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I, Samuel Wittekind, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:

A Novel Mechanism for Improved Exercise Performance in Pediatric Fontan Patients After Cardiac Rehabilitation

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**A novel mechanism for improved exercise performance in pediatric Fontan patients after
cardiac rehabilitation**

A thesis submitted to the
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by

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Abstract

Background: Patients with a Fontan circulation have impaired exercise capacity. Cardiac rehabilitation (CR) has shown promise in enhancing peak exercise parameters in this population, but an improvement in submaximal exercise has not been consistently demonstrated. We assessed the hypothesis that participation in CR will be associated with more efficient oxygen extraction and ventilation during submaximal exercise.

Methods: In this prospective study, pediatric Fontans completed two 60 minute CR sessions per week for 12 weeks. Cardiopulmonary exercise testing and stress echocardiography were performed at baseline and last CR session, then compared with a paired sample t-test.

Results: Ten pediatric Fontans completed the study. Five had tricuspid atresia and 5 had hypoplastic left heart syndrome. No serious adverse events occurred during CR sessions. Peak indexed oxygen consumption increased by a mean of 3.7 mL/kg/min (95% CI, 1.5 to 5.9; $p=0.004$), and peak oxygen pulse increased by a mean of 0.9 mL/beat (95% CI, 0.4 to 1.4; $p=0.004$). The peak respiratory exchange ratio did not change significantly. The significant difference in oxygen pulse became evident during submaximal exercise without a corresponding difference in echocardiographic stroke volume. Indexed oxygen consumption at ventilatory anaerobic threshold increased by a mean of 3.0 mL/kg/min (95% CI, -0.07 to 6.0; $p=0.055$). The slope for the volume of expired ventilation to volume of carbon dioxide production improved by a mean of 4.5 (95% CI, -8.4 to -0.6; $p=0.03$).

Conclusions: We observed significant improvements in both submaximal and peak exercise performance in pediatric Fontans undergoing CR with no serious adverse events. These changes appeared to be mediated, at least in part, by more efficient oxygen extraction and ventilation.

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Introduction

Patients with a Fontan circulation have impaired exercise capacity that is apparent in the first decade after surgery[1]. The reason for this is likely multifactorial including impaired chronotropic response [1], inability to increase stroke volume to meet metabolic demand [2], and right-to-left shunting during exercise stress [3]. There is robust evidence that regular physical exercise in the form of cardiac rehabilitation (CR) improves several indices of peak exercise performance in Fontans [4-6], but an improvement in submaximal exercise has not been consistently demonstrated. The slope for the volume of expired ventilation to volume of carbon dioxide production (VE/VCO_2 slope) is an index of ventilatory efficiency derived from submaximal exercise [7] which has prognostic value in adult Fontan patients [8]. Oxygen pulse, which is the amount of oxygen consumed per heartbeat [7], increases in submaximal stages after training [6,4]; however it is unknown whether this observation is due to higher stroke volume which can be estimated by multiple noninvasive techniques including stress echocardiography, or rather more efficient oxygen extraction which requires invasive measurement of the arteriovenous oxygen content gradient. We aimed to test the hypothesis that participation in CR will be associated with more efficient oxygen extraction and ventilation during submaximal exercise in young Fontan patients.

Materials and Methods

Study recruitment

Eligible study participants included children and adolescents with single ventricle physiology who had undergone the Fontan operation and were followed by pediatric cardiologists at Cincinnati Children's Hospital Medical Center. Inclusion criteria were: age range 7 - 18 years; ability to perform a cardiopulmonary exercise stress test (CPET); free of acute or

chronic respiratory illness or other conditions that might affect exercise performance; and at least 6 months post-Fontan procedure. Exclusion criteria were: documented life threatening arrhythmia without implantable cardioverter-defibrillator; moderate or severe ventricular dysfunction by echocardiography; history of pulmonary hypertension requiring treatment with vasodilators; acute inflammatory cardiac disease; documented coronary artery stenosis and/or myocardial ischemia; heart failure requiring hospitalization in the past year; evidence of systemic venous pathway obstruction by echocardiography or catheterization; resting oxygen saturation <90%; or systemic ventricular outflow tract stenosis with peak resting systolic gradient >50 mmHg. Patients' families were contacted with permission from their primary cardiologist.

Using an α value of 0.05 and the expected standard deviation of 0.15 in the mean difference of the outcome variables (VO_2 at peak exercise and at the ventilatory anaerobic threshold, oxygen pulse, and VE/CO_2 slope) pre- and post-CR, at least 10 subjects were required to detect the expected mean difference of 0.15 with a power of 0.8. Eighteen Fontans agreed to participate, but 3 of them did not reach maximal effort on baseline CPET due to physical incoordination related to young age, and another five could not attend a minimum number of CR sessions due to travel limitations. The remaining ten participants are the subject of this report. Written informed consent was obtained from the parent or guardian. Written assent was also obtained from participants younger than 18 years according to the guidelines established by the institutional review board at Cincinnati Children's Hospital Medical Center.

Study procedures: CPET and stress echocardiography

CPETs were performed within 2 weeks of the first and last CR sessions. A previously calibrated, upright cycle ergometer (Corival Lode Cycle 400) was used with the seat height adjusted to create a small knee angle at full extension. A standard 3 minute incremental cycle

exercise protocol developed for patients with single ventricle physiology [9] was used. The initial workload and increments were based on body surface area. Heart rate (HR) and a 12 lead electrocardiogram (ECG) were recorded at rest, during each minute of exercise, and post-exercise recovery (Marquette Model Case 8000). Arm blood pressure (BP) was measured at rest, during each stage, and post-exercise recovery using the auscultation method with a manual sphygmomanometer appropriately sized for the patient. All BP measurements were recorded in the right arm unless a Blalock-Taussig shunt had been performed on that side. Pulse-oximetry was measured continuously via a forehead probe (Masimo Radical 7). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured at rest and during each stage of exercise using a metabolic cart (Parvomedics Model True Max 2400). Perceived exertion was measured using the Borg scale (scale = 6 - 20). An exercise test was judged to be maximal if two of the following 3 criteria were met: respiratory exchange ratio ($\text{RER} = \text{VCO}_2 / \text{VO}_2$) ≥ 1.1 ; maximal HR $\geq 85\%$ of age predicted maximal HR[7]; maximal perceived exertion ≥ 18 . Early termination of the CPET occurred if patient safety was judged to be at risk by the test operator, if a serious arrhythmia occurred, or if systolic BP decreased more than 20 mmHg during the test.

Stress echocardiograms were performed in coordination with CPET. Images were obtained using a GE Vivid Seven (General Electric, Milwaukee, WI) imaging system. Echocardiography was performed at the end of each exercise stage, and during recovery. This consisted of two-dimensional echocardiographic views of the systemic ventricle and outflow tract in the apical view. Outflow tract area and pulse wave velocity-time integral (VTI) were measured in triplicate during post-processing. Stroke volume was calculated as the product of these two variables as previously described by Christie, et al. [10].

Intervention: Cardiac rehabilitation program

A personalized exercise program was designed per the standard of the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) [11]. Participants were instructed to attend two sessions lasting 1 hour per week for 12 weeks (24 sessions total). CR sessions took place at our hospital's satellite gym facility with one-on-one supervision by a trained exercise physiologist. Each CR session consisted of 5-10 minutes of warm-up and stretching activity, 30 minutes of aerobic training, 15 minutes of low-resistance high-repetition strength training, and 5 minutes of cool-down activity. The aerobic training component was conducted on stationary cycle or treadmill with a goal of sustaining 70-80% of the heart rate reserve as assessed by baseline CPET [12]. Age-appropriate games were incorporated into CR sessions for motivation and enjoyment. Participants were encouraged to remain active at home, but there was no exercise prescription and habitual physical activity was not monitored.

Statistical analysis

JMP Pro 12 (SAS) software was used for statistical analysis including the power calculation for sample size. Continuous demographic and clinical variables were summarized as mean $\pm$ standard deviation. Data from baseline and post-CR testing were compared with a two-tailed, paired sample t-test for statistical significance ($\alpha = 0.05$).

Results

The demographic and clinical characteristics of the participants are summarized in Table 1. Ten pediatric Fontan patients completed the study. The mean age at enrollment was 12 ± 2.8 years, 40% were male, and the mean BMI was 19.2 ± 3.2 kg/m². Five had tricuspid atresia (TA) and 5 had hypoplastic left heart syndrome (HLHS). All had either a lateral tunnel or extracardiac Fontan operation, with or without fenestration, at least 5 years prior to enrollment.

The systolic function of the single ventricle was normal for all participants, with either trivial or mild atrioventricular valve regurgitation as assessed by echocardiography. Only 1 participant had an open Fontan fenestration; the remaining fenestrations had undergone either spontaneous or percutaneous device closure. Most participants were taking aspirin and an angiotensin-converting enzyme inhibitor. All had normal resting HR in sinus rhythm and oxygen saturations greater than 90% (mean $97 \pm 2\%$). The baseline mean peak indexed oxygen consumption (VO_{2i}) was $31 \pm 3.9 \text{ mL/kg/min}$ ($78 \pm 18\%$ predicted).

Participants attended a mean 70% of scheduled CR sessions. The most common reason for a missed appointment was a scheduling conflict with a school-related activity. No prescribed medications were changed and no surgeries were performed during the study period. No serious adverse events occurred. Furthermore, no CR sessions were terminated prematurely for patient signs or symptoms. One patient had palpitations with corresponding premature ventricular contractions during the recovery stage of their baseline CPET which resolved spontaneously prior to leaving the exercise laboratory.

Maximal exercise performance improved significantly with exercise training. Figure 1 illustrates the change in peak VO_{2i} from baseline to post-CR as measured by CPET. Peak VO_{2i} increased by a mean of 3.7 mL/kg/min (95% CI, 1.5 to 5.9; $p=0.004$). In fact, all but one participant experienced an increase. Similar increases in peak VO_{2i} were observed in those with a single right ventricle (HLHS) versus left ventricle (TA). Total working capacity increased by a mean of 1497 kilopond-meters (kpm) (95% CI, 947 to 2047; $p=0.004$) as shown in Figure 2. The RER at peak exercise did not change after exercise training, suggesting this improvement in functional capacity was not due to increased voluntary effort.

Submaximal measures of cardiorespiratory fitness improved as well. The mean resting HR did not change; however, beginning in stage 1 and continuing through peak exercise, the mean HR was lower after CR ($p < 0.001$) (Figure 3). The corresponding oxygen pulse (VO_2 / HR) was higher during submaximal stages 2 through 5 (Figure 4) and the peak oxygen pulse increased by a mean of 0.9 mL/beat (95% CI, 0.4 to 1.4; $p = 0.004$). This augmentation in oxygen pulse after CR might predict increased stroke volume during submaximal effort; however, there was no significant difference in stroke volume as assessed by stress echocardiography. This is illustrated in Figure 5 by the flat stroke volume versus workload curves pre- and post-CR. Indexed oxygen consumption at ventilatory anaerobic threshold (VO_{2i} at VAT) increased by a mean of 3.0 mL/kg/min (95% CI, -0.07 to 6.0; $p = 0.055$), nearly meeting statistical significance (data not shown).

Figure 6 illustrates that the VE/VCO_2 slope improved by a mean of 4.5 (95% CI, -8.4 to -0.6; $p = 0.03$). The minute ventilation (VE) and oxygen saturation throughout exercise did not change after CR (data not shown). These observations are consistent with improved ventilatory efficiency derived from training.

Conclusions

This study demonstrates improved cardiorespiratory fitness in pediatric Fontan patients after participation in a CR program. Higher peak exercise parameters, such as VO_2 [4,5] and workload [6,4], have been reported previously. The 12% increase in peak VO_{2i} in the present study is consistent with these prior Fontan studies as well as other CR trials that included less serious forms of congenital heart disease [13,14]. Our observation is simpler to interpret because of the relatively uniform population (all pediatric Fontan patients with either HLHS or TA) and standardized CR program (12 weeks, facility-based) used in our study; previous studies had

significant variability in population [15,4] and exercise training setting and duration [15,5,6]. A review of the literature demonstrates that healthy children and adolescents experience a 5-6% increase in peak VO_2i with aerobic training [16]. Furthermore, less fit individuals ($\text{VO}_2\text{i} < 50 \text{ mL/kg/min}$) tend to experience greater gains in aerobic capacity and our study population of young Fontans certainly fits into this category. We also observed improved submaximal exercise parameters including lower HR and higher oxygen pulse curves throughout exercise. Others have reported similar results for these two variables [6,4], while Minamisawa et al. demonstrated a trend toward lower HR that did not reach statistical significance [5]. In theory, a higher oxygen pulse could be due to either elevated stroke volume (due to higher preload with an active skeletal muscle pump and increased myocardial contractility) or more efficient oxygen extraction by exercising muscle (higher arteriovenous oxygen content gradient) as illustrated by the Fick equation [17]. Our study explored this mechanism by measuring stroke volume by stress echocardiography. There was no significant increase in single-ventricle stroke volume after CR. This is perhaps not surprising since Fontan patients have impaired ability to augment stroke volume during exercise [2]. This suggests that the observed higher oxygen pulse is a reflection of more efficient oxygen utilization beginning in submaximal exercise. Proof of this mechanism would require measurement of the arteriovenous oxygen content gradient during exercise. More accurate measurement of cardiac output with the inert gas rebreathing method [18] or bioimpedance cardiography [19], for example, would also strengthen this theory.

Our study adds to the body of literature by including VE/VCO_2 slope in the assessment of submaximal exercise after CR in Fontan patients. Increased VE/VCO_2 slope is a strong predictor of death in adult Fontans [8]. A lower VE/VCO_2 slope after exercise training has been demonstrated in adults with acquired heart disease [20,21], but not in Fontans to date. In

studies by Rhodes et al. that included Fontan patients[4] no index of ventilatory efficiency improved after 12 weeks of CR. In contrast, we observed a significant decrease in VE/VCO_2 slope that cannot be attributed to less exercise-induced right-to-left shunting [22] because there was no significant change in pre- and post-CR oxygen saturation during exercise. Furthermore, only one patient had an open fenestration and this individual's data did not significantly skew the group trend. Aside from Fontan fenestration closure [3], the only intervention known to improve ventilatory efficiency in this population is phosphodiesterase 5 inhibition as shown in the Sildenafil After Fontan Operation (SAFO) trial [23] in which the VE/VCO_2 at the anaerobic threshold decreased by a mean of 2.09 (95% CI, -4.00 to -0.17; $p=0.03$) in 18 adolescents and young adults. The investigators hypothesized that this change is due to more optimal ventilation-perfusion matching. We propose that regular physical exercise induces a similar mechanism. The novelty of our finding warrants further investigation with a larger trial of CR in patients with a Fontan circulation.

The present study has several limitations. First, the sample size is small which is characteristic of all published, single-center CR trials involving youth with congenital heart disease. The obvious reason for this is that CR is a time and resource heavy therapy. To complete CR requires commitment from patients and families, significant travel and time cost, and dedicated gym space and staff. Notably, our current clinical CR program's experience with insurance coverage has been favorable with over 80% reimbursement, so financial concerns should not prevent the growth of pediatric CR referrals. Another limitation is the lack of a control group. The only related trial that contained a control group, by Rhodes et al. [4,24], demonstrated superior exercise performance compared to age-matched Fontan patients that did not complete CR. Next, the maximal cycle ergometry CPET protocol [9] used in this study has

not been used widely in clinical research. It was designed to allow more single ventricle patients palliated with a Fontan circulation to achieve a maximal test compared to traditional staged protocol, and in this regard it was successful. Lastly, we did not enroll adult Fontan patients which limits the generalizability of our findings to this vulnerable and growing population.

In summary, we report improvements in both peak and submaximal exercise performance in pediatric Fontan patients after a 12 week course of CR. The unchanged echocardiographic stroke volume suggests that more efficient oxygen utilization is the mechanism of the observed higher oxygen pulse after CR. The improved ventilatory efficiency in the form of lower VE/VCO_2 slope is intriguing and requires validation. Future trials will need to be multi-centered, controlled, and administer a standardized CR program and CPET protocol in order to address the aforementioned limitations and, more importantly, establish the efficacy and safety of CR for Fontan patients.

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Table 1: Baseline characteristics of study participants.

Baseline characteristics											
Age (y)	Sex	Weight (kg)	CHD	Stage 1 palliation	Stage 2 palliation	Fontan type	Years since Fontan	Fenestration status	Co-morbidities	Medications	Baseline peak VO _{2i} (mL/kg/min); percent predicted
9	F	31	HLHS	Norwood with mBTS	Hemi-Fontan	Fenestrated lateral tunnel	6	Spontaneous closure	None	Aspirin, lisinopril	29; 80%
12	M	39	HLHS	Norwood with Mee shunt	BDG	Fenestrated lateral tunnel	9	S/p device closure	None	Lisinopril, warfarin	31; 57%
12	M	35	HLHS	Norwood with mBTS	Hemi-Fontan	Fenestrated lateral tunnel	10	S/p device closure	None	Aspirin, lisinopril	30; 63%
14	M	41	HLHS	Norwood with mBTS	BDG	Fenestrated extracardiac	11	Spontaneous closure	None	Aspirin, enalapril	30; 55%
15	F	64	HLHS	Norwood with mBTS	Hemi-Fontan	Fenestrated lateral tunnel	14	Spontaneous closure	None	Aspirin	26; 65%
8	M	26	Tricuspid atresia with D-TGA	PA band	BDG and DKS anastomosis	Fenestrated extracardiac	5	Spontaneous closure	None	Aspirin, enalapril	41; 104%
8	F	33	Tricuspid atresia with NRG	PA band	BDG	Fenestrated extracardiac	5	Spontaneous closure	None	Aspirin, enalapril, furosemide, spironolactone	29; 85%
11	F	28	Tricuspid atresia with NRG	PA band	BDG	Nonfenestrated extracardiac	6	N/A	None	Aspirin, enalapril	31; 73%
15	F	59	Tricuspid atresia with NRG	PA band	BDG	Nonfenestrated extracardiac	7	N/A	None	Warfarin	33; 105%
15	F	65	Tricuspid atresia with NRG	PA band	BDG	Fenestrated lateral tunnel	12	Open	None	Aspirin, lisinopril	30; 92%

Table 1 legend. HLHS=hypoplastic left heart syndrome, NRG=normally related great arteries, mBTS=modified Blalock-Taussig shunt, PA=pulmonary artery, BDG=bidirectional Glenn, DKS=Damus-Kaye-Stansel, N/A=not applicable; VO_{2i}=indexed oxygen consumption.

Figure 1: Improved peak indexed oxygen consumption (VO_{2i}) after cardiac rehabilitation (CR).

Fig 1 legend. Dashed lines correspond to individual participants with hypoplastic left heart syndrome s/p Fontan, solid lines correspond to those with tricuspid atresia s/p Fontan. $P=0.004$ for the difference in means.

Figure 2: Increased total working capacity on cardiopulmonary exercise test after cardiac rehabilitation (CR).

Fig 2 legend. Mean $\pm$ standard error represented. Asterisk indicates $p < 0.001$.

Figure 3: Change in heart rate (HR) during progressive stages of exercise.

Fig 3 legend. Dashed line represents baseline mean values (pre-CR), solid line represents post-CR mean values, +/- standard error. Asterisk indicates $p < 0.001$.

Figure 4: Change in oxygen pulse (O2 pulse) during progressive stages of exercise.

Fig 4 legend. Dashed line represents baseline (pre-CR) mean values, solid line represents post-CR mean values, +/- standard error. Asterisk indicates $p = 0.004$.

Figure 5: Stroke volume as estimated by stress echocardiography during progressive stages of exercise.

Fig 5 legend. Dashed line represents baseline (pre-CR) mean values, solid line represents post-CR mean values, +/- standard error.

Figure 6: Lower slope for volume of expired ventilation to volume of carbon dioxide production (VE/VCO_2 slope) after cardiac rehabilitation (post-CR).

Fig 6 legend. Mean +/- standard error represented. Asterisk indicates $p=0.003$.