Sildenafil for Fontan Associated Liver Disease (SiFALD) Study

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Fontan associated liver disease (FALD) affect 50% of all survivor of the Fontan operation, about 3 decades after the initial operation. It is associated with significant mortality and morbidity, and currently there are no treatment strategies to halt progression of this disease. The purpose of this study is to determine the efficacy of phosphodierestate-5 inhibitor (sildenafil) in modifying the progression of FALD.

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A. Rationale

Background

The Fontan operation is an effective surgical palliation for patients with complex cyanotic heart disease.[1] The physiologic benefit of the Fontan operation is that it separates the systemic and pulmonary circulations, thereby eliminating cyanosis and ventricular volume overload. However, the absence of a subpulmonary ventricle results in an obligatory high central venous pressure and low cardiac output state.[2, 3] These hemodynamic derangements result in chronic hepatic congestion and reduced blood supply to the liver.[4, 5] The downstream effect is a spectrum of Fontan associated liver diseases (FALD) such as liver fibrosis, cirrhosis ad hepatocellular cancer.[4, 6-8]

Clinical and Public Health Significance

The prevalence of cirrhosis is 50% at 3 decades after their initial Fontan operation.[6, 8] The diagnosis of cirrhosis is a strong predictor of death in this population because more than two-thirds of the patients with cirrhosis are dead within 5 years.[6] Those who survive experience significant morbidities such as variceal bleeding, hepatic encephalopathy, liver failure and hepatocellular cancer.

The incidence of complex cyanotic heart disease such as single ventricle diagnosis is 91 per 100, 000 live births.[9, 10] Based on the annual birth rate of 4.2 million in the United States,[11] more than 4 thousand babies with complex single ventricle diagnosis are born every year, and most of them will undergo Fontan operation. More than 80% of patients undergoing Fontan

operation in the current era survive to adulthood, and most of these patients will develop FALD.[12]

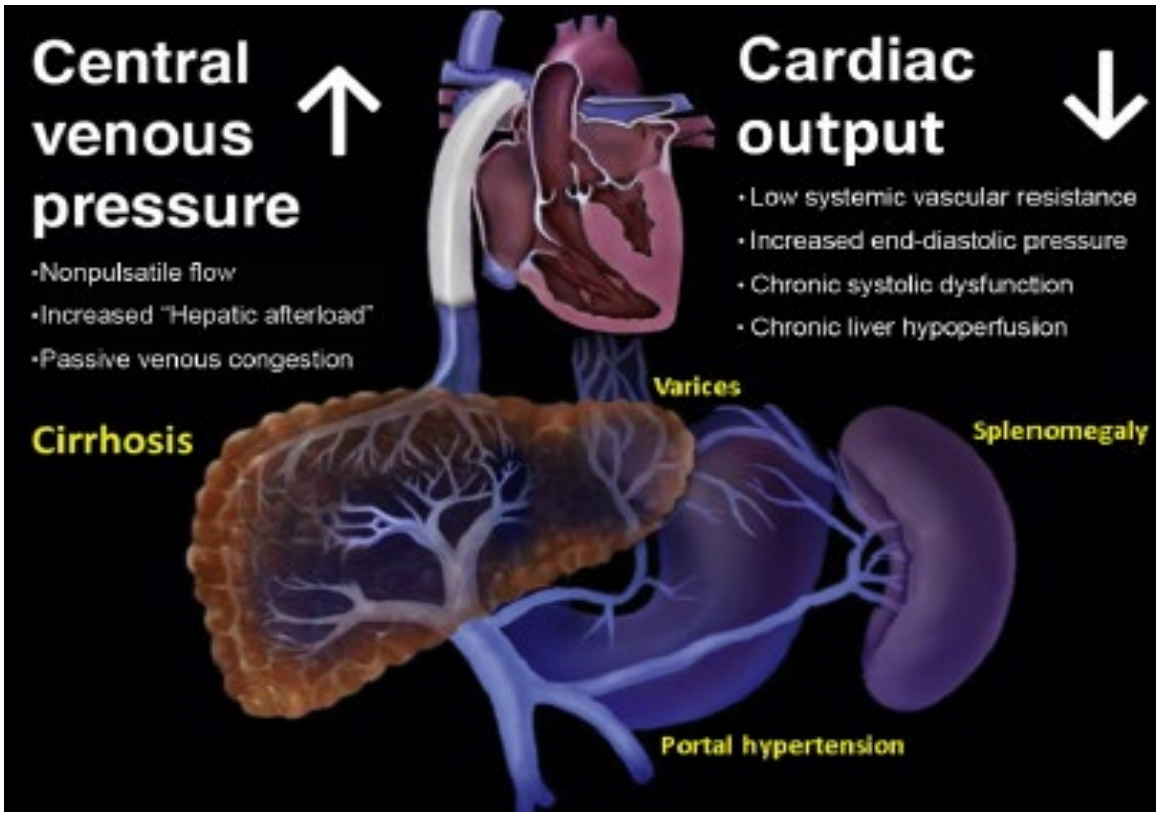

Figure 1: Schematic showing the hemodynamic interaction between the liver and the Fontan circulation. Adapted from Poterucha et al.[13]

B. Hypothesis

The use of pulmonary vasodilators will promote forward flow in the Fontan circuit, reduce hepatic congestion and halt the progression of liver fibrosis.

C. Innovation

(i) Available data suggest that chronic hepatic congestion, inherent in the Fontan physiology, is the precursor of early liver fibrosis and cirrhosis in the Fontan population. [2, 3]A recent study based on the Mayo Clinic Fontan

cohort show ed that half of the patients had liver fibrosis after 30 years from the time of initial Fontan.[6]

(ii) This proposed study would be the first study to assess the role of pulmonary vasodilators in the management of FALD.

D. Significance

(i) The adult congenital heart disease program at Mayo Clinic has the largest and oldest cohort of Fontan patients in the United States, and this places Mayo Clinic in a unique position to study this problem.

(ii) Data from this study will influence the management of FALD nationally and worldwide.

E. Brief Synopsis of Methods

(i) All patients enrolled in the study will undergo a baseline liver magnetic resonance elastography (MRE) prior to the initiation of phosphodiesterase-5 inhibitor (sildenafil).

(ii) A second MRE will be performed after 12 months of therapy.

F. Preliminary studies to support feasibility

(i) Several studies have shown that the use of pulmonary vasodilators in Fontan patients (even those with normal pulmonary vascular resistance) results in increased cardiac output and exercise tolerance by promoting forward flow in the Fontan circuit.[14-16]

(ii) A recent study from the Mayo Clinic showed that liver stiffness measured by MRE correlates with severity of fibrosis on liver biopsy.[13]

(iii) The proposed study is built on the foundation of these previous studies. Pulmonary vasodilators will be used to promote forward flow in the Fontan

circuit, and thereby reduce liver congestion. MRE will then be used to monitor treatment effect. We chose a phosphodiesterase-5 inhibitor instead of an endothelin receptor antagonist because the latter is associated with hepatotoxicity.

G. Study design

1. Inclusion criteria: All adult (age ≥ 18 years old) Fontan patients who have no contraindications for magnetic resonance imaging (MRI) will be eligible for the study. Informed consent will be obtained from potential participants by their primary cardiologist or dedicated study personnel.
2. Exclusion criteria: Subjects with implantable pacemakers, residual cardiac lesions (severe ventricular dysfunction, severe atrioventricular valve regurgitation, Fontan baffle or conduit obstruction), viral hepatitis, severe renal dysfunction, a history of sildenafil use in the six months prior to study enrollment, ongoing sildenafil therapy, or patients currently taking nitrates. Based on the stipulation from the Food and Drug Administration regarding the approved use of sildenafil, we also excluded patients with hypotension at baseline (BP <80/50 mmHg), pulmonary veno-occlusive disease, and pulmonary hypertension due to sickle cell disease. Women of child-bearing potential with a positive pregnancy test will additionally be excluded.
3. All participants may undergo the following baseline tests (+/- 4 weeks) as part of standard clinical care: transthoracic echocardiogram, electrocardiogram, cardiopulmonary exercise test, complete blood count, chemistry panel, INR, alpha-fetoprotein. All these tests are routine clinical tests in the Mayo Clinic Adult Congenital Heart

Disease program. Baseline clinical tests performed within 6 months prior to enrollment will be accepted as part of the study (data will be utilized if results are available). Any routine standard clinical tests or procedures that are not completed will not be considered a deviation.

4. Other additional baseline tests include:
    a. MRI studies: [cardiac MRI + Liver MRE + 4D phase contrast imaging of the abdomen]
    b. Abdominal ultrasound [full abdominal scan with Doppler of portal/hepatic/mesenteric vessels]
    c. Biomarkers [NT-proBNP, ST2, Galectin-3, ADMA, ceramides, hs-CRP, Cystatin C, electrolytes]
    d. Quality of life indices: MLHFQ: Minnesota Living with Heart Failure Questionnaire (for patients enrolled prior to protocol version 2, baseline MLHFQ will be administered at re-consent (+/-4 weeks).
5. This will be a double blinded placebo control study design. All participants will be randomized 1:1 to sildenafil or placebo for a total of 12 months therapy.
6. Sildenafil will be initiated at 5 mg 3 times per day for the first week, and titrated to 10 mg 3 times per day for the second week and 20 mg 3 times per day from the 3rd week to the end of the study period. The patients will be required to check their pulse rate and blood pressure daily during the first month of drug therapy. Patient who experience hypotension (blood pressure < 90/50 plus symptoms such as dizziness) during dose titration will be asked to remain on the previous tolerated dose. Patients who cannot tolerate 10 mg 3 times daily will be asked to withdraw from the study and will be asked to

continue checking their blood pressure for three days after stopping the medication.

7. After 12 months (+/- 4 weeks) of therapy, all tests listed in #3 and #4 will be repeated.
8. These same tests listed in #3 and #4 will be repeated for the patients who have follow-up up to 24 months (+/- 4 weeks).
9. Adverse event and compliance monitoring: During the first month of enrollment (initiation and dose titration), adverse events will be collected by subject report and by weekly telephone or email interview (±7 days) with dedicated research personnel. For the rest of the study period, adverse events will be collected by subject report and by monthly telephone or email interview (±14 days) with dedicated research personnel. The research personnel will be responsible for sending out the monthly supply of medications and obtaining a count of the remaining number pills as a measure of compliance. All participants will be provided with a pamphlet containing all the side effects of sildenafil, and contact information of research team for reporting any adverse event of concerns about the study.

   Up to three voicemail messages will be left for each follow-up.

H. Statistical analysis and power considerations:

Sample size and power

We have determined that a total of 40 patients who complete the study (20 patients in the treatment arm and 20 patients in the placebo) will adequately power the study accounting for approximately a 10% attrition rate. In a prior

study from the Mayo Clinic,[13] the distribution of MRE stiffness score in the adult Fontan population was 4,900 ± 1,100 Pa. Assuming that the standard deviation of MRE is 1,000 both for before and after treatment measures, and that the within subject correlation between before and after measures is at least moderate in strength and positive (i.e. $\rho \geq 0.5$), then the variance in the difference between pre- and post-treatment MRE stiffness score is no more than 250 Pa. A sample of 40 patients in the treatment arm will provide 80% power for a two-sided two-sample t-test with a 0.05 Type I error rate to detect a mean difference of at least 500 Pa in treatment effect, as measured by the difference within patient MRE stiffness score.

Interim Analysis

An interim analysis of subjects who have completed 12 months of Sildenafil vs. Placebo therapy will be conducted at the end of the grant period (August 2019). Those still on Sildenafil vs. Placebo at that time will remain blinded until their completion of 12 months on Sildenafil vs. Placebo.

I. Human studies issues (consent or research authorization)

Consent

An informed consent will be obtained from the patients at the time of enrollment in the study. The consent will authorize a member of the research team to contact each patient by phone, email, or questionnaire. The study participants will be notified of the very limited evidence supporting the use of sildenafil in this population.

Data and Safety Monitoring

The Food and Drug Administration approved Sildenafil for the treatment of pulmonary hypertension. The patients will be notified that the use of sildenafil in this study is off-label. We will implement an internal safety monitoring system consisting of two members (not immediately affiliated with the study) to review reported side effects of sildenafil at the mid-point and completion of the study. Finally, and as always, extreme caution and monitoring of study participants will be undertaken throughout the study and in follow up to ensure no untoward events as a direct result of the study substance. Please see data safety monitoring plan.

M. Literature cited

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