Sildenafil in Heart Failure with Reactive Pulmonary Hypertension (Sildenafil HF)

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Scientific Rationale

In 2007, Lewis et al[1] from Massachusetts General Hospital published a paper on sildenafil, a type 5 phosphodiesterase inhibitor, in heart failure (HF). A single oral dose of 50 mg reduced resting and exercise pulmonary arterial pressure, systemic vascular resistance, and pulmonary vascular resistance, and increased resting and exercise cardiac index ($P<0.05$ for all) without altering mean arterial pressure, heart rate, or pulmonary capillary wedge pressure. Peak VO2 increased (15+/-9%) and ventilatory response to CO2 output (VE/VCO2 slope) decreased (16+/-5%) just one hour after sildenafil treatment. Improvements were confined to patients with secondary pulmonary hypertension (PH). The study group was 13 patients, which was enough to demonstrate statistical significance of the findings.

Pulmonary hypertension (PH) in heart failure (HF) is associated with poor outcomes. In a Mayo Clinic study, there was a strong positive graded association between pulmonary artery systolic pressure (PASP) and mortality. Increasing PASP was associated with an increased risk of death (hazard ratio [HR]: 1.45, 95% confidence interval [CI]: HR: 2.07, 95% CI: 1.62 to 2.64 for the highest PASP tertile versus lowest PASP tertile. This association was independent of age, sex, comorbidities, ejection fraction, and diastolic function [2].

Elevated right sided pressures in HF usually result from elevated left ventricular filling pressures. In HF, there are two major components of PH: hydrostatic and vasoreactive[3]. Hydrostatic, or the passive component, reflects the backward transmission of elevated left ventricular end diastolic pressure. Therefore, pulmonary artery diastolic pressure correlates tightly with the pulmonary capillary wedge pressure (PCWP). Normally, the pulmonary vasculature is characterized by low pressure, low resistance and high distensibility. It can accommodate a significant increase in blood flow with a minimal elevation of pulmonary arterial pressure. When this compensatory capacity is exceeded, there is an elevation in pulmonary arterial pressure. The effective treatment for such PH is diuretic therapy or other means of fluid removal.

The vasoreactive component of PH develops with long-standing PH. It is characterized by vasospasm, vasoconstriction, and eventually morphologic changes of the pulmonary vasculature. The degree of PH is considered "out of proportion" to the PCWP. In other words, PH persists independently of the PCWP. Pulmonary vascular resistance and the transpulmonary gradient are elevated. Diuretics are, therefore, ineffective for treatment of reactive PH, and other medical treatment options are limited. In HF, reactive PH is associated with worst outcomes. In one study involving HF patients, the presence of reactive PH carried a higher risk of death (HR: 1.55; 95% CL: 1.11, 2.20; $p < 0.001$) [4].

Finally, no treatment option currently exists for reactive PH in the setting of HF. Multiple studies indicate that phosphodiesterase-5 inhibitors may be an effective therapy in this setting[5] [6-8]. In particularly, when patients with biventricular HF, poor right ventricular function, and increased transpulmonary gradient received sildenafil 20 mg three times a day, in addition to other HF medications, it resulted in a significant decrease of pulmonary pressures, improvement in right ventricular function, decrease in NTproBNP serum levels, as well a substantial improvement of the 6-minute walk distance by 91±54 m.[9] Importantly, there was a very modest reduction in pulmonary capillary wedge pressure, indicating that the reactive, and not the passive component of PH is the principal therapeutic target for sildenafil.

Clinical studies of sildenafil in HF are summarized in Table 1. The best results were obtained when the patients were selected based on the presence of reactive pulmonary hypertension, namely increased pulmonary vascular resistance and transpulmonary gradient.

No randomized controlled clinical trials, testing sildenafil in HF, selected patients based on these criteria. None of the trials, therefore, utilized the full potential of phosphodiesterase -5 inhibitors in HF. Specifically, the recent multicenter, double-blind, placebo-controlled, parallel-group, randomized RELAX trial included patients with unknown pulmonary pressures – they were not among inclusion criteria. Understandably, the trial failed to demonstrate favorable effects of sildenafil[10].

Many physicians, treating patients with advanced HF, use sildenafil empirically, based on the literature. Phosphodiestherase-5 inhibitors for PH in HF is currently not approved by the FDA and is used as an off label indication in patients with HF. A randomized controlled trial including patients with appropriate criteria can demonstrate benefits of sildenafil in this common and growing condition.

Table 1. Clinical studies of sildenafil in heart failure, grouped by outcomes

Study/Date	Patients	N	PH	Intervention	Duration	Outcome
Positive						
Zakliczynski et al 2007 [11] Case Series	Transplant candidates	6	TPG > 12 and/or PVR > 2.5 No reversibility with sodium nitroprusside	50 mg BID	1 month	3 - normal TPG and PVR 2 - acceptable responsiveness of pulmonary HTN to nitroprusside 1 – no difference
Guazzi et al, 2007[12]	NYHA II/III EF<45%	46	None	50 mg TID	6 months	Improved peak VO2, endothelial function, symptoms
Dumitrescu et al, 2011[9] Case series	Biventricular failure NYHA III/IV EF<40 TAPSE<17	9	PAP mean ≥ 25 PCWP ≥15 TPG >12	20 mg TID	5 months	Increased 6 minute walk distance, improved Echo, hemodynamics, BNP
Guazzi et al, 2011[13] double-blind, randomized, placebo-controlled	HFpEF	44	PASP>40 by echo	50 mg TID	12 months	Improvement in QOL, symptoms, hemodynamics, echo
Pons et al, 2012 [14] retrospective	Transplant candidates	15	MPAP>25 PVR >2.5 and/or TPG >12	20-60 TID	5-6 months	MPAP, PVR, and TPG decreased. All successfully transplanted
Reichenbach et al, 2012 [15] non-randomized, retrospective case–control study	Transplant candidates	32	TPG>15	20-60 TID	~1 year	Improved hemodynamics, clinical status, 60% transplanted
De Santo et al, 2012 [16] prospective, non-randomized, open label uncontrolled pilot trial	Transplant candidates	31	PVR >6 WU, unresponsive to vasodilators	25 mg TID→ uptitrated every 2 weeks to 75 mg TID	3 months	All successfully transplanted

Guazzi et al, 2011[17] Prospective, Randomized, Placebo-Controlled Study	NYHA II/III EF<40% E/e'>10	45	None	50 TID	12 months	Improved LV diastolic function and cardiac geometry, functional capacity and clinical status	
Guazzi et al, 2012[18] randomized, placebo-controlled	HF patients with exercise oscillatory breathing	32	None	50 TID	12 months	Improved peak VO2, hemodynamics	
Behling et al, 2008[19] double-blind, randomized, placebo-controlled	Outpatients with HF, EF<40%	19	None	50 TID	4 weeks	Improved peak VO2, decreased PASP	
Negative							
Redfield et al, 2013[10] double-blind, randomized, placebo-controlled	HFpEF	216 (113 sildenafil)	None	20 mg TIDx 12 weeks, followed by 60 mg TID for 12 weeks.	6 months	No improvement in exercise capacity or clinical status	
Amin et al, 2013 [20] double-blind, randomized, placebo-controlled	NYHA II/III EF<35%	106	None	25-50 mg TID	12 weeks	No improvement in exercise capacity or clinical status	

1. Specific hypotheses

Phosphodiesterase- 5 inhibitors in heart failure with secondary reactive pulmonary hypertension improve exercise capacity, hemodynamic, echocardiographic parameters, and quality of life

2. Trial design

Patients over 18 years of age with HF who have PH by right heart catheterization (mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary capillary wedge pressure ≥ 15 mm Hg, and pulmonary vascular resistance >3WU) will be eligible for randomization to sildenafil 20 mg, or placebo three times a day for 3 months. At baseline, a 6 minute walk test and quality of life questionnaire will be performed (Kansas City Cardiomyopathy Questionnaire) from 7 days prior to 3 days after qualifying right heart catheterization. If the echo was done for clinical indications within one month of enrollment, the data will be used. Laboratory tests are routinely obtained before right heart catheterization (comprehensive metabolic panel and NT-proBNP) and will be recorded for the study.

Participants will return for follow-up visits as needed for clinical indications. Our study coordinator will document changes of symptoms, changes in therapies, and capture clinical events like unscheduled hospital visits. For study purpose, the only follow-up visit will take place in 3 months. At that time, an echocardiogram, right heart catheterization, six minute walk, laboratory tests, and quality of life questionnaire will be repeated if clinically indicated. In addition, we will evaluate for signs and symptoms of HF (dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, increased heart rate) at baseline and at the follow-up visit. These assessments are part of routine care for HF patients. The 3 month assessments should take place from 80-97 days following randomization whenever possible.

Measurements and calculations by 2D echo will include left ventricular end systolic and end-diastolic dimensions, left ventricular ejection fraction by Simpson's method, left atrial volume, severity of mitral and tricuspid regurgitation, velocity of tricuspid regurgitation, diameter of inferior vena cava and its variability with respirations, and right ventricular function by tricuspid annular plane systolic excursion.

Measurements by right heart catheterization will include right atrial pressure, right ventricular systolic and end diastolic pressure, pulmonary arterial systolic, diastolic, and mean pressure, and pulmonary capillary wedge pressure. Cardiac output and cardiac index will be calculated both by Fick and thermodilution methods.

The majority of study information will be collected from routine care for standard clinical indications.

Primary outcome

6 minute walk distance

Secondary outcomes

Percent of change of pulmonary arterial pressures (systolic, diastolic, and mean) and pulmonary vascular resistance from the baseline

Percent of change of cardiac index from the baseline

Percent of change in tricuspid annular plane systolic excursion

3. **Objectives**

Primary Objective:

The primary objective of this study is to determine whether sildenafil for treatment of HF with reactive PH can improve exercise tolerance measured by 6 minute walk distance

Secondary Objectives:

The secondary objectives of this study are to determine whether sildenafil for treatment of HF with reactive PH can improve hemodynamics, right ventricular function, or quality of life

4. **Eligibility (include rationales for selecting or excluding particular cohorts)**

Inclusion criteria:

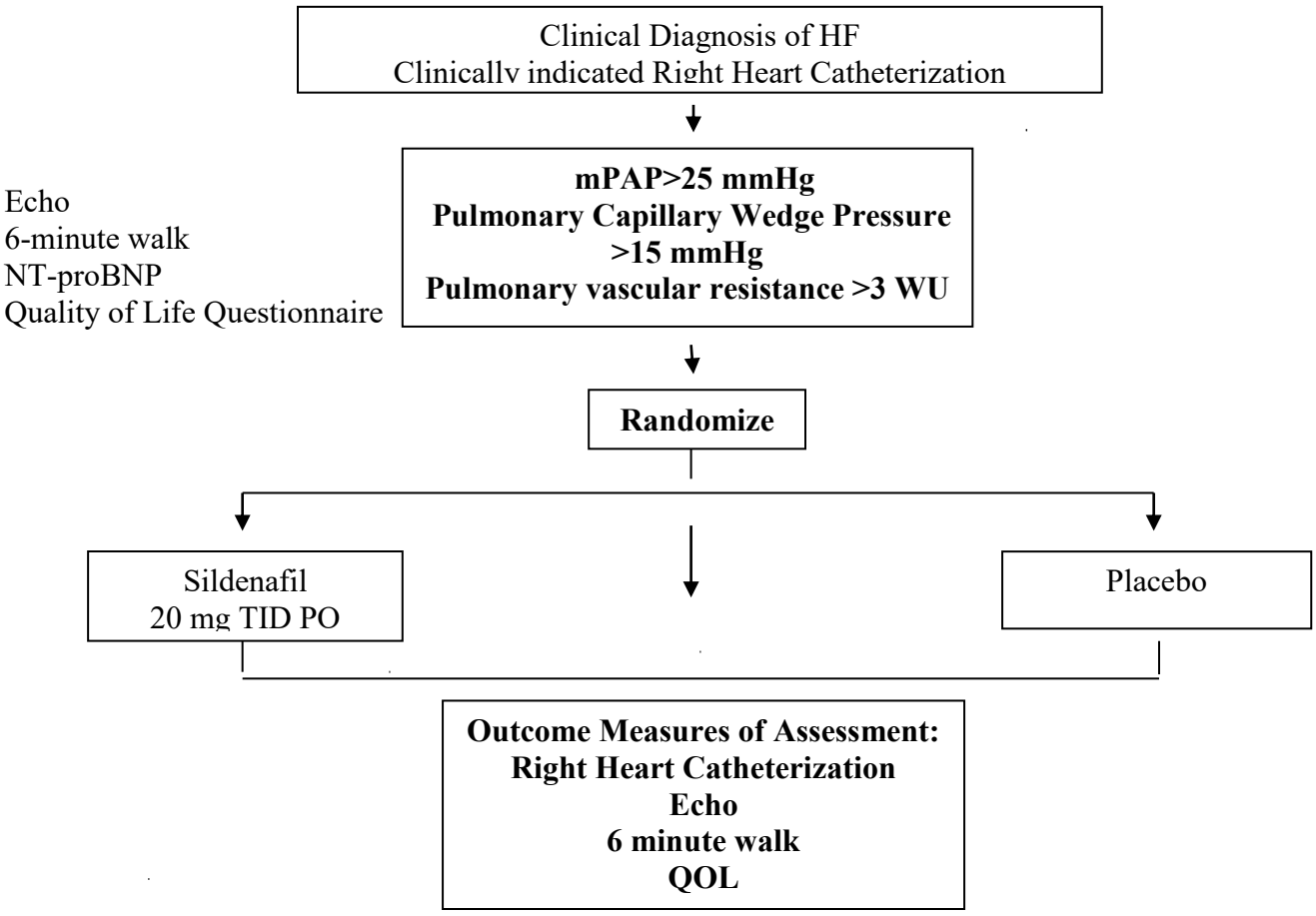
- ≥ 18 years of age
- Known chronic heart failure appropriately treated with angiotensin converting enzyme antagonists, angiotensin receptor blockers, and beta blockers, unless contraindicated, not indicated, or poorly tolerated
- Indications for right heart catheterization, other than for biopsy
- Pulmonary artery mean pressure >25 mm Hg, pulmonary capillary wedge pressure >15 mmHg, and pulmonary vascular resistance >3 WU as measured by right heart catheterization within 3 days of planned randomization

Exclusion criteria:

- Hypersensitivity, allergy, or intolerable side effects of sildenafil
- Contraindication to sildenafil including need for nitric oxide donors such as organic nitrates or organic nitrates in any other form regularly and/or intermittently or current nitrate therapy
- History of primary PH, connective tissue disorders, severe COPD, pulmonary embolism, or left to right shunts
    - Primary (idiopathic) Pulmonary Hypertension in patients without history of heart failure
    - Pulmonary hypertension in patients with systemic scleroderma
    - Pulmonary hypertension due to congenital heart disease
    - Pulmonary hypertension due to severe COPD
    - Pulmonary hypertension in patients with systemic scleroderma
    - Pulmonary hypertension due to congenital heart disease
    - Pulmonary hypertension due to severe COPD or interstitial lung disease
- History of heart transplant, VAD, or any other solid organ transplant
- Likely to have solid organ transplant or any other major surgery during study enrollment/treatment period
- Liver cirrhosis as primary diagnosis

- History of massive pulmonary embolism
- Acute pulmonary embolism
- Female subject who is pregnant, breastfeeding, or one who is unwilling to practice an acceptable method of birth control unless postmenopausal or sterile.
- Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject (eg, alcohol or other substance abuse, inability, unwillingness to adhere to the protocol, documented non-compliance or vulnerable population
- Currently enrolled in another investigational drug or device clinical study, or less than 30 days since completing study
- Current diagnosis of HIV or AIDS
- End stage renal disease undergoing dialysis
- End stage liver disease
- Co-morbidities, if it limits exercise tolerance
  - morbid obesity (BMI>40)
  - COPD with oxygen dependence
  - severe peripheral vascular disease with intermittent claudication
  - status post amputation of lower extremity(s) at any level
  - severe degenerative joint disease preventing normal walking
  - CVA with long term sequella affecting ability to walk

5. **Arms/regimens**



6. **Statistical design in detail (include one primary and any secondary endpoint(s), any stratification to be used in the randomization, sample size with power justification, analysis plan including plans for formal interim analysis, projected monthly accrual rate)**

Sample size was calculated at 32 patients per arm, 64 patients total

Primary and secondary endpoints are as noted above. Patients will be randomized to treatment versus placebo in a 1:1 ratio using permuted blocks of variable size, to which the principal investigator (and the patients themselves) will be blinded. Planned sample size is 64, as described below. Data will be analyzed on an intent-to-treat basis, as described below. An interim analysis will also take place after data have been acquired for (approximately) 32 subjects, using a temporary alpha of 0.01 to mitigate inflation of Type I error probability due to multiple testing. Results of interim data analysis will be shared with Data Safety Monitoring Board, which will advise the principal investigator on whether to continue with the study.

Planned sample size of 64 will provide nearly 80% power, using the final alpha of 0.05, to detect a difference between groups on a numerical outcome variable for which the effect size is approximately 0.7, in the sense that a typical person in the treatment group would be approximately seven-tenths of one standard deviation better than a typical person in the control group. This is slightly greater than the effect size of approximately 0.6 observed by Mathai and colleagues for the exercise endpoint, but we anticipate being able to reduce variability by considering change scores from baseline to 3 months rather than just the final results at 3 months.

Each numerical outcome variable will be examined for approximate normality, and appropriate corrective action (e.g., log transformation prior to further data analysis) will be considered if approximate normality is untenable. A linear mixed model will be fit relating each outcome variable to group (between-subjects factor: treatment vs. placebo) and time (within-subjects factor: baseline vs. 3 months), with random effects for subjects and embedded linear contrasts to compare groups on change from baseline to 3 months. Although randomization is anticipated to balance groups on demographic and clinical characteristics, in the unlikely event that groups are imbalanced we can modify the linear mixed modeling to adjust for any covariates on which groups are imbalanced. Loss to follow-up is anticipated to be small, but in the unlikely event of more than 10% attrition from either group we can employ multiple imputation or another method for handling missing data. Groups will be compared on adverse events (e.g., re-hospitalization) using Fisher's exact test.

7. **Source of agents:** investigational pharmacy at UK (Chandler Hospital)

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