cardiac output syndrome despite repair with preserved biventricular systolic function (20). Echocardiographs typically show evidence of restrictive right ventricle physiology, which is related to the degree of myocardial damage from the surgical repair (20). Early post-operative restrictive physiology, characterized by antegrade diastolic flow in the pulmonary artery, requires prolonged inotropic support, longer stay in an intermediate care station and higher doses of diuretics (20). Pulmonary regurgitation and right ventricle dilation are well described in later postoperative years (20).

Gatzoulis et al. (51) claimed pulmonary regurgitation was the most important hemodynamic determinant of symptomatic arrhythmia and risk for sudden death. A prolonged QRS duration is efficient in predicting increased risk for ventricular arrhythmias and was strongly associated with pulmonary regurgitation (35, 51, 52). The QRS duration has been shown to be positively correlated with right ventricle volume and wall mass and inversely related to ejection fraction and VO_{2peak} (35, 51, 52). Additionally, moderate to severe left ventricle dysfunction has been shown to have predictive value of sudden cardiac death for a QRS duration >180 ms. (51, 53). Pulmonary valve replacements have been shown to improve ventricular function, stabilize QRS duration and reduce ventricular arrhythmias in patients with severe pulmonary regurgitation (51, 52). Pulmonary valve replacements are commonly performed in children and adults with repaired ToF who have symptomatic pulmonary regurgitation or objective evidence of severe right ventricle dilatation or progressive

right ventricular dysfunction. Studies have shown that dilation of the right ventricle undermines left ventricle systolic performance, therefore a strong negative correlation between right ventricular volume and left ventricular ejection fraction exists after repair of ToF (20, 24, 54). However, the findings of Mercer-Rosa et al. (55) suggest that pulmonary regurgitation alone does not explain the impaired aerobic capacity in ToF patients. These authors compared ToF patients to valvular pulmonary stenosis patients post valvotomy and found lower aerobic capacity, higher rght ventricular mass and lower right ventricular ejection fraction in ToF patients despite similar degrees of pulmonary regurgitation. Based on these findings, the authors proposed that ToF patients may have intrinsic right ventricular cardiomyopathy from prior cyanosis, abnormalities of the distal pulmonary arterial tree or, as a consequence of transannular patching and surgical repair that alters the right ventricular performance during exercise. Interestingly, elimination of pulmonary regurgitation by surgical or transcatheter implantation of a prosthesis is not associated with an improvement in aerobic capacity (56). Some investigators have implicated that a pre-existing impairment of lung function may cause a ventilation limitation to VO_{2peak} in adult CHD (ACHD) patients with pulmonary valve replacements (57). Thus, for adolescent and adult ToF patients, follow-up assessments focus on the degree of pulmonary regurgitation and its effect on exercise tolerance, ventricular remodeling, arrhythmia and sudden death (20).

Because of the increasing number of patients with ToF surviving into adulthood, the risk of comorbidities and coronary artery disease is increasing (58). ToF patients may have an increased risk for coronary artery disease, ventricular arrhythmias and death, due partially to a decreased aerobic capacity (27). Aerobic capacity is considered one of the most important health markers and predictors for morbidity and mortality (59). Van den Berg et al. (48) reported a reduced global ventricular diastolic function at rest in ToF patients, but with prolonged exercise training and acute stress, neither regional ventricular diastolic function

nor systolic performance are negatively affected. Evaluation of CHD patients' aerobic capacity may prove an effective prognostic measure for risk of future disease (32, 60, 61).

2.2 Assessment of Aerobic Capacity.

Symptom Limited Graded Exercise Test (SL-GXT): To determine the aerobic capacity of an individual a lab based SL-GXT or a field based exercise test (such as a 6 Minute Walk Test [6MWT]) is typically used. Assessing aerobic capacity is useful in helping estimate prognosis, as well as return to work and disability assessment (13). There is no consensus as to the best form of aerobic capacity testing. For lab based SL-GXTing the most commonly used modalities are treadmills and cycle ergometers. Treadmills utilize walking and accommodate a wide spectrum of fitness levels (13). For treadmill SL-GXTing, the Bruce protocol is commonly conducted, using endurance time to estimate aerobic capacity (15, 62). The Bruce protocol increases in intensity in relatively large increments of 2-3 METs per stage (i.e., every 3 minutes) (13). However, as a result of the large MET increments per stage used in the Bruce protocol, aerobic capacity may be markedly overestimated by the Bruce protocol (13). By contrast, it has been proposed that protocols such as the Naughton or Balke-Ware (i.e., ≤ 1 MET increase per stage) may be better suited for the elderly and patients with chronic disease (13).

Regardless of the modality, most lab based exercise tests involve either incremental protocols or ramp protocols. For instance, the Bruce, Naughton or Balke-Ware protocols all involve incremental stages which last 2-3 minutes whereas ramp protocols increase exercise intensity/work rate at a constant rate every minute through to volitional fatigue (13). Advantages to ramp protocols include: reduced testing time, avoidance of large and unequal increments in workload, uniform increase in hemodynamic and physiologic responses, and more accurate estimates of aerobic capacity (13). Typically these SL-GXT incorporate continuous 12 lead ECG-monitoring for the assessment of heart rate (HR), arrhythmias and ST segment changes, blood pressure (BP) monitoring (at each stage of the SL-GXT) and the patient's rating of perceived exertion (RPE) at rest, during exercise and during the immediate post-exercise recovery period (e.g., the first 5 minutes of recovery) (13).

During a SL-GXT, HR should increase linearly with increments in workload from baseline to HR_{peak} (13, 62, 63). Age predicted HR_{max} may be estimated from the equation: $HR_{max} = 220 - age$ (years) provided the patient is not on medication that impact HR (e.g., beta blockers) (13). The inability to increase HR during progressive exercise (i.e., chronotropic incompetence; < 85% age predicted HR_{max}) is associated with the presence of heart disease and increased mortality (13, 64) and is commonly observed in patients after CHD surgery (62). Chronotropic incompetence may be due to conduction system malfunction due to injury to the sinoatrial (SA) node secondary to intervention, by drug therapy or chronic pacing (15). As such, HR reserve (HRR) and chronotropic index should be assessed in ACHD patients (65). The HRR, defined as $HR_{peak} - HR_{rest}$, may be a predictor of mortality in patients with CHD (66). The chronotropic index, used to predict a normal HR response to submaximal exercise, is calculated as $HRR/[(220\text{-age}) - HR_{rest}]$ and is independent of age, resting HR, and functional state (64).

In patients with CHD, augmentation of cardiac output during exercise may be limited, either by chronotropic incompetence or a reduced stroke volume (20, 24, 67). The O_2 pulse, defined as VO_{2peak} divided by HR_{peak}, may be used a surrogate indicator of stroke volume in patients with CHD (68-70). The O_2 pulse is lower than predicted in CHD patients affected by hypoxemia and abnormal peripheral oxygen extraction (68, 71). Patients with severe deconditioning also tend to have a depressed O_2 pulse because the normal augmentation of preload and stroke volume by pumping action of the exercising muscles are impaired in addition to mild impairment of oxygen extraction (15). Normal values for O_2 pulse at peak exercise are dependent on patient size, age and gender (72).

Blood pressure is typically measured throughout the SL-GXT (pre-, during each exercise stage and immediately post-exercise). Systolic BP (SBP) should increase and with each increment in workload while little to no change in diastolic BP (DBP) is expected (13). If SBP appears to be decreasing with increments in exercise intensity, it should be reassessed immediately. If a drop in SBP > 10 mmHg occurs with an increase in exercise

intensity, or if it drops below the value obtained in the same position prior to the SL-GXT the test should be stopped, particularly if accompanied by adverse signs and symptoms. The SL-GXT should also be terminated if a hypertensive response is observed (i.e., SBP >250 mmHg and/or DBP >115 mmHg). The BP response to exercise is variably attenuated in patients on vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors, and alpha- and beta-adrenergic blockers (13). An important indicator of myocardial oxygen demand may be derived from the rate pressure product which is defined as SBP x HR (13). Signs and symptoms of ischemia generally occur at a reproducible rate pressure product (13).

During a SL-GXT with concurrent ventilator gas analysis, oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) may be measured. These variables are used to determine peak oxygen uptake (VO_{2peak}), ventilatory anaerobic threshold (VAT), oxygen uptake efficiency slope (OUES) and the ventilatory equivalent for CO_2 (VE/VCO_2). The measurement of these parameters provides a detailed physiologic understanding of the underlying mechanisms of exercise impairment and subsequent improvements which may accompany a program of aerobic training.

2.3 Outcome Measures

Peak VO_2 (VO_{2peak}): VO_2 reflects the integrated ability of an individual to transport oxygen from the atmosphere to the mitochondria to perform physical work (73). As such, VO_2 encompasses a chain of processes that include gas exchange in the lungs, right and left ventricular cardiac output, oxygen transport in the blood through the vascular system, as well as peripheral factors that include the metabolic efficiency and vascularization of skeletal muscles (73).

The assessment of VO_{2max} may be considered the gold standard for measuring aerobic capacity and the overall health of the cardiorespiratory system. VO_{2max} is effort-dependent and defined as the plateau in VO_2 despite increasing workload (46). The achievement of VO_{2max} is verified by a respiratory exchange ratio (RER;

VCO_2/VO_2) of $\geq$ 1.1 and has been shown to be an important predictor of health outcome and survival in diverse groups of cardiac patients including ACHD (24, 27, 34, 60, 65, 74).

Because VO_{2max} is effort dependent and is not typically achieved by ACHD patients during a SL-GXT, therefore a surrogate for VO_{2max}, VO_{2peak} is used. The inability to achieve VO_{2max} during a SL-GXT may be attributed to the caution employed during the testing and/or the fact that patients experience volitional fatigue before achieving the physiological markers associated with VO_{2max}. In these tests, the highest VO_2 observed during the test, termed VO_{2peak}, is reported (70, 75). Like VO_{2max}, VO_{2peak} also has prognostic significance for ACHD. Like most congenital heart lesions, adults with repaired ToF have reduced VO_{2peak} (e.g., 26 $\pm$ 9 ml/kg/min) compared to age-matched healthy controls (e.g., VO_{2peak} of 45 ± 9 ml/kg/min) (24, 65). It should be noted that a VO_{2peak} of <15 mL/kg/min has been shown to be an independent predictor of hospitalization and increased mortality (24, 66).

While an assessment of VO_{2peak} provides an index of aerobic capacity, respiratory parameters such as ventilatory anaerobic threshold (VAT), oxygen uptake efficiency slope (OUES) and a ventilatory equivalent (e.g., VE/VCO_2 slope) may also be assessed during the submaximal portion of the SL-GXT and are valuable in the assessment of cardiorespiratory fitness and in prescribing aerobic exercise (75, 76).

Ventilatory anaerobic threshold (VAT): The VAT reflects the point at which aerobic metabolism is substantially supplemented by anaerobic processes (15). During a SL-GXT, the ratio of ventilation to CO_2 production (VE/VCO_2) remains relatively stable with increasing workloads, whereas the ratio of ventilation to VO_2 (VE/VO_2) starts to increase. The VAT is defined as the workload at which there is an increase in VE/VO_2 and no change in VE/VCO_2. The regression analysis of the VCO_2 and VO_2 slopes (the so called V-slope method) indicating the beginning of excess VCO_2 as a means of buffering excess $[H^+]$ is also used to determine the VAT (16). The VAT is not affected by patient effort or motivation and may be determined during the submaximal phase of the SL-GXT, thus VAT is considered an excellent index of the cardiovascular system's capacity to support the

hemodynamic demands of exercise (15). Often described as a percentage of VO_{2peak}, VAT is useful for predicting the ability of the patient to sustain a given work rate for a prolonged period of time (77). Using the VAT as a basis for prescription allows for matching the unique physiological responses of different exercise intensities to the individual pathology and clinical status (36). In healthy, untrained populations the VAT typically occurs at a workload of approximately 50-60% of VO_{2peak} (13). However, in the presence of cardiovascular disease, the VAT may be as low as 40% of VO_{2peak} (15). Additionally, a lower VAT has been associated with an increased risk for mortality in ACHD (15, 66).

Oxygen Uptake Efficiency Slops (OUES): OUES measures the distribution of systemic blood flow and peripheral oxygen extraction (17). The OUES provides an objective index of cardiopulmonary function that is practical, easily attainable, and less influenced by subjective, motivational factors. The OUES integrates the functional capacities of the cardiovascular, pulmonary and musculoskeletal systems during progressive exercise and does not require maximal effort (18, 78). Major factors that influence OUES are CO_2 production derived from muscle aerobic metabolism, as well as from the pH buffering function of bicarbonate, the arterial CO_2 and the physiological pulmonary dead space VE (18). As measured by plotting VO_2 versus $\log_{10}$ VE, a linear slope has been reported, in which the steeper the slope or higher OUES value, the more efficient oxygen uptake is (17). A large OUES or steep slope depends on a substantial mass of working muscle, a vigorous and unimpaired blood flow to the muscles, efficient oxygen extraction and utilization of oxygen by the working muscles and the delayed appearance of lactate and lactic acidosis (18). Of all submaximal measures, VAT and OUES were found to have significant correlations with VO_{2peak} in CHD patients (75).

Ventilatory equivalent: The ventilatory equivalent (for CO_2) is calculated from the slope of the line of VE/VCO_2. This slope is an indicator of ventilatory efficiency, and reflects pulmonary perfusion, ventilation/perfusion mismatch and ventilatory reflex sensitivity (19). The VE/VCO_2 slope becomes abnormally elevated in

cardiovascular or pulmonary disease, including those with pulmonary hypertension (73). Studies have shown that the VE/VCO_2 slope exhibits a high prognostic value for cardiac-related events in patients with coronary artery disease, and the risk of mortality increases as the VE/VCO_2 slope rises. For example, Arena et al. (79), reported that the quartiles of VE/VCO_2 slope in heart failure patients can predict cardiac outcomes, where <30 implies negligible risk of a major cardiac event; 30–35, a low risk of major cardiac event, 36–45, moderate risk of major cardiac event; and ≥45, high risk of major cardiac event.

The VE/VCO_2 slope has been shown to be higher in adults with ToF than in healthy controls (75, 80). Even young ACHD patients have been observed to have elevated VE/VCO_2 slopes (> 30) (15). A linear relationship has also been reported between VE/VCO_2 and New York Heart Association (NYHA) classification, suggesting a link between ventilatory responses to exercise and the occurrence of symptoms (19). Similar to the findings of Arena et al. (79), Dimopoulos et al. (19) noted a VE/VCO_2 slope of >38 was a prognostic marker associated with a ten-fold increase in the risk of death within 2 years. Interestingly, Inuzuka et al. (66) found no predictive value in cyanotic patients, however, non-cyanotic patients had an increased risk of death with a slope > 39, concluding a slope of 39 as an optimal cut-off value based on the authors time-dependent ROC analysis. Moreover, since one of the most important pathophysiological processes affecting VE/VCO_2 slope is maldistribution of pulmonary blood flow causing ventilation/perfusion mismatch, it is not surprising that patients with repaired ToF, who often have pulmonary artery stenosis, have been found to have elevated VE/VCO_2 slope attributable to pulmonary blood flow maldistribution (15, 23, 60, 80, 81).

2.4 Response to Acute Exercise in CHD

Patients with ToF may lack the ability to supply the body with adequate amounts of oxygen due to pulmonary regurgitation, ventricular dysfunction and musculoskeletal adaptations all contributing to exercise intolerance (82). The diminished aerobic capacity observed in ToF patients may be an important predictor for

morbidity and mortality (60). Indeed, Diller et al. (24) reported that aerobic capacity of patients with CHD was comparable to what has been reported for heart failure patients. Moreover, similar to heart failure patients, ToF patients experience an increase in oxygen debt and prolonged recovery (e.g. VO_2 and VE) post-exercise (82). Aerobic capacity may be lower in those with ToF because of their inability to increase cardiac output during exercise, either due to the inability to increase stroke volume or chronotropic incompetence (67). Rhodes et al. (83) suggests a number of non-cardiac factors that may also contribute to the reduced aerobic capacity in CHD patients which include: presence of restrictive and/or obstructive lung disease, pulmonary vascular disease, systemic vascular disease, skeletal muscle dysfunction (including deconditioning), anemia, and iron deficiency.

2.5 Physical Activity Levels in CHD.

One of the desired outcomes of exercise programs is that patients assume the responsibility to maintain their own PA once the exercise program is completed. Unfortunately, there is ample data suggesting that one year post-cardiac rehabilitation, many patients discontinue structured exercise training (84-86). Since even simple unstructured activities at modest intensity may elicit significant health benefits (87), ACHD patients should be encouraged to engage in a physically active lifestyle, which includes both structured exercise and unstructured PA such as walking, cycling or other leisure activities that involve continuous movement of large muscle groups (87).

According to the World Health Organization (WHO), adults (aged 18-64 years) should accumulate 150 minutes of moderate PA (i.e. ≥ 3.0 METs) each week and the activities should be performed in bouts of ≥ 10 minutes (88, 89). Sandberg et al. (90) reported that approximately half of ACHD patients did not achieve the WHO recommendation. However, these authors used 1.75 x HR_{rest} as a minimum cut-off point for MVPA (90). Dua et al., (30) noted that while ACHD patients in NYHA Class I were more active than NYHA Class II or III patients, overall only a small percentage of participants met the current WHO PA recommendation. Even those with complex lesions may still safely achieve daily activity recommendations (33).

One way to monitor and encourage ACHD patients to complete daily unstructured PA is through the use of accelerometers, which can assess daily step counts. Tudor-Locke et al. (91) suggested that, for optimal health benefits from PA, healthy young adults should achieve ≥ 10,000 steps per day. Several reports have documented that ACHD patients typically do not achieve this step goal (29, 90, 92). Interestingly, for heart failure patients, who have a similar aerobic capacity to ACHD patients, a goal of ≥ 7,500 steps/day may be a more appropriate goal (92, 93).

Sedentary behaviour (defined as <5,000 steps per day or waking time spent ≤ 1.5 METs) is known to be problematic for ACHD patients and this sedentary behavior is linked to a reduced aerobic capacity (26, 33, 41, 75, 94). Since there is evidence indicating that sedentary behaviour is often replaced with light PA rather than more vigorous PA (95), patient care-teams may wish to encourage ACHD patients to reduce their sedentary behaviour by increasing their time spent in light PA (95-98). Further, by simply implementing more frequent breaks in sedentary time patients may achieve greater engagement in light PA, which in turn is an important step toward a more active lifestyle (99). Indeed, Manns et al. (98) has suggested that focusing on reducing sedentary behaviour and increasing light PA may be a more feasible first step in PA behavior change and may lead to more successful and sustainable behaviour change. PA counselling and ensuring good communication between clinician, therapist and caregivers regarding PA recommendations should be emphasized (34).

Few studies have objectively assessed PA using accelerometers (29, 33, 90, 100). Two studies reported significant improvements in PA after formal training programs (29, 100). In fact, in contrast to previous studies (40, 90, 101) Muller et al. (33) found regular MVPA (i.e., ≥ 3.0 METs) was positively related to VO_{2peak} in CHD patients. Because of the health benefits regular PA may provide, measuring daily PA should be a part of a strategy to improve ACHD overall health.

2.6 Measuring Physical Activity.

Accelerometers provide an objective assessment of daily PA (102). Accelerometers use sensors to measure acceleration and deceleration in one or more planes of movement, which in turn can provide evidence of sedentary behavior, activity counts and intensities (102). Commercial devices such as ActiGraph, SenseWear Armband and FitBit accelerometers have been validated against the Cosmed $K4b^2$, the gold-standard indirect calorimetric devices (102). The most valid method for assessing energy expenditure (EE) is the double labelled water method, which involves the participant ingesting two stable isotopes of water that reflect the metabolism of the body (102, 103). One to three weeks after ingestion, the rate of loss of isotopes are analyzed to determine the kilocalories (Kcal) burned over the given period (104). Although valid, this PA assessment method is costly, and only provides EE over the two week period (103, 104). As such, personal accelerometers provide a less costly and invasive method for monitoring PA levels (105). The SenseWear Armband (SWA) has been validated against the double labelled water method in both healthy populations and elderly adults (106, 107). Furthermore, the SWA has been shown to provide accurate estimates of total EE across most treadmill speeds (103).

The SWA gathers data from a heat flux sensor, galvanic skin response sensor, skin temperature sensor and a three-axis accelerometer. Information from the four sensors are recorded second by second and entered into an algorithm to calculate minute by minute EE each day (106, 107). These data can then be assessed to determine sedentary time (≤ 1.5 METs) or time spent in mild (> 1.5 - < 3.0 METs) or moderate-vigorous PA (≥ 3.0 METs) (108). Because personal accelerometer use is becoming increasingly popular, user friendly and inexpensive, using accelerometers is feasible for tracking sedentary behavior and PA (105).

2.7 Level of Risk with Exercise and CHD.

Bergman and Stamm (109) found that patients with CHD may be less active than their healthy peers because of over-restriction from parents and educators. A frequently mentioned reason for not inquiring about

PA restrictions for CHD patients was the assumption that all types of exercise were safe to perform (110). Adding to the confusion regarding exercise recommendations is the fact that a significant proportion of children with CHD believe that they can participate in PA that is more intense than those actually recommended by their cardiologist (111). Takken et al., (34) suggested that the lack of agreement between parents and cardiologists regarding PA restrictions appropriate for a child with complex CHD may play a role in elevating the child's sedentary behavior. Evidence supporting the relative safety of exercise for patients with complex CHD may be drawn from a study by Duppen et al., (27) who reported 1 cardiac arrest every 115,000 hours in cardiac rehabilitation and 1 death every 750,000 patient hours of PA participation. However, there are other limitations linked to CHD that hinder exercise tolerance that need to be taken into consideration with exercise rehabilitation (112).

2.8 Benefits of Exercise Training for CHD.

Because ACHD patients have a reduced aerobic capacity, an obvious question is whether exercise training can reduce symptoms and improve exercise tolerance. A growing body of evidence supports the efficacy of exercise training programs in improving aerobic capacity in ACHD patients (27). In a report from Norway of 55 children and adolescents with CHD, a 5-month sport and recreation intervention performed at 60-85% HR_{peak} yielded slight improvements in exercise duration and VO_{2peak} (101). In a similar study involving 61 ACHD participants, Dua et al., (30) used a 10-week home-based walking program and demonstrated significantly increased walking time and VO_{2peak}. This implies that regular PA can improve aerobic capacity in patients with ToF. A systematic review by Duppen et al., (27) on the impact of cardiac rehabilitation in ACHD patients noted an average increase in VO_{2peak} of 2.6 mL/kg/min. Conversely, several studies have reported that ACHD patients who had lower PA scores, also recorded a lower VO_{2peak} (89, 92).

Improved aerobic capacity is considered an important health marker that may predict risk for morbidity and mortality (59). Several studies have also shown the associations between PA and aerobic capacity in healthy

participants (113-115) and in addition to the physical benefits of MVPA, studies have shown improvements in mental health, self-esteem, resilience to stress, and sleep patterns, and reduced anxiety and depression (27, 31).

Two randomized controlled trials evaluating cardiac rehabilitation for patients with ToF demonstrated an improvement in aerobic capacity post-training (31, 32). In a small study of 18 ToF adults, Therrien and colleagues (31) randomized patients to 12-weeks of moderate continuous aerobic training (MCAT) versus usual care. They found a 2 mL/kg/min improvement in VO_{2peak} in the training group. Duppen et al. (32) conducted a randomized trial of 12-weeks of MCAT versus usual care in 47 young adults with ToF (mean age of 15 years). Their results supported the findings of Therrien and colleagues (31) as MCAT produced a 3 ml/kg/min improvement in VO_{2peak} compared to controls (32).

The current study sought to evaluate the relationship between VO_{2peak} and daily time spent in moderate-to-vigorous PA (MVPA ≥ 3.0 METs) in patients with ToF or ToF-like physiology and to compare these findings with healthy age and gender matched controls. Further, this study evaluated the relationship between submaximal cardiopulmonary exercise measures (i.e., VAT, OUES, and VE/VCO_2 slope) and daily time spent in MVPA across the two groups.

Chapter 3

METHODS.

3.1 Study Design.

This was a cross-sectional single center observational study evaluating the relationship between VO_{2peak} and daily PA in adults with ToF or ToF-like physiology versus healthy, sedentary, age and gender matched controls. This study was approved by the University of Alberta Health Research Ethics Board.

3.2 Sample Size.

To date, few studies have objectively measured PA levels in patients with CHD. Mueller et al., (33) published objective PA results across the spectrum of CHD diagnoses. As a result, we chose to base our sample size calculation on the reported correlation between daily PA and aerobic capacity as reported in Mueller et al.'s paper (33). Using the correlation coefficient found in Mueller et al.'s paper (33) of r = 0.437, a 90% power and a 2 sided-alpha of 0.05, we calculated a required sample size of 19 participants per group (116).

Inclusion/Exclusion criteria. For ToF participants, medically stable patient's ≥ 16 years of age with moderate or greater pulmonary regurgitation were included. Patients with ToF-like physiology such as double outlet right ventricle (DORV) with pulmonary stenosis, pulmonary atresia with a ventricle septal defect, or Rastelli procedure were also included. Exclusion criteria included uncorrected ToF, severe outflow tract obstruction (peak Doppler gradient > 50 mmHg), or sustained arrhythmia.

The ToF participants aged 16 and 17 years were recruited from the pediatric cardiology clinic at the Stollery Children's Hospital by a study coordinator. Adult ToF patients were recruited from the Northern Alberta Adult Congenital Heart (NAACH) Clinic, which facilitated enrollment. The CHD patients were recruited by the principle investigator, research coordinator, or research nurse upon the patients clinical visit to determine their

interest in the study. Patients interested in participating completed a consent form prior to completing baseline physiological measurements.

Healthy, age and gender matched controls were recruited via word-of-mouth and posters located throughout the University of Alberta and the surrounding community. As the majority of CHD patients are sedentary (26, 33, 41, 42, 90), we recruited sedentary (self-reported PA < 150 min per week of exercise participation) healthy controls. The healthy control participants had to be free of any health issues as determined by Physical Activity Readiness Questionnaire (PAR-Q) (117). The healthy control participants interested in participating completed a consent form prior to participating in the physiological measurements.

3.3 Outcome Measures

The primary outcome measures were VO_{2peak} and time spent in MVPA (i.e., METs ≥ 3.0). Secondary outcomes include VAT, OUES and VE/VCO_2 slope. Measurements were completed at the Alberta Cardiovascular & Stroke Research Centre (ABACUS) within the Mazankowski Alberta Heart Institute at the University of Alberta Hospital within 1-2 weeks following recruitment. Participants' characteristics, including date of birth, gender, height, weight and BMI were recorded at the initial visit. Assessments included anthropometric measures, a SL-GXT and an objective measurement of daily PA.

Symptom Limited Graded Exercise Stress Test: The SL-GXT was completed using a stationary, electronically braked upright cycle ergometer. Prior to starting the SL-GXT, after 5 minutes of quiet rest on the bicycle ergometer, resting VO_2 (VO_{2rest}), heart rate (HR_{Rest}) and blood pressure (BP_{Rest}) were recorded.

The exercise portion of the SL-GXT involved a ramp protocol beginning at 20 watts (W) with increments of 20 W/min while maintaining a pedalling rate of 50-70 revolutions per minute (rpm). This ramp protocol was chosen based on previous studies (118, 119). Heart rate was recorded every minute throughout the SL-GXT using a 12-lead electrocardiogram (ECG) (CASE Exercise Testing System, General Electric Company® Electrocardiography, USA). Oxygen uptake (VO_2) was measured via breath-by-breath expiratory gas analysis

using a Vmax Encore Metabolic Cart (SensorMedics, CareFusion Corp, San Diego, CA, USA). Blood pressure, measured via auscultation, and the rate of perceived exertion (RPE; using the Borg 1-10 scale) were assessed every 2 minutes throughout the SL-GXT.

The SL-GXT end-point criteria included: a respiratory exchange ratio (RER) > 1.1, a HR response > 85% age-predicted maximal heart rate, volitional fatigue (defined as maximal perceived exertion; i.e., RPE = 10/10), inability to maintain a pedalling rate of 50 rpm on the cycle ergometer or signs and symptoms of exertional intolerance (13). VO_{2peak} was defined as the highest oxygen uptake observed over a 30 second interval during the SL-GXT. Upon completion of the SL-GXT, participants completed 7 minutes of passive recovery while sitting quietly on the cycle ergometer. During this time, HR, VO_2, and BP were measured following the same protocol as during the exercise portion of the SL-GXT. After completion of the SL-GXT, each participant's chronotropic index and submaximal measures (i.e., VAT, OUES, VE/VCO_2 slope) were determined using recorded data over 30 second intervals using the breath-by-breath expiratory gas data. The ventilatory anaerobic threshold was defined as the disproportionate increase in VCO_2 relative to the increase in VO_2 and was determined using the V-Slope method (15, 16). The oxygen uptake efficiency slope was determined by the equation $VO_2 = a \times \log VE + b$; where "a" represents the OUES (18, 78). The VE/VCO_2 slope was determined by linear regression analysis of the data acquired throughout the entire period of exercise (66).

*Level of Physical Activity***.** Daily PA levels were objectively measured using a SenseWear Mini Armband (SWA; BodyMedia, Pittsburgh, Pennsylvania). The SWA has been validated against the double labelled water method in both healthy populations and elderly adults when estimating daily energy expenditure (r = 0.89) (106, 107, 120).

The SWA has a three-axis accelerometer with additional sensors, (i.e., heat flux sensor, galvanic skin response sensor and skin temperature sensor) to estimate energy expenditure (EE). Information from the four sensors are recorded second by second and entered into an algorithm to calculate minute by minute EE each

day (106, 107). The EE data were then used to categorize sedentary time (≤ 1.5 METs), time spent in light (> 1.5 - < 3.0 METs) and MVPA (≥ 3.0) based on previous studies using objective accelerometry on adults with congenital heart disease (29, 33, 90, 108, 115). The SWA also provides information about step counts (steps/day).

Participants were given the SWA after baseline testing and were instructed to wear it on the upper left triceps for at least 4 consecutive days, with a minimum of 1 weekend day; in the hope that 3 full days (midnight to midnight) of data was collected. They wore the monitor at all times except for water submersion. Participants who wore the SWA for ≥ 2 days were included for analysis (106). Only days where the SWA was worn for a minimum of 95% of the day (22 hours, 48 minutes) were included for analysis to ensure accurate representation of PA levels (106). Using the SWA data, steps/day was calculated by averaging the total number of steps taken each minute for all days. PAEE was equal to the sum of EE between 1.6 – 2.99 METs and ≥ 3.0 METs each minute for all days. PA participation was reported in steps per day, EE (Kcal), time spent sedentary (≤ 1.5 METs), in light (> 1.5 to < 3.0 METs), moderate to vigorous (≥ 3.0 METs) activity and number of MVPA bouts ≥ 10 min (2, 6, 29, 121). The accelerometer was returned by envelope with postage stamps and return address provided.

3.4 Statistical analysis

All data are presented as mean $\pm$ standard deviation. All data were managed using REDCap™ software. Analyses were performed using SPSS Statistics. Baseline characteristics of the participants are summarized using descriptive statistics (e.g., means, medians, standard deviations [SDs], frequencies, and proportions).

The primary hypothesis was evaluated using Pearson correlation and Fisher r to z transformation to determine the relationship between VO_{2peak} and daily time spent in MVPA within both groups. Secondary hypotheses were evaluated using Pearson correlation to determine the correlations between submaximal cardiopulmonary exercise measures (i.e., VAT, OUES and VE/VCO_2 slope) and daily time spent in MVPA within the two groups. Correlation coefficients are characterized as strong (r ≥ 0.700), moderate (r = 0.400 - 0.699), and

weak ($r \leq 0.399$) (122, 123). Given that the SL-GXT was completed on a cycle ergometer (i.e., a non-weight-bearing activity), the correlations conducted in this study were based on absolute VO_{2peak} (i.e., L/min). Two-tailed unpaired t tests were used to evaluate differences between groups in VO_{2peak}, daily time spent in MVPA and submaximal cardiopulmonary exercise measures (i.e., VAT, OUES, and VE/VCO_2 slope). Significant results were defined as $p < 0.05$.

Chapter 4

RESULTS.

4.1 Sample.

A total of 38 participants were included in the final analysis, 19 ToF patients and 19 healthy sedentary controls. The mean age of the ToF patients was 27.3 ± 7.3 years (M:F = 12:7) versus 27.6 ± 6.8 years (M:F = 12:7) for the healthy sedentary controls. The demographics and characteristics of the two groups are presented in Table 1. All participants completed the SL-GXT. Accelerometer data was collected for all patients however, two ToF patients' SWA data were not included in final analysis due to insufficient wearing time or technical problems with the SWA. Thus, in total there was SWA data from 17 ToF patients and 19 healthy sedentary controls for final analysis.

Table 1: Descriptive Characteristics.

	ToF (n = 19)	Controls (n = 19)	p value
Age (years)	27.3 ± 7.3	27.6 ± 6.8	0.909
Male (%)	12 (63%)	12 (63%)	-
Height (cm)	173.2 ± 9.6	172.8 ± 9.3	0.897
Weight (kg)	74.3 ± 21.3	79.4 ± 19.3	0.438
BMI (kg/m^2)	24.6 ± 5.9	26.5 ± 5.8	0.317
Cardiac Diagnosis:			
ToF	11 (58%)		
PS + post valvotomy with PR	4 (21%)		
VSD + PA	2 (11%)		
Ebstein's Anomaly	2 (11%)		
Prescribed Medications:			
ASA	8 (73%)		
Beta Blocker	3 (27%)		
Diuretic	2 (18%)		
ACE Inhibitor	1 (9%)		
Calcium Channel Blocker	1 (9%)		

Data are presented as mean ± SD or number (N) and percentage (%) unless otherwise indicated. BMI indicates body mass index, determined by weight (kg)/height (m^2). Significant difference between groups ($p < 0.05$). ToF= Tetralogy of Fallot. PS, pulmonary stenosis. PR, pulmonary regurgitation. VSD, ventricle septal defect. PA, pulmonary atresia. ASA, acetylsalicylic acid. ACE, angiotensin converting enzyme. Patients may be prescribed ≥ 1 medication.

4.2 Aerobic Capacity and MVPA.

The healthy sedentary controls had a significantly higher VO_{2peak} (L/min) compared to the ToF participants (Table 2; $p = 0.019$). Similarly, the healthy sedentary controls recorded a significantly higher amount of time spent in MVPA each day versus the ToF participants ($p = 0.015$). For the ToF patients, there was no correlation between VO_{2peak} (L/min) and daily time spent in MVPA (Table 3; $r = 0.094$, $p = 0.720$). However, for the healthy sedentary controls, a moderately strong positive correlation was observed between VO_{2peak} (L/min) and daily time spent in MVPA (Table 3, $r = 0.685$, $p = 0.001$).

Table 2: Cardiovascular Responses to Graded Exercise and the Assessment of Daily Physical Activity in ToF Patients and Healthy Sedentary Controls.

	ToF (n = 17)	Controls (n = 19)	p value
Response to Graded Exercise			
VO_{2peak} (ml/kg/min)	27.2 ± 6.0	31.2 ± 7.6	0.077
VO_{2peak} (L/min)	2.0 ± 0.5	2.5 ± 0.7	0.019*
Predicted VO_{2peak} (%)	76.1 ± 0.08	82.1 ± 0.08	0.029*
Work (Watts)	177.9 ± 44.2	210.5 ± 60.1	0.065
Peak METs	7.8 ± 1.7	8.9 ± 2.2	0.084
Peak HR (bpm)	171.1 ± 17.0	180.7 ± 13.0	0.057
Chronotropic Index	0.8 ± 0.1	0.9 ± 0.1	0.069
O_2 Pulse (mL/beat)	11.4 ± 2.4	13.5 ± 3.7	0.052
RER	1.3 ± 0.1	1.3 ± 0.1	0.170
VAT (L/min)	1.0 ± 0.3	1.2 ± 0.5	0.156
OUES (L/min)	1.0 ± 0.2	1.2 ± 0.3	0.018*
VE/VCO_2 slope	28.1 ± 2.7	26.7 ± 3.4	0.187
Measure of Daily Activity			
Waking Time (hrs/day)	16.5 ± 1.1	16.4 ± 1.1	0.666
Steps/day	6,829 ± 3060	7,806 ± 3,084	0.354
Daily EE (Kcal)	2,575 ± 658	2,821 ± 788	0.319
Sedentary Time (hrs/day)	10.5 ± 2.3	10.3 ± 1.5	0.794
Light PA (hrs/day)	4.6 ± 1.8	3.8 ± 1.0	0.108
MVPA (hrs/day)	1.4 ± 0.8	2.2 ± 1.2	0.015*
Bouts (≥ 10 min/day)	2.4 ± 1.6	4.0 ± 2.3	0.031*

Data are mean ± SD. Work, defined in watts (W). ToF, Tetralogy of Fallot. METs, metabolic equivalent. SenseWear Armband (SWA). VO_{2peak}, defined as the highest oxygen uptake observed during SL-GXT. Chronotropic index, calculated as $HRR/[(220\text{-age}) - HR_{rest}]$ (64) Volume of Oxygen Consumed (VO_2), defined as oxygen levels observed SL-GXT. Volume of Carbon Dioxide (VCO_2), defined as volume of carbon dioxide during the SL-GXT. Respiratory Exchange Ratio (RER). Ventilatory Anaerobic Threshold (VAT). Oxygen Uptake Efficiency Slope (OUES). VE, Ventilation. EE, Energy Expenditure. PA, Physical Activity. Sedentary (≤ 1.5 METs), Moderate-Vigorous PA (MVPA) (≥ 3.0 METs) (108). Kcal, kilocalories. Significant difference between groups ($p < 0.05$). Significant results are marked *.

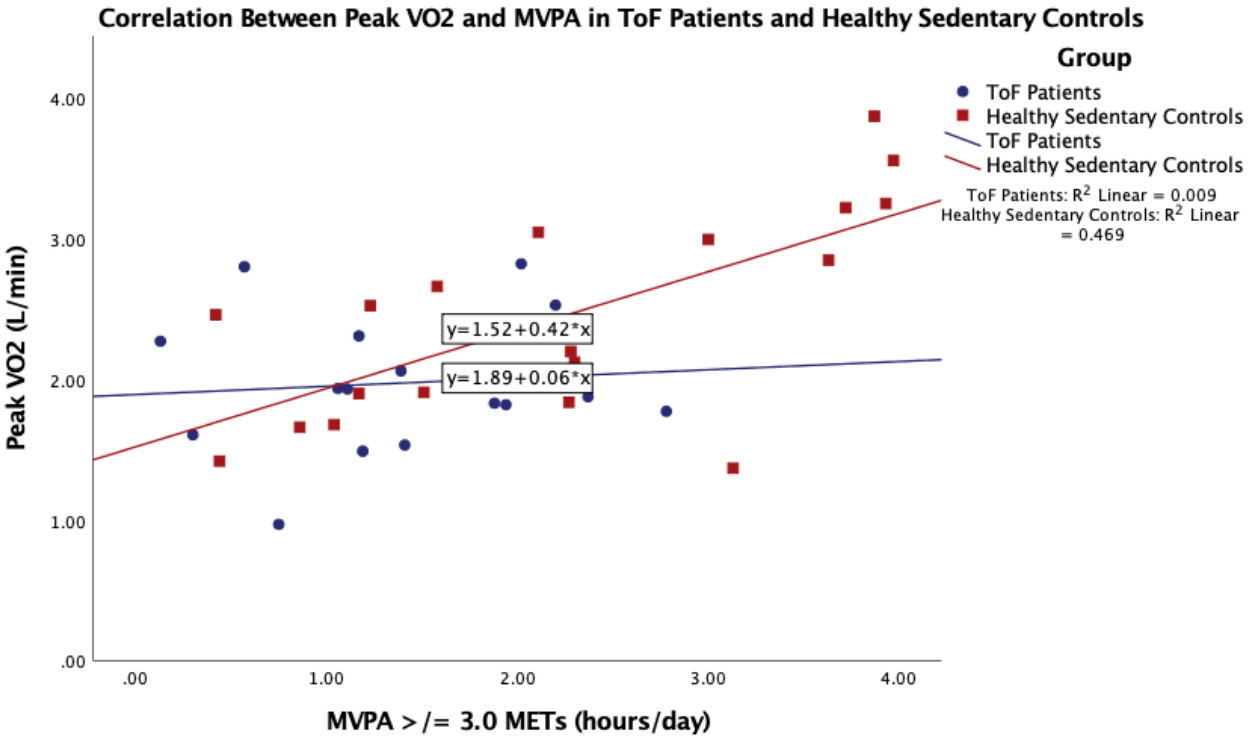

Figure 1: Relationship between MVPA and VO_{2peak} in ToF Patients and Healthy Sedentary Controls

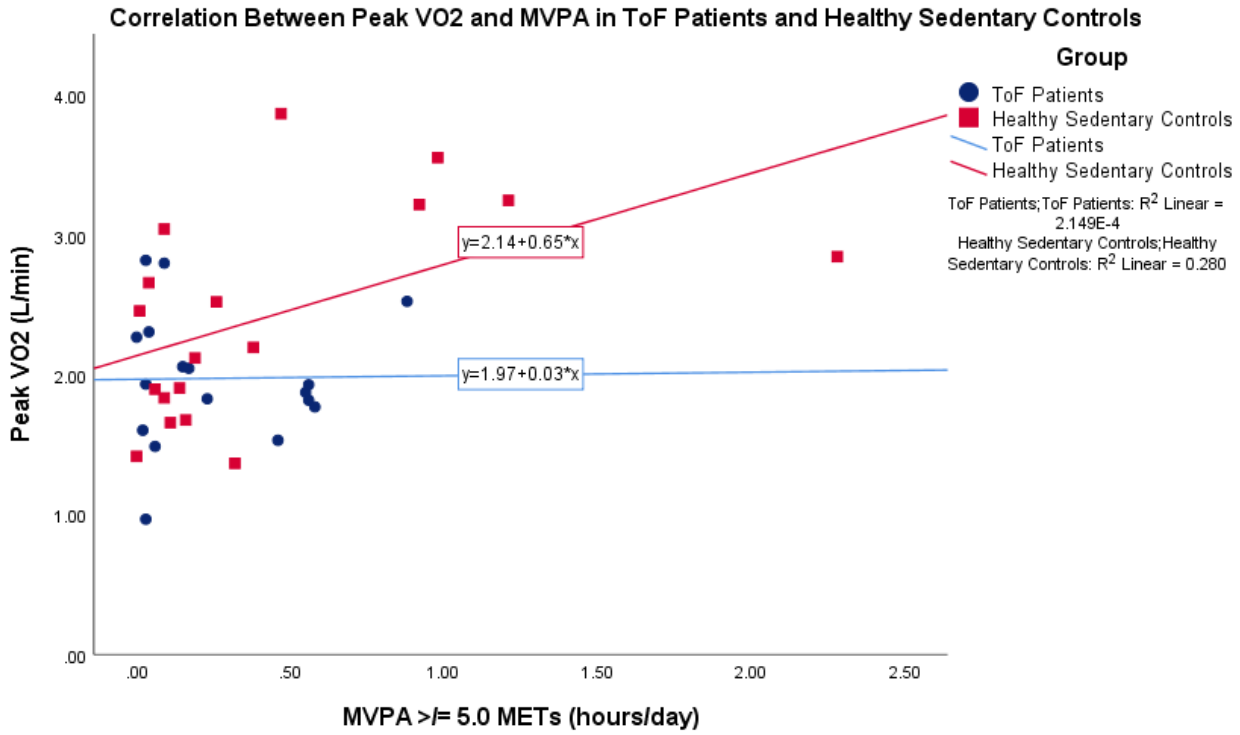

Figure 2: Relationship between MVPA (≥ 5.0 METs) and VO_{2peak} in ToF Patients and Healthy Sedentary Controls.

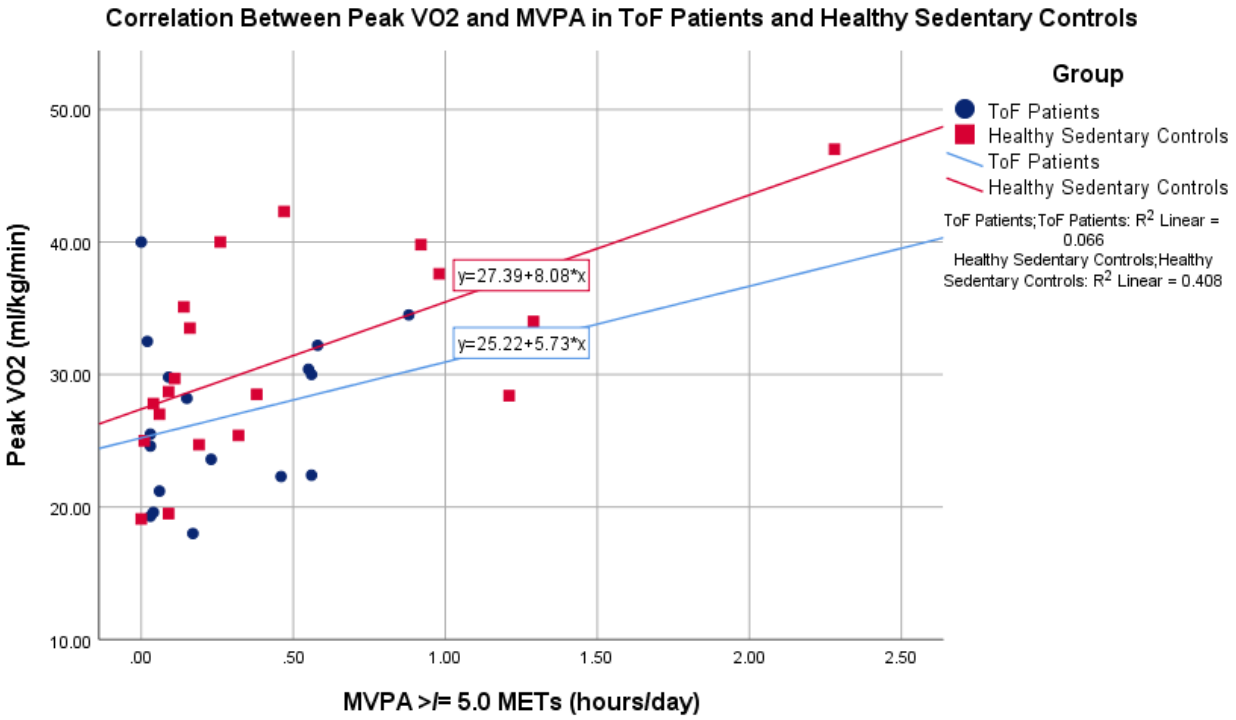

Figure 3: Relationship between PA (≥ 5.0 METs) and VO_{2peak} (mL/kg/min) in ToF Patients and Healthy Sedentary Controls.

4.3 Submaximal Cardiopulmonary Exercise Capacity.

The VAT and the VE/VCO_2 slope were comparable across the two groups (Table 2). Conversely, the OUES was lower in the ToF patients versus the healthy sedentary controls (Table 2; p = 0.018). There was a strong positive correlation between VO_{2peak} (L/min) and OUES in both the ToF patients (r = 0.989, p = 0.000) and the healthy sedentary controls (r = 0.995, p = 0.000) (Table 3). However, no correlation was found between VO_{2peak} (L/min) and VE/VCO_2 slope in the ToF patients (r = 0.278, p = 0.281) or in the healthy sedentary controls (r = -0.231, p = 0.342) (Table 3).

Two healthy sedentary healthy controls failed to reach a VAT because the participant remained in an anaerobic dominant metabolism (i.e., RER ≥ 1.0) from the onset of exercise through volitional fatigue during the SL-GXT or the participant stopped the SL-GXT due to localized muscle fatigue of the quadriceps before a VAT was reached. There was a moderate positive correlation between VO_{2peak} and VAT found in ToF patients (r = 0.675, p = 0.003). As well, a strong positive correlation was found between VO_{2peak} and VAT in the healthy sedentary controls (r = 0.746, p = 0.001).

Table 3: Correlation between Aerobic Capacity and Submaximal Cardiopulmonary Exercise Capacity Measures and Daily PA in ToF Patients and Healthy Sedentary Controls.

		ToF		Healthy Controls	
	VO_{2peak} (L/min)	**r**	**p value**	**r**	**p value**
VAT		0.675	0.003	0.746	0.001
OUES		0.989	0.000	0.995	0.000
VE/VCO_2 slope		0.278	0.281	- 0.231	0.342
Daily Time Spent in MVPA		0.094	0.720	0.685	0.001
Sedentary Time		0.397	0.115	- 0.278	0.248

ToF = Tetralogy of Fallot. VAT = Ventilatory Anaerobic Threshold. OUES = Oxygen Uptake Efficiency Slope. VE = Ventilation. VCO_2 = Volume of Carbon Dioxide. PA = Physical Activity. Sedentary (≤ 1.5 METs), Moderate-Vigorous PA (MVPA) (≥ 3.0 METs) (108).

4.4 Submaximal Cardiopulmonary Exercise Capacity and MVPA

There were no relationships observed between daily time spent in MVPA and VAT and daily time spent in MVPA and OUES in ToF patients (Table 4). Similarly, there was no correlation observed between daily time spent in MVPA and VE/VCO_2 slope in ToF patients (Table 4). In the healthy sedentary control group, a strong positive correlation between daily time spent in MVPA and VAT ($r = 0.912$, $p = 0.000$), as well as MVPA and OUES ($r = 0.702$, $p = 0.001$) was observed. Lastly, there was no correlation between daily time spent in MVPA and VE/VCO_2 slope (Table 4) found in healthy sedentary controls.

Table 4: Correlation between MVPA and Submaximal Cardiopulmonary Exercise Capacity Measures in ToF Patients and Healthy Sedentary Controls.

	ToF		Healthy Controls	
MVPA	**r**	**p value**	**r**	**p value**
VAT	0.352	0.166	0.912	0.000
OUES	0.144	0.582	0.702	0.001
VE/VCO_2 slope	-0.200	0.441	- 0.219	0.367

ToF = Tetralogy of Fallot. VCO_2 = Volume of Carbon Dioxide. VAT = Ventilatory Anaerobic Threshold. OUES= Oxygen Uptake Efficiency Slope. VE = Ventilation. (108).

4.5 Daily Sedentary Time.

There was no difference in daily sedentary time across the ToF patient and the healthy sedentary control groups (Table 2). Sedentary time accounted for 64% and 63% of waking time for the ToF and control groups, respectively. There were no correlations between daily sedentary time and VO_{2peak} (Table 3; r = 0.397, p = 0.115), VAT (r = 0.075, p = 0.776) and OUES (r = 0.340, p = 0.182) in ToF participants (Table 5). Lastly, no relationship was observed between daily sedentary time and VE/VCO_2 slope (Table 5) in ToF patients.

For the healthy sedentary controls, there was no correlation between daily sedentary time and VO_{2peak} (r = - 0.278, p = 0.248). Additionally, there were no correlations observed for the healthy sedentary controls between daily sedentary time and OUES and VE/VCO_2 (r = - 0.315, p = 0.189; r = 0.393, p = 0.096, respectively) (Table 5). Lastly, within the healthy control group, a moderate negative correlation between daily sedentary time and VAT (r = - 0.631, p = 0.007) was observed.

Table 5: Correlations between Daily Sedentary Time and Submaximal Cardiopulmonary Exercise Measures in ToF Patients and Healthy Sedentary Controls.

	ToF		Healthy Controls	
Daily Sedentary Time	**r**	**p value**	**r**	**p value**
VAT	0.075	0.776	- 0.631	0.007
OUES	0.340	0.182	- 0.315	0.189
VE/VCO_2 slope	0.474	0.055	0.393	0.096

ToF = Tetralogy of Fallot. VO_{2peak} = Peak VO_2. VCO_2 = Volume of Carbon Dioxide. RER = Respiratory Exchange Ratio. VAT = Ventilatory Anaerobic Threshold. OUES = Oxygen Uptake Efficiency Slope. VE = Ventilation. (108).

Chapter 5

DISCUSSION.

5.1 Aerobic Capacity and MVPA. The purpose of this study was to evaluate the relationship between VO_{2peak} and daily time spent in moderate-to-vigorous PA (MVPA ≥ 3.0 METs) in patients with ToF or ToF-like physiology and to compare these findings with sedentary healthy age and gender matched controls. The observed VO_{2peak} (27 mL/kg/min) recorded in our ToF participants was comparable to what has been reported previously (27, 33, 65, 119). Further, the aerobic capacity (mL/kg/min) of our ToF participants was similar to what was observed in our healthy control participants (i.e., 31 mL/kg/min). This observed VO_{2peak} in the healthy sedentary controls was ~ 14 mL/kg/min lower than average healthy adults between 20-29 years old (124).

Given that the SL-GXT was completed on a cycle ergometer we felt it was important to also report aerobic capacity in absolute terms, where we noted that the VO_{2peak} (L/min) was significantly lower in our ToF participants (Table 2). Additionally, a significant difference in the percentage of predicted VO_2 (L/min) was observed between healthy controls, who achieved 82% of predicted VO_{2peak}, and ToF patients who achieved 76% of predicted VO_{2peak} (Table 2). This lower VO_{2peak} observed in ToF patients compared to healthy controls may be attributed to the subtle differences observed in HR_{peak}, chronotropic index and oxygen pulse (i.e., an indirect measure of SV, thus a lower SV at peak exercise in ToF patients) which, based on the Fick equation, may indicate a limitation to the augmentation of CO at peak exercise (Table 2) (125). Additionally, VO_{2peak} has been shown to be negatively correlated with body fat percentage (126, 127). Although we did not measure fat mass versus muscle mass in any participants, our healthy controls may have had a higher percentage of muscle mass, which may increase oxygen extraction from working muscle during the SL-GXT, resulting in a higher observed absolute VO_{2peak}.

With regard to daily PA we noted that neither group accumulated the 10,000 steps/day recommended for healthy young adults in order to achieve health benefits associated with PA (91). Indeed, both groups

averaged less than 8,000 steps/day and although our healthy control group accumulated more steps/day, the difference was not significant. With respect to time spent in the various levels of PA, we noted that both groups spent approximately 63% of their waking time sedentary, while light activity accounted for 28% of waking time for our ToF participants and 23% of waking time for our control group ($p > 0.05$). The only difference observed in daily PA was in the MVPA category.

These findings confirm our secondary hypothesis, which stated ToF patients would spend significantly less daily time in MVPA (i.e., $\geq$ 3.0 METs) than healthy sedentary controls. These findings may be due to restrictions placed on ToF patients by a concerned physician or the ToF patient themselves, fearing the possibility of increased risk of morbidity and mortality (33, 38). Interestingly, when we compared the MVPA of our ToF patients to previous reports, we observed that our ToF patients spent more time in daily MVPA than previously reported (29, 33, 38, 40, 90, 100). The results found in this study were determined using a SWA, which has been validated against the double labelled water method in both healthy populations and elderly adults when estimating daily energy expenditure (106, 107, 120). The previous studies lacked consistency in objective PA measurement (i.e., using a variety of accelerometers, such as the RT3, Actigraph or self-reporting PA). Indeed, we noted that 71% of our ToF patients met the WHO PA recommendations (i.e., ≥ 3.0 METs for ≥ 30 min/day) (88, 115). Similar findings have been reported by Muller et al. (33) who found that 76% of their ACHD patients reached these PA recommendations. Muller et al. (33) went on to suggest that while ToF patients may have a lower aerobic capacity due to their underlying lesion they can still achieve the daily PA recommendations and gain the health benefits associated with regular daily PA.

Although the majority of our ToF patients met WHO PA recommendations (≥ 3.0 METs for ≥ 30 min/day) they did so in ~ 2 bouts/day of MVPA >10 min, indicating that ToF patients may have spent the rest of their day in light PA or sedentary. Conversely, the healthy sedentary controls completed significantly more bouts per day (~4 bouts/day) of MVPA > 10 min. Although the current PA guidelines recommend MVPA should be

accumulated in bouts of ≥ 10 min, some studies have showed similar associations with metabolic syndrome, waist circumference and body mass index between bouted MVPA (< 10 min) versus continuous MVPA (≥ 10 min) (128-132). Additionally, Saint-Maurice et al. concluded that greater total time spent in MVPA was strongly associated with lower mortality, independent of how PA was accumulated (132).

Sedentary time was comparable across the two groups, accounting for 63% and 64% of waking time for the control and ToF groups, respectively. This observation is consistent with findings from Sandberg et al. (90) who reported that sedentary time accounted for 64% and 65% of daily waking time in complex ACHD patients and healthy controls, respectively. Further, Healy et al. (133) reported that healthy adults spend approximately 50-60% of waking time sedentary. Increasing sedentary time may elevate the risk for negative health outcomes, independent of MVPA (114, 133). Interestingly, in the present study, no relationships were found between VO_{2peak} (L/min) and sedentary time for either group, an observation that differs from previously reports, which included a large, diverse group of CHD patients and longitudinal studies on healthy participants (27, 114). The one notable difference between the present and previous studies was the methodology of assessing sedentary behaviour. The previous studies on ACHD patients used self-reported PA levels (27, 114), while the present study assessed sedentary time using accelerometers. Self-reporting PA may over estimate PA levels due to recall bias, whereas accelerometers provide an objective measure of PA (102).

Increasing light PA (i.e., > 1.5 – < 3.0 METs) has been found to be effective in reducing total sedentary time (95-99). Upon evaluating light PA, we found no differences between groups (Table 2). The volume of light PA observed in the present study is similar to results previously reported for healthy adults (134) and represents the first objective measurement of time spent in light PA in adult ToF patients. The time spent in light PA observed in our ToF patients' may help lower the risk for negative health outcomes associated with sedentary behavior (114, 133).

When the relationship between VO_{2peak} (L/min) and MVPA was examined, we found a moderately strong positive correlation in our healthy sedentary control group; a finding that is consistent with what has been reported in the literature (87, 114, 135). However, when we examined the same relationship in the ToF patients, no correlation was found. The present finding differs from what has been reported previously (27, 30, 33) and we must therefore reject our primary hypothesis. The inconsistency between studies may be due to differences in daily PA measurement. The present study used a SWA accelerometer to objectively measure daily PA; this was different from previous reports (29, 33, 38, 40, 90, 100). Although the definition for MVPA (i.e., $\geq$ 3.0 METs) is consistent with previous studies, methods for measuring PA was different. Dua et. al., (29) used the Actigraph accelerometer with cut-off points of >2100 counts/min as a measure of MVPA, while Muller et. al. (33) evaluated daily PA using a triaxial accelerometer by RT3 with cut-off points of >984 counts/min as an indication of MVPA (i.e., $\geq$ 3 METs). Lastly, Sandberg et al.'s (90) evaluated habitual PA and sedentary time using an Actiheart monitor, a combined uniaxial accelerometer and HR monitor where MVPA was defined as time spent with a HR $\geq$ 1.75 times HR_{rest} and individual HR response at 3 minutes into a baseline step-test.

Interestingly, after adjusting the cut-off points for MVPA to ≥ 5.0 METs, a similar finding was observed in the relationship between MVPA and VO_{2peak} (L/min) in our ToF patients (Figure 2). Additionally, when evaluating the relationship between VO_{2peak} (mL/kg/min) and MVPA defined as ≥ 5.0 METs, no correlation was found in our ToF patients (Figure 3). These results may be a reiteration of Muller et al. (33) which stated that while ToF patients may have a lower aerobic capacity due to their underlying lesion they can still achieve the daily PA recommendations and gain the health benefits associated with regular daily PA. However, our results do not support increases in time spent in MVPA may increase VO_{2peak}.

5.2 Responses to Submaximal Exercise. The VAT expressed as a percentage of VO_{2peak} (L/min), was comparable across the two groups (ToF = 53% vs. Healthy = 49%). There are few reports on VAT in adult ToF patients (66, 75) however, Buys et al. (75) found their ToF patients typically achieved a significantly lower VAT compared to

healthy controls suggesting that ToF patients' ability to deliver and utilize oxygen is lower than healthy controls, resulting in a greater dependence on anaerobic metabolism at lower exercise intensities (66, 75). Buys et al. (75) findings may be due to the control group having a higher VO_{2peak} than the control group in the present study (i.e., 38.6 mL/kg/min versus 31.2 mL/kg/min) during the same SL-GXT protocol. Our observations may suggest relatively comparable capacity to perform sustained submaximal aerobic exercise between our ToF group and the healthy sedentary controls due to the relatively similar exercise intensities at which a greater dependence on anaerobic metabolism occurs during a SL-GXT.

The correlation observed between VO_{2peak} and VAT for our healthy sedentary controls was consistent with previous reports (75, 136-140). Similarly, the correlation between VO_{2peak} and VAT in our ToF patients has been observed previously (66, 75). The relationship found between VO_{2peak} and VAT in ToF patients may suggest that increasing VO_{2peak} may result in a greater capacity to perform submaximal exercise as a higher VO_{2peak} is an indication of improved capacity to uptake, deliver and utilize oxygen during exercise, decreasing the dependence on anaerobic metabolism (66, 83, 137, 138, 140, 141).

Although VO_{2peak} is commonly used as a measure of aerobic capacity, it is effort dependent and may be influenced by patient apprehension to complete maximal exercise (142). Hence, using OUES may give an objective and reproducible indication of aerobic capacity at submaximal intensities in ToF patients (142). Our observation of a lower OUES in the ToF group may suggest a reduced efficiency in oxygen delivery and uptake within the periphery and increased dead space ventilation compared to the healthy controls (75). As Giardini et al. (60) showed, cyanotic adult Fontan patients have substantial differences in OUES throughout the entirety of exercise compared to Fontan patients with normal saturation. We also observed a strong positive correlation between VO_{2peak} and OUES in both the healthy controls and our ToF patients. These findings have been reported previously (75, 143).

Lastly, the VE/VCO_2 slope was comparable across the two groups suggesting that the interplay between aerobic and anaerobic metabolism during incremental aerobic exercise is essentially the same across the two groups. These findings have been reported in ToF patients by Buys et al. (75). In the present study, we observed no correlations between the VO_{2peak} and VE/VCO_2 slopes for either group. Although the VE/VCO_2 slope may be used for prognostic purposes, using the VE/VCO_2 slope as a measure of aerobic capacity may not be appropriate (66, 75).

To our knowledge, this is the first study to evaluate the relationship between daily time spent in MVPA and submaximal cardiopulmonary exercise measures (i.e., VAT, OUES, and VE/VCO_2 slope) in ToF patients. Interestingly, no correlations between MVPA and submaximal cardiopulmonary exercise measures were found in our ToF patients. Conversely, our healthy controls had strong correlations between MVPA and VAT and between MVPA and OUES. Thus, while confirming our secondary hypotheses that a relationship between MVPA and submaximal cardiopulmonary exercise measures would be greater in healthy sedentary controls (versus ToF patients), our data does not suggest that MVPA may improve submaximal cardiopulmonary exercise capacity measures in ToF patients.

5.3 Limitations: Unlike previous studies (30, 33, 41, 90), our sample size was small and focused on ToF and ToF-like adults. We chose to base our sample size calculation on the correlation between daily PA and aerobic capacity reported by Mueller et al. (33, 116). Because the current study is a sub-study of the *PhiT Study*, our ToF patients may be more conscious of the benefits of PA and actively engage in an increased time spent in MVPA and thus more likely to enroll in a training study compared to the ToF population as a whole (144).

We elected to recruit self-reported sedentary healthy controls because previous literature suggests ACHD patients do not achieve the WHO PA recommendation of $\geq$ 150 min/week of MVPA (27, 88). Interestingly, we found a majority of our healthy controls exceeded the WHO recommendations for MVPA, while self-reporting a sedentary lifestyle prior to enrollment. As well, participants from both groups were educated (high

school graduates, completed and/or attending college/university/technical school), and recruited primarily from the University of Alberta community. Higher education and socioeconomic status have been related to higher PA participation and aerobic capacity (145). Our ToF patients had a lower average age versus previously reported (i.e., 27 years vs. 32 years) (24, 65). Older CHD patients have been shown to have lower VO_{2peak} than younger CHD patients (68, 70, 72).

The most common subjective reason for stopping the SL-GXT was localized leg fatigue of the quadriceps muscles for both groups. This was expected as using a cycle ergometer may elicit 10-20% lower observed VO_{2peak} when compared to treadmill protocols due to localized leg fatigue as people are generally not as conditioned on a cycle as they are walking/running (13). No adverse signs or symptoms were observed and all participants reached the end point criteria, defined as a respiratory exchange ratio (RER) > 1.1, a HR response > 85% age-predicted maximal heart rate, volitional fatigue (defined as maximal perceived exertion; i.e., RPE = 10/10) or inability to maintain a pedalling rate of 50 rpm on the cycle ergometer (13).

5.4 Conclusion: Our ToF patients had a lower aerobic capacity (L/min) compared to our sedentary controls. The ToF patients achieved PA recommendations for daily time spent in MVPA of ≥ 3.0 METs, ≥ 30 min/day, however the ToF group spent less time in daily MVPA compared to healthy controls. Additionally, no relationship was found between VO_{2peak} and MVPA in our ToF patients. These results may be a reiteration of Muller et al.'s (33) findings which stated that while ToF patients may have a lower aerobic capacity due to their underlying lesion but may still achieve the daily PA recommendations and gain the health benefits associated with regular daily PA.

The VAT and VE/VCO_2 slope were comparable across the two groups. This may suggest relatively comparable capacities to perform sustained submaximal aerobic exercise and the interplay between aerobic and anaerobic metabolism during incremental aerobic exercise is similar between our ToF group and the healthy sedentary controls. Conversely, the lower observed OUES in the ToF group may suggest a reduced

efficiency in oxygen delivery and uptake within the periphery and increased dead space ventilation compared to the healthy controls (75). A relationship was found between VO_{2peak} and submaximal exercise capacity measures (VAT and OUES) in our ToF group. This relationship between VO_{2peak} and VAT and OUES are consistent with what is typically seen in healthy populations. However, when evaluating maximal aerobic capacity and PA habits in CHD patients, other factors should be considered (75, 149).

5.5 Recommendations for Clinical Practice and Future Research: One of the desired outcomes of cardiac rehabilitation programs is that patients assume the responsibility to maintain their own PA once the formal exercise program is completed. Unfortunately, there is ample data suggesting that by one year post-exercise intervention many patients discontinue structured exercise training (84-86). Since even simple unstructured activities at modest intensity may elicit significant health benefits (87), ToF patients should be encouraged to engage in a physically active lifestyle, which includes both structured exercise and unstructured PA such as walking, cycling or other leisure activities that involve continuous movement of large muscle groups (87). It is important to determine PA levels of ToF patients and what may be limiting these patients from being more physically active. Because PA appears to be safe for ToF patients, decreasing total sedentary time, while increasing PA and exercise participation should be encouraged. Thus, an exercise prescription should be individualized to the patients' interests and goals, while encouraging increased PA outside of formal exercise training.

High intensity interval aerobic exercise has been shown to improve VO_{2peak} in healthy, CAD and HF populations (150-156) better than moderate intensity continuous aerobic exercise. Additionally, PA at higher intensities (i.e., $\geq$ 5.0 METs) has been shown to be of particular benefit to patients with chronic lung disease where dyspnea may limit exercise (152). High intensity interval training, which consists of alternating high intensity aerobic work bouts (i.e., 90-100% VO_{2peak}, HR_{peak}, peak power output) with periods of rest of active recovery at relative low intensities (i.e., 30-60% VO_{2peak}, HR_{peak}, peak power output) has been shown to increase

VO_{2peak}, O_2 pulse, post training power output in healthy populations (151). Guiraud et al. (150) reported that heart failure patients with severely reduced VO_{2peak} were able to spend a considerably longer period of time at 85% VO_{2peak} during 30 second bouts of HIIT. These authors added that HIIT is better tolerated and allows patients to increase their total exercise time compared to longer exercise intervals (150). Based on these findings, high intensity interval aerobic training programs may improve VO_{2peak} in ToF patients better than moderate continuous intensity training programs and needs to be further investigated. Additionally, further research is needed on the potential positive effects of increasing daily time spent in unstructured vigorous PA (i.e., $\geq$ 5.0 METs) on aerobic capacity in ToF patients.

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Appendix A: Ethical Approval

10: Pro00059680_AME5

Name: PhiT Study

Status: Approved

Submission Type: Amendment

Instructions

1. Check the Submission Type above. Based on the descriptions below, if the submission type is appropriate to the changes or renewal you wish to file, click "Continue"
2. If the Submission Type is incorrect, click the "Back" button and in the amendment workspace, click on the activity button appropriate to your needs.

Change Personnel and Funding

These changes can be done using the buttons on the left side of study workspace under the heading "My Activities" and do NOT require the submission of an amendment. Please close this window and simply use the activity buttons on the main study workspace to make these changes to the study personnel or funding, with one exception. If you wish to change the study PI you MUST submit an Amendment.

Amendments

An amendment should be submitted to outline ANY changes from the approved study (other than changes to the study personnel or study funding).

Renewals

A renewal should be submitted if the ethics approval for your study is due to expire, and you still need ethics certification to continue your study (ie. you are continuing to work with human participants and/or their data and/or you may need to go back to your human participants to collect more data.

Clarification on Requesting Amendments or Renewals

A request for Amendment or Renewal involves two parts: fill in the Amendment or Renewal form; and modify the ethics application form, as required
Important: Only one request for any type of amendment or renewal is allowed at any given time. For example, if you have an amendment currently in process, you cannot create a New Renewal submission.

Appendix B: ToF Consent Form

PARTICIPANT CONSENT FORM

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

Principal Investigator:	Dr. Isabelle Vonder Muhll, 780-407-3107
Co-Principal Investigator:	Dr. Andrew Mackie, 780-407-2101
Co-Investigators:	Dr. Jonathan Windram Dr. Bob Haennel Dr. Gabor Gyenes
Study Coordinator:	Ms. Kathryn Rankin, 780-407-1327
Study Staff:	Mr. John (JP) Willner, 780-492-2609

Why am I being asked to take part in this research study?
You are being asked to be in this study because you have you have Tetralogy of Fallot (TOF) or a heart defect like TOF. Heart defects are usually treated with repair in early childhood. Despite successful surgery, there is a risk of problems later in life, such as leaking pulmonary valve. Leaking valves in congenital heart patients cause heart enlargement and other problems. As a result, patients have difficulty performing exercise. The purpose of this study is to see if exercise will help congenital heart patients, and what form of exercise works best.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?
This study will assess physical activity and exercise training in TOF patients and patients with heart defects like TOF. Other researchers have found low exercise ability in congenital heart patients. You will either receive one of two forms of exercise training or no training. We will compare moderate exercise to high intensity exercise to no exercise. We hope to learn what form of exercise works best. We think that this study will provide important information about the role of exercise in congenital heart patients. There will be 51 participants in this study.

What will happen in the study?
If you decide to take part, you will have assessments at the beginning and end of the study. We will test your exercise ability and measure your physical activity. We will assess your heart function with MRI and/or echocardiography (ultrasound of the heart). You will complete questionnaires about quality of life. These procedures will take about half a day. You will then be assigned at random (like flipping a coin OR like rolling a dice) to one of three groups. You have a 1 in 3 chance of being in the group that receives moderate exercise training. You have a 1 in 3 chance of being in the group that receives high intensity exercise training. You have a 1 in 3 chance of being in the group that receives no exercise training. You can continue your usual activities, including exercise, whatever group you are in.

Participants in the exercise groups will come to the Jim Pattison Center for Cardiac Rehabilitation for exercise training. The Jim Pattison Center is on the ground floor of the Mazankowski Alberta Heart Institute. Training will occur 3 times per week for 12 weeks. Each training session will be one hour.

Baseline assessment:
At the time of your first visit:

- The research staff will record your date of birth, gender, email and telephone number. Your cardiologist will provide medical information about you. This includes the types of surgery you have had.
- Exercise ability will be assessed with a cardiopulmonary exercise test. During this test you will exercise on a bicycle while breathing into a special mask. You will be encouraged to give the test your best effort.
- Heart function will be assessed with an echocardiogram and/or a cardiac MRI (magnetic resonance imaging study of the heart). Both of these tests take 1 hour each to complete.
- Surveys with questions about your symptoms and quality of life will be given to you. The surveys will take 15 minutes.
- You will be lent an arm-band activity tracker to wear for four days which measures how active you are. It should not be worn in the water or while showering. You should return it when you come for your next visit.
- You will be informed which of the 3 groups you will be in.

Exercise training:
If you are assigned to an exercise group, you will come for 3 one-hour sessions per week. The training will occur for 12 weeks with a group of 6-8 other participants.

- Moderate exercise group: You will receive instruction by exercise specialists how to use exercise equipment. The exercise program will be similar to what patients do after a heart attack.
- High intensity exercise group: You will receive instruction by exercise specialists how to use exercise equipment. The exercise program will be short bursts of activity

with breaks. This is similar to how athletes train.

Non-training group:
If you are assigned to the no exercise group, you will continue your usual activities for 12 weeks. If you normally exercise, you may continue to do so. We ask that you do not change the type of activities you normally do.

12 week Assessment:
After 12 weeks in one of the groups you will return for follow-up tests. These include a cardiopulmonary exercise test, an echocardiogram and/or a cardiac MRI. You will repeat the surveys with questions about your symptoms and quality of life.

Final Assessment:
Six months from the start of the study, we will ask you to repeat the surveys. You will wear the arm-band activity tracker for four days. You will receive a fitbit Zip fitness monitor for your use afterward.

What are the risks and discomforts?
Exercise testing carries a slight risk of heart attack or death (1 in10, 000). Rarely abnormal heart rhythms can occur during an exercise test. MRI can cause claustrophobia (fear of being in a confined space). There is a possibility that the MRI may identify something abnormal in the chest. If anything unexpected is found, you will be referred for follow-up. Echocardiography has no known risks.

Exercise training carries a risk of causing joint or muscle problems. Rarely, an abnormal heart rhythm or heart attack could occur from exercise (1 in 1000). Staff at the Jim Pattison Center will supervise your exercise training. They have expertise in training heart patients. Urgent care is available for any heart emergency.

What are the benefits to me?
Exercise training is expected to be helpful. If you are in an exercise group, you may have improved exercise ability and general wellbeing. However, you may not get any benefit from being in this research study. This study may help other people with congenital heart conditions in the future.

If you complete the study, you will receive a fitbit Zip fitness monitor to thank you.

What will I need to do while I am in the study?
It is important to remember the following things during this study:

- Tell study staff if your health has changed.
- If you think that you might be pregnant, a cardiac MRI should not be performed. If one is scheduled for you, please let study staff know.
- If you are in the non-training group, try not to change your activity levels during the

12-week period.

What happens if I am injured because of this research?
If you become ill or injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigators or institution from their legal and professional responsibilities.

Do I have to take part in the study? Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the care or treatment that you are entitled to.

Can my participation in the study end early? In addition to your being able to stop the study at any time, the study doctor may withdraw you from this study if new health problems arise.

Will I be paid to be in the research?
Your costs to park or take transit to be in the study will be covered. If parking is needed, you will receive a parking voucher to cover the parking fee at each visit. If you take transit, you will receive a transit pass each time for the next visit.

Will my information be kept private?
During the study we will be collecting health data about you. We will do everything we can to make sure that this data is kept private. No data relating to this study that includes your name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private

The study doctor/study staff may need to look at your personal health records held at the study doctor's office, and/or kept by other health care providers that you may have seen in the past (i.e. your family doctor). Any personal health information that we get from these records will be only what is needed for the study.

During research studies it is important that the data we get is accurate. For this reason your health data, including your name, may be looked at by people from the University of Alberta Health Research Ethics Board and clinical auditors.

By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose information about you from your personal health records as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for 5 years after the end of the study.

If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

What if I have questions?
If you have any questions about the research now or later, please contact Dr. Vonder Muhll at 780-407-3107, Ms. Kathryn Rankin (coordinator) at 780-407-1327 or Mr. John Willner (staff) at 780-492-2609**.**

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office is independent of the study investigators.

CONSENT

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

Principal Investigator: Dr. Isabelle Vonder Muhll **Phone Number: 780-407-3107**

Study Coordinator: Ms. Kathryn Rankin **Phone Number: 780-407-1327**

	Yes	No
Do you understand that you have been asked to be in a research study?	D	D
Have you read and received a copy of the attached Information Sheet?	D	D
Do you understand the benefits and risks involved in taking part in this research study?	D	D
Have you had an opportunity to ask questions and discuss this study?	D	D
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	D	D
Has the issue of confidentiality been explained to you?	D	D
Do you understand who will have access to your records, including personally identifiable health information?	D	D
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	D	D

Who explained this study to you? _____

_____

I agree to take part in this study:

Signature of Research Participant _____

(Printed Name) _____

Date:_____

Signature of Witness _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee_____Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

Appendix C: Control Consent Form

PARTICIPANT CONSENT FORM

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

Principal Investigator:	Dr. Isabelle Vonder Muhll, 780-407-3107
Co-Principal Investigator:	Dr. Andrew Mackie, 780-407-2101
Co-Investigators:	Dr. Jonathan Windram
	Dr. Bob Haennel
	Dr. Gabor Gyenes
Study Coordinator:	Ms. Kathryn Rankin, 780-407-1327
Study Staff:	Mr. John (JP) Willner, 780-492-2609

Why am I being asked to take part in this research study?

You are being asked to be in this substudy of the Physical Activity in Tetralogy (PhiT study): a Randomized Trial of Interval Training Versus Moderate Continuous Training Versus Usual Activity because you are a healthy, age and gender matched control for a participant enrolled.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?

Regardless of the complexity, patients with congenital heart disease should be encouraged to participate in regular physical activity and patients with tetralogy of Fallot (ToF) may benefit their health from increasing daily physical activity. Although research has been conducted on the effects of formal training regimes, little research has evaluated the associations between exercise capacity and physical activity in ToF patients. Thus, while the health benefits of regular physical activity are well documented in many cardiac patient populations, there remains a need for examining the effect of daily physical activity levels on the health and fitness of ToF patients.

The primary purpose of this study is to evaluate the relationship between exercise capacity (VO_{2peak}) and daily time spent in moderate-to-vigorous physical activity in patients with ToF or ToF-like physiology compared to healthy age-matched controls. The secondary purpose is to evaluate the relationship between submaximal cardiopulmonary exercise measures and daily physical activity.

What will happen in the study?

If you decide to take part, you will complete one assessment at the beginning of the study. We will test your exercise ability and measure your physical activity. You will complete questionnaires about quality of life.

Baseline assessment:

At the time of your first visit:

- The research staff will record your date of birth, gender, email and telephone number. You will complete the Physical Activity Readiness Questionnaire (PAR-Q).
- Exercise ability will be assessed with a cardiopulmonary exercise test. During this test you will exercise on a bicycle while breathing into a special mask. You will be encouraged to give the test your best effort.
- Surveys with questions about your quality of life will be given to you. The surveys will take 15 minutes.
- You will be lent a SenseWear Armband activity tracker to wear for one week. This is a strap-on device you wear throughout the day. It measures how active you are in a week. It should not be worn in the water or while showering. You will be given a stamped and addressed envelope in order to return the device.

What are the risks and discomforts?

Exercise testing carries a slight risk of heart attack or death (1 in 15,000 tests). Rarely abnormal heart rhythms can occur during an exercise test. If anything unexpected is found, you will be referred for follow-up. Exercise testing carries a risk of causing joint or muscle problems. Rarely, an abnormal heart rhythm or heart attack could occur from exercise (1 in 10,000 exercise hours). Staff at the Mazankowski Alberta Heart Institute will supervise your exercise testing. They have expertise in training heart patients. Urgent care is available for any heart emergency.

What are the benefits to me?

Exercise training is expected to be helpful. However, you may not get any benefit from being in this research study. This study may help other people with congenital heart conditions in the future.

What happens if I am injured because of this research?

If you become ill or injured as a result of being in this study, you will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigators or institution from their legal and professional responsibilities.

Do I have to take part in the study? Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the care or treatment that you are entitled to.

Can my participation in the study end early? In addition to your being able to stop the study at any time, the study doctor may withdraw you from this study if new health problems arise.

Will I be paid to be in the research?

Your costs to park or take transit to be in the study will be covered. If parking is needed, you will receive a parking voucher to cover the parking fee at each visit. If you take transit, you will receive a transit pass each time for the next visit.

Will my information be kept private?

We will do everything we can to make sure that data collected is kept private. No data relating to this study that includes your name will be released outside of the study doctor's office or published by the researchers. Sometimes, by law, we may have to release your information with your name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your health information is kept private.

During research studies it is important that the data we get is accurate. For this reason your health data, including your name, may be looked at by people from the University of Alberta Health Research Ethics Board and clinical auditors.

By signing this consent form you are giving permission for the study doctor/staff to collect, use and disclose data collected about you as described above.

After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for 5 years after the end of the study.

If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

What if I have questions?

If you have any questions about the research now or later, please contact Dr. Vonder Muhll at 780-407-3107, Ms. Kathryn Rankin (coordinator) at 780-407-1327 or Mr. John Willner (staff) at 780-492-2609**.**

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office is independent of the study investigators.

CONSENT

Title of Study: Physical Activity in Tetralogy (PhiT Study): A Randomized Trial of Interval Training Versus Moderate Continuous Training Versus Usual Activity.

Principal Investigator: Dr. Isabelle Vonder Muhll **Phone Number: 780-407-3107**

Study Coordinator: Ms. Kathryn Rankin **Phone Number: 780-407-1327**

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	☐	☐

Who explained this study to you? _____

_____

I agree to take part in this study:

Signature of Research Participant _____

(Printed Name) _____

Date:_____

Signature of Witness

_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT

Appendix D: PAR-Q

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→ **DELAY BECOMING MUCH MORE ACTIVE:**

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT _____ WITNESS _____
or GUARDIAN (for participants under the age of majority)

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

Appendix E: Patient Instructions

Patient Instructions

Thank you for participating in our study, "Physical Activity in Tetralogy (PhiT Study): A Randomized Trial of Interval Training Versus Moderate Continuous Training Versus Usual Activity".

Because the baseline testing includes a maximal exercise test, it may be beneficial to have arrangements for transportation to and from the Mazankowski Alberta Heart Institute in case of fatigue.

For all appointments, we ask you arrive roughly **15 minutes** prior to the beginning of assessment.

Parking

In order for hassle free arrival, we will compensate your parking. Parking passes will be given at the end of your measurement appointment or exercise session. You will be able to park at **P1 – the East Public Parkade located on 83 avenue and 112 street** (the entrance is off 83 Ave.) An enclosed pedestrian pedway connecting the parking garage to the Mazankowski Alberta Heart Institute is available on the **4th level** of the parking garage. If you are taking the pedway access to the Mazankowski Alberta Heart Institute, you will enter the Mazankowski on the second level **(Level 2)**.

If entering the Mazankowski from the front entrance, Level 1, take a **right** upon entering. There is elevator and stair access to the **second floor** of the Mazankowski Alberta Heart Institute. **John (J.P.) Willner will meet you at the registration area on Level 2 to escort you through the testing procedure.**

Testing will be completed in the Alberta Cardiovascular and Stroke Research Centre (**ABACUS**) on **Level 0**. Maps are attached. The **ABACUS** is located through a set of double doors adjacent to the Shaw 3-I Auditorium.

Baseline and Final Measurements

For all measurements, you will be in the Mazankowski Alberta Heart Institute at the University of Alberta Hospital. Questionnaires and Cardiopulmonary Exercise

Test will be completed on the **lower level (Level 0)** of the building in the Alberta Cardiovascular and Stroke Research Centre for research studies and clinical trials (**ABACUS**). Due to the length of time needed for measurements, we ask that you arrive **15 minutes** before your appointment and anticipate being with us for **1 hour**. The test order is: Anthropometric/resting measurements, cardiopulmonary exercise test and physical activity monitoring (explained in detail after the completion of the cardiopulmonary exercise stress test). In addition, we ask that you:

- Please refrain from ingesting food, alcohol, caffeine, or tobacco within 2 hours of testing.
- Avoid significant exertion or exercise on the day of the assessment.
- Wear comfortable, free moving clothing and running shoes. Women may choose to wear a short-sleeved blouse that buttons down the front and should avoid restrictive undergarments.
- If taking medications, continue to take them as per usual.

For any questions, comments or concerns, please contact John (J.P.) Willner at willner@ualberta.ca or by phone at work: (780) 492-0563 cell: (306) 520-4456 (No, this is not a long distance call).

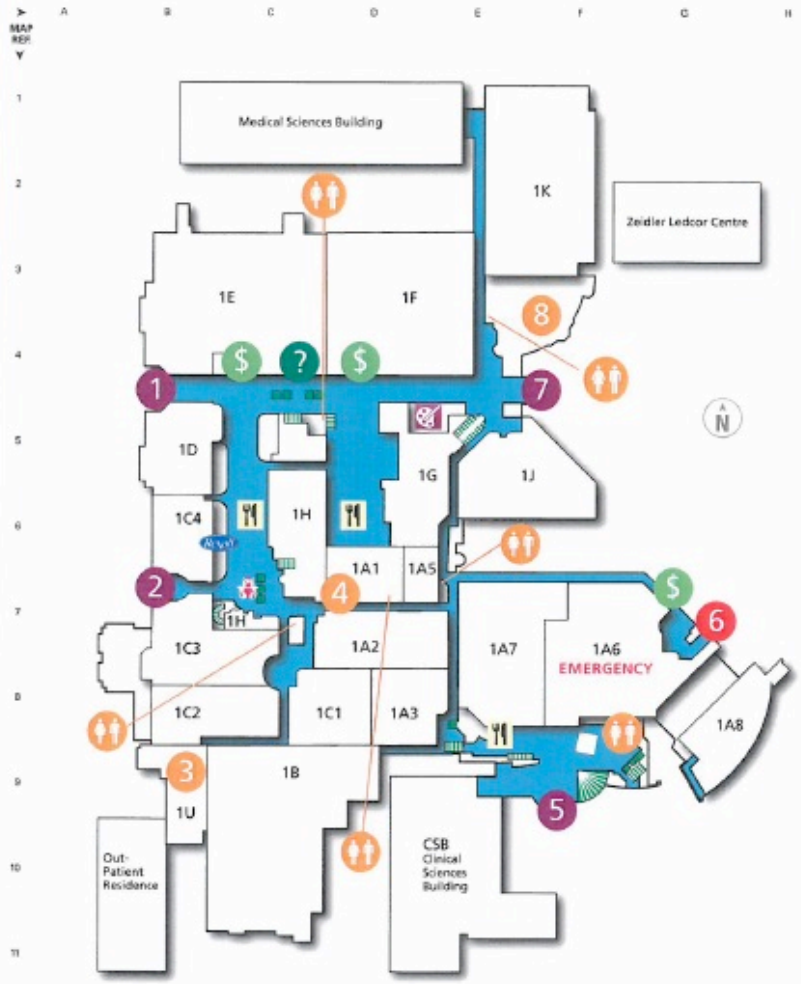

LEVEL
0
Walter C. Mackenzie
Health Sciences Centre
Elevators/Stairs
Public Route
Washrooms
Parking
1 Security Office
2 Parking Office
3 Human Resources
4 Shipping & Receiving
5 Shaw 3i Auditorium
6 ABACUS
7 Health Records
MAP REF:
A
B
C
D
E
F
G
H
1
2
3
4
5
6
7
8
9
10
11
N
W
E
S
0E2
0E1
P
0D2
0G1
0H1
0H3 / 0H4
0J1
0D1
0H2
0C3
0C2
0A2
0A6
0A1
0A3
0C1
0A8
0B2
0B3 / 0B4
0B1
CSB Clinical Science Building

Alberta Health Services

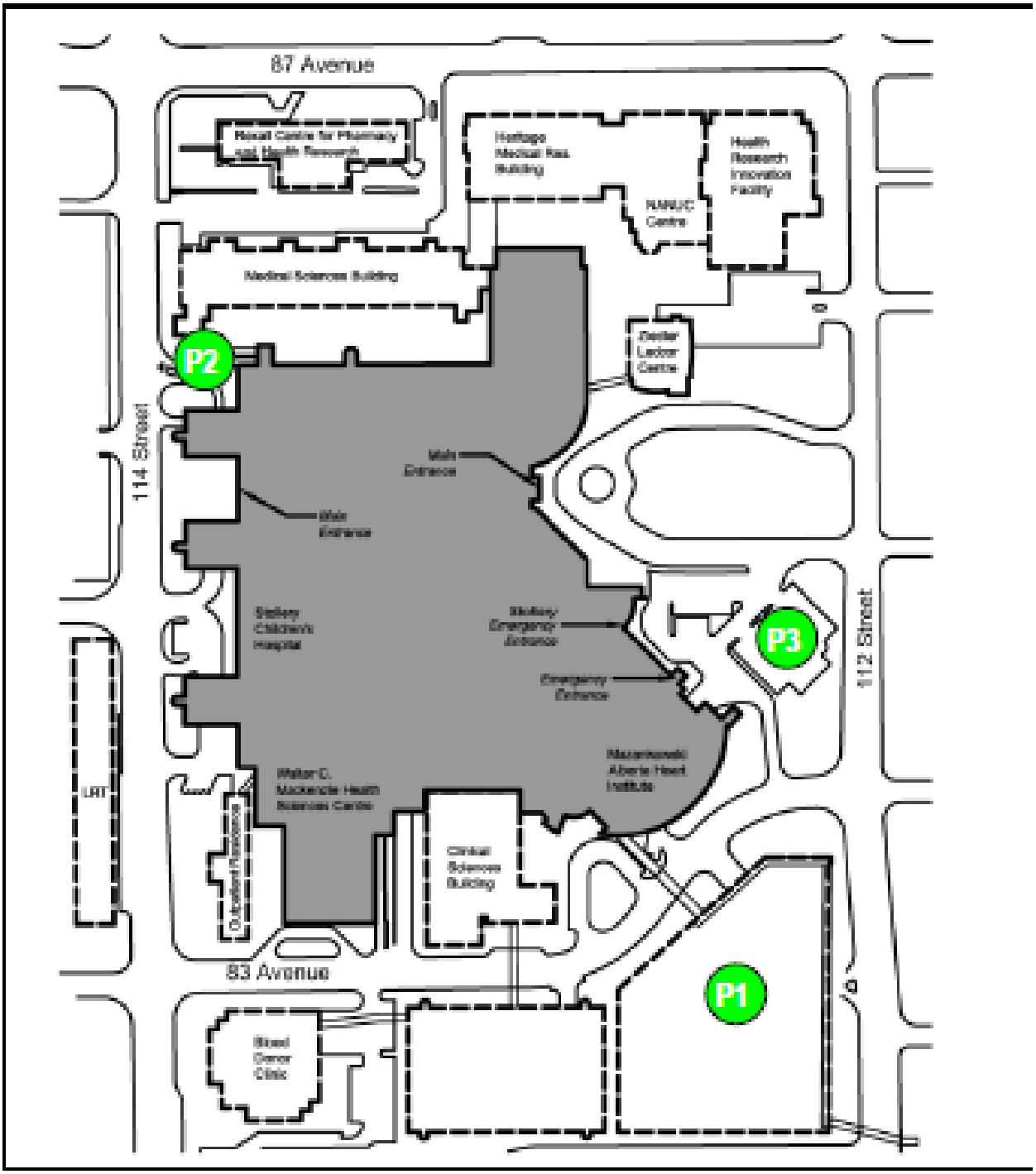
LEVEL 1

Walter C. Mackenzie Health Sciences Centre

- Elevators/Stairs/ Escalator
- Public Route
- Washrooms
- Information
- 1 114 St Entrance
- 2 Stollery Entrance
- 3 MRI
- 4 Admitting
- 5 Mazankowski Entrance
- 6 Emergency Entrance
- 7 112 St Entrance
- 8 Bernard Snell Hall
- $ ATM




LEVEL 2
Elevators/Stairs/ Escalator
Public Route
Atrium Area
Washrooms
Pedway to Parking
John W. Scott Health Sciences Library
Faculty of Medicine and Dentistry
Diagnostic Imaging
ATM
Heart Institute Unit Areas
Anti-coagulation Management Services
Cardiac Outpatient Services
Cardiac Catherization Labs/ Electrophysiology Labs
87 Ave
112 Street
Medical Sciences Building
Zeidler Ledcor Centre
2K
2F
2E
2G
2D
2J2
2H
2G2
2C1
2A1
2A2
2C2
2C3
2A3
Elko Cardiac MRI
2A5
2A6
2A9
2A7
Public Parkade
2B
CSB Clinical Science Building
Out-Patient Residence
MAZANKOWSKI
W
E
S

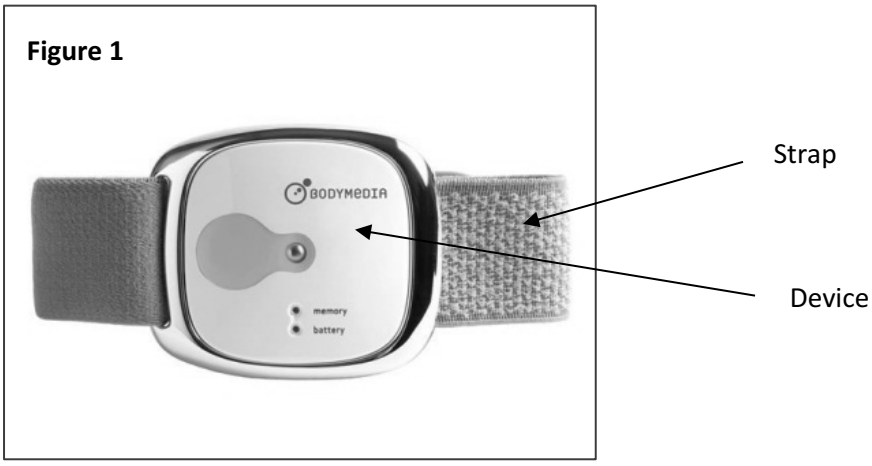

87 Avenue
Heritage Medical Res. Building
Health Research Innovation Facility
NANUC Centre
Medical Sciences Building
P2
Zeidler Ledcor Centre
114 Street
Main Entrance
Main Entrance
Stollery Children's Hospital
Stollery Emergency Entrance
Emergency Entrance
P3
112 Street
LRT
Walter C. Mackenzie Health Sciences Centre
Outpatient Pharmacy
Clinical Sciences Building
83 Avenue
P1
Blood Donor Clinic

Appendix F: SWA Wearing Instructions

Armband Step-by-Step Instruction

1) Take the armband out of envelope and make sure that it contains the strap and the device. As shown in figure-1. Keep the smaller envelope to return the armband later (see #8 below)

Figure 1



2) **You do not** need to do anything else. The device is charged and ready to be worn.

3) Strap the armband so the device is on the back of **your upper left** arm. It will be worn underneath your clothes as shown in figure-2.

Figure 2

4) The sensors on the back should always be in contact with your skin. If your arm ever feels uncomfortable or tingly, readjust the strap but **make sure the armband remains in contact with your skin**.

5) Counting the day you put it on, wear the armband for **4 days**. Wear it **all the time** during the day and night (i.e., at work, during exercise, while sleeping).

6) **Remove the armband if you shower, bathe or go swimming.** Put it back on after you are dried off.

7) **It is really important if you feel any itching, rash or any abnormal skin conditions under the armband, please remove the armband immediately and contact us.**

8) On the 5th day remove the armband. Place it in the smaller, self-addressed envelope you have received as shown in figure-3(you will receive self-addressed envelope in another mail). Make sure the armband strap is completely flat.

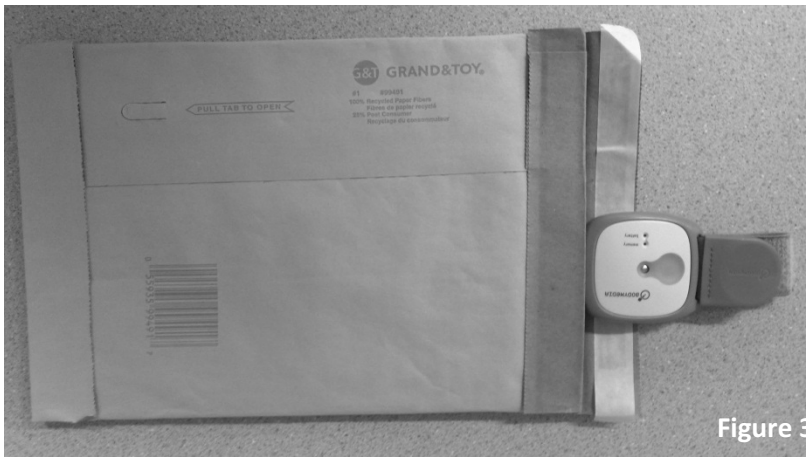


Figure 3

……

9) Fill out the date you put the armband on your body here …….

And the date of last day you have worn it, here ……

Tear off this part of the paper and place it in the envelope. Seal the envelope and post it.

If you have any **questions** please call **J.P. Willner** at **780-492-2609** (Exercise Physiology lab, Rehabilitation Medicine Faculty, U of A).

Thank You for participating in this study.