Externally applied compression therapy for Fontan patients

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Background: Limited therapeutic options are available for Fontan patients with dysfunctional or failing single ventricle physiology. This study describes the evaluation of an alternative, non-invasive, at-home therapeutic compression treatment for Fontan patients. Our hypothesis is that routinely administered, externally applied compression treatments to the lower extremities will augment systemic venous return, improve ventricular preload, and thus enhance cardiac output in Fontan patients.

Methods: To initially evaluate this hypothesis, we employed the NormaTec pneumatic compression device (PCD) in a pilot clinical study (n=2). This device is composed of inflatable trouser compartments that facilitate circumferentially and uniformly applied pressure to a patient's lower extremities. Following an initial health screening, test subjects were pre-evaluated with a modified-Bruce treadmill exercise stress test, and baseline data on cardiorespiratory health was collected. After training, test subjects conducted 6 days of external compression therapy at-home. Subjects were then re-evaluated with a final treadmill stress test and data acquisition of new cardiorespiratory parameters.

Results: Both subjects demonstrated improvement in exercise duration time, peak oxygen volume, and ventilator threshold, as compared to the baseline evaluation.

Conclusions: These findings are promising and provide the foundation for future studies that will focus on increasing study participation (sample size) to better assess the clinical benefit of compression therapy for Fontan patients.

Keywords: Enhanced external counterpulsation (EECP); single ventricle physiology; congenital heart disease (CHD)

Introduction

Pediatric and adult patients having single ventricle physiology are a small subset of patients with complex cardiac defects and congenital heart disease (CHD) (1). The current treatment paradigm for these patients involves a set of staged surgical cardiac procedures. These surgeries result in the creation of a Fontan physiology where the right side of the heart is bypassed and the single functioning ventricle draws and drives blood flow through the systemic and pulmonary circulations, respectively (*Figure 1*). These patients live with a compromised circulatory system and can develop late stage pathophysiology in the months and years after the Fontan operation, generally leading to a decompensation to congestive heart failure (CHF) (1,3). Significant progress in pharmacologic and novel surgical
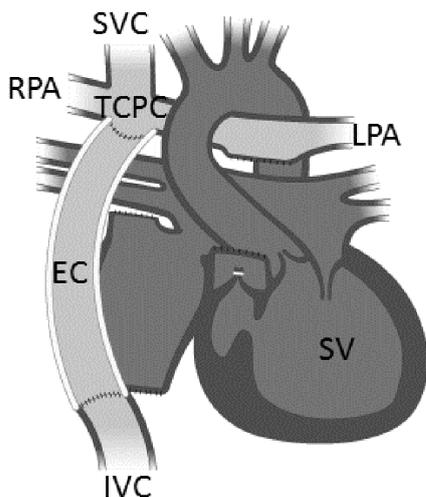
Figure 1 Single ventricle Fontan physiology (2). SV, single ventricle; RPA, right pulmonary artery; LPA, left pulmonary artery; TCPC, total cavopulmonary connection; EC, extra-cardiac; IVC, inferior vena cava; SVC, superior vena cava.
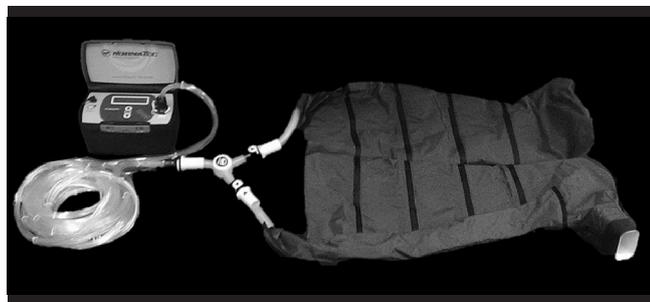
Figure 2 NormaTec pneumatic compression device (PCD).

treatments has occurred over the years. However, new therapeutic options are needed since heart transplantation is a limited option due to donor numbers, pre-existing antibodies due to prior blood product exposure, and the waiting period (4,5).

There is growing interest in the use of mechanical circulatory assistance for Fontan patients (6). By introducing a pressure boost to the pulmonary circulation analogous to the native right ventricle, it is conceivable that the deleterious complications of the Fontan palliation might be reversed, and the circulation might revert to more normal physiologic levels (7,8). Although mechanical circulatory support devices have been shown to mitigate the failing Fontan physiology prior to heart transplantation, current research indicates device success as only a short term

bridge-to-transplant therapy, not for use over an extended period of time (9-11). Additionally, these devices require an invasive, open-heart procedure for implementation, and no clinically available device to-date has been designed to specifically augment the unique circulatory demands of a Fontan physiology. Although cavopulmonary assist devices are currently under development, all are far from reaching clinical use (4,12).

To address this unmet clinical need, we are investigating the feasibility of a non-invasive, at-home therapy to improve hemodynamic circulation and quality of life for these patients. Our hypothesis is that regularly applied, external compression therapy will augment systemic blood flow to the pulmonary arteries and improve cardiac output. The purpose of this research study is to evaluate the effectiveness of applying external pressure to the patient's legs using a NormaTec pneumatic compression device (PCD) (NormaTec, Inc. Newton Center, MA, USA) and to compare at-home therapeutic findings to an exercise study. We measured how externally applied pressure over a 1-week time-period may improve cardiovascular health. This study involved three stages, which included an initial evaluation, at-home compression treatment using the NormaTec device for one week, and then a post-treatment treadmill test.

Methods

NormaTec pneumatic compression trousers

The NormaTec PCD (NormaTec, Inc.) has received U.S. Food and Drug Administration 510(k) clearance (PMA #013436) for use to treat patients having venous insufficiency, which Fontan patients exhibit as they decompensate to CHF. *Figure 2* illustrates this device as composed of inflatable trouser compartments that facilitate circumferentially and uniformly applied pressure to a patient's lower extremities. A controller is easily programmed to a target externally applied pressure level and to a rate of inflation and deflation of the trouser compartments, facilitating improved venous return, as displayed in *Figure 3*. Other programmable parameters include the duration of compression cycles and rest periods before compression cycles. The trousers have 5 separate compartments in which compression is initiated in the feet (i.e., compartment 1) and ends at the top of the thighs. For subjects with an inseam measurement less than 30 inches, only the lower 4 of the 5 compartments are required for successful compression treatment.

Compression study methods

The Institutional Review Board (HM# 13521) at Virginia Commonwealth University (VCU) reviewed and approved of this pilot clinical study. *Figure 4* describes the clinical study methods and timeline of events with respect to the compression therapy as well as pre-study and post-study cardiorespiratory measurements. Two study subjects (n=2) were identified by pediatric cardiologists at the VCU Medical Center for enrollment (*Table 1*). Following an initial health screening, neither of the subjects met any of the exclusion criteria. After receiving informed consent, the test subjects were pre-evaluated with a treadmill exercise stress test based on a modified-Bruce protocol, and relevant cardiorespiratory baseline data was collected. They were then fitted and trained on how to use the NormaTec PCD at-home. The subjects returned to their residences and began their at-home compression treatment for 6 consecutive days.
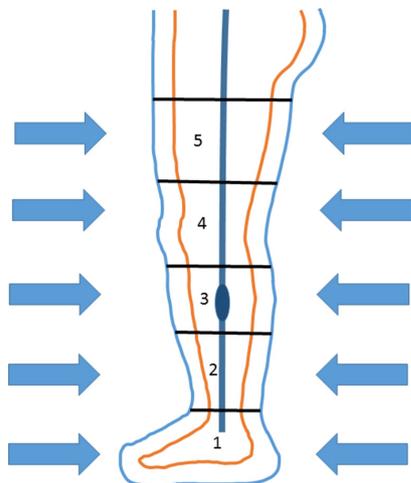
Figure 3 NormaTec PCD action. Initial compression of the feet and ankles results in an upward push of blood volume that is supported by subsequent compartment compressions from 2 to 5. PCD, pneumatic compression device.

Prior to initiation of compression, a baseline blood pressure reading was taken of the subject. The level of external pressure applied during compression was set to a pressure of +15 mmHg above the measured diastolic pressure. Subjects performed the compression treatments daily for 140 minutes on each of the first 4 days at-home and then 280 minutes over the last 2 days at-home based on the discretion of the subject. Full compression cycle time consisted of 30 minutes with a rest period of 5 minutes between each set. Each compression cycle began with inflation of the trouser compartment around the feet and ankles, following inflation of the next compartment and deflation of prior compartment in order to move blood volume back toward the heart; compression rates from lowest compartment 1 to 4 took approximately 165 seconds. Four compression cycles were completed to constitute a day of treatment. A member of the study team was present to assist with the compression treatments each day. On day 7, after the last at-home compression treatment, the subjects returned to the VCU Medical Center for a post-study evaluation, which involved a second treadmill exercise stress test and collection of another set of relevant cardiorespiratory data for comparison to the pre-study levels.

Results

Data from two test subjects are displayed in *Table 2*. Both subjects demonstrated the following: (I) an improvement in exercise duration time, peak oxygen volume, and ventilation threshold; (II) an ability to exercise to exhaustion without adverse events; and (III) a 10% improvement their total exercise duration time based on a peak respiratory exchange rate (RER peak) ≥1.0 as indicative of maximal performance. During the graded stress test, oxygen consumption was measured to increase linearly as exercise intensity increased. In general, total aerobic capacity (VO_2 peak) was achieved at a lower level than normally found in a healthy subject with a biventricular circulation. No cardiopulmonary or vascular

At-home compression therapy

Patient selection	pre-Eval	140 minutes	140 minutes	140 minutes	140 minutes	280 minutes	280 minutes	Post-Eval
Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
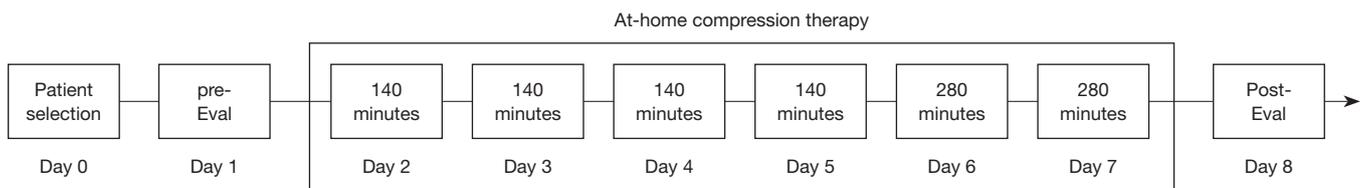
Figure 4 Clinical study timeline of events.

Table 1 Characteristics of study subjects

Characteristics	Subject #1	Subject #2
Gender	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 (LT) TCPC	Extracardiac conduit (ECC) TCPC
Age at Fontan procedure (months)	46	52

TCPC, total cavopulmonary connection.

Table 2 Cardiopulmonary exercise test results for study subjects

Parameter	Subject #1			Subject #2		
	Pre-	Post-	% change	Pre-	Post-	% change
Exercise duration (s)	690	760	10.1	670	730	9.0
Heart rate (BPM) @ Rest	70	71	1.4	60	67	11.7
Heart rate (BPM) @ Max	147	153	4.1	67	108	61.2
MAP (mmHg) @ Rest	112.0	96.0	14.3	90.3	94.7	4.8
MAP (mmHg) @ 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

MAP, mean arterial pressure; VO_2 peak, peak oxygen consumption; VE peak, peak minute ventilation; VCO_2, CO_2 production; RER peak, peak respiratory exchange rate; VT, ventilatory threshold; VT/VO_2, ventilatory threshold versus oxygen consumption; VE/VCO_2, ventilation versus CO_2 elimination; VT/VCO_2, ventilatory threshold versus O_2 consumption; OUES, oxygen uptake efficiency slope; BPM, beat per minute.

complications were noted by either subject. Neither subject complained of a headache that could have been contributed by retrograde blood flow into the SVC. Also, neither subject complained of any discomfort during the study.

In consideration of the first subject, *Figure 5* illustrates the RER as a function of time for the pre- and post-compression treatment stress test. As seen in *Figure 5*, the RER peak for the first subject occurred slightly after the exercise phase. A positive impact from the compression treatment was measured due to the significant improvement in aerobic capacity (47%), as shown in *Figure 6*. Since the RER peak was not reached until after the exercise phase, it was difficult to discern if this measured improvement is due primarily to increased exercise duration or the 6-day long compression treatment.

The second subject was able to achieve maximal exercise levels during the stress test. The RER peak occurred at 8 minutes and 20 seconds during the pre-treatment test
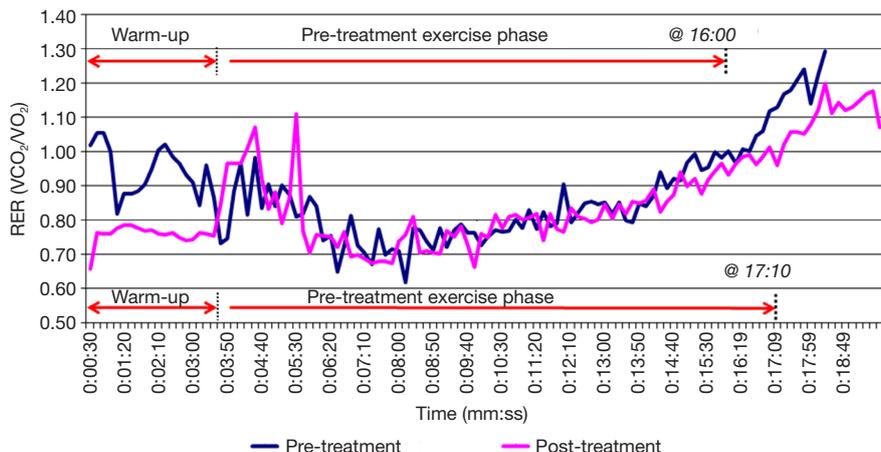
Figure 5 RER (VCO_2/VO_2) *vs.* time (mm:ss) subject #1 (pre- and post-treatment stress test). RER, respiratory exchange rate.
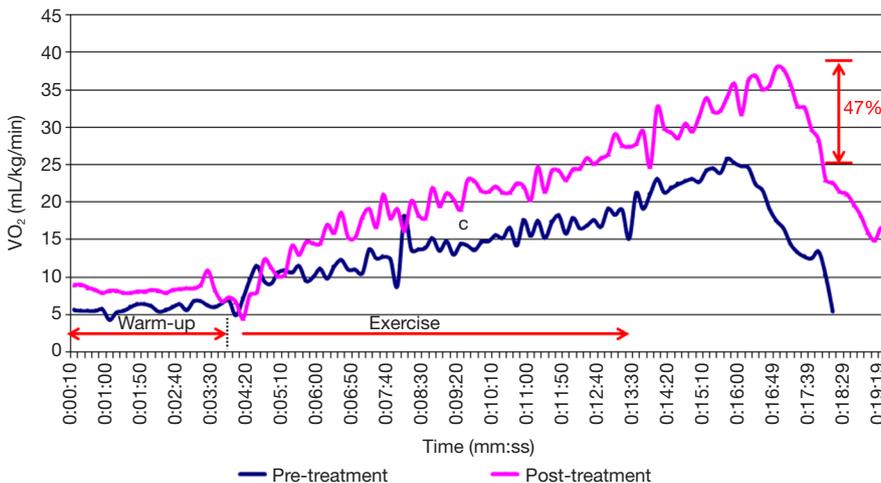
Figure 6 VO_2 (mL/kg/min) *vs.* time (mm:ss) subject #1 (pre- and post-treatment stress test).

(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). A modest improvement in VO_2 peak occurred for the second subject, increasing capacity by 13.9%, as shown in *Figure* 7.

Ventilatory threshold (VT) 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 measured VT noninvasively by analyzing the continuous measurements of ventilatory and gas exchange variables during the stress test. Since peak respiratory exchange rate was only reached after the exercise test for the first subject, it is a not a reliable indication of improved exercise capacity for this

subject. The second subject was able to achieve maximal exercise levels during testing, and thus the maximal exercise parameters were included in the analysis of the second subject. Although the heart rate response was blunted, positive trends in the ventilation threshold data were observed.

Ventilatory equivalent ratios were measured to assess if the subjects reached their anaerobic threshold later after going through the treatment regimen. Here we investigated 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
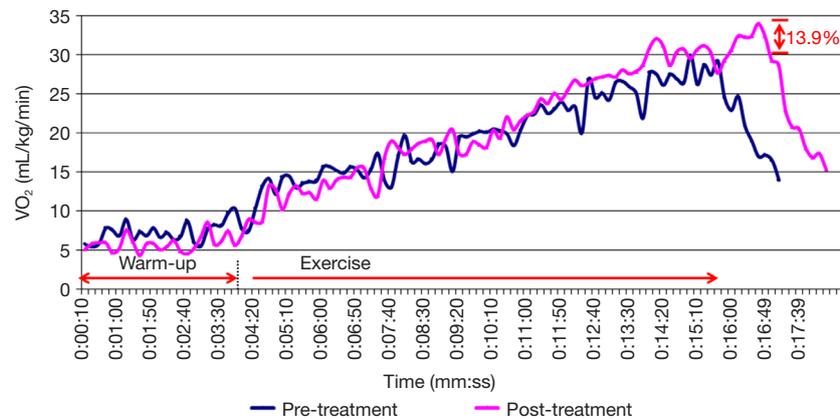
Figure 7 VO_2 (mL/kg/min) *vs.* time (mm:ss) subject #2 (pre- and post-treatment stress test).

week, the subjects were able to reach their aerobic capacity later, around 8 minutes and 50 seconds, improving their time by 8%. The subjects increased the VO_2 at which VT occurred by 3.7 mL/kg/min. The first subject demonstrated a modest improvement in VE/VCO_2 slope of 9.8%. The second subject had an increase of VE/VCO_2 slope after the compression therapy of 16%.

Post-treatment, both subjects were found to achieve more efficient oxygen consumption as indicated by a steeper slope in the oxygen uptake efficiency slope (OUES). OUES measurements were started at 90 seconds until 90% of the test phase had been reached (13). The first subject experience an increase in OUES of approximately 32%, and the second subject showed an increase as well, although to a lesser degree (7.2%).

Discussion

The absence of the right ventricle as a preloader for the systemic circulation leads to a reduced pulmonary blood volume being driven through the lungs to the left atrium. This condition leads to chronically elevated central venous pressure, which is a hallmark of the Fontan physiology and contributes to limited systemic venous return, liver congestion and cardiac arrhythmias (14,15). Following the Fontan surgery, single ventricle patients have a lower exercise capacity and tolerance than individuals with two ventricles. At rest, these patients will have normal or slightly subnormal levels of cardiac index, stroke index, and systolic blood pressure as compared to healthy subjects. However, during dynamic exercise, notable differences are observed, showing that these patients are unable to adequately

respond to exercise.

Beyond adolescence, exercise tolerance continues to fall at a rate of about 2.6% per year. It is well known that during intense exercise Fontan patients reach exhaustion much faster than their healthy counterparts with a biventricular circulation. Respiratory and ventilation rates are known to spike as they exhale more CO2 and reach anaerobic metabolism much faster. This effect is primarily driven by a low cardiac output response during intense exercise resulting in a lower VO_2 max among Fontan patients. They have a limited ability to increase stroke volume with exercise, due to impaired ventricular function and an inability to increase ventricular preload exercise (16). Cardiac Index has been measured to be 22% lower in Fontan patients than those with healthy biventricular circulations (14); in consideration of older adults with Fontan physiology, clinical reports indicate myocardial dysfunction and Grade II failure in approximately 70% of patients (15). As Fontan patients age, the single ventricle becomes dilated, hypertrophic, and hypocontractile, resulting in systolic and diastolic dysfunction. When exercise capacity crosses a threshold of about 45% of predicted, as typically occurs in the third decade of life, hospitalization rates and symptoms increase significantly.

Given the known studies on limited exercise tolerance of Fontan patients and clinical experience in the evaluation and treatment of Fontan patients, we sought to evaluate the benefit of at-home compression treatments on the cardiorespiratory function and capacity of Fontan patients. By introducing a pressure boost to the pulmonary circulation similar to the native right ventricle, it is conceivable that the deleterious complications of the Fontan

palliation might be reversed. We hypothesize that regularly applied external compression therapy will enhance systemic venous return to the pulmonary arteries and improve left atrial return volume. This study demonstrated an improvement in exercise capacity after compression therapy in two subjects. There are, however, several limitations of this pilot study. For a compelling case of improvement to be made, additional study subjects are required, and an appropriate statistical evaluation of the pre-treatment and post-treatment measurements are needed with sufficient power.

There is an inherent bias in the exercise protocol that seems to favor subject experience with the equipment. It is known that the majority of test subjects tend to perform better the second time on the treadmill. The first study subject did not reach the RER peak of greater than 1.0 during the treadmill study, which means that it is unreliable to use the change in VO_2 peak as an indication of increased exercise capacity. This result has been observed in other external compression studies and exercise studies, including Fontan patients. Feldman *et al.* (17) showed in a 6 month follow up that subjects who received a treatment regimen of 35 1-hour sessions over a period of 7–8 weeks using enhanced external counterpulsation (EECP) technology were able to improve their exercise time, although peak VO_2 did not improve with therapy. Both Bossers *et al.* (13) and Akkerman *et al.* (18) report that finding VO_2 Max is limited to healthy adult subjects who can actually perform maximally during a graded exercise stress test. Subjects must continually push themselves long enough for VO_2 to reach the plateau in the face of increasing workload. Both studies indicate that in the pediatric population and Fontan patients a true plateau in oxygen uptake is seldom attained. Bossers *et al.* (13) conducted a large multi-center study with 110 Fontan patients and showed that as much as 20% of the subjects were not able to reach a maximal exercise state (RER ≥1.00), and thus sub-maximal exercise parameters were used in the evaluation (e.g., VE/VCO_2 slope and OUES slope).

Although the second subject was able to perform at a sufficient level of effort, as indicated by RER peak, there was still no clear plateau of VO_2, thus no conclusion can be drawn for certain that a true VO_2 max level was reached. Hence, it was essential to analyze sub-maximal exercise parameters, which included VE/VCO_2 slope, VT, and OUES. 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. Larger studies have shown an average VE/VCO_2 slope for Fontan patients to be around approximately 127% greater than their healthy counterparts (13). This observation is in agreement with the results seen in this OUES analysis, and these two subjects seem to be relatively healthy Fontan patients. As measured, an elevated slope is expected from CHD patients since an elevated VE/VCO_2 slope is inversely related to cardiac output. In the Fontan population, a diminished pulmonary perfusion also contributes to this elevated slope state. As cardiorespiratory measurements improve with long-term pneumatic compression therapy, a reduction in VE/VCO_2 slope is expected.

VT was also measured noninvasively by analyzing the continuous measurements of ventilatory and gas exchange variables during the stress test. VT for CHD patients occurs closer to VO_2 max/peak than does for healthy subjects; the VT/VO_2 ratios for CHD subjects are higher than healthy subjects (67.6 % *vs.* 44.6%) (19). At rest, these patients have near normal ventilation (9–10 L/min); however, during peak exercise, the minute ventilation rate is significantly less than that of normal subjects (20).

Due to a scheduling conflict, the second subject was not able to perform the post-treatment stress test immediately following the last day of treatment. 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 variation between the two subjects results post treatment. Nevertheless, both subjects showed an improvement in exercise duration time, peak oxygen volume, and ventilation threshold, as compared to the baseline evaluation. These findings are promising and provide the foundation for future studies that will focus on increasing study participation (sample size) to better assess the clinical benefit of compression therapy for Fontan patients.

Conclusions

A consistent attenuation of the chronic venous insufficiency found in the Fontan patients is required to avoid long-term complications, such as liver congestion, cardiac arrhythmias, and other co-morbidities. Limited therapeutic options exist to achieve this attenuation. This study describes the initial evaluation of an alternative, non-invasive, at-home therapeutic option for Fontan patients. Routinely administered, externally applied compression treatments

to the lower extremities is expected to augment systemic venous return, improve ventricular preload, and thus enhance cardiac output in Fontan patients. Two subjects received at-home compression therapy for 6 days for which the cardiovascular benefit was evaluated using an exercise stress test. Both subjects demonstrated an improvement in exercise duration time, peak oxygen volume, and ventilation threshold, as compared to the baseline evaluation. The findings of this study provide the foundation for future studies of at-home external compression therapy for Fontan patients.

Acknowledgements

Footnote

Conflicts of Interest: Joseph Hernandez is now the Director of Research for the Frederick Banting Foundation. The other authors have no conflicts of interest to declare.

Ethical Statement: The Institutional Review Board (HM# 13521) at Virginia Commonwealth University (VCU) reviewed and approved of this pilot clinical study and written informed consent was obtained from all patients.

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