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**A PRELIMINARY STUDY ON EXTERNAL COUNTERPULSATION SYSTEM: AN
ALTERNATIVE THERAPEUTIC OPTION FOR FONTAN PATIENTS**

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Biomedical Engineering at Virginia Commonwealth University.

by

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I am using this opportunity to express my gratitude to everyone who supported me through the course of my work as a graduate student at Virginia Commonwealth University. I would never have been able to finish the clinical study or this dissertation without the help of my committee members, colleagues and support from my family and wife.

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Dr. Sam Lee has been instrumental in carrying this study forward and I'm in his debt for his involvement. Accepting the role of principal investigator, Dr. Lee has moved this project forward even during uncertain times. In collaboration with Dr. William Moskowitz they both worked hard at recruiting subjects to the clinical study. A much more difficult process than I had anticipated and now have come to appreciate.

The Frederick Banting Foundation, a Richmond, Virginia based organization that funds innovative medical research, has graciously partnered with VCU and taken up this cause as their own. I am grateful for their financial support and for the vision that made this work possible.

Finally, I would like to thank Dr. Gerald Miller for taking me on as his student and being my advisor. Only through his steady patients could all the parts come together and come to fruition.

There were many moving pieces that amounted to the completion of this work. A significant amount of energy went into designing the protocol, attaining IRB approval, recruiting subjects, conducting the study and finally compiling results to produce this paper. Each person played a valuable role and this team's value is truly worth more than the sum of their parts.

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Abstract

A PRELIMINARY STUDY ON EXTERNAL COUNTERPULSATION SYSTEM: AN ALTERNATIVE THERAPEUTIC OPTION FOR FONTAN PATIENTS

By Joseph J. Hernandez, B.S.

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
in Biomedical Engineering at Virginia Commonwealth University.

Virginia Commonwealth University, 2014

Director: Dr. Gerald E. Miller
Professor and Chair, Department of Biomedical Engineering

In order to address the long-term complications that arise from poor venous return, a hallmark of the Fontan physiology, we assessed the feasibility of a non-invasive, home therapy that will improve the health of the patient during the heart transplant waiting period and ameliorate the quality of life. In order to achieve this goal we tested a device that applies pressure to the lower extremities of the body (legs and abdomen) in a pulsating fashion with the goal of augmenting systemic blood flow to the pulmonary arteries. This treatment will enhance flow from the great veins and through the lungs and serve as adjunctive clinical treatment of single ventricle physiology.

The specific aim of this study was to show improvements in cardiorespiratory measurements after applying external pressure as a proxy for improved health in the Fontan patient. Various studies have shown the impaired exercise capacity of post-operative Fontan patients, but very

little data exists focusing on a period much later after the surgery. Our results among the two subjects completed so far have shown a moderately beneficial improvement in exercise capacity after the compression therapy.

Subjects performed a treadmill exercise stress test at VCU that was followed by six days of applied external pressure treatment and finished with a final post-treatment stress test. Cardiorespiratory data was collected and analyzed for improvements from base level.

Overall an improvement in exercise duration time, VO_2 peak, ventilatory threshold, and OUES was observed, with only VE / VCO_2 slope having mixed results. Both subjects seem to be relatively healthy Fontan patients, as indicated by their VO_2 peak, VE/VCO_2 slope and OUES. As a result, benefits of treatment may vary among a cohort of Fontan patients with poor health condition; a failing Fontan physiology for instance. The improvement in exercise capacity suggests that this therapy could be very beneficial to Fontan patients. These results warrants follow up studies to explore the extent of the clinical benefits of compression treatment among the Fontan population.

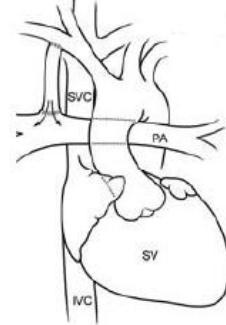
CHAPTER 1: Motivation and Significance

1.1 BACKGROUND

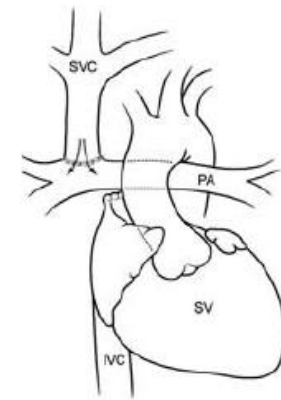
In the U.S., approximately 1 million babies are born annually with a heart defect in need of corrective treatment. 40,000 of these are born with congenital heart disease (CHD) requiring surgical intervention [45]. A further subset, approximately 8,000 to 9,000 children (or 2 per 1,000 births), are born with a malformed heart that only has a single ventricle, essentially half a heart. In the first year of life, single ventricle heart defects are the leading cause of death from all birth defects in the U.S. [46].

This particular heart defect causes oxygenated and deoxygenated blood to mix in the heart and immediate surgical intervention is required for survival. The standard surgical procedure attempts to redirect the major veins (that would have connected to the missing portion of the heart) directly to the lungs in order to separate the oxygen-/deoxygenated blood flow going into the body (Fontan Surgery). While this new blood flow system is life saving, in the long run, it will contribute to deteriorating health for the patient.

Norwood Procedure



Glenn Procedure



Fontan Procedure

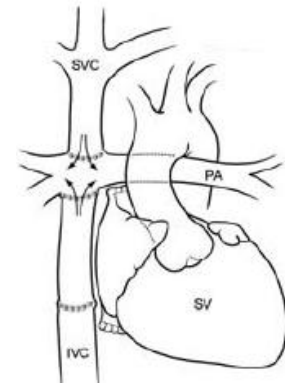


Figure 1: Three successive heart surgeries

1.2 THE FONTON PROCEDURE

In patients born with this single-ventricle malformation of the heart, 3 successive heart surgeries are required. Each stage is named after the surgeon who pioneered the technique. The single ventricle has to maintain both the systemic and the pulmonary blood circulation, prior to these heart surgeries. In order to correct the two major problems with single-ventricular physiology, (1) arterial desaturation and (2) chronic volume overload to the single ventricle, these surgeries separate the systemic and pulmonary circulation, achieving near normal arterial saturation and eliminating the volume overload problem.

The primary reason for a staged approach is that at birth the pulmonary vascular resistance is still elevated for several weeks. A cavopulmonary shunt would also be impossible, considering the caval veins and pulmonary arteries are usually too small at this point. This staged approach also allows the body to adopt progressively to this new physiology and reduces operative morbidity and mortality.

Norwood Procedure

Immediately after birth, the patient undergoes the first of three procedures, the Norwood procedure. Here a "systemic-to-pulmonary" arterial shunt is used to provide blood flow to the lungs. The main goal in this step is to provide pulmonary blood flow sufficient to allow adequate oxygen delivery to tissues and pulmonary arterial growth.

Glenn Procedure

Once the older infant displays low risk of elevated pulmonary vascular resistance, the shunt is removed and the superior vena cava is subsequently attached to the pulmonary artery. At age 4-12 months, the cavopulmonary connection, or the bidirectional Glenn shunt will be performed. If no other blood flow is allowed to the lungs, the volume load to the heart is significantly decreased to slightly less than normal. At this stage, the patient will remain slightly cyanotic, as the desaturated blood from the inferior caval vein is still allowed to flow to the aorta. This will be corrected in the third and final stage.

Fontan Procedure

This is the final procedure and usually occurs between the ages of 3 and 5 years old. The inferior vena cava is now connected to the pulmonary artery, completely bypassing the right heart in this step and completing a Total Cavopulmonary Connection (TCPC). Here the caval veins are connected to the pulmonary artery, bypassing the right ventricle and the right atrium. The superior caval vein was connected to the pulmonary artery during the second stage surgery (the Glenn Procedure).

Immediately after the Fontan surgery, ventricular preload will significantly decrease, subsequently increasing pulmonary blood flow. Exercise capacity has been shown to increase significantly immediately following the Fontan surgery, with exercise duration by approximately 40% and VO_2 max by 20% [1].

1.3 SINGLE-VENTRICLE / FONTON PHYSIOLOGY

These surgeries are a high-risk operation with survival rates ranging from 50% to 70% [2]. The end result is a surgeon-made physiology in which a single ventricle drives blood flow through the systemic and pulmonary circulations without a subpulmonary pressure source. These patients live with an abnormal circulatory status and are at high risk of developing congestive heart failure [43].

This surgeon-made physiology has a single functional ventricle, which drives blood flow through the systemic circulation to the body, and no right ventricle exists to pump blood through the lungs. This profound alteration of blood flow or venous return contributes to early and late Fontan pathophysiology, including premature failure of systemic venous return, liver congestion and cardiac arrhythmias.

1.4 WHY IS A NON-INVASIVE SOLUTION NEEDED?

A major health challenge for this redesigned blood flow path is the lack of pressure available to properly and efficiently pump blood through the lungs; since only half a heart exists. Over time this leads to morbidity and other major complications. Today, a heart transplant is the only therapeutic option for these patients and medically stabilizing them in order to survive the organ waiting period presents a major challenge. This leads to high healthcare cost consumptions and a high mortality rate. The 10-year survival rate is only 60% [47].

Cardiac transplantation for patients with failing Fontan physiology is a treatment option, if they can be medically stabilized and survive the waiting period for a donor organ. Transplantation, however, has an average waiting period of 6 months with a pretransplant mortality of 14% and an operative mortality of 27%, including a lifetime of immunosuppressive therapy and potential for noncompliance and graft rejection [44].

1.5 GOAL OF CLINICAL STUDY

In order to address these major concerns we assessed the feasibility of a non-invasive, home therapy with the potential to reduce the complications during the heart transplant waiting period and ameliorate the quality of life for Fontan patients. To achieve this we tested a device that applies pressure to the lower extremities of the body (legs and abdomen) in a pulsating fashion with the goal of augmenting systemic blood flow to the pulmonary arteries. This in turn reduces ventricular workload, increases venous return and pulmonary perfusion, and reduces cardiac after load. The idea is to optimize the use of this low-cost treatment that, with the increase blood flow, will lead to improved health in this patient population and reduce overall healthcare cost over time.

Specifically we attempted to reduce the chronic venous insufficiency, a hallmark of the Fontan physiology, by routinely administering lower body compression therapy, which we hypothesize will enhance flow from the great veins through the lungs. This enhancement of flow, in turn, should materialize into improved functional and exercise capacity. We performed a clinical pilot

study to evaluate this hypothesis, building on Dr. Amy Throckmorton's earlier work (n=2 feasibility study) [48]. Our specific aims for this study included:

1. Measure the acute physiologic benefit of external pulsation (n=2) in Fontan patients and assess functional improvement through exercise evaluation on a treadmill using the Ramp protocol.
2. Characterize and optimize the existing pulsation technology for Fontan patients to readily use in the comfort of their home, rather than having to attend regular, outpatient appointments.

Our hypothesis of augmenting systemic blood flow to the pulmonary arteries through the application of external compression originates from studying skeletal musculature during exercise [3 - 8]. The extension and contraction of skeletal muscle during exercise is shown to augment blood flow through this pumping action. This muscle pump and muscle vasodilatory mechanisms play important roles in increasing muscle perfusion and cardiac output during exercise. Jose Gonzalez-Alonso demonstrated that cardiac output can increase by 8.7 l/min during maximal exercise (incremental knee-extensor and cycle ergometer exercise) [3].

Compression therapy not only has similar effects on cardiovascular function during exercise [16, 18] but similar vasodilatory effects on blood vessels [9]. Hence, we hypothesize that by applying external pressure to the lower extremities of the body we will not only mimic the hemodynamic response of the skeletal muscle pump during exercise but replicate much of the long-lasting benefits of exercise achieved during endurance training (e.g., increasing VO_2 max, increased

stroke volume). Improving exercise capacity in Fontan patients, a group that suffers from compromised cardiovascular function, particularly during exercise [10] is expected to reduce the long-term mortality and morbidity rates among this patient population.

The knowledge gained from this research will allow us to develop transformative technology which is usable for the immediate post-operative period after Fontan surgery in the home setting. This pneumatic device will aid patients struggling to cope with the new circulation and serve as a novel clinical management strategy for long-term use.

1.6 PNEUMATIC COMPRESSION DEVICE/THERAPY

The concept of applying external compression in order to elevate systemic pressures and manipulate blood flow has been well documented using various technologies and therapies. Applying external pressures to the lower body can produce similar cardiovascular results as performing passive leg exercises in healthy subject, increasing cardiac output, on average by 1 ml / min [3, 16].

Applying ambulatory compression therapy that is commonly used in phlebology, J. Veraart (University Hospital Maastricht) conducted a study measuring the pressure augmentation in the deep vein (popliteal vein) when compression stockings of various pressures were worn. Subjects experienced an increase in venous pressure of as much as 75% when applying a compression stocking of 40 mmHg equivalent pressure [17]. Table 1 gives a list of some studies

conducted where various technologies were applied to achieve pressure augmentation and other hemodynamic changes after applying external compression device.

Table 1: Hemodynamic changes for Various Applied Pressures

Author	Year Published	Total Subjects	Technology	Applied Pressure	Results					Notes
					Systolic Arterial Pressure (Avg.)	Diastolic Arterial Pressure (Avg.)	Right Atrial Pressure / CVP (Avg.)	Left Atrial Pressure (Avg.)	Cardiac Output / Cardiac Index (Avg.)	
Herman A. Heck	1981	9	MAS Trousers (Lower Body - Phasic)	45-50 mmHg	69 to 89 mmHg (30% increase)	-	RAP: 17 to 24 mmHg (41% increase)	9 to 16 mmHg (78% increase)	-	Post Operative Fontan patients ages 7-26 years
Jeffrey C. Milliken	1986	16	MAS Trousers (Abdominal Compression - Phasic)	30 - 45 mmHg	91 to 118.2 mmHg (30% increase)	54.3 to 67.6 mmHg (24% increase)	RAP: 15 to 22.9 mmHg (53% increase)	7.4 to 14.9 mmHg (101% increase)	-	Post Operative Fontan patients; 23 months - 31 years
Alexander V. NG	1987	12	MAS Trousers	50 mmHg	119 to 129 mmHg (8% increase)	84 to 85 mmHg (1% increase)	-	-	4,034 to 4,907 ml/min (22% increase)	Healthy male subjects (mean age 28). Inflated before and during graded arm cranking exercise
William Ma	2002	10	External Counter pulsation	-	-	-	CVP: Avg. increase of 15.3%	-	CI avg. increase of 7.4% from baseline	Pediatric Post operative Fontan patient (age 2 - 8)
J C J M Veraart	2003	7	Compression Stockings (Supine position)	18 - 40 mmHg	-	-	Pressure increase in deep veins (popliteal vein) vs. applied: 20% for 18 mmHg; 31% for 29 mmHg; 75% for 40 mmHg	-	-	Adult patients with severe venous insufficiency

Various studies show the resulting hemodynamic changes during applied external pressures using different compression technologies.

1.6.1 Medical Anti-Shock Trouser (MAST)

Medical anti-shock trousers were designed to stop or significantly reduce severe blood loss during hypovolemic or hemorrhagic shock. This is primarily accomplished by applying a fixed external pressure to the lower extremities of the body. This fixed pressure maintains a systolic pressure of 100 mmHg by increasing impedance of blood flow to the lower half of the body. The result of this treatment is an increase in both interstitial and tissue pressure and decrease in vessel size, resulting in a reduction of transmural pressure beneath the area where pressure is applied. In the case of trauma circulating blood is redirected to the vital areas and allowing a quick stabilization of the patient [4, 16].

Various studies have shown that the use of MAST while upright causes blood volume redistribution from the lower body to the thorax, which results in increase venous return and SV [19-21]. A paper by Alexander V. NG at the University of Wisconsin [16] demonstrated that applying this pressure to the lower extremities of the body of healthy male subjects during standing rest and arm exercise, MAST inflation resulted in significant increases in SV, cardiac output, and MABP, and a decrease in HR. The investigators inflated the MAST device to 50 mmHG on 12 healthy male subjects and found, on average, a consistent increase in cardiac output of 800 ml/min and an increase in SV of ~8-13 ml, compared to MAST deflation. Mean arterial blood pressure was also shown to increase ~6 mmHg with MAST inflation with increasing work.

Although to a lesser degree, Fontan patients have also show significant beneficial hemodynamic changes during compression therapy, on average increasing cardiac index by 7.4 % [18] and right atrial pressure between 40% - 50% [22, 23]. Heck et al. [22] showed that the application of 45 – 50 mmHg of pressure through MAS trousers to post-operative Fontan patients (7-26 years) on average increased right atrial pressure by 44%.

1.6.2 Enhanced External Counter Pulsation (EECP)

Another compression technology utilizing this blood flow redistribution principal is the Enhanced external counter pulsation (EECP). This device has been FDA approved as a treatment modality for ischemic heart diseases. This treatment mimics the inflation and deflation of a

pressure-cuff, wrapped around the patient's lower extremities (from the abdomen to the patient's feet). The device consists of the use of a sequential inflation of 3 sets of cuffs and the inflation-deflation cycle is timed to the patient's electrocardiogram; the arterial pressure waveform is monitored noninvasively.

The EECP therapy is usually carried out in an outpatient setting. Applied pressures range from 200 mmHg to 300 mmHg. A course of EECP treatment typically involves 35 1-hour sessions at the physician's office, usually 5 days a week over a 7-week period, though treatments twice per day have been effective as well [24].

The clinical benefits of EECP for patients with refractory angina pectoris have been well established [24 - 28]. The overall hemodynamic effect is to provide diastolic augmentation and thus increasing coronary perfusion pressure, venous return and, subsequently, cardiac output. In 2002, William Ma published results from a study his team conducted at the Dallas Children's Medical Center where they study the effects of external counterpulsation (EC) in the pediatric Fontan population [18]. His safety and efficacy study attempted to show an improved cardiac output in the early postoperative period after the Fontan procedure. The results of this study showed an average increase for all enrollees in cardiac index of 7.4 L/min/m² and 15.3 mmHg for central venous pressure during EC treatment.

1.7 EARLY STUDY RESULTS

While various studies have documented the hemodynamic effects of applying external compression to the lower body, very few, if any, have considered the modern Fontan patient population. As such, an early feasibility study (n=2), conducted by the VCU BioCirc Laboratory in early 2009, set out to explore this relationship among this specific study population [48]. The results of this study served as a starting point in setting the applied pressures for our current at home pilot study.

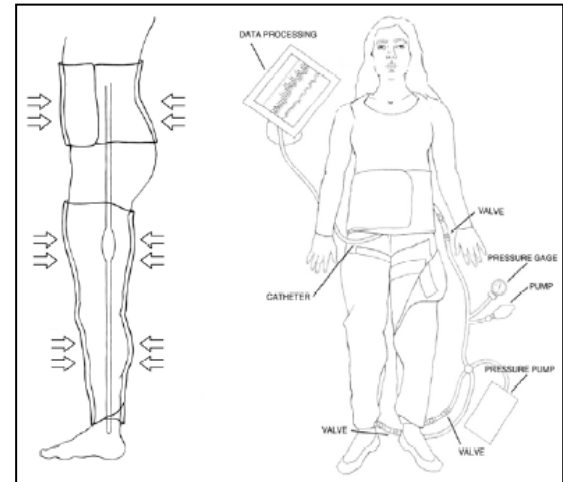


Figure 2: Concept of timed compression to drive flow toward the heart using the retrofitted MAS trousers and cyclic inflation / deflation.

This earlier study used retrofitted commercial medical antishock (MAS) trousers (David Clark Company, MA) to apply circumferential pressure to the lower extremities. While in the supine position, subjects had a catheter inserted into the femoral vein and/or artery and the compression treatment was carried out. The MAS-trouser pressures were set based on the patient's diastolic blood pressure, and with the catheter in place, the increase in venous pressure and cardiac output was measured.

Both subjects in the study showed a significant increase in pressure levels during the application of the compression treatment. The data demonstrated that an almost linear relationship exists with the applied external pressure, satisfying the hypothesis that this treatment can increase venous pressure and in turn increase the blood flow to pulmonary

circulation. Table 2 below shows the average pressure increase for each subject compared to their baseline measurements.

Table 2: Average Pressure Augmentation for Feasibility Study Patients as compared to Baseline Measurement

	Cycle Number	Applied Pressure (mmHg)	Systolic BP (mmHg)	Systolic Change (mmHg)	Systolic Change (%)	Diastolic BP (mmHg)	Diastolic Change (mmHg)	Diastolic Change (%)	MAP (mmHg)	MAP Change (mmHg)	MAP Change (%)
Patient 1	Baseline	0	82	--	--	47	--	--	59	--	--
	1	37	91.6	9.6	11.7	51.1	4.1	8.7	64.6	5.6	9.5
	2	47	94.9	12.9	15.7	54.2	7.2	15.3	67.8	8.8	14.9
	3	57	97.3	15.3	18.7	57.1	10.1	21.5	70.5	11.5	19.5
Patient 2	Baseline	0	117	--	--	79	--	--	92	--	--
	1	79	130.1	13.1	11.2	86.5	7.5	9.5	101	9	9.8
	2	89	127	10	8.5	85.6	6.6	8.4	98.9	6.9	7.5
	3										

This feasibility study demonstrated the augmentation of pressure by compressing the lower extremities in the Fontan patients and thus served as the basis for the clinical study conducted in this thesis.

CHAPTER 2: Methods and Materials

2.1 AT HOME CLINICAL STUDY

Given the beneficial cardiovascular response during compression therapy that has been well documented we developed a study protocol that specifically looks at the period following treatment to better assess if a lasting effect occurs. Equipped with the results from the earlier feasibility study (n=2), we obtained VCU IRB approval (HM #13521) in May of 2011 to test our hypothesis and carry out the proposed pilot study. The study was approved for five CHD patients with single ventricular physiology (Fontan). The results will serve as the foundation for evaluating this treatment in a chronic outpatient setting in adult Fontan patients where the treatment regimen can be optimized.

Project Highlights

- This is a novel project; the concept of using external pulsation to support pediatric and adult patients with this particular CHD has not been explored. A heart transplant is the only therapeutic option.
- The NormaTec device used in this study is already FDA approved and commercially available for a related therapy. This will ensure a rapid approval for this particular application.
- This device will be a low cost, non-invasive at home therapy that will drastically improve the health of this pediatric patient population. No home therapy exists today.

2.2 NORMATEC PNEUMATIC COMPRESSION DEVICE

We used the NormaTec Pneumatic Compression Device (PCD). This is an FDA cleared external compression device that applies pressure to the extremities of the body, in a peristalsis process. The inflatable trousers are connected to a controller that is programmed to the patient's specifications. Various parameters are entered, such as pressure, compression time and rest time.



Figure 3: NormaTec's Pneumatic Compression Device (PCD)

Our choice to use the NormaTec technology was strongly driven by its programmable controller and ease of use. NormaTec's PCD stands apart from other technologies as part of a treatment option that is truly ambulatory with real clinical translatability. While, EECP technology has been studied extensively, its relatively high risk and operational complexity limit it as a viable option for an at home therapy. EECP treatment is administered in either an in-patient or medical office setting and will usually apply very high pressures in the range of 200-300 mmHg. With this in mind, the NormaTec device was a good choice for this study.

The pants that were provided to us by NormaTec consisted of 5 separate cells that started at the feet and finished at the top of the thighs. Depending on the subject's height, the pants can be programmed to inflate all five cells or less. For subjects with an inseam measurement less than 30 inches, the pants are programmed to inflate only up to the 4th cell, as was the case for the first patient in our group.

Under typical prescription to a patient, NormaTec delivers the controller preprogrammed to medical mode, where the physician can choose from a number of already loaded preset treatments. As our protocol called for a lot tighter control of the parameters, we deviated from standard factory settings and programmed our controller under the classic mode. The settings for programing our controller under the classic mode setting included:

- Total time set for the treatment session can be set in 15 minute incremental steps
- Rest time can be set in 15 second incremental steps
- Pressure hold time at each cell can be set in 15 second incremental steps
- Pressure values are set in 10 mmHg incremental steps (starts at 30 mmHg and has a max at 100 mmHg).

The peristaltic compression should lead to an improvement in venous return. As the trousers become inflated, the portion of the body under compression is pinched closed (or "occluded"), forcing the blood / lymphatic fluid to move further up the leg. It is expected that, after applying over time, this improved venous return should manifest in improved exercise capacity.

2.3 STUDY PROTOCOL

The IRB approved the participation of five to ten subjects in this study. Through direct contact, Dr. Sam Lee, and in collaboration with Dr. William Moskowitz, recruited our subject cohort. An initial screening of potential study candidates was completed on the basis of age, interest, health status, and congenital diagnosis. Our target age for the study was between 15 – 45 years old. Once the subject was recruited, they were scheduled to come into Dr. Lee's office for the Pre-Evaluation portion of the study. This consists of:

- Orientation on the device and how to use it.
- Signed the consent form
- If the subject does not meet any of the exclusion criteria, the patient will undergo a doppler ultrasound of the lower extremities to exclude deep vein thrombosis as a concern.
- Baseline treadmill stress test, conducted on the 10th floor of the Main Hospital in the Pauley Heart Center.

The subject was then discharged to their home and began the home treatment using the NormaTec compression device for 6 consecutive days. Daily compression treatments was performed for 2-3 hours for the first four days, and for 4-5 hours over the last two days for at least 2 hours per day, at the discretion of the patient. The day after the last treatment day, day 8, exactly one week from the pre-evaluation, the study participants returned to the VCU Medical Center for a post-treatment evaluation and study conclusion. The figure below illustrates the treatment regimen over the eight days.

Clinical Study Protocol

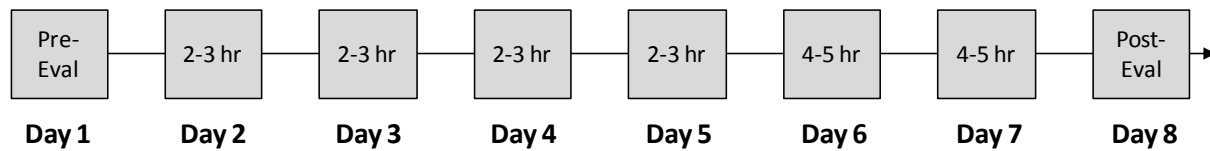


Figure 4: Clinical Study Protocol. Treatment regimen from pre-stress test to post-stress test.

At the end of the post-treatment medical evaluation, we conducted an exit-interview and asked the study participants to fill out a Quality of Life-based survey about their use of the pneumatic trousers.

2.4 STUDY SUBJECT AND CLINICAL CHARACTERISTICS

As of November 2014, two subjects have been successfully recruited and undergone the pneumatic compression treatment. Dr. Sam Lee, our principal investigator, with the help of Dr. William Moskowitz, spent a significant amount of time attempting to recruit Fontan patients. Very few patients have been willing to participate primarily due to the time spent away from work or school required during the pre- and post-treatment exercise testing. To-date, both subjects have completed the treatment regimen and final evaluation. The remainder of this paper discusses the methods and results of these two subjects with the hope of highlighting initial conclusions that can be used to better analyze and assess the benefits of this treatment for future work, with a larger subject cohort.

The clinical characteristics are summarized below (Table 3). Both subjects are TCPC Fontan patients with one having an ILT and the other an ECC connection. The mean age at the Fontan operation was 4 years with an interval from Fontan operation to this exercise study of 16 years.

Table 3: Study Subject Characteristics

	Subject #1	Subject #2
Sex	F	M
Age (years)	17	23
Height (cm)	152	160
Weight (kg)	47	42
Cardiac Diagnosis	Double Inlet Left Ventricle	Double Outlet Right Ventricle
Fontan Type	Lateral Tunnel (ILT) TCPC	Extracardiac Conduit (ECC) TCPC
Age at Fontan Procedure (months)	46	52
Time b/w Study & Fontan Procedure (years)	14	19

The only clinical condition that complicated the analysis was a heart block that was discovered in the second subject later in the study (Figure 12).

2.4.1 Pre-Treatment Evaluation

The pre-treatment evaluation involved a reiteration of the study objectives and a medical assessment of each subject to rule out any existing symptoms or conditions that meet the exclusion criteria.

Table 4: Exclusion Criteria for clinical trial

Exclusion Criteria:
• uncontrolled arrhythmias
• history of pulmonary embolism and/or deep vein thrombosis
• uncontrolled hypertension
• uncontrolled congestive heart failure
• clinically significant valvular disease
• acute myocardial infarction
• excessive tachycardia or marked bradycardia bleeding diathesis
• a significant abdominal aortic aneurysm.

Other Screenings Consisted of:

- Electrocardiograms were completed to exclude patients with persistent and significant atrial dysrhythmias.
- Patients were questioned about any recent episodes of chest discomfort or shortness of breath as well as recent prescription adjustments to medication dosages.
- An additional screening was done to assess the patient, including blood pressure, heart rate, oxygen saturation, skin integrity, presence of peripheral edema, any shortness of breath or other discomfort, liver size, and lung auscultation.
- As stated earlier, if the subject did not meet any of the exclusion criteria, the patient underwent a doppler ultrasound of the lower extremities to exclude deep vein thrombosis as a concern.

2.5 TREADMILL STRESS TEST

The primary aim of this study was to test the hypothesis that through this pneumatic compression therapy at home, the subject experiences an increase in systemic and pulmonary circulation. The effectiveness of this therapy can best be measured through a demonstrable improvement in exercise capacity of each subject. For this reason, we decided to conduct a treadmill stress test both before the treatment regimen, to serve as the baseline, and after for purposes of comparison.

During Exercise Phase			
Stage	Duration (S)	Speed (mph)	Grade (%)
1	30	1.0	0.0%
2	30	1.1	0.5%
3	30	1.2	1.0%
4	30	1.3	1.5%
5	30	1.4	2.0%
↓ ↓ ↓ ↓			

Figure 5: Treadmill stress test using the ramp protocol.

Treadmill stress test was executed according to a Ramp protocol [42]. This protocol was selected because it is routinely performed in the evaluation of 40-50 pediatric and adult patients per year at VCU and because it brings the subjects to their tolerance limit in approximately 10 minutes, thereby providing ample time for data collection and evaluation. Figure 5 illustrates further the details of this protocol. The workload increases progressively over the exercise duration. Both the speed and incline increase every 30 seconds until the subject reaches exhaustion and decides to stop the test. During the testing period, inspired and expired gases were collected with a mouthpiece the subject wore. The data was used to calculate the oxygen consumption and other important parameters.

Primary measurements of interest during the stress test included O_2 consumption (VO_2), CO_2 production (VCO_2), minute ventilation (VE) and heart rate (HR). Our analysis included evaluation of the change in peak exercise capacity by looking at parameters such as VO_{2max} , exercise time, Ventilatory Equivalent Ratios (VE/VO_2 & VE/VCO_2), Respiratory Exchange Ratio (VCO_2/VO_2) and max heart rate.

The day after concluding the treatment regimen, subjects returned to the 10th floor Main Hospital for a post-treatment stress test in the VCU Pauley Heart Center. Results were directly compared to the baseline measurements of the pretreatment evaluation. The desired outcome was a demonstrable improvement in functional and exercise capacity as indicated by an improved ability to withstand the treadmill exercise for a longer time and at a higher VO_2 peak value.

2.6 NORMATEC PULSATION TREATMENT

The treatment for the subjects occurred daily over a 2-3 hour period and a total of 4-5 hours over the last two days. I was present at the subjects house each day, with the medical personnel, to program the device and ensure compliance with this protocol. I also maintained daily communication with the subject to discuss any questions or concerns that may arise during the treatment.

This device is currently FDA cleared (through the 510(k) premarket notification process; #K013436) for use in patient with venous insufficiency; a common issue with Fontan patients. Nursing staff and technical personnel at NormaTec were available 24-hours a day in the event assistance was needed.

A blood pressure measurement was taken at the patient's home, prior to starting treatment, and the pneumatic compression device was set to apply an external pressure of +15 mmHg above the patient's measured diastolic pressure. The compression was automatically and cyclically applied for 30 minutes with a 5 minute rest period before having another 30 minute treatment, until completion of the treatment duration.

A major difference between the technology used in this study and the first feasibility study, was the use of a peristaltic pulse pattern for applying the external pressure. This is more complicated than manually inflating and deflating the trousers, but yields better results in

increasing venous return. The following outlines the steps in one full inflation / deflation cycle of the compression device.

1. **Cell 1:** rhythmic inflation/deflation up to the set pressure and pulse time for that cell
2. **Cell 1:** After pulse time for **Cell 1** is reached, **Cell 1** holds a pressure for 10 mmHg higher than it pulses during the pulsing time for the next two cells (**Cells 2 & 3**).
3. **Cell 2:** rhythmic inflation/deflation up to the set pressure and pulse time for that cell
4. **Cell 2:** After pulse time for **Cell 2** is reached, **Cell 2** holds a pressure for 10 mmHg higher than it pulses during the pulsing time for the next two cells.
5. **Cell 3:** rhythmic inflation/deflation up to the set pressure and pulse time for that cell
6. **Cell 3:** After pulse time for **Cell 3** is reached, **Cell 3** holds a pressure for 10 mmHg higher than it pulses during the pulsing time for the next two cells.
7. **30 second pause – Cell 1 deflates**
8. **Cell 4:** rhythmic inflation/deflation up to the set pressure and pulse time for that cell
9. **Cell 4:** After pulse time for **Cell 4** is reached, **Cell 4** holds a pressure for 10 mmHg higher than it pulses during the pulsing time for the next cells (**Cell 5**).
10. **15 second pause – Cell 2 deflates**
11. **Cell 5:** rhythmic inflation/deflation up to the set pressure and pulse time for that cell
12. **Cell 5:** After pulse time for **Cell 5** is reached, **Cell 5** holds a pressure for 10 mmHg higher than it pulsed for, until the end of the full inflation / deflation cycle.
13. **15 second pause – Cell 3 deflates**
14. **Cell 4 & 5** now both deflate
15. **Rest time begins.**

Figure 6 below provides an illustration of a full peristaltic pulse inflation / deflation cycle for a given set of parameters.

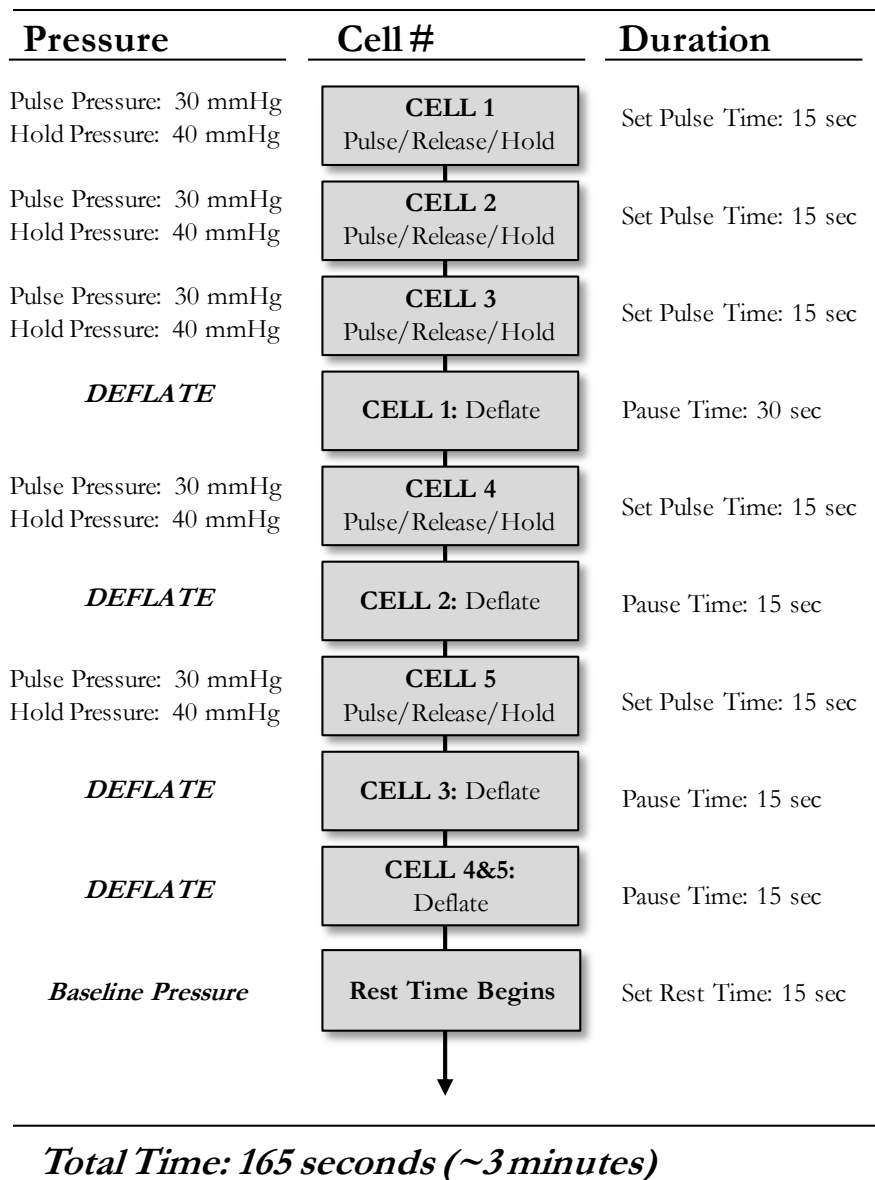


Figure 6: Example of a full peristaltic pulse cycle using the NormaTec Pneumatic Compression device (PCD). Assumptions include: (1) set pulse time to 15 seconds; (2) set cell pressure to 30 mmHg, and (3) set rest time to 45 seconds. From start to finish, the total time lapse will be around 165 seconds.

2.7 MILESTONES / TIMELINE

This clinical study, titled "Pilot Study of External Pulsation Treatment for Fontan Patients" was approved by the IRB on September 6, 2013 with the current team in place (VCU IRB Protocol Number: HM13521). The team consists of:

- Sam Lee, M.D.; Assistant Professor of Pediatric Cardiology (Principal Investigator)
- William B. Moskowitz, M.D.; Chairman, Pediatric Cardiology (Sub/Co-Investigator)
- Joseph Hernandez; Biomedical Engineering Graduate Student (Graduate Student).

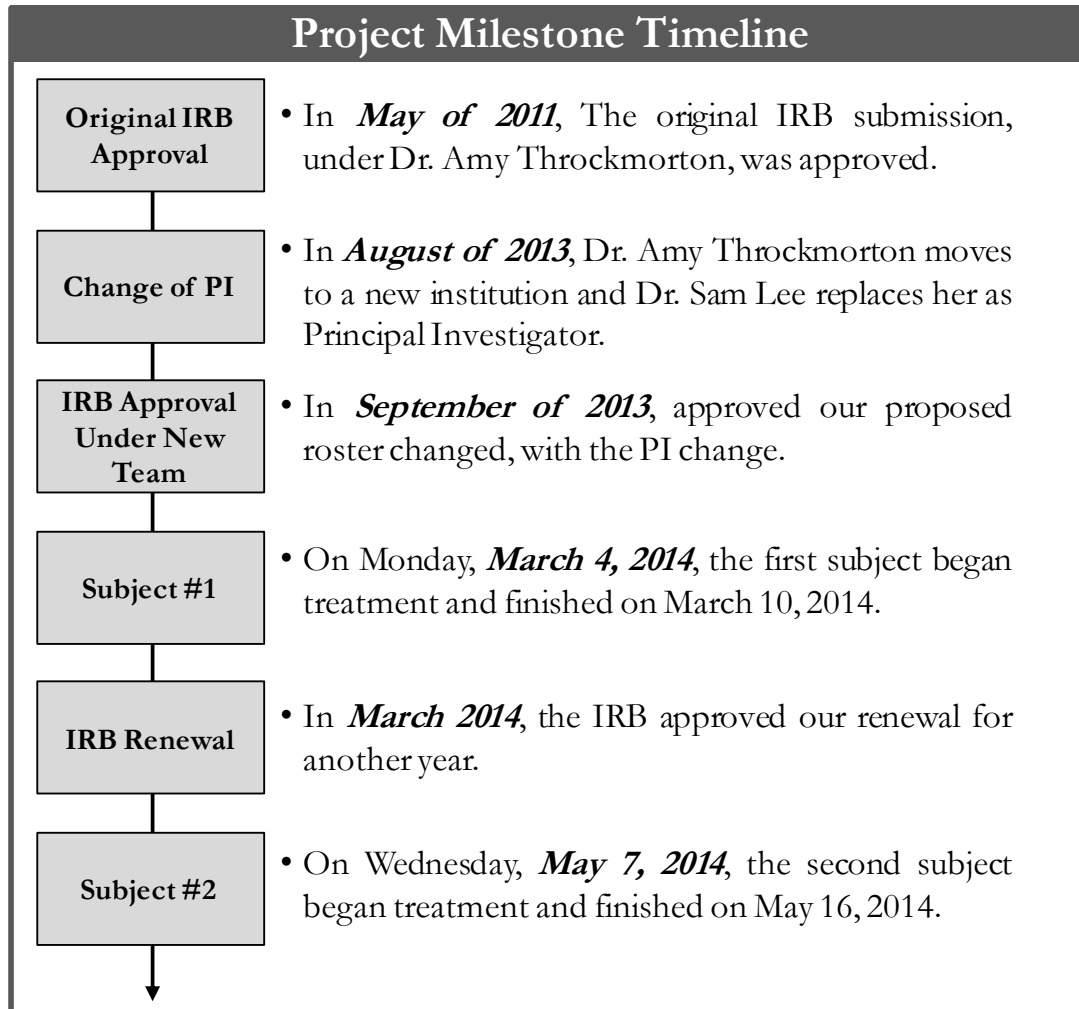


Figure 7: Project milestone timeline. Starting from the original IRB approval through the second subject.

The results of this study will allow development of technology that is usable for the immediate post-operative period after Fontan surgery. Following this pilot study, extramural funding could be sought in order to conduct larger multi-center trials.

2.8 CALCULATIONS AND ANALYSIS

In order to validate the success of the treatment on the Fontan physiology, we assessed improvements in a number of parameters related to improved exercise capacity. Below are the primary endpoints that were compared among the pre- and post- treatment stress test results.

1. Increase in exercise duration.
2. Increase in maximal/peak oxygen uptake (VO_2 peak).
3. A decrease in the slope of minute ventilation versus total CO_2 production (VE/VCO_2 slope). As measured at the point before anaerobic threshold is reached.
4. An increase in the Oxygen Uptake Efficiency Slope (OUES). A steeper slope represents a more efficient VO_2 , showing that a smaller ventilation quantity is required for a given VO_2 value.
5. Improved anaerobic threshold (AT) capacity:
 - a. Increase in the VO_2 at which AT occurs
 - b. A decrease in AT as a % of VO_2 Max

Because we sought to improve exercise capacity, our primary end points included VO_2 max as a proxy for energy expenditure and an increase in exercise time to show an increase in work load. Because it is commonly difficult among CHD patients to reach a true $\text{VO}_{2\text{max}}$, VO_2 peak was used instead. This can be seen in Figures 9 and 11, where no plateaus in VO_2 were ever reached.

Exercise tests that reached a peak respiratory exchange ratio ($\text{VCO}_2 / \text{VO}_2$) of ≥ 1.0 during the exercise phase were considered maximally performed [10]. The peak oxygen uptake (VO_2 peak) and peak minute ventilation was used (instead of maximal values) and calculated by averaging the final 30 seconds of the test. The slope of ventilation versus carbon dioxide elimination (VE/VCO_2 slope) was determined using measurements from minute 6 and 1.5, for subjects 1 and 2 respectively, of the exercise phase until the ventilatory threshold point had been reached.

The oxygen uptake efficiency slope (OUES) was calculated from the linear relationship of VO_2 versus the logarithm of minute ventilation using the equation $\text{VO}_2 = a \log(\text{VE}) + b$. The data was used starting at the second minute of the exercise phase until the end [29 - 30]. A steeper slope, reflects a more efficient oxygen consumption, where a smaller ventilation quantity is required for a certain VO_2 value.

The ventilatory threshold (VT), the moment that the VCO_2 increased out of proportion compared with VO_2 , was determined using the ventilatory equivalent method $\text{VT}(\text{VE})$ [31]. VT is

an important index of cardiorespiratory function during exercise in patients with CHD [32 - 33].

Ventilatory threshold has been widely applied clinically as an index of the functional state of patients with various cardiorespiratory diseases, used to predict the ability of a subject to sustain a given work rate for a prolonged period without metabolic (lactic) acidosis.

Since both VO_2 and VCO_2 fluctuate breath to breath, due to irregularities in ventilation, this data has been processed by a 9-s moving average filter in order to visually identify the VT [34].

CHAPTER 3: Results

The VCU IRB approved a total of 5 – 10 subjects for this study. Due to difficulty in recruiting, we have only successfully recruited two subjects so far. Although a small sample size, we attempted to fully analyze the results from this group with the hopes of establishing a frame of reference for future work. We anticipate that results will vary with additional subjects, but will provide us with additional data sets for drawing more exact conclusions from data generated so far. Treadmill stress-test Results for both subjects are listed in Table 5.

Table 5: Cardiopulmonary exercise test results for both subjects

	Subject #1			Subject #2		
	Pre-	Post-	% Change	Pre-	Post-	% Change
Exercise Duration (Sec)	690	760	10.1%	670	730	9.0%
Heart Rate (bpm) at Rest	70	71	1.4%	60	67	11.7%
Heart Rate (bpm) at Max	147	153	4.1%	67	108	61.2%
MAP (mmHg) at Rest	112.0	96.0	(14.3%)	90.3	94.7	4.8%
MAP (mmHg) at Max	120.3	103.3	(14.1%)	107.7	105.7	(1.9%)
VO ₂ Peak (ml/Kg/min)	24.93	36.75	47.4%	27.35	31.15	13.9%
VE Peak (L/min)	35.43	53.75	51.7%	46.15	59.88	29.7%
RER Peak	0.99	1.01	2.6%	1.20	1.29	7.4%
VO ₂ at VT (ml/Kg/min)	17.87	30.5	-	22.6	26.38	-
% VT/ VO ₂ Peak	71.7%	83.0%	-	82.6%	84.7%	-
VE/VCO ₂ Slope	27.838	25.099	(9.8%)	27.36	31.763	16.1%
OUES	1,850.1	2,442.9	32.0%	1,903.4	2,039.8	7.2%

3.1 COMPRESSION THERAPY

The first subject showed the most compelling results from the therapy. This subject was able to reach the desired applied external pressures, in line with the study protocol. Follow up evaluation was conducted immediately following the last day of treatment. The treatment was not tolerated well by either patient initially. Similar complaints of discomfort of the lower

extremities were made by the subjects. The applied external pressure had to be initially adjusted and ramped up to the desired level that the protocol called for.

Table 6: PCD treatment Regimen for subject 1

Day #	Day	Time of Day	Blood Pressure (mmHg)	# of Cells Activated	Applied Pressure (mmHg)		Treatment Duration (minutes)	Notes
					Initial	Final		
1	Tuesday	Night	125 / 73	4	90	60	120	Applied pressure < diastolic after 30 minutes
2	Wednesday	Night	108 / 70	4	60	80	120	Applied pressure > diastolic after 60 minutes
3	Thursday	Night	118 / 68	4	70	80	120	Applied pressure > diastolic for the entire treatment
4	Friday	Night	118 / 72	4	70	80	150	Applied pressure > diastolic after 30 minutes
5	Saturday	Morning	115 / 73	4	70	80	150	Applied pressure > diastolic after 30 minutes
6	Sunday	Morning	110 / 65	4	70	80	240	Applied pressure > diastolic for the entire treatment

For the second subject, the target applied external pressures (+15 mmHg above diastolic) was only achieved for three of the six treatment days. Because of scheduling related issues, we were not able to get the subject into the Pauley Heart Center for the stress test and post-treatment evaluation until three days after the last day of treatment; a factor that could have potentially contributed to the more subtle improvements in exercise capacity.

Table 7: PCD treatment Regimen for subject 2

Day #	Day	Time of Day	Blood Pressure (mmHg)	# of Cells Activated	Applied Pressure (mmHg)		Treatment Duration (minutes)	Notes
					Initial	Final		
1	Thursday	Night	110 / 65	5	70	40	120	Started at 70 mmHg, dropped to 60 mmHg after 10 min, after 30 min reduced to 40 mmHg
2	Friday	Night	128 / 75	5	50	70	120	Started at 50 mmHg, raised to 70 mmHg after 30 min, raised again to 80 mmHg after 60 min, but had to immediately drop back to 70 mmHg
3	Saturday	Morning	122 / 70	5	60	80	120	Applied pressure > diastolic after 30 minutes
4	Sunday	Morning	118 / 70	5	70	70	120	Applied pressure < diastolic for the entire treatment
5	Monday	Night	125 / 67	5	70	80	120	Applied pressure > diastolic for the entire treatment
6	Tuesday	Night	127 / 65	5	70	70	210	Applied pressure > diastolic for the entire treatment

* Subject's applied pressure was above diastolic pressure for only 3 out of the 6 treatment days.

3.2 EXERCISE DURATION AND OXYGEN UPTAKE

Both subjects exercised to exhaustion without any adverse events during the exercise testing. Total exercise duration time during the exercise phase improved by approximately 10% for each subject (Table 5).

We considered exercise tests with a peak respiratory exchange rate (RER peak) ≥ 1.0 during the exercise phase as maximally performed. As can be seen in Figure 8, this occurred at or slightly after the exercise phase for the first subject. It was therefore difficult to use maximal exercise parameters like VO_2 peak and Max heart rate to demonstrate the improvements on exercise capacity for the first subject. However, we did include this analysis to show a complete and thorough analysis.

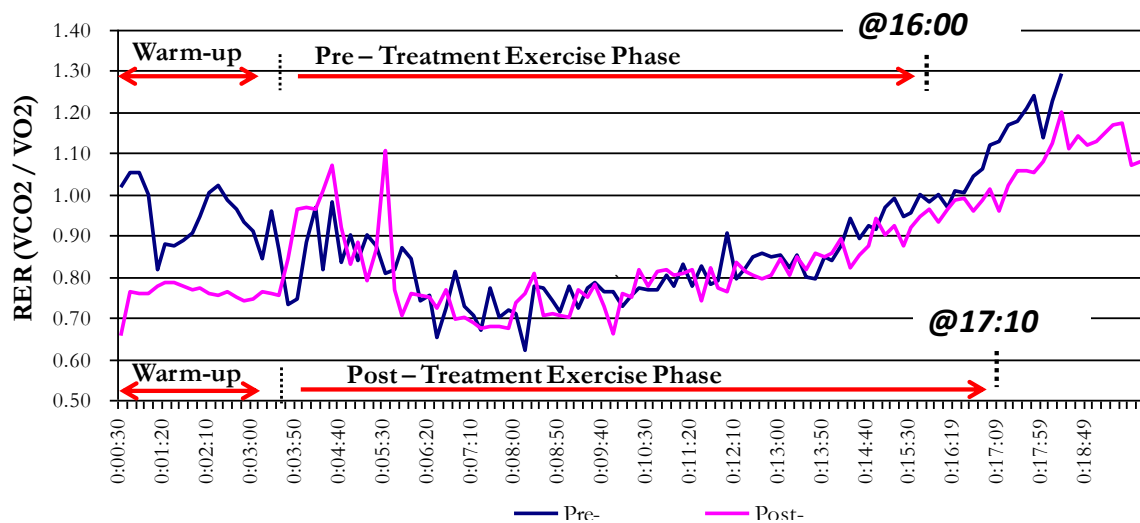


Figure 8: RER (VCO₂/VO₂) vs. Time (HH:MM:SS) for subject 1. Showing both pre- and post- stress test results.

As can be seen in Table 5, because of this single ventricular physiology, blood perfusion is compromised and a lower VO_2 peak is reached compared to a healthy subject. Typical VO_2 max seen in Fontan patients are around 30 ml/kg/min; half of a healthy subject [1]. The primary means of improving this in our study is by increasing venous return and therefore cardiac output.

As expected, during the graded exercise test, oxygen consumption increases linearly with increases in exercise intensity. Total aerobic capacity (VO_2 peak) is reached at a lower level than a healthy subject, primarily because of blood flow deficiency. We can see the effects of the compression treatment, improving aerobic capacity by 47% (Figure 9). Since $RER \geq 1.00$ was not reached until the end (or after) of the exercise phase, we do not know if this improvement is due primarily to increased exercise duration and not the treatment itself.

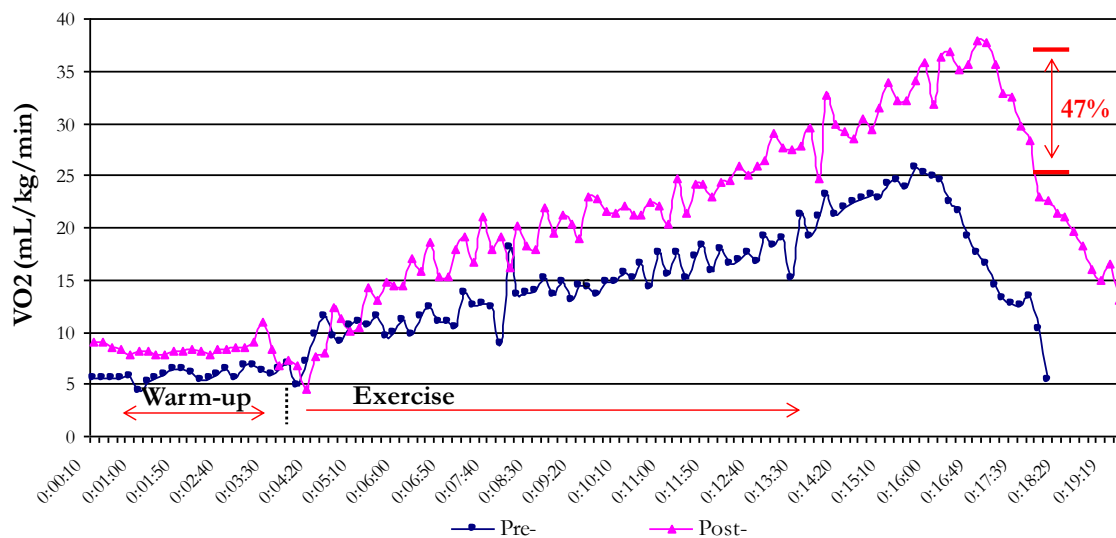


Figure 9: VO_2 (ml/kg/min) vs. Time (HH:MM:SS) for subject 1. Showing pre- and post- stress test results.

As can be seen in Figure 10 there was a modest improvement in the max heart rate achieved for the first subject. The time it took to reach max HR increased by 7%. These values are in line with published results. Fontan patients maximal heart rate during exercise tends to be reduced by approximately 80% of what is expected in a health subject [1].

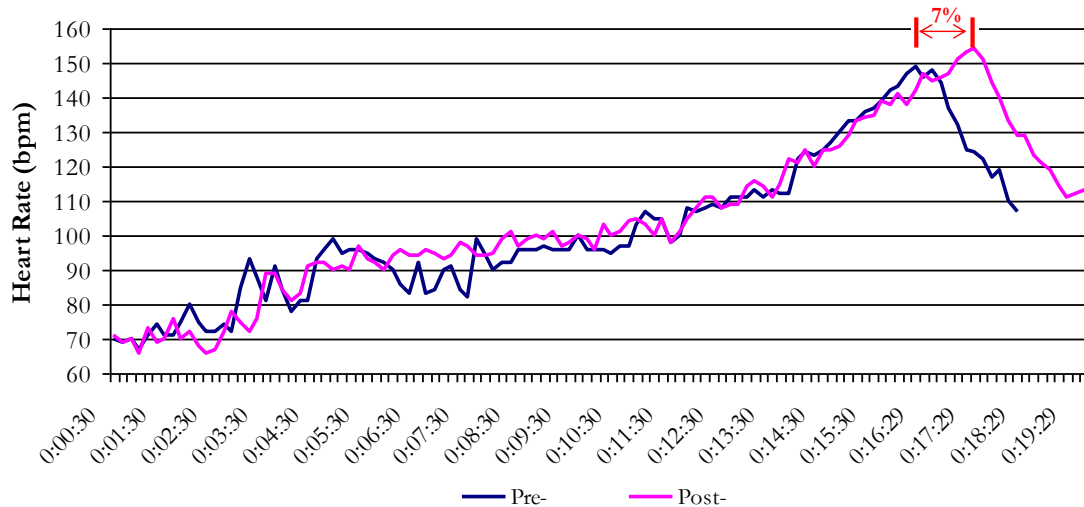


Figure 10: Heart Rate (bpm) vs. Time (HH:MM:SS) for subject 1. Showing pre- and post- stress test results.

The second subject was able to achieve maximal exercise levels during the treadmill test. RER crossed 1.0 at 8 minutes and 20 seconds during the pre-treatment test (170 seconds before the end of the exercise phase) and at 9 minutes during the post-treatment test (190 seconds before the end of the exercise) (Figure 15). A modest improvement in VO_2 peak occurred for the second subject, increasing capacity by 13.9% after the treatment regimen (Figure 11).

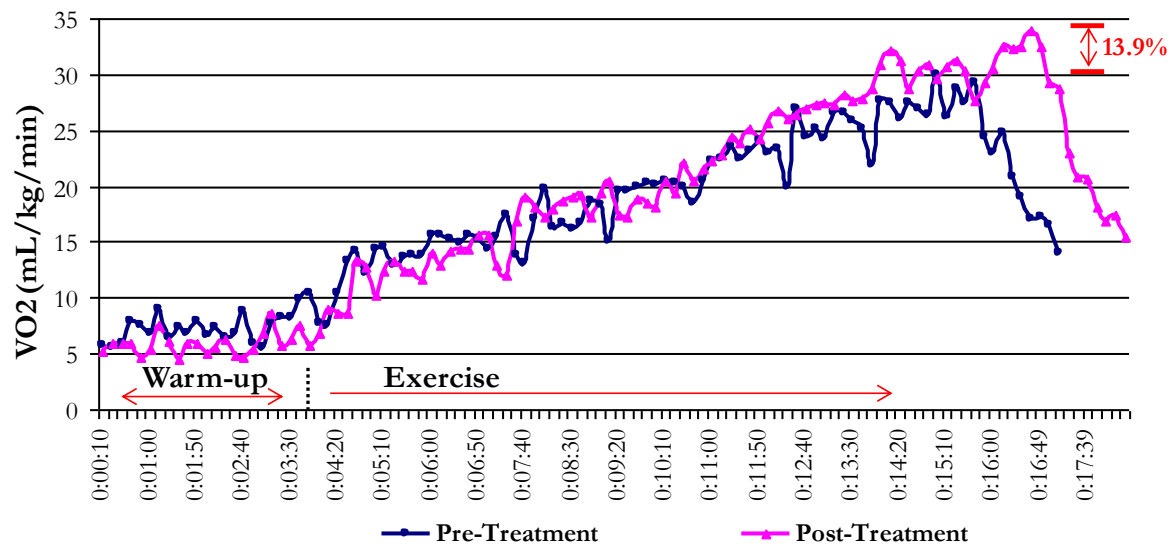


Figure 11: VO2 (ml/kg/min) vs. Time (HH:MM:SS) for subject 2. Showing pre- and post- stress test results.

The second subject showed no real heart rate response to the exercise stress test (Figure 12). It was not until after the study started that the medical team identified a heart block (AV Nodal block) that caused these skewed results. Because of this almost constant heart rate, cardiac output must have augmented primarily on the back of a marked increase in blood pressure (given a constant resistance). Systolic blood pressure increased by 40% during the pre-treatment stress test and by as much at 64% during last test.

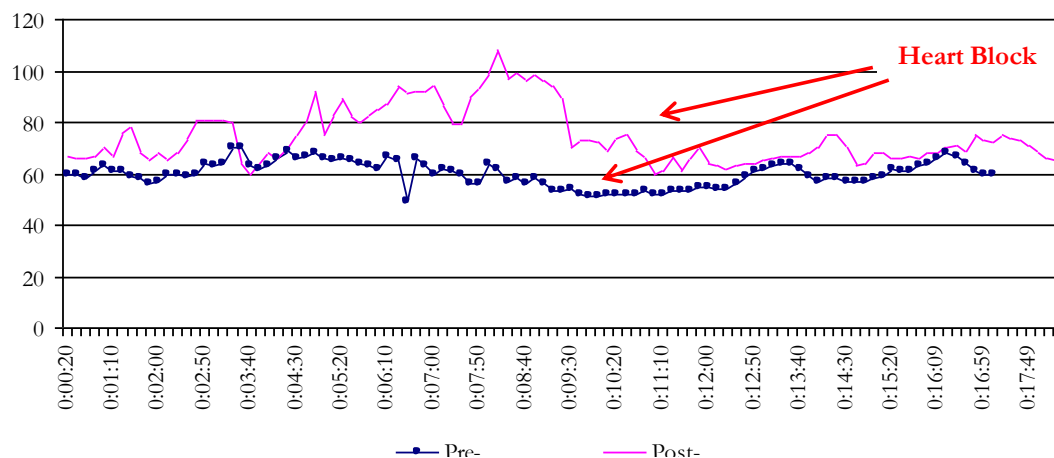


Figure 12: Heart Rate (bpm) vs. Time (HH:MM:SS) for subject 2. Showing pre- and post- stress test results.

3.3 VENTILATORY THRESHOLD AND OXYGEN UPTAKE EFFICIENCY SLOPE

Ventilatory threshold is an important parameter to measure as it can be used to predict the ability of a subject to sustain a given work rate for a prolonged period without metabolic (lactic) acidosis. In our study we measure VT noninvasively by analyzing the continuous measurements of ventilatory and gas exchange variables during the stress test.

VT for CHD patients seem to occur closer to VO_2 max / peak than does for healthy subjects; the VT/Peak VO_2 ratios for CHD subjects are higher than healthy subjects (67.6 % vs. 44.6%) [35]. Although the first subject was not able to reach a maximal exercise lever during stress testing, we include analysis on ventilatory threshold to show a complete data set for our group. As discussed earlier, peak respiratory exchange rate (RERpeak) of ≥ 1.00 was only reached after the exercise test for the first subject. Therefore, this is not a reliable indication of improved exercise capacity for this subject.

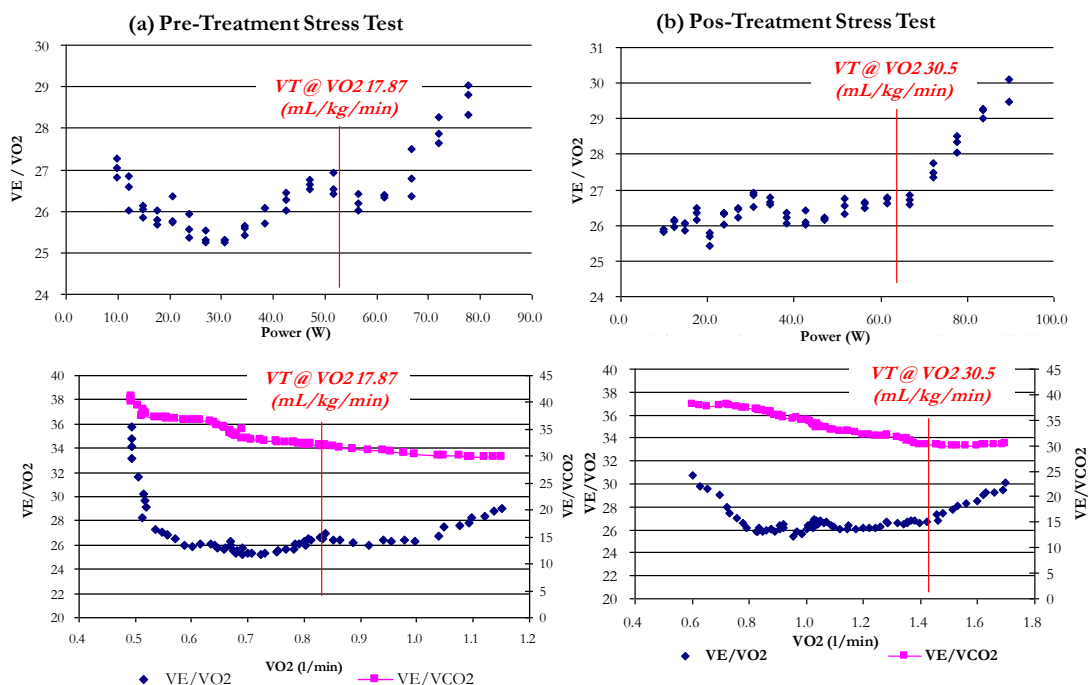


Figure 13: Determination of Ventilatory Threshold for subject 1. Showing pre- and post- stress test results.

Among Fontan patients, minute ventilation is notably altered during an exercise bout. At rest, these patients seem to have near normal ventilation (9 – 10 L/min), however during peak exercise; the minute ventilation is significantly less than that of normal subjects [1]. This altered cardiorespiratory response to exercise, in many cases, makes it difficult to utilize VT as a parameter for exercise testing. We therefore include other submaximal exercise parameters in this analysis.

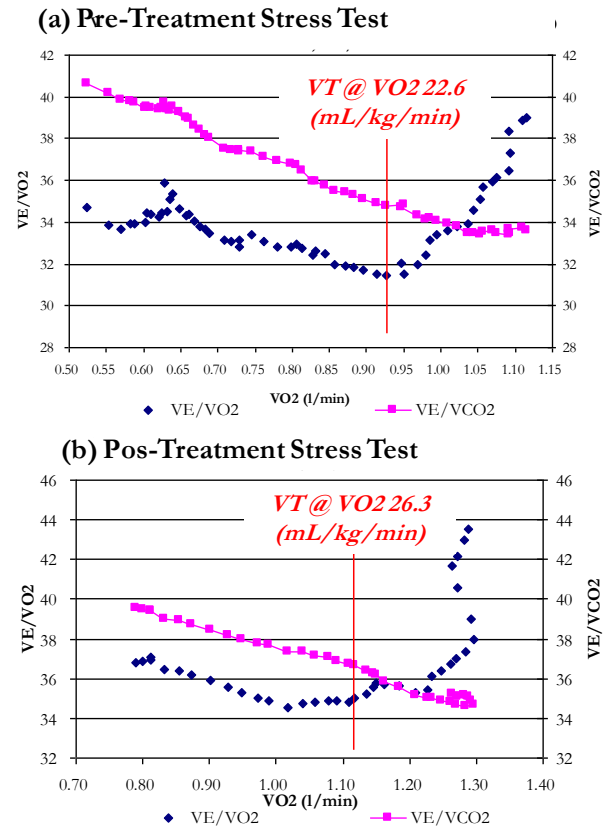


Figure 14: Determination of Ventilatory Threshold for subject 2. Showing (a) pre- and (b) post- stress test results.

The second subject was in fact able to achieve maximal exercise levels during testing (Figure 15) and we found it appropriate to include maximal exercise parameters in our analysis of the second subject. Although the heart rate response was blunted, we observed positive trends in the ventilatory threshold data.

To obtain a better sense of overall improvement in exercise capacity for the second subject, we looked at the ventilatory equivalent ratios to understand if the subject reached their anaerobic threshold later after going through the treatment regimen (Figure 14). Here we are looking for the point where a marked change in slope occurred between VE/VO_2 and VE/VCO_2 . Before treatment this threshold was reached around 8 minutes and 10 seconds into the stress test.

This VO_2 of 22.6 ml/kg/min represents 82.6% of the VO_2 peak, pre-treatment. By the end of the week, the subject was able to reach their aerobic capacity later, around 8 minutes and 50 seconds, improving their time by 8%.

As confirmed by both sets of graphs (Figure 14), the subject increased the VO_2 at which VT occurred by 3.7 ml/kg/min.

We were able to visually identify the points where the VE/VO_2 curve, which has been flat or decreasing from the beginning until after 8 minutes into the exercise phase, and now, begins to rise as the VE/VCO_2 curve remains constant or decreasing.

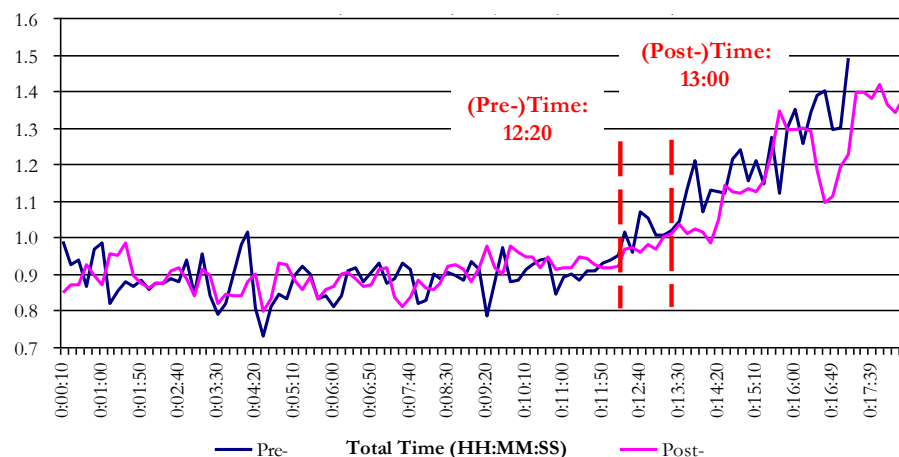


Figure 15: RER (VCO_2/VO_2) for subject 2. Showing pre- and post- stress test results.

The primary clinical assessment of interest is the evaluation of aerobic capacity as a response to compression therapy. While VO_2 peak provides an accurate and objective indication of maximal aerobic capacity, it is only useful if the patient is able to perform at maximal effort. This level is rarely reached by Fontan patients. As an alternative, we have included analysis on the Oxygen Efficiency Slope (OUES) as a proxy for aerobic capacity. Figure 16 provides visual details on the resulting OUES changes after the treatment.

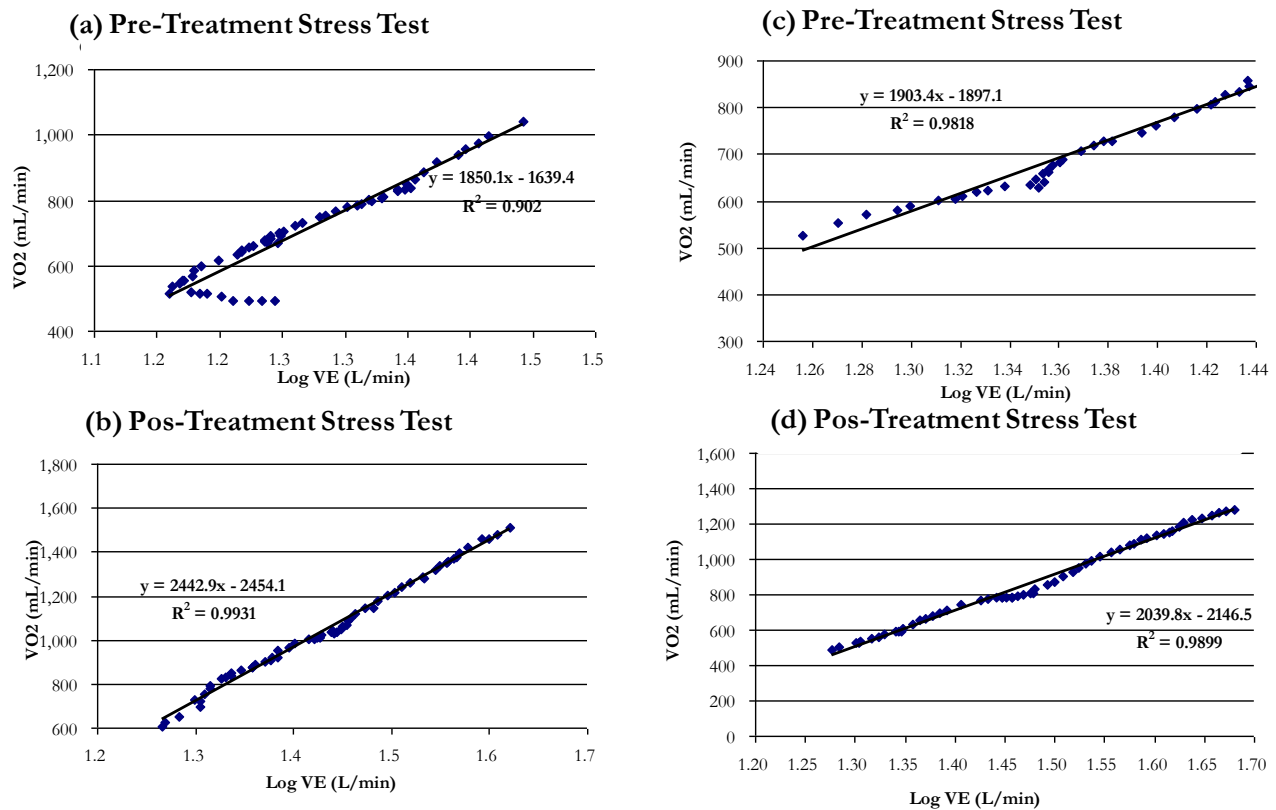


Figure 16: Oxygen efficiency slope (OUES). (a) pre-treatment subject 1, (b) post-treatment subject 1, (c) pre-treatment subject 2, (d) post-treatment subject 2.

Both subjects were able to achieve more efficient oxygen consumption post-treatment as indicated by a steeper slope in OUES. The first subject experience an increase in OUES of approximately 32% (2,443 vs. 1,850) and the second subject showed an increase as well, although to a lesser degree (7.2%).

OUES measurements were started at 90 seconds (because of 9-s moving average) until 90% of the test phase had been reached [10]. These values show that both subjects are relatively healthy as compared to other Fontan subjects. Healthy subjects tend to have OUES values in the range of 1,500 to 2,000 with CHD patients experiencing 75% - 80% of those values [10, 29].

3.4 VE/VCO₂ SLOPE

The first subjects demonstrated a modest improvement in VE/VCO₂ slope. The slope of ventilation versus carbon dioxide elimination was determined using measurements beginning from minute 6 of the test phase (due to a large amount of noise in the beginning), up to the VT determined from the graphs. The true stopping point is the respiratory compensation point, but due to difficulty in accurately identify this point visually, we utilized VT instead. The second subject had an increase of VE/VCO₂ slope after the compression therapy of 16%. For this subject measurements began at 1 minute and 30 seconds (as as result of using a 9-s moving average).

As far as this parameter is concerned, these two subjects seem to be relatively healthy Fontan subjects. Larger studies have shown and average slope for Fontan patients to be around 34.5

and approximately 127% greater than their healthy counterparts [10]. This observation is in agreement with the results seen in the OUES analysis above.

An elevated slope is expected from CHD patients since an elevated VE/VCO_2 slope is inversely related to cardiac output. In our patient population, a diminished pulmonary perfusion leads to this elevated slope state. Ideally, as cardiorespiratory measurements improve with long-term pneumatic compression therapy, a reduction in VE / VCO_2 slope should be experienced.

3.5 CHAPTER SUMMARY

The pressure applied during the treatment regimen was not well supported by the test subjects. The recommended external pressure of 15 mmHg above the diastolic was not achieved and adjusted down for the comfort of the subject. On average, 70 mmHg was the highest pressure applied that was tolerated by either participant.

Only one of the two subjects performed maximally during the exercise stress test. As such, it is appropriate to assess the viability of this treatment using submaximal exercise parameters across both study subjects. These parameters do show, particularly OUES, an improvement in exercise capacity after compression treatment. OUES improved by 32% and 7.2% for the first and second subject, respectively.

The second subject was able to perform maximally during the stress test. Considering both maximal and submaximal parameters we did observe an improvement in all parameters, with the exception of VE / VCO_2 slope.

Regardless of the point at which true VO_2 max occurs, we can confidently see an improvement in ventilatory threshold as a result of the compression treatment. Both subjects increased their aerobic capacity, demonstrating greater oxygen consumption at the time of anaerobic metabolism transition than during pre-treatment stress test. VO_2 at the point of VT increased by 70% and 17% for the first and second subject, respectively.

These preliminary results are encouraging and suggest that this therapy could be very beneficial to Fontan patients. Overall, there was an improvement in exercise duration time, VO_{2peak} , ventilatory threshold, and OUES with only VE / VCO_2 slope having mixed results for our patient cohort.

CHAPTER 4: Discussion

The aim of this study was to show improvements in cardiorespiratory measurements among Fontan patients after applying external pressure to the lower extremities of the body. Our results among the two subjects so far have shown a moderately beneficial improvement in exercise capacity after the compression therapy.

The objective is to mitigate complications that result from long-term single-ventricle physiology. The primary strategy is to increase venous return and thus stroke volume. Improved exercise capacity, and hence cardiorespiratory measures, can be observed as a proxy for improved health among this patient population. The result of the Fontan surgery tends to be a diminished exercise tolerance and ventricular dysfunction [12-15]. At rest, (cardiac index, stroke index and systolic blood pressure) these subjects will have normal or slightly subnormal parameters as compared to healthy subjects. However, during dynamic exercise, notable differences are observed, showing that these patients are unable to adequately respond to exercise. This is why, when compared to healthy subjects, single ventricular patients tend to have an abnormal cardiorespiratory response to exercise. This can include:

- A blunted heart rate response.
- Limited ability to increase stroke volume with exercise, due to impaired ventricular function and difficulty in increasing ventricular preload. Cardiac Index has been found to be as much as 22% greater during exercise for healthy, age-matched subjects as compared to Fontan patients [36].

- Most 10 year follow-up studies document myocardial dysfunction and grade II failure in about 70% of patients [37].
- The ventricle becomes dilated, hypertrophic, and hypocontractile, with deterioration in both systolic and diastolic function.

The absence of the pulmonary ventricular pump results in a low pulmonary blood flow, considering that at this point blood flow is primarily driven by venous pressure. Because of the redirection of the vena cava to the pulmonary arteries, there is very little pressure gradient to push along blood flow to the lungs. Studies have shown very little, if any, pressure gradients exists across the surgical connections (e.g., RA-PA) for Fontan patients [36]. With so little hydrostatic pressure contributing to venous return, blood flow is mainly being driven passively (osmotic pressure) into the lungs. This pressure increase upstream leads to chronically elevated central venous pressure, a hallmark of the Fontan physiology. Common CVP at rest among this patient population can be 3 times that of their healthy counterparts (14 mmHg vs. 4 mmHg) [38]. This is why the dominant limiting determinant of ventricular function is preload in these patients.

During an intense exercise bout, Fontan patients reach exhaustion much quicker than their healthy counterparts. They will produce lactic acid much quicker and lactic acidosis may occur. Respiratory rates and ventilation are expected to spike as they expire off more CO₂ and reach anaerobic metabolism much quicker. This effect is primarily driven by a low cardiac output response during intense exercise resulting in a lower VO₂ max among Fontan patients. Stroke

volume, not heart rate has been found to be responsible for this depressed cardiac output during exercise [38].

Maximal Vs. Sub-Maximal Exercise Parameters

There is an inherent bias in the exercise protocol that seems to favor experience with the equipment. The majority of test subjects perform better, as it relates to exercise time, the second time on the treadmill equipment. In a scenario where maximal exercise was not reached ($\text{RER peak} \geq 1.0$), then it is unreliable to look at the change in VO_2 peak as an indication of increased exercise capacity since all that is being captured is improved duration on the treadmill where a higher VO_2 peak should be expected. This was the case with the first subject (Figure 8 and 15).

Both Bossers [10] and Akkerman [30] argue that finding true VO_2 Max is mainly limited to healthy adult subjects who can actually perform maximally during a graded exercise testing. These subjects have to keep pushing themselves long enough for VO_2 to reach the plateau in the face of continuing exercise and increasing workload. Both argue that in the pediatric population and Fontan patients, a true plateau in oxygen uptake is seldom attained. Bossers conducted a large multi-center study with 110 Fontan patients less than 18 years old and showed that as much as 20% of the subjects were not able to reach a maximal exercise state ($\text{RER} \geq 1.00$) and "Submaximal" exercise parameters were used (e.g., VE/VCO_2 slope and Oxygen Uptake Efficiency slope).

Akkerman goes as far as stating that for these patients, using VO_2 peak during exercise is not appropriate as a proxy for improved cardiovascular health since this measurement can in fact be strongly influenced by the patient's motivation, the selected exercise protocol, and the experience of the tester.

Although the second subject was able to perform at a sufficient level of effort, as indicated by $\text{RER}_{\text{peak}} \geq 1.0$, there was still no clear plateau of VO_2 . Thus, it is not certain that a true VO_2 max level was ever reached (Figure 11). Therefore, if both subjects did not achieve a true VO_2 max, we then were really measuring VO_2 peak. If the subjects improved their exercise duration primarily because of their experience with the equipment, an improvement in $\text{VO}_{2\text{peak}}$ should then be expected but reveals very little about whether or not the pneumatic compression treatment was in fact effective at improving the patients exercise capacity. For this reason, it is important to additionally analyze submaximal exercise parameters, which includes VE/VCO_2 slope, Ventilatory Threshold, and Oxygen Uptake Efficiency Slope (OUES).

Other Considerations

The second subject was not able to perform the post-treatment stress test immediately following the last day of treatment, due to scheduling conflicts at the lab. The post-treatment stress test was performed three days after the last day of treatment. Although not the primary reason, this could have caused some major variation between the two subjects results post treatment. However, both of the subjects seem to be relatively healthy Fontan patients, as indicated by their VO_2 peak, VE/VCO_2 slope and OUES. This may also lead us to believe that our

current cohort of patients may not experience as much of an improvement as one might see in Fontan patient with poor health, a failing Fontan physiology for instance. Until a greater sample size is studied we cannot be sure that this data represents the extent of the clinical benefit of this compression treatment.

CHAPTER 5: Future work and Conclusion

Various studies exploring the effects of applying external pressure mainly focus on the post-operative period of the Fontan procedure. Very little data exists on a much later period after the surgery. This study presents results on exercise capacity after applying a compression therapy regimen on a modern Fontan population. Most studies focus on the result of compression during the therapy.

With only two subjects, there is not enough data to draw a statistically significant conclusion. Although we have been able to thoroughly analyze the results so far with the hopes to gain additional clarity once other subjects are recruited and further studied. With a larger cohort of subjects we aim to lay the ground work for future chronic outpatient studies. If successful this technology could serve as a preventive measure and long-term clinical treatment alternative for Fontan patients.

Recruiting Efforts

Our team had difficulties successfully recruiting subjects to this study. There are a number of reasons that could have contributed to the poor participation. Principal among this is the time commitment required. Not only did the patient have to block off two full weekdays for the pre- and post-treatment stress test, but also a portion of every evening and weekend. A study stipend could help address this issue by partly off-setting the subjects' expense for the time spent participating in the study. This is particularly important when time off work or missed school is required.

Target Applied Pressure

The applied external pressures used during the treatment were based on the clinical results of the first feasibility study. The protocol called for an applied external pressure set to 15 mmHg greater than their diastolic pressure. In many instances this meant applying pressures greater than 85 mmHg. This was not well tolerated and patients complained of discomfort, having to stop treatment and adjust the applied pressure. We attempted to reach pressures as close to the protocol as was tolerated by the subject. For future studies, an appropriate applied pressure should be explored. It is conceivable to think that one would only have to apply enough pressure to distribute blood flow from the lower extremities of the body to the central venous system and large enough to provide a gradient across the surgical connection and increase blood flow. This could be between 30 – 40 mmHg, but more work needs to be done.

Testing Bias

Most subjects perform better on the treadmill stress test after the initial test since they are better acquainted with the equipment. This was not a factor that was anticipated during the study protocol designed. As a way to reduce this bias, before the initial baseline stress test is conducted, each subject could first perform the treadmill exercise test at least once. We can then establish a true base-line once the study begins.

Starting Early

The impact the therapy has related to the age of the Fontan patients is worth considering for future work. Studies have shown that VO_2 peak decreases over time with an annual decline between 1.25% [11] and 2.6% [14]. In order to see the maximal benefit from this kind of therapy, an early start might be important to consider. The time between this study and the Fontan procedure among our subjects was 14 and 19 years. With our limited sample size, we do not have the benefit of observing results across various age groups and results might be poorer than the mean observed results for other published data. Average time since the Fontan procedures ranged anywhere from 4 months post operation to 14 years [1, 10, 36, 38].

In order for the proposed treatment to have true clinical application it will need to have lasting benefits that are materialized in improved exercise capacity in the long-run. A consistent attenuation of the chronic venous insufficiency found in the Fontan patients will need to be achieved in order to avoid long term complications such as liver congestion, cardiac arrhythmias and other morbidity.

Long-term Treatment Benefits (Exercise Training Like Results)

The benefits of exercise training on various exercise parameters have been well documented including improving VO_2 max by 16% - 46% in a cohort of healthy subjects performing a 2-3 times per week for 8-16 week exercise regimen [39]. Exercise training has shown improved cardiorespiratory responses to exercise over time by increasing blood volume and thus a greater venous return. Increased maximal cardiac output in endurance trained athletes has

been shown to be primarily a result of greater stroke volume, rather than an increase in maximal heart rate, which in fact tends to be lower in these athletes. Training can lead to an increase in efficacy of systolic contraction and essentially a more complete emptying of the heart by a forcible systolic contraction. It is not unreasonable for us to think that with the proper treatment regimen for our pneumatic compression device, a Fontan patient can experience a similar, albeit to a lesser degree, improvement in long-term exercise capacity and reduction of venous insufficiency.

There will need to be some discussion on a proposed long-term treatment regimen for future studies using this pneumatic compression therapy. Arthur M. Feldman [40] showed in a 6 month follow up that subjects who received a treatment regimen of 35 1-hour sessions over a period of 7 to 8 weeks using the EECF technology were able to improve their exercise time, although peak VO_2 did not improve with therapy.

There is also a genetic component that has been identified which can dictate how effective exercise training can be on improving exercise capacity and cardiovascular adaptability [41]. It has been suggested that as much as 25% - 50% of the general population's variability in VO_2 Max is due to genetic differences. Subjects who are predisposed to responding to exercise training have increased VO_2 max by as much as 50% and those that are not predisposed have show no improvements. While the Fontan patient will benefit from an improved venous return during treatment, there might be a similar genetic factor that might limit the long-term conditioning effect seen in exercise training among endurance athletes.

Possible reason for subject to subject variability:

The total capopulmonary connection (TCPC), a modified version of the original Fontan operation, is most often performed using either an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC). It has been demonstrated that ILT patient group tends to have diminished cardiovascular function as compared to their ECC counterpart. VO_2 peak has been found to be significantly lower in this group as well as a steeper VE/VCOs slope [10]. This may describe some of the differences in results among our group. The first subject, an ILT Fontan patient, was not able to perform maximally in either pre- or post-treatment exercise test. More data needs to be collected before definitive conclusions can be made.

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APPENDIX A: IRB Approval & Subject Consent Form



Office of Research
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DATE: March 10, 2014

TO: Sam Lee, MD
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Box 980342

FROM: Lea Ann Hansen, Pharm D *Lea Ann Hansen, Pharm D/EP*
Chairperson, VCU IRB Panel D
Box 980568

RE: VCU IRB #: HM13521
Title: Pilot Study of External Pulsation Treatment for Fontan Patients

On March 7, 2014, this research study was approved for continuation by expedited review according to 45 CFR 46.108(b) and 45 CFR 46.109(e) and 45 CFR 46.110 Category 8(b). This research involves children and is approved under 45 CFR 46.405. This determination reflects the revisions received in the Office of Research Subjects Protection on March 4, 2014.

PROTOCOL: Pilot Study of External Pulsation Treatment for Fontan Patients

- Research Plan (Version dated 8/21/2013; received by ORSP January 29, 2014)

VCU IRB APPROVED CONSENT/ASSENT FORM (attached):

- Research Subject Information and Consent Form (Version dated 8/21/2013, 7 pages; received by ORSP January 29, 2014)

ADDITIONAL DOCUMENTS:

- VCU IRB Study Personnel Roster (Version date: 8/24/2013; received by ORSP March 4, 2014)

This approval expires on February 28, 2015. Federal Regulations/VCU Policy and Procedures require continuing review prior to continuation of approval past that date. Continuing Review report forms will be mailed to you prior to the scheduled review.

The Primary Reviewer assigned to your research study is Antonio Abbate, MD. If you have any questions, please contact Dr. Abbate at aabbate@mcvh-vcu.edu or 828-0513; or you may contact Elicia Preslan, IRB Coordinator, VCU Office of Research Subjects Protection, at IRBPanelD@vcu.edu or 827-0899.

Attachment – Conditions of Approval

Conditions of Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (*as applicable*):

1. Conduct the research as described in and required by the Protocol.
2. Obtain informed consent from all subjects without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).
3. Document informed consent using only the most recently dated consent form bearing the VCU IRB "APPROVED" stamp (unless Waiver of Consent is specifically approved).
4. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translated version.
5. Obtain prior approval from VCU IRB before implementing any changes whatsoever in the approved protocol or consent form, unless such changes are necessary to protect the safety of human research participants (e.g., permanent/temporary change of PI, addition of performance/collaborative sites, request to include newly incarcerated participants or participants that are wards of the state, addition/deletion of participant groups, etc.). Any departure from these approved documents must be reported to the VCU IRB immediately as an Unanticipated Problem (see #7).
6. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.
7. Report Unanticipated Problems (UPs), including protocol deviations, following the VCU IRB requirements and timelines detailed in VCU IRB WPP VIII-7:
8. Obtain prior approval from the VCU IRB before use of any advertisement or other material for recruitment of research participants.
9. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.
10. All protocols that administer acute medical treatment to human research participants must have an emergency preparedness plan. Please refer to VCU guidance on <http://www.research.vcu.edu/irb/guidance.htm>.
11. The VCU IRBs operate under the regulatory authorities as described within:
 - a) U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
 - b) U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
 - c) Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE OF RESEARCH: PILOT STUDY OF EXTERNAL PULSATION TREATMENT FOR FONTAN PATIENTS

VCU IRB PROTOCOL NUMBER: HM13521

INVESTIGATORS:

Principal Investigator: Sam Lee, M.D.

Sub/Co-Investigator: William B. Moskowitz, M.D.

Student: Joseph Hernandez, B.S.



After carefully reading and understanding the information listed below, if you would like to participate in this research study please sign this consent form indicating your consent.

This consent form may contain words or information that you do not understand. Please ask one of the investigators to explain any words or information that you do not understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE RESEARCH STUDY:

The purpose of this research study is to evaluate the effectiveness of applying external pressure to your legs using a NormaTec compression device and compare the results using an exercise study. The NormaTec compression device has pants or trousers that have air filled pockets inside of them; they function similar to blood pressure cuffs and can be inflated, only around the lower extremities or legs, as opposed to the upper arm. We will have you slip on the pants and then, using air, inflate these trousers. This will apply pressure to the outside of your legs. In doing so, we will measure how this externally applied pressure over a one week time-period may improve blood flow conditions in the circulation on the right side of your heart. Fifteen subjects will participate in this study.

You are being invited to participate in this study because you have been diagnosed with single ventricle physiology or a closely related congenital heart defect. This study will involve three stages, which include an initial evaluation, at-home external pulsation using the NormaTec device for one week, and then a post-treatment treadmill test and exit interview.

Approved
3/7/14 / AA / EP

WHAT YOU WILL DO IN THE STUDY:

Your participation in this study will last for one week. The study will begin on a Monday morning and conclude on the following Monday afternoon. You will visit the VCU Medical Center for an initial pre-evaluation that will be finished by mid-morning, be fit with the NormaTec compression pants, and then you will be discharged to home on all other ongoing therapies (i.e. medications, diet). You will use the NormaTec compression device for 6 consecutive days. You will perform daily treatments using the device in the afternoons for 2-3 hours during the week, and weekend treatments will be performed for 4-5 hours over the entire weekend for at least 2 hours per day. Thus, on Saturday and Sunday, you are allowed complete the compression treatments based on your schedule with at least 2 hours per day. On that Monday, exactly one week after the initial evaluation, you will return to VCU for a post-evaluation to see if the compression treatments had any measurable benefit on blood flow. A more detailed timeline of the study is listed below for your review. Please ask questions at any time.

Sample Procedural Timeline:

Initial / Pre-Treatment Assessment

- You will come to the VCU Medical Center on a Monday. One of the investigators will contact you by phone to inform you of the appropriate location on Friday before the Monday appointment.
- We will assess your weight, blood pressure, heart rate, oxygen saturation, skin integrity, presence of peripheral edema, breathing rate, and electrocardiogram.
- We will then perform an ultrasound of your legs to rule out any blood clots.
- After the ultrasound, you will undergo a treadmill stress test to determine baseline exercise performance. During this procedure, we will measure vessel diameters and breathing conditions according to the standard protocol for the hospital.
- Upon completion of the stress-test, we will then work with you to become familiar with the Normatec trousers. This step will involve a training session on the device, especially about the safety features of the trousers. We will also coordinate and assist with the first compression treatment at your home in the afternoon.
- We will ask you about any recent episodes of chest discomfort or shortness of breath as well as any recent changes to your medication(s).

Compression Treatment

- You will carry out the compression daily for 2-3 hours and 4-5 hours in total over the weekend (minimum of 2 hours per weekend day).
- An investigator will be present to assist with the treatments each day.
- We will already have the applied pressure level determined from your medical evaluation.
- The compression treatment will occur in 30-minute intervals as follows: 1) pants are deflated, 2) inflation, 3) increase to applied external pressure for 20 seconds, 2) hold this pressure for 40 seconds, and 3) decrease or release applied pressure over 20 seconds, 4) back to 1). A 5-minute rest period will occur between 30-minute treatment intervals.
- You will perform these treatments from Monday afternoon until Sunday evening.

Post-Treatment Assessment

- After the six days of treatment, you will return to the VCU Medical Center for a final assessment.

- We will repeat the initial or pre-treatment evaluation measurements and testing.
- In conclusion, we will also conduct an exit-interview and ask the study participants about their use of the pneumatic trousers.

RISKS AND RISK REDUCTION:

The Normatec compression device has FDA clearance for use in patients with compromised blood flow on the right side of their heart. An investigator will be present during the pre-treatment assessment, compression treatment, and post-treatment assessment to assist. The safety features of the compression device are designed to protect you from harm.

You will also be carefully monitored for any sign or symptoms of shock, such as dizziness or pale skin. During the procedure, we will determine whether abnormal findings are being observed. If the observed results are not compliant with the hypothesized results, the procedure and study will be immediately terminated. If you are in any discomfort or wish to stop the study or treatment at any time, then please feel free to do so.

You may experience discomfort and risks associated with the compression pants may include a tightness around the legs, feet, and toes at different times; muscle cramps; rubbing of the skin on the legs, feet, and toes; dizziness; and overall displeasure with sitting for so long during the study. A representation from the research team will be present during the compression treatment. If you are in any pain or discomfort, then you may stop the test and appropriate treatment will occur. We may call your doctor, the trouser company help-line, and 911 in the unlikely event of an emergency.

You may also experience discomfort and risks associated with the exercise stress-test including a feeling of weakness, being dizzy, fainting, falling down on the treadmill, chest pain, leg and muscle cramps, unusually strong heart beat, and abnormal heart rate. Please notify medical personnel if any of these occur, and you may stop the test at any time. Medical personnel will be present to help you if any of these discomforts or conditions occur.

BENEFITS TO YOU AND OTHERS:

We expect that the participants in this study will feel better during this study. We expect patients to experience a comparable physiological benefit of low intensity exercise each day when undergoing the PCD treatment. We will compare the physiological benefit after one week of treatment to their performance during a stress-test. It is possible, however, that you will experience no improvement during the study.

This procedure may even temporarily worsen your symptoms, although this is a highly unlikely possibility, and in such case treatment will be interrupted and we expect no long-term consequences for your health. The information from this research study may lead to better treatment in the future for patients with single ventricle physiology or a closely related congenital heart defect.

ALTERNATIVES:

If you decide to not enter this study, routine exercise is a potential alternative treatment. With that stated, however, Fontan patients are unable to tolerate most forms of exercise. Therefore, the PCD technology offers an alternative technique for patients to reap the benefit of low intensity exercise

without the inherent levels of exertion. The study doctor will discuss this with you. You do not have to participate in this study to be treated for your condition.

COMPENSATION:

No compensation will be provided for this study. The knowledge gained from this study will be used to improve the design of existing technology as a clinical management tool for patients with single ventricle physiology or a closely related congenital heart defect similar to yours.

CONFIDENTIALITY:

Your confidential information will be protected at all times. For this study, only nonspecific information will be collected, including your age, sex, and diagnosis.

Data being collected is for research purposes only. Your data will be identified by ID numbers, **NOT** names, and stored separately from medical records in a secured spreadsheet with the principle investigator. Only key personnel will have access to these files with the principle investigator present.

COMPENSATION FOR INJURY:

Virginia Commonwealth University and the VCU Health System have no plan for providing long-term care or compensation in the event that you suffer injury as a result of your participation in this research study.

If you are injured or if you become ill as a result of your participation in this study, contact one of your investigators immediately. Your investigator will arrange for short-term emergency care or referral if it is needed.

Fees for such treatment may be billed to you or to the appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:

You do not have to participate in this study. If you choose to participate, you may stop at any time without any penalty or loss of benefits to which you are otherwise entitled. If you do participate, you are free to withdraw at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Your principle investigator, co-investigators, or student investigator can stop your involvement in the study at anytime without your consent. This could occur due to:

- 1.) The investigators believe it to be necessary for your health or safety.
- 2.) You are unable to comply with study instructions.
- 3.) Administrative reasons requiring your withdrawal.

QUESTIONS:

In the future you may have questions about your participation in this study. If you have questions, complaints, or concerns about the research, contact:

Sam Lee, M.D.
Assistant Professor, Pediatric Cardiology
Department of Pediatrics
VCU/Medical College of Virginia
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Office (804)-828-9143
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You may also contact this number for general questions, concerns or complaints about the research. Please call this number if you cannot reach the research team or wish to talk to someone else.

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 113
PO Box 980568
Richmond, VA 23298
(804) 827-2157

ASSENT for a patient between the ages of 15 and 18

I have read the description of the study entitled, "Pilot Study of External Pulsation Treatment for Fontan Patients," which is printed above. I understand the procedures and what will happen to me in the study. I have received permission from my parent(s) to participate in the study, and I agree to participate in it. I know that I can quit the study at any time.

Signature of Child

Date

Do not sign this assent/consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. Additional information about participation in research studies can be found at: <http://www.research.vcu.edu/irb/volunteers.htm>

Approved
3/7/14 AA EP

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

Please read if you are the Parent/Legal Guardian of a patient participating in this study:

You are making the decision to allow your child to participate in this study. Your signature below indicates that you have read the information provided above and have decided to allow him or her to participate. If your child is between the ages of 15 and 18, your signature below indicates that you have talked with your child about the study and believe he or she fully understands what will happen during the study. If you later decide that you wish to withdraw your permission for your child to participate, simply tell an investigator or the doctor. You may discontinue his or her participation at any time.

Subject Name, printed

Subject Signature

Date

Name of Parent or Legal Guardian
(Printed)

Parent or Legal Guardian Signature

Date

Name of Person Conducting Informed Assent/Consent
Discussion / Witness
(Printed)

Signature of Person Conducting Informed Assent/Consent
Discussion / Witness

Date

Investigator Signature (if different from above)

Date

Do not sign this assent/consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. Additional information about participation in research studies can be found at: <http://www.research.vcu.edu/irb/volunteers.htm>

Approved
3/2/14 AA EP

Vita

Joseph Hernandez was born October 6, 1982 in Huntsville, AL. He graduated from Virginia Polytechnic Institute and State University with a Bachelors of Science degree in Electrical Engineering in May of 2007. Upon graduation he accepted a job with BB&T Capital Markets in Richmond, VA as an investment banking analyst. After three years of working with various technology and life science companies on mergers and acquisitions and raising capital, he entered the Masters of Science program in Biomedical Engineering at Virginia Commonwealth University in August of 2010. He currently works as the director of research for the Frederick Banting Foundation in Richmond, VA. The foundation funds innovative medical research focused on improving treatment or finding a cure for type 1 diabetes.