Effect of Carvedilol on Exercise Performance in Fontan Patients

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EFFECT OF CARVEDILOL ON EXERCISE PERFORMANCE IN FONTAN PATIENTS

OVERVIEW (ABSTRACT)

Until the late 20th century patients with a diagnosis of a functional single ventricle (SV) circulation was uniformly fatal. The development of staged surgical palliation including the initial neonatal procedure, Glenn shunt, and modified Fontan procedure, has dramatically improved survival.[1-3] Despite advances in surgical techniques and medical care, these patients still suffer from lower quality of life, decreased exercise capacity, poorer neurodevelopmental outcomes, need for heart transplantation and other co-morbidities.[4-12] Although patients with SV circulation comprise a small portion of all congenital heart disease, 2-4% of congenital heart disease, they require a great deal of resource utilization.[4,13-15] Improvements in management of this small population will have a large impact on patient and societal costs.

Although carvedilol and other beta-blockers are well-established medications for adults with biventricular ventricular dysfunction, these agents are used less frequently in pediatric patients with heart failure, especially in patients with congenital heart disease. Similar to biventricular heart failure patients, circulating levels of norepinephrine are higher in Fontan patients with few or no signs and symptoms of heart failure compared to age-matched controls.[16] Circulating levels of norepinephrine are associated with poorer outcomes in Fontan patients.[16,17] Increased concentrations of circulating catecholamines are known to have deleterious effects on myocardial function, and blocking of this process reduces mortality in patients with biventricular heart failure. A multicenter randomized trial of carvedilol versus placebo in pediatric heart failure patients with multiple different etiologies including some with SV failed to show an improvement in the primary endpoint of improved functional state.[18] However, a smaller non-blinded study indicated improvement in ventricular function in Fontan patients with carvedilol.[19] Therefore, it is reasonable to hypothesize that beta blockers will improve functional status in Fontan patients. Carvedilol has α1 in addition to β1, β2, receptor–blocking properties making this agent the preferred beta-blocker in patients with

increased systemic vascular resistance. Systemic vascular resistance is increased Fontan patients which may adversely affect function of the single ventricle. [20,21] Therefore, carvedilol may provide more physiologic benefit than other more selective beta blockers.

Potential participants in this study are patients with SV who have undergone Fontan palliation, who are now between the ages of 10 years and 35 years. Participants will initially undergo a screening phase which will include an exercise test to determine if they can adequately perform a maximal exercise test (RER>1.0 at maximal exercise) and safety laboratories. Participants who are able to exercise as described and who have acceptable safety laboratories will be randomly assigned to receive either carvedilol or placebo for the first 12 week treatment period. After a 6 week washout period, all participants will cross over to the other treatment arm for 12 weeks. Exercise data will be collected at baseline and at 12, 19, and 30 weeks after randomization. The primary aim of the study is to compare the effect of carvedilol therapy to that of placebo therapy on exercise performance as measured by peak oxygen consumption per kilogram. Secondary endpoints include the following: peak heart rate during exercise, submaximal exercise capacity, ventilatory efficiency of carbon dioxide, and safety profile of carvedilol in Fontan patients. The total sample size target of 30 participants will be recruited over approximately 24 months.

There is a lack of controlled clinical trials that have systematically investigated whether carvedilol will benefit Fontan patients. The results of this study will provide preliminary efficacy data for carvedilol in Fontan patients and inform the design and sample size calculations necessary for a large multicenter trial.

A. SPECIFIC AIMS

There is an unmet need for a better understanding of the effects of traditional heart failure medications in patients with Fontan circulation. It is now standard practice in developed nations for patients with a functional single ventricle (SV) circulation to undergo a three-stage surgical palliation. Survival to stage III palliation, the Fontan procedure, has greatly improved in recent decades.[5] Despite complete physiologic palliation, Fontan subjects suffer from lower exercise capacity than their peers and have a poorer quality of life.[6,8] The emphasis of SV care has evolved from preventing mortality to improving quality of life. The utility of traditional heart failure medications the SV population is not completely understood. Exercise testing is a frequently used measure of cardiovascular health, as it allows insight into cardiac and pulmonary responses to exercise and is a robust tool for predicting poorer cardiovascular outcomes in heart failure, including patients with Fontan circulation. The specific aims of this research are as follows.

Primary Aim 1: To compare the effect of carvedilol to that of placebo on peak exercise capacity.

Rationale: Peak exercise capacity is directly related to cardiovascular health and has been shown to be predictive of outcomes in patients with cardiovascular disease.

Primary and Secondary Measures: Peak volume of oxygen consumption indexed to patient weight (peak VO_2) is the primary outcome measure. Secondary measures will include maximum watts performed, respiratory exchange ratio at peak exercise.

Hypothesis: Carvedilol will increase peak exercise capacity.

Secondary Aim 1: To compare the effect of carvedilol to that of placebo on chronotropy.

Rationale: Beta-blockers are sometimes avoided in Fontan patients because of a theoretical concern of worsening chronotropic incompetence. However, this has never been studied systematically.

Measures: Primary outcome measure is peak heart rate during exercise. Secondary measures will be heart rate reserve (heart rate at peak exercise minus baseline heart rate) and chronotropy reserve (peak heart rate minus baseline heart rate divided by the difference of predicted peak heart rate and baseline heart rate).

Hypothesis: Carvedilol will decrease peak heart rate

Secondary Aim 2: To compare the effect of carvedilol to that of placebo on submaximal exercise capacity

Rationale: Submaximal exercise capacity is directly related to cardiovascular health and has been shown to be prognostic of outcomes in cardiovascular disease.

Measures: Primary outcome measure will be the volume of oxygen consumption at anaerobic threshold indexed to patient weight. Secondary measures will include watts and respiratory exchange ratio at anaerobic threshold.

Hypothesis: Carvedilol will increase volume of oxygen consumption at anaerobic threshold.

Secondary Aim 3: To compare the effect of carvedilol to that of placebo on ventilatory efficiency of carbon dioxide.

Rationale: The ventilatory efficiency of carbon dioxide has prognostic value in patients with heart failure.

Measures: Primary measures will be ventilatory equivalent of carbon dioxide at anaerobic threshold (VE/VCO_2 at anaerobic threshold). Secondary measure will be slope of minute ventilation to volume of carbon dioxide production (VE/VCO_2 slope).

Hypothesis: Carvedilol will improve ventricular mechanics and therefore decrease ventilatory efficiency of carbon dioxide.

Secondary Aim 4: To evaluate the safety of carvedilol in Fontan patients over an intermediate time period.

Rationale: Limited data are available regarding the safety profile of carvedilol in the Fontan population has not been previously described.

Measures: Laboratory data and the number of serious adverse events and adverse events reported during the two different treatment periods (carvedilol v. placebo).
Hypothesis: Carvedilol will have a similar side effect profile compared to placebo.

B. BACKGROUND

B.1 Management and Outcomes of Single Ventricle Patients

B.1.1 Surgical Palliation of Single Ventricle Patients.

A multitude of different congenital anatomical cardiac defects can result in single ventricle physiology. The most common and well known is hypoplastic left heart syndrome, but others include double-inlet left ventricle, unbalanced atrioventricular canal, and tricuspid atresia. Currently the management of these patients involves a three step staged surgical palliation. No anatomically corrective procedure other than heart transplantation exists for this population.

Although the type of 1st stage palliation varies based upon anatomy, subsequent surgeries focus on creating surgical anastomoses enabling passive flow of systemic venous blood to the pulmonary circulation so that the functional SV pumps only to the systemic circulation. The third stage of palliation (modified Fontan procedure) typically is done between age 18 months to 6 years depending on institutional preference and patient characteristics. The Fontan procedure, connects the inferior vena cava to the pulmonary arteries to create a complete total cavopulmonary anastomosis. The Fontan circulation results in elevated central and peripheral venous pressures, which in turn, leads to an elevated systemic vascular resistance. [21-24]

B.1.2 Complications of Current Single Ventricle Palliation.

Although the Fontan procedure is the goal for palliation for the patient with SV, this abnormal circulation results in multiple unique situations that may deleteriously affect the patient. Fontan patients often develop ventricular dysfunction leading to heart failure symptoms and heart transplantation. Heart transplantation is a possible therapeutic option, however, patients with previous single ventricle palliation are at higher risk for complications (death, rejection and infection) after transplantation than patients with a biventricular circulation.[9] Even without important signs or symptoms of heart failure, Fontan patients' quality of life is lower than their peers, evidenced by decreased

exercise capacity, lower neurodevelopmental quotients, and lower rates of medical insurance coverage.[6-8,25-27]

Exercise performance is decreased in Fontan patients when compared to patients with a biventricular circulation.[11,13] It has been hypothesized this is related to the inability to increase ventricular filling during exercise, however, the exact mechanism is not known.[10] It is possible that only having passive blood flow to the pulmonary arteries, with no pulmonary pumping chamber, leads to a situation where the Fontan circulation cannot sufficiently augment ventricular filling to the systemic ventricle during exercise. However, chronically increased systemic vascular resistance likely contributes to impaired exercise capacity. Additionally, it has been well described that Fontan patients suffer from chronotropic incompetence.[28] The degree of chronotropic incompetence has been associated with mortality in this population.[29]

Although carvedilol and other beta-blockers are well-established medications for adults with biventricular ventricular dysfunction, these agents are used less frequently in pediatric patients with heart failure, especially in patients with congenital heart disease. Similar to biventricular heart failure patients, circulating levels of norepinephrine are higher in Fontan patients with no or few signs and symptoms of heart failure compared to age-matched controls.[16] Circulating levels of norepinephrine are associated with poorer outcomes in Fontan patients.[16,17] Increased concentrations of circulating catecholamines are known to have deleterious effects on myocardial function, and blocking of this process reduces mortality in patients with biventricular heart failure. A multicenter randomized trial of carvedilol versus placebo in pediatric heart failure patients with multiple different etiologies including some with SV failed to show an improvement in the primary endpoint of improved functional state.[18] However, a smaller non-blinded study indicated improvement in ventricular function in Fontan patients with carvedilol.[19] Therefore, it reasonable to hypothesize that beta blockers will improve functional status in Fontan patients. Carvedilol has α1 in addition to β1, β2, receptor–blocking properties making this agent the preferred beta-blocker in patients with increased systemic vascular resistance. Systemic vascular resistance is increased in

Fontan patients which may adversely affect function of the single ventricle. [20,21] Therefore, carvedilol may provide more physiologic benefit than other more selective beta blockers.

B.1.3 Animal Models of Single Ventricle Heart Disease

There are no animal models of SV and therefore preliminary data for this population using such models is not available. Therefore, this highly vulnerable population is not significantly studied.

B.1.4 Carvedilol treatment of patients with SV

Carvedilol has proven safe and effective for the treatment of congestive heart failure and hypertension in adults. A study by Albers et al. showed that carvedilol pharmacokinetics in adolescents was similar to that of adults.[30]. Ishibashi and colleagues described using carvedilol in patients with SV with an age range of 1 month to 35 years (mean 10 years). The average maximum dose of carvedilol was 0.42mg/kg ± 0.29. In this study, only one patient out of 51 discontinued carvedilol because of an adverse side effect.[19]

B.2 Rationale for this Trial

Despite the major advances that have been made in the medical and surgical management of SV, morbidity and early mortality persist. Moreover, medical therapies often used in patients with Fontan without good data regarding safety and efficacy in this population. Existing medical therapies are used because they have been shown to be effective in other patient populations. Furthermore, we are only beginning to appreciate the "new" natural history of Fontan patients who are now surviving into young adulthood. There is emerging knowledge that these patients show a chronic inability to provide adequate preload the systemic ventricle, significantly lowered maximal heart rates and chronically elevated systemic vascular resistance, combined with elevated levels of catecholamines and activation of the renin-angiotensin system. Therefore, this study aims to systematically study the effects of a commonly available and often used medication in patients with Fontan physiology.

B.3 Rationale for Selection of Outcome Measures

B.3.1 Peak Oxygen Consumption per Kilogram

Exercise testing with metabolic cart analysis has been proven one of the best prognostic tests in heart failure and pulmonary hypertension, often superior to other traditional cardiovascular tests.[31,32] Reports have confirmed that prognostic capability of exercise testing with metabolic cart applies to Fontan population.[29,33] Specifically, peak oxygen uptake per kilogram has been shown to be associated with significant outcomes in Fontan patients.[33] Also, normative equations for predicted peak oxygen uptake have been developed and validated.[34]

B.3.2 Effect of Carvedilol on Chronotropy

Carvedilol is a beta blocker and therefore reduces the augmentation of heart rate as a result to released circulating catecholamines concentrations. Peak heart rate during exercise is associated with outcomes in patients with CHD.[35] Therefore, congenital heart disease cardiologists are concerned about starting beta blockers in the SV population. However, the chronotropic incompetence seen in SVs is similar to the chronotropic incompetence seen in adults with heart failure. In that population, the discontinuing carvedilol was not associated with improvements in chronotropic competence.[36] Therefore, it is possible that carvedilol will not have a negative impact on chronotropic incompetence which would eliminate a significant barrier to its use in the SV population.

B.3.3 Submaximal Exercise

Submaximal exercise is measured by the oxygen uptake at anaerobic threshold. Anaerobic threshold is the point where carbon dioxide production increases at a rate faster than oxygen consumption indicating the point in which a patient begins to produce measurable amounts of lactic acid. This time point in exercise testing may reflect more usual activities of daily living and has been associated with outcomes in the Fontan population.[35]

B.3.4 Ventilatory Efficiency of Carbon Dioxide

The ventilatory efficiency of carbon dioxide has been shown to have a prognostic value in adult heart failure, independent of other exercise testing variables. [37] The ventilatory efficiency of carbon dioxide is measured by the ratio of minute ventilation of to carbon dioxide production at anaerobic threshold. Ventilatory efficiency of carbon dioxide is also measured by calculating the slope of the regression line created by plotting minute ventilation to carbon dioxide production throughout the exercise test. In a recent study, the ventilatory efficiency of carbon dioxide was associated with unscheduled hospitalization and mortality in Fontan patients.[38]

B.3.5 Safety Profile of carvedilol

Carvedilol is a commonly used medication in heart failure. Due to efficacy studies in different populations, cardiologists often use carvedilol in the Fontan population. However, there is a lack of data regarding the safety profile of carvedilol specific to the Fontan population. Adverse events will be recorded. While hepatic and renal dysfunction are rare adverse events (<1%) of carvedilol, they are of severe consequence in the Fontan population. Possible hepatic or renal dysfunction associated with carvedilol in Fontan patients has not been previously described. Therefore a comprehensive metabolic panel will be monitored throughout the study. B-type natriuretic peptide (BNP) is a seromarker of heart failure that is associated with important outcomes in the Fontan population. Therefore, BNP will be measured during the study to assess the effect carvedilol has on serum BNP in Fontan patients.

B.4 Rationale for Study Drug

Carvedilol is a well studied non-selective beta blocker with alpha-1 blocker activity as well. In adult heart failure trials it has been proven superior to other form of beta-blockers in preventing mortality and hospitalizations. Given it's superiority in treating heart failure, carvedilol was chosen as the beta blocker for this study.

B.5 Rationale for Screening Laboratories

B.5.1 B-type natriuretic peptide (BNP)

BNP is a seromarker made in response to ventricular or atrial myocardial stretch. It is a well-studied seromarker shown to be associated with heart failure in multiple different populations. Decreases in BNP have been associated with improved outcomes in the SV population.[40] A BNP >300pg/mL has been associated with a significant increase in chances of needing heart transplant, heart failure admission or death.[44] BNP will be used in the screening phase to determine eligibility for randomization as outlined below.

B.5.2 Complete Blood Count (CBC)

CBC will be obtained to measure hematocrit and hemoglobin. Significant anemia (hemoglobin <7gm/dL) or polycythemia (hemoglobin >18gm/dL) affects oxygen consumption during the exercise test. Therefore significantly abnormal hemoglobin (>18gm/dL or <7gm/dL) will introduce significant bias in the results. Therefore,, anemia (hemoglobin <7gm/dL) and polycythemia (hemoglobin >18gm/dL) is an exclusion criteria as later outlined reduce confounding factors in comparisons of oxygen consumptions.

B.5.3 Comprehensive Metabolic Panel (CMP)

CMP will give the study investigators valuable information. Serum albumin will be used to assess if patients meet exclusion criteria #17 (serum albumin <2.0g/dL). AST/ALT will be used to assess for the presence of hepatic dysfunction as described in exclusion criteria #8. Serum creatinine will be used to assess for renal dysfunction (creatinine >2.0mg/dL) as later outlined, and is an exclusion criteria (#7).

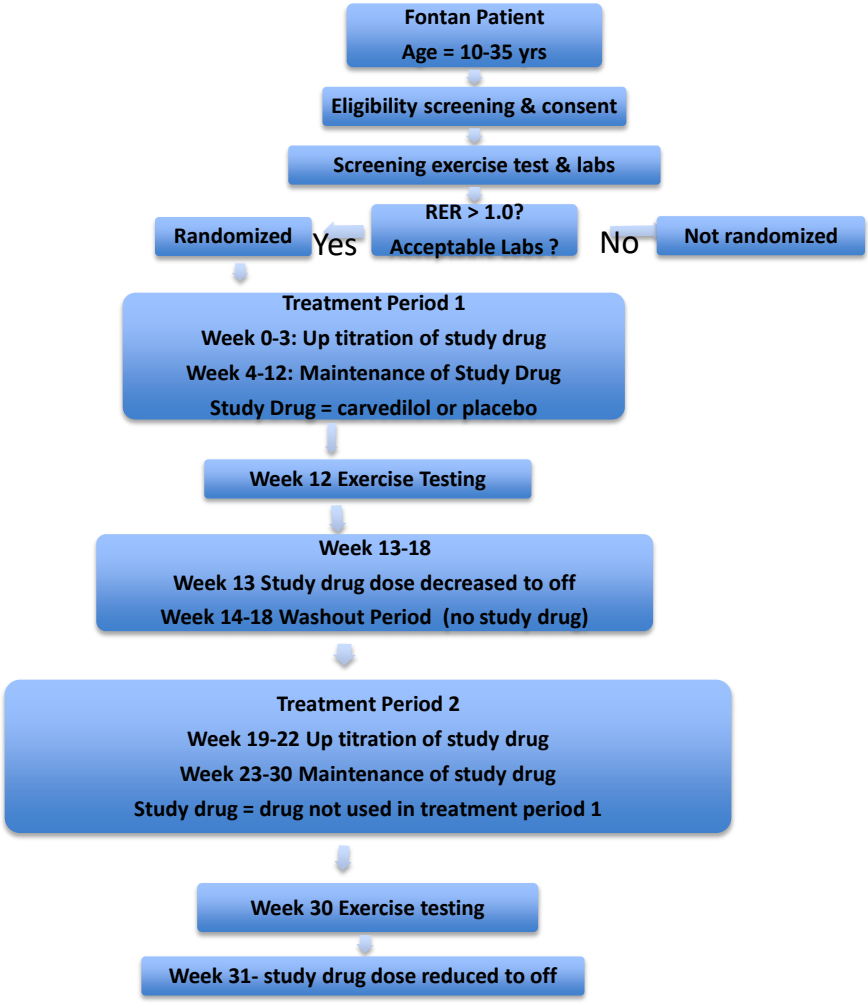
B.5.4 Pregnancy Test

Carvedilol is classified as pregnancy class C. Rat models have shown increased chance of skeletal developmental delay. However, this occurred only when rats were given 50 times the current recommended dose. There are currently no adequate studies assessing safety during pregnancy and therefore pregnant patients will be excluded.

C. STUDY DESIGN AND METHODS

C.1 Overview

A randomized crossover trial of carvedilol vs. placebo in individuals with single ventricle physiology who have undergone a Fontan procedure **(Figure. 1)**.



C.2 Human Subjects Considerations

This section includes information on the human subjects aspects of the research design and methods.

C.2.1 Human Subjects Involvement and Characteristics

Children and young adults will be enrolled for this trial from among patients followed by cardiologists at UT Southwestern Medical Center or local pediatric cardiologists in Dallas who have a Fontan circulation.

C.2.1.a Inclusion Criteria Screening Phase

To be eligible for this trial the subjects must meet all of the following inclusion criteria at the time of enrollment:

1) Informed consent of parent(s) or legal guardian; informed consent or assent of subject as applicable.
2) Male or female children between the ages of 10 and 35 years with congenital heart disease that has been palliated with a Fontan circulation.

C.2.1.b Inclusion Criteria Treatment Phase

To proceed to randomization and treatment phase of the trial the subjects must meet the following criteria after the screening phase:

1) Ability of perform a maximal exercise test as defined by a respiratory exchange ratio (RER) greater than 1.0 at the time of maximal exercise

C.2.1.c Exclusion Criteria Screening Phase

To be eligible for this trial, the subjects must meet none of the following exclusion criteria at the time of enrollment:

1) The use of beta blockers within 2 months of randomization
2) Patients actively listed for transplantation at time of entry into the study or anticipated to undergo heart transplantation, interventional catheterization, or corrective cardiac surgery during the 7 months following entry into the study
3) Sustained or symptomatic ventricular dysrhythmias uncontrolled by drug therapy or the use of an implantable defibrillator, and/or significant cardiac conduction defects, e.g., 2nd degree or 3rd degree AV block, or sick sinus syndrome, unless a functioning pacemaker is in place

4) Uncorrected obstructive or severe regurgitant valve disease, nondilated cardiomyopathy, or significant systemic ventricular outflow obstruction
5) Known renovascular hypertension or evidence of pulmonary hypertension (pulmonary vascular resistance > 6 Wood units) unresponsive to vasodilator agents such as oxygen, nitroprusside, or nitric oxide
6) History or current clinical evidence of moderate-to-severe fixed obstructive pulmonary disease or severe reactive airway diseases (e.g., asthma) requiring hospitalization within the past 2 years or patient currently using long-term inhaled bronchodilators
7) Renal, hepatic, gastrointestinal, or biliary disorder that could impair absorption, metabolism or excretion of orally administered medication
8) Concurrent terminal illness or other severe disease (e.g., active neoplasm) or other significant laboratory value(s) which, in the opinion of the investigator, could preclude participation or survival
9) Endocrine disorders such as primary aldosteronism, pheochromocytoma, hyper- or hypothyroidism, insulin-dependent diabetes mellitus
10) Unwillingness or inability to cooperate, or for the parents or guardians to give consent, or for the child to give assent, or any condition of sufficient severity to impair cooperation in the study
11) Pregnancy or possible pregnancy at time of randomization, or female of child bearing potential who are lactating, or sexually active and not taking adequate contraceptive precautions (e.g., intrauterine device or oral contraceptives for 3 months prior to entry into the study)
12) Use of an investigational drug within 30 days of randomization, or within 5 half-lives of the investigational drug (the longer period will apply)
13) History of drug sensitivity or allergic reaction to 〈-blockers or ß-blockers
14) Use of any of the following medications within two weeks of randomization: MAO inhibitors, Calcium channel blockers, alpha

blockers, beta blockers, disopyramide, flecainide, encainide, moricizine, propafenone, sotalol, or beta adrenergic agonists

15) Hospital admission for protein losing enteropathy or plastic bronchitis within 3 months of randomization
16) Active and/or chronic protein losing enteropathy or plastic bronchitis (on inhaled medication to control the plastic bronchitis).

C.2.1.d Exclusion Criteria Treatment Phase

To proceed to randomization and treatment phase of the trial the subjects must meet none of the following criteria after the screening phase:

1) Hypoalbuminemia defined as serum albumin <2.0g/dL
2) Renal dysfunction defined as serum creatinine >2.0mg/dL
3) Hepatic dysfunction defined as serum AST and/or ALT> 3 times upper limit of normal (approximately 120 IU/L however, will vary depending on age),
4) Significant anemia or polycythemia defined as hemoglobin >18gm/dL or hemoglobin <7gm/dL
5) Severely elevated serum BNP defined as BNP>300pg/ml

C.2.1.e Subject Availability

The estimated number of patients who meet trial eligibility criteria is approximately 150. Fontan patients are seen on an annual basis. Therefore, assuming a consent rate of 20%, the required 30 subjects can be enrolled within the two year timeframe.

C.3. Recruitment and Eligibility Phases

The Principal Investigator or designee at Children's Medical Center and the study coordinator will be responsible for case finding and subject recruitment.

For patients who meet inclusion criteria for the eligibility phase, the patient's cardiologist will be approached. Then potential study participants (if over 18 years of age) or the parent(s) or legal guardian of potential participants, will be approached about participation. At this time, a final determination about eligibility for the screening phase

of the study will be made, and eligible patients or parents will be asked to participate in the study.

A cardiologist experienced in the treatment of patients with Fontan circulation will be involved in obtaining consent. Data (demographic, eligibility criteria and informed consent status) will be recorded on a screening form for all patients with Fontan circulation, regardless of their inclusion in the study, for definition of the study population. The screening data will be obtained and stored in a confidential manner, in compliance with HIPAA requirements and local national regulations.

Each subject enrolled in the trial will be assigned a study identification (ID) number so that study information will be confidential. The link between subject name and ID number will be stored only in an encrypted password protected database at Children's Medical Center and will only be accessible to the PI, study investigators and research coordinators. Data that will be obtained on study participants includes demographic data and family history, information about their past and current medical care, echocardiographic imaging data, and information on adverse drug reactions and adverse events. The stress test data will be interpreted at Children's Medical Center by a study investigator and will contain the patient's name. The consent form will state this clearly. All study procedures are conducted in accordance with local and HIPAA requirements and regulations.

C.3.1. Gender and Minority Inclusion

Based on current rosters of patients with Fontan circulation at Children's Medical Center of Dallas, it is estimated that 50% of patients will be female and 15-35% of the patients will be of minority race/ethnicity. Race, gender and other patient characteristics will not be considered when targeting enrollment.

C.4 Screening Phase

A screening exercise test and safety laboratories will be performed. If the study participant meets inclusion criteria for the treatment phase (RER>1.0 at maximal

exercise test) and does not meet exclusion criteria for the treatment phase (serum albumin <2.0g/dL, hemoglobin <7gm/dL or hemoglobin >18gm/dL, AST and/or ALT > 3 times upper limit of normal, BNP>300pg/ml, or serum creatinine greater than 2.0mg/dL) s/he enter the treatment phase of the study within 14 days from screening testing. Study participation will be terminated for all subjects who do not enter the treatment phase of the study.

C.5 Treatment Phase

C.5.1 Masking of Treatment Group Assignment

The primary endpoint and most of the secondary endpoints will be measured by the study investigator, who will be unaware of each subject's treatment group assignment. Randomization to treatment arm (carvedilol first versus placebo first) will be determined by Children's Medical Center investigational drug pharmacy.

No one else including subjects, their families, and primary care providers will be informed of the subject's treatment assignment.

The Data Safety and Monitoring Board (DSMB) will determine their preference for receipt of blinded or unblinded trial results prior to the interim look. No clinical investigators will review trial outcomes, by arm or in aggregate, until the end of the trial.

C.5.2 Randomization

After eligibility has been confirmed as described above in C.2.1.a-d and the trial consent has been signed, subjects will be randomly assigned in a 1:1 ratio to receive carvedilol or placebo first using randomly permuted blocks. All eligibility criteria must be confirmed, and written informed consent obtained, before randomization. Randomization will be accomplished by Children's Medical Center of Dallas Investigation Drug Pharmacy.

C.5.3 Study Drugs

C.5.3.1 Uptitration Period

After the baseline clinical evaluation, all subjects will be entered into the uptitration period, during which they will receive carvedilol or placebo in addition to their usual medications. The goal of the uptitration period is to reach the effective dose (defined below) that will then be continued throughout the maintenance phase. Based upon the subject's body weight, the pharmacist will determine the appropriate initial dose of carvedilol. Starting doses and the up-titration are shown in Table 1. Dose ranges are provided but actual doses will be rounded up or down according to the available pill sizes (3.125mg increments). Each drug will be administered twice a day, at about the same time of day.

Table 1. Uptitration Schedule (all dose ranges in mg/kg/dose)

Weight Classification		Initial Dose	Uptitration 1	Uptitration 2
20-<30kg	Absolute Dose	1.56 mg	3.125 mg	6.25 mg
	Dose Range	(0.06-0.08)	(0.10-0.16)	(0.20-0.32)
30kg-<40kg	Absolute Dose	3.125 mg	6.25 mg	9.375mg
	Dose Range	(0..08-0.10)	(0.16-0.2)	(0.23-0.31)
40kg-60kg	Absolute Dose	3.125 mg	6.25 mg	12.5 mg
	Dose Range	(0.05-0.08)	(0.10-0.16)	(0.20-0.32)
>40kg	Absolute Dose	6.25 mg	12.5 mg	25 mg

C.5.3.2. Down-titration of Study Drug

During the washout period, after treatment period 2 (Table 5) or if it is necessary for a subject to stop the study drug, the subject should optimally be weaned off the drug as follows. Per manufacturer's guidelines, carvedilol will be down-titrated over one week:

Day 1: 50% of previous dose
Day 3-5: 25 % of regular dose
Day 7-10: Stop drug

In the event of severe clinical instability or inability to take the study drug (i.e., severe vomiting), weaning may need to occur over a shorter period of time, at the discretion of the study physician and care providers. Reinitiation of study drug will be considered

after the PI has consulted with the study participant (or legal guardians) and attending cardiologist.

C.5.3.3 Protocol Deviations in Treatment

All deviations from the above schedules will be noted and described on a study report form. In addition, for all non-study drugs, the dosage, treatment period, and reason for use will be recorded. For modified and interrupted therapy, the length of and reason for the modification/interruption will be recorded. Every attempt will be made to keep protocol deviations and non-protocol treatment to a minimum.

C.5.3.4 Dispensing of Study Drug and Compliance Monitoring

All study drugs (placebo and carvedilol) will be dispensed through the investigational drug pharmacy at Children's Medical Center of Dallas.

Pill Dispensing: The family will receive a medication bottle. Study drug in the form of pills will be dispensed by the pharmacy at visits 1, 2, 3, 4, 7, 8, 9, and 10.

Unused study drug will be returned to the pharmacy to monitor compliance. Study drug compliance will be assessed by comparing the expected to the measured number of doses in pill form of study drug returned.

Once measurement the pill count by the pharmacy is complete, the pharmacy will destroy the returned study medication according to standard operating procedure.

C.5.3.5 Subject Monitoring

Subjects will be monitored for adverse events at each study visit. If, during the study, the study investigator determines that the subject has developed an adverse reaction, further monitoring will be performed as clinically indicated.

C.5.4 Indications for Permanent Discontinuation of Study Drug

- Intolerance to study drug
- Continued administration of study drug felt to be not indicated by the attending cardiologist or study investigator
- Pregnancy or planned pregnancy
- Other adverse events that require discontinuation of study drug in the judgment of the study investigator

The reason and the circumstances for permanent discontinuation of study drug will be documented. If study drug is permanently discontinued, the subject will continue to be followed and undergo expected tests and measurements through the planned completion date (31 weeks after randomization), unless an indication for withdrawal from trial is met.

C.5.5 Indications for Withdrawal from the Trial

- Subject/guardian refusal to continue in the trial, including refusal of the subject to sign the adult informed consent form upon reaching the age of consent
- Subject failure to return for scheduled appointments

The reason for withdrawal and the circumstances of withdrawal will be documented for all subjects withdrawn from the study.

C.5.6 Trial Completion

Subjects will be considered to have completed the study if they have completed the assessment scheduled for 31 $\pm$ 2 weeks post-randomization. Down-titration of the study drug will be performed as described in C.5.3.2.

C.5.7 Other Treatments/Interventions

Subjects will receive non-study medical care as recommended by their cardiologist and other care providers. The need for additional procedures and all prescription medications will be recorded on study forms

C.6. Potential Risks, Benefits, Adverse Events and Protections

C.6.1. Potential Risks

The possible risks or discomforts to the subjects include those listed below.

1. Treatment with carvedilol may rarely induce adverse drug reactions including symptomatic bradycardia, dizziness, postural hypotension, fatigue, lethargy, mental depression, headache, nausea, diarrhea, sleep disturbances, and asthma exacerbation.
3. Self-limited exercise tests pose very small risks of syncope, arrhythmias, hypotension, emesis, dizziness, leg or other muscle cramping.
4. Risks associated with drawing blood from a vein include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely. Less than 5 ml of blood is needed for the 3 safety laboratories (CBC, CMP, and BMP).
5. Study investigators from UT Southwestern and Children's Health will have access to the medical record for 5 years after each subject completes the study to review the results of follow-up clinical course, surgical intervention, and other relevant studies.

C 6.2 Protection Against Risks

Protection of study subjects is implicit in all studies at UT Southwestern and Children's Medical Center of Dallas, and is achieved through sound study design, patient education, strict adherence to informed consent principles, careful monitoring of subjects, and compliance with International Conference on Harmonisation (ICH) Good Clinical Practices, including HIPAA regulations or local national laws and regulations.

C.6.2.a Informed Consent

Consent will be obtained from the parent(s) or legal guardian and consent or assent, as applicable, will be obtained from the subject. This will be facilitated by IRB-approved study brochures, and information about the trial that will be placed on the clinical trials Web site, www.clinicaltrials.gov. The site study investigators, study coordinators, or assigned designees will obtain consents, documented by the subject, parent(s) or legal

guardian's witnessed signature on an informed consent document that is compliant with HIPAA regulations and local and national laws and regulations. The potential study participant will be informed of possible adverse effects from carvedilol some of which are transient, including: fatigue (20%), bradycardia (9%), hypotension (9%), syncope (3%), dizziness (6%), chest pain (2%), nausea (9%), vomiting (6%), cough (8%), insomnia (3%), headache (8%). If potential subjects or parents decline to participate, their or their child's medical care will not be adversely affected in any way. If they agree to participate, they are free to withdraw from the study at any time. Additionally, subjects who reach the age of consent during their participation in the trial will be re-consented with the adult informed consent form.

C.6.2.b Protection Against Risks

To minimize the potential risks listed in Section C.6.1 the following steps will be taken:

1. The starting doses of carvedilol will be low and will be up-titrated carefully (see Table 1).
2. Subjects with known renal dysfunction will be excluded from the study.
3. Blood draws, to the extent possible, will be performed after the application of a topical anesthetic cream.
4. Serum creatinine, BNP, hemoglobin, hematocrit, AST and ALT will be measured as during the screening phase. Serum creatinine, BNP, AST and ALT will be measured during the treatment phase (Table 5).
5. Pregnancy or a planned pregnancy during the trial are exclusion criteria. A urine pregnancy test will be obtained during the screening phase. A statement regarding the potential risk of one of the study drugs will be given to female subjects of child-bearing potential and to the parents of female subjects less than 18 years of age. They will be asked questions about the subject's sexual activity. In addition, this risk is listed in the consent and the assent. Written documentation of birth control measures will be required for female subjects who are sexually active.
6. The study sponsor will pay for all testing that is not part of routine care.

C.6.3 Potential Benefits of the Proposed Research

The possible benefits of participation in the proposed study to the subject are:

1. The subject's family, primary care provider, and cardiologist will receive extensive information regarding the subject's cardiac status.

C.6.4 Risk/Benefit Ratio

The risk/benefit ratio of the study is favorable. The risk of adverse drug reactions is low, and most are relatively minor in nature and reversible with a decrease in the dose of study drug or cessation of therapy. There is a small risk of privacy being compromised in this study. Subject identities will be coded to insure confidentiality and all data will be stored and communicated according to the code to protect against loss of privacy. There will be some unavoidable inconvenience to subjects and families because of study visits and blood draws. However, subjects and families will be compensated within the limits of the study budget and local IRB guidelines for travel and related expenses for study visits. All study costs not related to standard clinical care will be paid for. Given the anticipated benefits to subjects and others with the Fontan circulation, the risks are reasonable.

C.6.5 Importance of Knowledge to be Gained

Current data are very limited to support or refute the utility of carvedilol in this population. The variable practices in the use of carvedilol in management of SV patients underscore the need for further research. Data collected in the proposed study will provide important information regarding safety profile, as well as efficacy data crucial to the development of multicenter trials of carvedilol in Fontan patients.

C.6.6 Data and Safety Monitoring Plan

Throughout the performance of this study and during the performance of all procedures, subjects will be carefully monitored in accordance with current medical practices. Treatment with carvedilol as proposed in this study has had few if any reported side effects. Based upon the extensive experience with all aspects of the study protocol procedures, it is anticipated that that the risk of adverse events associated with the

study will be acceptably low and therefore will be monitored by the PI, the DSMB (see below), and the IRB. Maximum efforts will be undertaken to ensure the safety of all study participants. All personnel involved in performance of the study and its procedures will be fully trained and extensively experienced. All serious adverse events will be required to be reported to the IRB within 24 hours of it being brought to the attention of the attending physician of the subject as well as the principal investigator of the study. The DSMB will oversee progress and safety of the project and will consist of a congenital heart disease specialist, pediatric pharmacist and statistician. The DSMB will meet every 6 months to review the study. Non severe adverse events will be reported according to IRB protocol.

A major component of safety monitoring is ascertainment and reporting of adverse events, including adverse drug reactions. The approach to these activities for this trial is summarized in the sections that follow.

C.6.6.a Definition of Adverse Event and Adverse Drug Reaction

International Conference on Harmonisation Good Clinical Practice guidelines define an *adverse event* as any untoward medical occurrence experienced by a subject administered a pharmaceutical product, regardless of its causal relationship to the study treatment. An event can be any unfavorable and unintended sign, symptom, laboratory abnormality, or disease temporally associated with the use of the product. An *adverse drug reaction* is a response to a drug that is noxious and unintended, and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

C.6.6.b Classification of Adverse Events

Monitoring adverse events requires that they be classified as to seriousness, expectedness, and potential relationship to the study drugs, all of which drive the reporting process.

Seriousness

A serious adverse event is one that:

(a) Results in death,

(b) Is life-threatening (the subject was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred),

(c) Requires inpatient hospitalization or prolongation of existing hospitalization,

(d) Results in persistent or significant disability/incapacity, or

(e) Is a congenital anomaly/birth defect in the offspring of a participant.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (http://ctep.cancer.gov) provides a grading system that is used to categorize the severity of adverse events, as follows:

(a) Grade 1 Mild: transient, requires no special treatment or intervention, does not interfere with daily activities

(b) Grade 2 Moderate: alleviated with simple treatments, may limit daily activities

(c) Grade 3 Severe: requires therapeutic intervention and interrupts daily activities

(d) Grade 4 Life-threatening or disabling

(e) Grade 5 Death.

A serious adverse event, as defined above, encompasses CTCAE grades 4 and 5, and any Grade 3 event that requires or prolongs hospitalization, or that is disabling.

Expectedness

The purpose of reporting is to provide new, important information on serious reactions or events previously unobserved or undocumented. Therefore, all adverse events will be evaluated as to whether their occurrence was unexpected.

1. Unexpected: An unexpected adverse event or adverse drug reaction is one for which the nature or severity is not consistent with information in the protocol, consent form, or product brochure.

2. Expected: An event is considered expected if it is known to be associated with the study drugs. For this protocol, expected events include the following:

a. Bradycardia

b. Dizziness

c. Syncope
d. Hypotension
e. Palpitations
f. Fatigue
g. Lethargy
h. Mood changes
i. Behavior changes
j. Sleep disturbances
k. Nightmares
l. Headache
m. Nasal congestion
n. Gastrointestinal pain
o. Dysgeusia
p. Nausea
q. Emesis
r. Diarrhea
s. Constipation
t. Myalgias
u. Back pain
v. Peripheral edema
w. Wheezing
x. Shortness of breath
y. Cough
z. Chest pain
aa. Renal dysfunction
bb. Anemia
cc. Hepatic dysfunction

Causality

Causality assessment is required in clinical investigations to help determine which events require expedited reporting. The following criteria will be used to determine causality:

1. Not Related: The event is clearly related to other factors, such as the subject's clinical state, or non-study drugs or interventions.
2. Possibly Related: The event follows a compatible temporal sequence from the time of administration of the study drug, but could have been produced by other factors such as the subject's clinical state or non-study drugs or interventions.
3. Probably Related: The event follows a reasonable temporal sequence from the time of drug administration, and cannot be reasonably explained by other factors such as the subject's clinical state, or non-study drugs or interventions.

C.6.6.c Identification of and Data Collection Procedures for Adverse Events

In this trial, a primary safety concern as well as one of the secondary end points is to capture and compare adverse drug reactions between carvedilol versus placebo. In addition, following standard clinical trial procedures, information on other adverse events will be collected.

Adverse drug reactions will be assessed at baseline, at the end of up-titration, and at each study visit through a standardized questionnaire that will be administered by the study coordinators or investigators. The assessment at baseline will be obtained while the subject is not taking any study drug and is essential to accurate assessment of drug effects. *Adverse event*s that are not considered adverse drug reactions will be identified when they are reported to the clinical center or during scheduled study visits by study coordinators and investigators. Subjects and families will be encouraged to report any serious event to study personnel as soon as the event occurs, rather than waiting for scheduled visits.

C.6.6.d Reporting Procedures (Table 2)

1. Fatal or life-threatening adverse events are to be reported to the IRB within three working days after knowledge of the event. Those that are unexpected and considered

possibly or probably related to the study drug will be reported, by the PI to the DSMB Chair but no later than 7 calendar days after first knowledge of the event, followed by a complete report within 15 calendar days. All other fatal or life threatening events will be reported to the DSMB within 15 days,

2. All other serious (i.e., non-fatal or not life-threatening) adverse events that are unexpected and considered possibly or probably related to the study drug will be reported to the IRB within 7 days of learning of the event. The PI will report the event to the DSMB within 15 calendar days after first knowledge of the event.

3. All other adverse events not meeting the criteria for expedited reporting will be reported quarterly to the DSMB.

4. The following events do NOT need to be reported:
    - Planned hospitalizations for non-cardiovascular surgical, diagnostic, or other procedures.
    - Planned cardiac catheterization.
    - Social admissions in the setting of foster care or other similar circumstances.
    - Otitis media
    - Streptococcal pharyngitis
    - Allergic rhinitis
    - Uncomplicated upper respiratory infections
    - Short-term (<36 hours) fever with no other symptoms after immunizations
    - Uncomplicated gastroenteritis
    - Uncomplicated urinary tract infections
    - Hospitalizations or emergency room care for trauma, including broken bones, evaluation after motor vehicle accident, or similar incident.

The site investigator or designee will report all serious adverse events to the IRB according to IRB policies.

Table 2. Reporting of Adverse Events

Seriousness	Relatedness	Expectedness	Reporting Timeframe
Fatal or life threatening	Related or Unrelated	Expected or Unexpected	Within 3 days of learning of the event
Serious, but not fatal or life threatening	Related	Unexpected	Within 7 days of learning of the event
All other			At least quarterly

C.6.6.e Reporting Adverse Events to the Institutional Review Board

After each DSMB meeting, a Summary Report of Adverse Events will be prepared and submitted at the continuing review to the IRB. The Summary Report will contain the following information:

- A statement that a DSMB review of outcome data, adverse events, and information relating to study performance took place on a given date
- A statement as to whether or not the frequency of adverse events exceeded what was expected and indicated in the informed consent
- A statement that a review of recent literature relevant to the research took place
- The DSMB's recommendation with respect to progress or need for modification of the protocol or informed consent. If the DSMB recommends changes to the protocols or informed consent, the rationale for such changes and any relevant data will be provided
- A statement that if safety concerns are identified, the NHLBI Program Official will communicate these promptly to the investigators.

C.6.6.f Post-Study Procedures for Adverse Events

All adverse events unresolved at the time of the subject's termination from the study will be followed by the investigators until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained or has stabilized. At the last scheduled contact, the investigator will instruct each subject or parent/guardian to report any subsequent event(s) occurring in the next 30 days that the subject, parent, or the subject's personal physician believes might reasonably be related to the study drugs.

Any death or other clinically serious adverse event that may be related to the study drugs and that occurs at any time after a subject has discontinued study drug or terminated study participation will be reported.

C.7 Measurements

C.7.1. Study Data and Measurements are outlined in Table 4 and 5

Table 4. Screening Measures

	Screening Phase
	Visit 0 (week -2-0)
Exercise Test	x
Pregnancy Test	x*
BNP, CBC, CMP	x

*to be performed on females of child bearing age only (12 years of age or older)

Table 5. Treatment Phase Measures

	Treatment Period 1 (week 0-12)					
	Visit 1 (week 0)	Visit 2 (week 1)	Visit 3 (week 2)	Visit 4 (week 3)	Visit 5** (week 8)	Visit 6 week 12
Duration (hrs)	1-1.5	<1	<1	<1	<1	2
Vital signs	x	x	x	x		x
NYHA HF Classifications	x	x	x	x		x
Adverse Drug Effect	x	x	x	x	x	x
Compliance Check		x	x	x	x	x
Safety Labs (CMP, BNP, CBC)	X					x
Exercise Test	x*					x
Study Drug Medication	X_initiate	X-uptitration 1	X-uptitration 2	X-no change		X-after visit stop study medication***
	Washout Period (Week 13-18)					
	Treatment Period 2 (week 19-30)					
	Visit 7 (week 19)	Visit 8 (week 20)	Visit 9 (week 21)	Visit 10 (week 22)	Visit 11** (week 26)	Visit 12 (week 30)
Duration (hrs)	2	<1	<1	<1	<1	2
Vital Signs	x	x	x	x		x
NYHA HF Classifications	x	x	x	x		x
Adverse Drug Effect	x	x	x	x	x	x
Compliance Check	x	x	x	x	x	x
Safety Labs (CMP,BNP, CBC)	X					x
Exercise Test	x					x
Study Drug Medication	X-initiate	X-uptitration 1	X-uptitration 2	X-no change		after visit stop study medication***

*-exercise test from screening phase may be used if visit 1 exercise test if done within 14 days of visit 1,
**-may be phone visit
***dose of study medication decreased during weeks 6 and 31 and then stopped

C.7.2. Windows for measurements

To ensure adequate time for patients obtaining maximum tolerated dose of carvedilol prior to visit 6 and visit 12 exercise testing, visits 1,2,3,4,7,8,9,10 and will occur as outlined ± 7 days. Visit 5 and 11 will occur as outlined ± 14 days. Visit 6 and visit 12 will occur as outlined ± 14 days.

C.7.3. Exercise Testing

All Exercise Tests for study purposes will be performed at the Children's Medical Center of Dallas. Studies will be performed by experienced pediatric EKG technicians and exercise physiologists. An attending cardiolgist will be immediately available per institutional protocol for any adverse event experienced during the exercise test. The exercise test will provide peak oxygen consumption, peak heart rate, ventilatory efficiency of carbon dioxide as well as submaximal exercise test performance. As previously described these data are associated with outcomes in the SV population and therefore were chosen as the primary and secondary endpoints. Exercise tests will be performed on Visit 1, 6, 7, and 12.

C.7.4. Vital Signs

Vital signs will include heart rate, blood pressure and pulse oximetry. Vital signs will be obtained by a pediatric research coordinator or appropriate designee. As previously described, bradycardia and hypotension are possible adverse events of treatment with carvedilol.

Bradycardia will be defined as:

1. Heart rate that is less than two standard deviations below age normal that is associated with <u>at least one</u> of the following:
    1. New symptoms of syncope, pre-syncope, lightheadedness, dizziness or nausea
    2. Hypotension
    3. Heart block (2^{nd} or 3^{rd} degree)
    4. New symptoms of dyspnea, fatigue or palpitations
    5. Development of any new symptom that is deemed to be due to bradycardia by a study investigator

Hypotension will be defined as:

1. For patients < 18 years of age, systolic and/or diastolic blood pressure less than 2 standard deviations from the age/sex/height normal values[43]; for patients 18 years of age or older a systolic blood pressure of less than

85mmHg and/or diastolic blood pressure of less than 55 mmHg; and is associated with at least one of the following:

1. Syncope, pre-syncope, dizziness, lightheadness or nausea
2. Newly developed bradycardia
3. Heart block
4. New symptoms of dyspnea, fatigue, or palpitations
5. Development of any new symptom that is deemed to be due to hypotension by a study investigator

Response to Bradycardia or Hypotension:

1. Heart rate and/or blood pressure will be confirmed by two repeat measures after initial measurement with at least 5 minutes between measurements, the average of all three measurements will be recorded
2. The study investigator will reduce the dose of study drug back to previously tolerated dosing
3. If hypotension or bradycardia develop after initiation prior to uptitration, study drug will be stopped

C.7.5. NYHA Classification

New York Heart Association classification of heart failure symptoms is a frequently used method of classifying the degree of heart failure symptoms a patient is experiencing. The NYHA classification is shown below in Table 6. The classification will be assessed on visits 1, 2, 3, 4, 6, 7, 8, 9, 10, 12. It will help objectively measure the degree of heart failure symptoms and the response of heart failure symptoms to carvedilol versus placebo in the study population. NYHA classification will be assessed by the principal investigator, study investigator, research coordinator or appropriate designee.

Table 6. NYHA Heart Failure Symptom Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

C. 7.6. Adverse Drug Reaction Screening

At all study visit, the principal investigator, study investigator, research coordinator or other appropriate designee will assess the presence of possible side effects from carvedilol. The study participant will be screened for the presence of the following symptoms: dizziness, syncope, palpitations, fatigue, lethargy, mood changes, behavior changes, sleep disturbances, nightmares, headache, gastrointestinal pain, nausea, emesis, constipation, peripheral edema, wheezing, shortness of breath, myalgias, back pain, cough, chest pain. CMP and BNP will be reviewed at visits 6 and 12 for presence of hepatic or renal dysfunction as previously described. If the patient is experiencing any of the listed side effects and it is felt by the study investigator and/or PI to be from the study drug, then the dose of study drug will be reduced to previously tolerated dose

C.7.7 Laboratories

CBC, CMP and BNP will be performed as part of the screening phase (Visit 1) as previously outlined. CMP, BNP will be performed at visits 6, 7, and 12. All laboratories will be drawn at the Children's Medical Center by a medical professional experienced in phlebotomy. As previously mentioned, topical anesthestic will be used when deemed appropriate. After proper labeling, blood will be sent to the Children's Medical Center laboratory for immediate analysis. Urine pregnancy tests will be performed only on female participants 12 years of age and will be performed at Children's Medical Center during the screening phase.

C.8. Statistical Analysis Plan

C.8.1. Statistical Analysis

Each exercise outcome is a continuous variable. Linear mixed-effects models will be used to estimate the difference in the average post-phase outcomes between Carvedilol and placebo, adjusting for pre-phase values, study phase (treatment phase 1 or 2) and treatment sequence. Exploratory subgroup analyses will be performed by grouping patients according to ventricular morphology (right/mixed versus left), baseline serum B-type natriuretic peptide (≥100pg/ml vs. <100pg/ml). P-values < 0.05 will be considered statistically significant.

C.8.2. Power Calculations

All power calculations were done with consultation from a biostastician, assuming an alpha level of 0.05 and 2-sided hypothesis testing. Average peak VO_2 for Fontan patients in a large multi-institutional study was 26ml/kg/min.[28] A previous study in adult heart failure demonstrated that a 6% increase in peak VO_2 was associated with reduction in cardiovascular mortality and cardiovascular hospitalization.[41] Therefore we conservatively chose a 10% change in peak VO_2 to be clinically meaningful, setting the desired detectable difference in the change in peak VO_2 to be 2.6ml/kg/min. The standard deviation of peak VO_2 in the before mentioned multi-institutional study was 6.3ml/kg/min. Prior research in a different study of adults with pulmonary and cardiac disease suggests that repeated $V0_2$ measurements are highly correlated (r=0.95).[42] To be conservative, for the purposes of power calculations we used an r-value of 0.8, allowing us to estimate the standard deviation of the $V0_2$ change scores to be ~3.98. Under these assumptions, enrolling n=20 subjects in this cross-over trial provides 80% power to detect a clinically significant difference between subjects' peak $V0_2$ under the 2 treatment conditions' (Carvedilol vs. placebo). Therefore, a goal of 30 enrolled study participants was set to account for potential non-completion of the trial.

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