

PAHTCH Pulmonary Arterial Hypertension Treatment with
Carvedilol for Heart Failure (Carvedilol)

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Introduction

Pulmonary arterial hypertension (PAH) is a serious condition characterized by endothelial dysfunction leading to pulmonary vascular constriction, smooth muscle and endothelial proliferation, and progressive right-sided heart failure. The severity of pulmonary hypertension is mostly determined by the response of the right ventricle (RV) to the increased afterload or pulmonary pressures, and RV failure is the leading cause of death in PAH.

Most accepted therapies for PAH have been aimed at vasodilation of the pulmonary vasculature, and there has been little thought that PAH patients would benefit from traditional left heart failure treatments. A cornerstone therapy in left heart failure is β -adrenergic receptor blockade because of its ability to reverse cardiac remodeling and improve clinical outcomes, despite decades of concern regarding its propensity to exacerbate heart failure. It has been reported to reduce mortality by about 30% in patients, and while the precise mechanisms that contribute to its beneficial effects remain to be elucidated, there is evidence that patients with underlying contractile reserve (*i.e.*, via recruitment of viable myocardium with β -adrenergic receptor stimulation) may experience greater recovery of their cardiac function. The current treatment recommendations regarding the use of β blockers in pulmonary hypertension state that there are possible unfavorable consequences on hemodynamics and functional exercise capacity, particularly when a relatively diminished and fixed stroke volume can be compromised. With a decreased stroke volume and an inability to increase it, patients with PAH depend on their heart rate response to increase cardiac output during exercise. In patients with severe mitral stenosis and pulmonary hypertension undergoing valvuloplasty, intravenous administration of atenolol was associated with further increase in pulmonary vascular resistance due to reduction in cardiac output. These observations have led to the belief that β -adrenergic blockers are detrimental in patients with PAH. This was supported by a small study of 10 patients with portopulmonary hypertension, in whom withdrawal of propranolol was associated with an increased exercise tolerance. However, only the β -blockers metoprolol and carvedilol have FDA approval for the treatment of left heart failure, and many studies have shown that the negative short-term effects such as fatigue and decreased exercise capacity of β blockade are overcome by a reversal of unfavorable cardiac remodeling. In a study using rats with pulmonary hypertension treated with β blocker, RV function improved, and maladaptive myocardial remodeling was prevented. Hence, in the same manner, in patients with PAH who are not destabilized and have preserved cardiac output and hemodynamics, the true short-term risks versus long-term benefits on reducing progressive RV dysfunction remained untested.

While the exact etiology for PAH is not known, the pulmonary endothelial dysfunction in PAH is associated with an impaired production of nitric oxide (NO) and activation of hypoxia-inducible factor 1 α (HIF-1 α). HIF-1 α , the subunit of the HIF-1 transcription factor regulated by both iron and hypoxia, is upregulated in PAH endothelial cells, and HIF-inducible hormones such as erythropoietin (Epo) are elevated and correlate with disease severity. Preliminary data from our lab suggests the same pathobiology occurring in the pulmonary vasculature also occurs in the myocardium of PAH patients, including increased levels of HIF-1 α , impairment of eNOS activation, and a switch to glycolytic metabolism. For example, in patients with PAH compared to control subjects, FDG-uptake in the heart is greatly elevated. We also find decreased amount of β -adrenoreceptors (β AR) and cAMP in circulating mononuclear cells in PAH patients, identifying β AR dysfunction. In primary PAH pulmonary artery endothelial cells in culture, promising preliminary data demonstrate the ability of β -blocker to rescue eNOS activity as measured by the amount of NO production, restore β AR density and function on cell surfaces, and reverse the metabolic switch to aerobic glycolysis. Correspondingly, in patients, cross-sectional data showed that PAH patients who were taking low doses of β -blocker had a decreased ventricular FDG-uptake compared to other PAH patients not taking β -blocker. Given the retrospective cross-sectional data, effects on clinical status are unclear, but initial review of the small population

indicates no significant adverse effect on clinical functional status (NYHA class, walk distance, cardiac output, pulmonary artery pressure, pulse, blood pressure). Thus, we propose to determine whether treatment with a β -blocker reverses biochemical abnormalities in PAH that lead to maladaptive right ventricular remodeling and failure, utilizing a blinded, placebo-controlled, randomized trial of carvedilol in PAH patients for six months. We will also evaluate clinical parameters of cardiovascular function in relation to changes in the biochemical effects of treatment. Because PAH patients ultimately die of heart failure, carvedilol was chosen as the β -blocker in this study, as it is one of the two β blockers currently FDA-indicated for the treatment of heart failure, and has been extensively well-studied for use in very severe heart failure. Carvedilol blocks β 1AR and β 2AR, as well as α 1AR, the latter blocks vasoconstriction and may benefit for PAH patients by decreasing afterload. Additionally, carvedilol is inexpensive and generally well-tolerated; specifically, during long term treatment, intolerance to drug in patients with severe heart failure (class III-IV) did not differ from patients with mild-to-moderate heart failure (class II).

Specific Aims and Hypothesis

We hypothesize that use of carvedilol in patients with PAH will reverse loss of, and resensitize β -adrenoreceptors, increase production of NO, and reduce activation of HIF-1 α , which altogether will improve right and left ventricular function, decrease right and left ventricular size, and improve exercise and functional capacity. To test this, we propose a blinded, placebo-controlled, randomized trial of carvedilol at a fixed low-dose or dose-escalating pattern of therapy in PAH patients for six months with a one-week open-label run-in phase.

A. Primary Aim

To determine whether treatment with carvedilol reverses biochemical abnormalities associated with PAH, we will assess the following:

1. **Activation of HIF-1 α (co-primary end points):** We will assess activation of HIF-1 α via measurement of plasma erythropoietin and myocardial glucose uptake during fasting gated FDG-PET. We already know that erythropoietin is elevated in PAH and that FDG-uptake is high. We expect both to decrease on drug.
2. **NO synthesis:** We will determine if carvedilol restores eNOS activity and NO synthesis by measuring the global arginine bioavailability ratio (GABR), exhaled NO, and circulating nitrogen oxides (plasma nitrite, nitrate and urinary nitrate). We will use GABR, exhaled NO and plasma nitrite and urinary nitrate to monitor responses to our strategy for restoration of NO synthesis. We expect GABR and all measures of nitrogen oxides to increase with Carvedilol, just as in LV failure treated with β -blockers.
3. **β AR recovery:** We will assess β AR numbers and activation by measurement of levels of β AR on the surface of cells, and the intracellular messenger cAMP via flow cytometric analysis of circulating mononuclear cells before, during, and after treatment with Carvedilol. We will also use circulating mononuclear cells to determine phospho- β AR levels. These novel tests were innovated by our group for this study. We anticipate that receptor numbers and cAMP will increase, while phospho- β AR levels will decrease in the circulating mononuclear cells of patients on drug.

B. Secondary Aim

To determine whether reversal of the biochemical abnormalities as above correlate with an improvement in clinical parameters of disease severity, including right ventricular function, heart chamber size, exercise and functional capacity, and quality of life, we will assess the following:

1. **Ventricular function and structure:** We will utilize echocardiogram to evaluate cardiac chamber size and function, including estimation of RV systolic pressure (RVSP) and measurement of RV fractional area change (RVFAC), RV ejection fraction, myocardial performance index (MPI) of the RV, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived systolic velocity of the lateral tricuspid annulus (S' velocity), three-dimensional RV ejection fraction, and longitudinal strain and strain rate with tissue Doppler techniques. Because dynamic physiologic insights into RV function will be valuable, we will capitalize on the ability to obtain radionuclide ventriculography measure of RV ejection fraction using the

cardiac-gated FDG. Although software packages are available for measurement of LV ejection fraction by PET, they do not allow for corresponding RV measurements, and new software is needed for this task. We plan to develop software for calculation of RV ejection fraction by the FDG-PET, and it will be available for the clinical trial.

2. **Quality of Life:** Measuring health-related quality of life is a key indicator of high-quality care. We will use two different, well-validated questionnaire to measure quality of life: The Kansas City Cardiomyopathy questionnaire and Camphor questionnaire. These are easy to complete and important to determining the effectiveness of therapy. [*Questionnaires uploaded*]

3. **Functional capacity & biomarkers:** Other traditional clinical parameters to assess therapy will be performed, including clinical status (WHO class), 6-minute walk, and aminoterminal B-type natriuretic peptide (NT-proBNP). All cause mortality and hospitalizations will be recorded for all participants in the study.

Study Design and Methods

A. Study Design

This will be a double-blinded, randomized, controlled intervention with three arms preceded by an open-label 1-week run-in period. This is a multi-center trial with the Cleveland Clinic being the leading site. After screening and consent, all eligible patients will have their first visit at the Clinical Research Unit to start the open-label challenge of carvedilol at a dose of 3.125 mg twice daily. The patient will be monitored for at least 3 hours and if a patient tolerates this dose (assessed by symptoms and vital signs including blood pressure and pulse), a patient will then be discharged home to continue on the drug at 3.125 mg twice daily for the remainder of the week. Patients will receive a follow up phone call the day after their first randomization visit. Patients will be provided with a blood pressure monitor for home and will measure their blood pressure and pulse as directed, and will be contacted daily during the first week to check on vital signs and symptoms. Patients who are able to complete the 1-week run-in phase without adverse effects will return to clinic for assessment by history and physical exam. Stable patients will be randomized to one of three arms for 24 weeks of treatment with placebo, fixed low-dose Carvedilol, or dose-escalating carvedilol to maximum tolerated dose. The first group will receive a placebo drug for the remainder of the study. The second group will continue with carvedilol at a dose of 3.125 mg twice daily. The third group of patients will receive carvedilol 3.125 mg twice daily one week, then 6.25 mg twice daily for second week, 12.5 mg twice daily for third week with the option to increase to the maximal dose of 25 mg bid for the remainder of the study period. If a dose is not tolerated, the dose will be decreased to the prior week's tolerated dose for the remainder of the study. Subjects will receive weekly phone calls after starting the study and a study visit at weeks 1, and months 1, 3 and 6 to evaluate for side effects, to monitor clinical status, and to collect outcome data. Patients will be provided a home blood pressure monitoring device and asked to record pulse and blood pressure in the morning and evening with instructions to call at any time if systolic BP<85 mm Hg or pulse<55, or if there is any adverse event such as hospitalization or unscheduled doctor visits.

B. Population

We will enroll 68 subjects with pulmonary arterial hypertension Class 1,3,4 and 5 (Nice 2013) with symptoms consistent with NYHA Class I-III.

Inclusion criteria

- Men and women age 18 or older not greater than age 65 years
- Diagnosis of pulmonary arterial hypertension class 1,3,4 and 5 (Nice 2013)
- NYHA/WHO Class I-III
- PAH medications must have been initiated according to the latest consensus statement recommendations and remained stable for the last 30 days
- Women of child-bearing age must use a double-barrier local contraception till completion of the study

- Subjects must demonstrate understanding of the study, sign the informed consent, and have a reliable method of communication for contact and ability to comply with the study requirements.

Exclusion criteria

- Participation in any other treatment studies during enrollment
- Significant illness in the past 30 days requiring hospitalization
- Hepatic insufficiency (transaminase levels >4 fold the upper limit of normal or bilirubin >2 fold the upper limit of normal),
- History of HIV, Hepatitis B or C
- Serum creatinine >2.8 mg/dl
- Pregnancy, breast-feeding, or lack of safe contraception
- Acute decompensated heart failure within past 30 days
- Known allergy or intolerance to carvedilol or other β blockers
- Significant, persistent bradycardia (resting heart rate <50 bpm) or hypotension (systolic blood pressure <100 mmHg or mean blood pressure <70 mmHg) at the time of enrollment
- Second or third-degree AV block without pacemaker
- Use of hypotensive drugs that deplete catecholamines (such as reserpine and monoamine oxidase inhibitors) which may lead to greater signs of hypotension or bradycardia
- Use of amiodarone, diltiazem, verapamil, clonidine
- Active bronchospasm
- Other medical and psychosocial conditions as determined by principal investigator deemed unsuitable for enrollment

C. Sample Size Rationale and Estimate

Target enrollment for this study will be 68 patients. The primary outcomes FDG-PET uptake and erythropoietin, are anticipated to have positively skewed distributions, amenable to the use of ratios of 6-month measures relative to baseline to measure changes over time. Log transformed ratios are then anticipated to have approximately normal distributions. For secondary measures demonstrating less skewness or even approximate normality without the log transformation, absolute changes from baseline to 6 months will be used to measure change over time. Sample size is determined taking into account the power of the T-test for comparing the placebo and low dose carvedilol groups with respect to the reduction in FDG-PET uptake, as measured by the ratio of 6-month uptake to baseline uptake. Variability in FDG-uptake measures over 6 months suggests an expectation that the coefficient of variation in uptake ratios will not exceed 50%. Using a Bonferroni correction to adjust for multiple time points with $\alpha=0.025$, the T-test comparing log-ratios has 90% power to detect a difference in groups such that ratios have a 50% lower median for the low dose carvedilol group relative to the placebo group, if the groups contain $n=14$ subjects each. This effect size was selected based on previously observed reductions in FDG-PET uptake of roughly 50% among patients on β -blocker. Considering 10% potential dropout after randomization and a 30% potential dropout during the run-in phase, we intend to enroll 68 patients into the run-in phases, to achieve at least 48 patients eligible for randomization into the placebo, low dose Carvedilol, or dose escalation groups.

D. Enrollment

Recruitment Strategy

Patients who are diagnosed with PAH will be identified as potential subjects by either a nurse or doctor involved in the patient's disease management. These patients will be referred to the study investigators for screening and to obtain informed consent. Subjects will be recruited as they become available and without regard to gender, race, or ethnicity.

Informed Consent

All volunteers will be approached by the study investigators or their designee. The consent interview will take place the day of a patient visit to the Pulmonary Department. In a private examination room, one of the research investigators will explain the details of the study, to the

potential subject and supply the informed consent form. The patient will be given the opportunity to ask any questions they may have, as well as to take the consent form home to read before making a decision. The investigator will ensure that subjects have a clear understanding of all tests involved in the study, are able to sign the consent form, and have all their questions answered. If the patient decides freely to participate in the outlined study, he or she will be asked to indicate his or her consent by signing the informed consent form. All original, signed consent forms will be kept in a study binder maintained by the study coordinator, and an informed consent procedure note will be entered in the electronic medical record as documentation of the subject's informed consent. Subjects will be given a copy of the signed consent form for their records.

Eligibility Assessment & Determination

After a potential subject has been identified, the investigator will review past right heart catheterization reports and the following parameters with the patient to ascertain eligibility based on the inclusion/exclusion criteria:

- Patient age
- Women of child-bearing age: whether she would be able to comply with using two methods of contraception for the duration of the study
- Past medical history and current medical conditions
- Medication allergies
- Recent illness/hospitalization
- Tobacco, alcohol, and substance usage
- Patient medications: all medications that a subject has taken, both over-the counter within the last month (including herbal medications) and prescribed within the last two months, will be reviewed. Doses, routes of administration, and duration of therapy will be recorded.

If the patient is still eligible after this initial assessment, and the patient has consented to participate as indicated by the signing of the consent form, the patient will undergo brief screening physical examination, to include blood pressure, heart rate, respiratory rate, height, weight, and pulse oximetry. The following tests will also be performed prior to official entrance into the study:

- Urine pregnancy test
- HIV & hepatitis screening if not performed within past 3 years or following any potential exposure (e.g., needle stick, high risk sexual behavior)
- Chest X-ray (if not done within past 1 year)
- Electrocardiogram
- Spirometry & diffusion capacity
- 6 minute walk test
- Blood draw for CBC & complete metabolic panel

Final eligibility will be determined by the investigator after review of the medical record and data gathered during the screening visit. Eligible, enrolled subjects will undergo additional baseline procedures:

- Quality of life questionnaires
- Fasting Gated FDG-PET scan
- Echocardiography
- Blood draw for flow cytometry, plasma nitrite and nitrate, global arginine bioavailability ratio (GABR), Erythropoietin, & NT-proBNP
- Urine for nitrate
- Exhaled NO

E. Intervention

Open-label Run-in Phase

All enrolled, eligible subjects will receive an open-label carvedilol therapy at starting dose of 3.125 mg twice daily for one week and be monitored at the Clinical Research Unit for the first-dose challenge of Carvedilol. Upon discharge, enough carvedilol to complete the 1-week run-in period will be dispensed by a licensed provider. Subjects will be instructed to return in 1 week with any

unused medication. Those individuals who are eligible for randomization to the trial will undergo the procedures summarized in Table A1 "Run-in Week".

Double-blinded Randomized Phase

At the end of the 1-week run-in phase, subjects who have tolerated the low-dose carvedilol without severe or limiting side effects, still meet the inclusion and exclusion criteria, and who wish to continue in the study will be randomized to one of three arms: placebo, low-dose carvedilol, or escalating dose carvedilol for 6 months. Subjects and the investigators will be blinded to their group assignment for the duration of the study.

- Group 1 will receive a placebo drug to take twice daily for 6 months.
- Group 2 will receive carvedilol at a dose of 3.125 mg twice a day for 6 months.
- Group 3 will receive carvedilol in a dose escalation scheme. They will be given 3.125 mg tablets to take bid for 1 week, followed by 6.25 mg bid for 1 week, followed by 12.5 mg bid for 1 week with the option to increase to the max dose of 25 mg bid for the remainder of the study. During up titration, if a dose is not tolerated, the dose will be decreased to the previous tolerated dose for the remainder of the study.

Because study physicians are blinded to groups, if patients are determined to be intolerant of drug (based on symptoms, signs such as sitting systolic BP<85 mm Hg or resting pulse<50, or severe adverse event such as hospitalization for heart failure), a request for dose reduction to the prior week will be requested from the research pharmacist (John Petrich), who is aware of treatment assignment. He will provide a new week's worth of medications at the "lower" dose. In the case of placebo, placebo will again be provided. In the case of fixed low-dose of carvedilol, placebo will be provided. In the case of dose-escalating carvedilol, the prior week's dose will be provided. Regardless of changes in dose, all three randomized study groups will be compared, based on the intent-to-treat principle, and thus subjects will be maintained in their original assigned study group for analyses.

Randomization scheme

Blocked randomization will be used. The block sizes will also be random and known only to the research pharmacist (John Petrich, Cleveland Clinic Research Pharmacy), who will perform the randomization and know treatment assignment at time of enrollment. The research pharmacist will ensure that a disproportionate subclass (idiopathic, familial or associated PAH) and/or severity of PAH are not entered into any single arm of the study.

Blinded Medication Dispensing

After randomization, all subjects will receive the study medication/placebo for the first 4 weeks in 4 separate bottles labeled "week 1," "week 2," "week 3" and "week 4" to blind subjects to whether they are assigned to the dose escalation group. All pills will be encapsulated so that dosing or medication cannot be discerned by patients or study investigators. Enough medication/placebo will be dispensed to last until the next scheduled follow-up visit. Subjects will be instructed to bring all unused medication and the medication bottles (even if empty) to each follow-up visit.

If any patients in any arm of the study appear intolerant of drug (based on symptoms such as persistent light-headedness, sitting systolic BP<85 mm Hg or resting pulse<50, or hospitalization for heart failure), they will be provided a new bottle of pills labeled "week-dose reduction" as follows: subjects on dose-escalating carvedilol will be provided a new bottle of carvedilol at the prior week's dose, subjects on fixed low-dose of carvedilol will be provided placebo pills, subjects on placebo will be provided a new placebo pill bottle. Once dose reduction has occurred in the dose-escalating arm, subjects will be maintained on that set dose throughout the remainder of the study, with no further escalation of dose. If signs or symptoms of subjects in any arm persist despite the dose reduction, dose reduction will again be implemented as follows: subjects on dose-escalating carvedilol will be provided a new bottle of carvedilol at half the current reduced dose, subjects on fixed low-dose carvedilol will again be provided placebo pills, subjects on placebo will again be provided a new placebo pill bottle. Of note, only 3 total dose reductions will be allowed during the entire 6 month study. Following 3 dose reductions are implemented, if subjects are still intolerant, they will be removed from all study drug.

Subject Instruction

All subjects will be advised to take the study medication with a small meal. All subjects will receive a daily phone call for the first week after start of carvedilol during the run-in. Thereafter, patients will be called weekly to screen for side effects and to monitor their clinical status. Patients will be provided a home blood pressure monitoring device and asked to record pulse and blood pressure in the morning and evening at the same time each day with instructions to call at any time systolic BP < 85 mm Hg or pulse < 55. Lightheadedness is expected to occur, but in 99.5% of cases in prior studies of severe heart failure, this resolves without problems. Patients will be instructed to sit up and rise slowly. Patients will also be instructed to call if they experience any new or worsening symptoms, or require hospitalization or unscheduled doctor visits.

F. Follow-up Schedule

Subjects will be scheduled for follow-up visits at week 1, and months 1, 3, and 6. There is no scheduled follow-up of subjects after completion of the exit visit; subjects will then resume their standard of care clinical course. If patients were on carvedilol, the option to remain on therapy will be allowed based on patient and physician preference. If removal from therapy is requested by patient or physicians caring for the patient, carvedilol dose will be reduced by half every week until the patient is on 3.125 mg twice daily, at which time drug will be stopped.

At follow-up visits, subjects will bring their medications to check for compliance and correct dosage. At each visit, the subjects will undergo a physical exam including BP and pulse, pregnancy test, EKG, breathing tests, 6-minute walk, and echocardiogram, fill out questionnaires, and give a blood and urine sample. Please see Table A1 below for details.

At the study teams discretion and for patient's convenience study visits Screening Baseline and Run in may be combined.

G. Data Collection

Outcome data will be collected at the baseline visit and at follow-up visits at week 1, and months 1, 3 and 6. Safety monitoring parameters will be collected at all visits and via weekly phone calls throughout the study period.

Table 1. Procedures Performed at Each Visit

Procedure	Screening	Baseline	Run-in Week	Month 1	Months 3 & 6 (or upon study exit)
Chest X-ray	X*				
Blood draw for CBC, Complete metabolic panel, HIV, Hepatitis	X				
Blood draw for Erythropoietin		X			X
Cardiac-gated fasting FDG-PET		X			X (6 month only)
Blood draw for flow cytometry, plasma nitrite & nitrate, and GABR		X	X	X	X
Urinary nitrate		X	X	X	X
Exhaled NO		X	X	X	X
Saliva Collection		X			X (6 month only)
Quality of Life Questionnaires		X	X		X
Blood draw for NT-proBNP		X	X		X
Six Minute Walk Test	X		X		X
Echocardiogram		X	X		X
Electrocardiogram	X		X	X	X
Urine pregnancy test**	X	X	X	X	X

Spirometry & Diffusion capacity	X		X		X
Anticipated length of visit:	1 hour	5 hours	2 hours	2 hours	5 hours

*if not done in past year

**only women of child-bearing age

*** screening, baseline, run-in may be combined

Blood draws

For measurement of laboratory parameters, blood will be drawn from a peripheral vein. Complete blood cell count (CBC), metabolic panel, and NT-proBNP, will be measured using standard laboratory techniques. The remaining laboratory parameters will be measured by the investigators in the laboratory. Erythropoietin (mIU/mL) will be measured via enzyme-linked immunosorbent assay (ELISA). The proportion of cells positive for cAMP will be determined via flow cytometry. Circulating mononuclear cells will also be assessed for phospho- β AR content by immunoprecipitation and western blot, to evaluate resensitization of the receptor. Plasma nitrite and nitrate will be measured, and fasting levels of arginine, ornithine, and citrate in order to calculate the GABR [Arg / (Orn + Cit)].

Urine collection

A urine specimen will be obtained in a sterile urine specimen cup for use of measuring urine nitrate and for pregnancy testing of women who are peri- or premenopausal.

NYHA/WHO Functional Classification

The patient will be classified into class I-IV based on a subjective assessment of their symptomatology and limitation of physical activity, as described below:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope.
- Class II: Slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
- Class III: Marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.
- Class IV: Inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Six Minute Walk Test

The six-minute walk test is a simple means of assessing functional capacity utilizing a 100-foot hallway¹. The distance that a patient can walk as quickly as possible on a flat, hard surface in six minutes will be measured in meters & feet. The test will be done according to American Thoracic Society recommended guidelines.

Echocardiogram

Doppler echocardiography will be performed by a single well-experienced echo technologist (M. Park) for all studies to estimate PAP, RV and LV function using previously validated methods. Right ventricular function will be assessed via measurement of RV fractional area change (RVFAC), RV ejection fraction, myocardial performance index (MPI) of the RV, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived systolic velocity of the lateral tricuspid annulus (S' velocity), three-dimensional RV ejection fraction, and longitudinal strain and strain rate with tissue Doppler techniques (conventional technique, 2-dimensional speckle tracking and velocity vector imaging). Among these methods, the most used parameters are RVFAC, TAPSE, S' velocity of the lateral tricuspid annulus, and RV MPI.

Exhaled NO measurement

The participant will take in a deep breath and exhale through a mouthpiece attached to the nitric oxide analyzer (Aerocrine). This will be repeated for a total of three exhaled NO readings. NO is measured using the American Thoracic Society recommended guidelines.

FDG-PET scan

Cardiac-gated fasting FDG-PET scans will be conducted on fasting patients at baseline and 6 months. Finger stick blood sugar will be measured to assure fasting state (blood sugar < 120 mg/dl). Patient data will be acquired using a clinical PET/CT scanner (Biograph mCT 128) having time-of-flight capable PET detectors. First, a low-dose CT scan will be acquired to provide an attenuation map for PET data corrections. Then, a PET scan will be acquired in list mode for fifteen minutes with ECG signals obtained during the scan. Both static and gated images will be reconstructed using advanced iterative algorithms available on the scanner. All subjects will be fasting 8 h prior to and during the study, then injected with 370 MBq (10 mCi) FDG and scan performed at 1.5 h post-injection. Images will be analyzed in a blinded fashion by D. Neumann using an image fusion workstation (MSViewer, CPS Innovations, Knoxville, TN) with region-of-interest (ROI) measuring tools. A total of five ROI will be measured in heart (left & right atria, RV, LV and IVS). In addition, ROI will be measured for the blood pool of the thoracic aorta. FDG uptake depends on factors including time between injection and scan, blood glucose, and body mass. For consistency, relative uptake will be normalized to blood pool FDG in thoracic aorta.

Safety and tolerability outcomes

Safety monitoring parameters will be collected via daily and/or weekly phone calls and at all follow-up visits. Subjects will be asked whether they have experienced any side effects and to describe these symptoms and to provide the BP and heart rate home records, which will be recorded in the electronic medical record. We will also monitor subjects throughout their enrollment and record whether there have been any deaths or hospitalizations during the study.

Compliance

Subjects will be asked to bring the study medication and bottles with them to each follow-up visit. A tablet count will be performed to estimate compliance. Subjects will also be asked how many tablets per day they have been taking on average, and how many times a week they miss a dose.

H. Early Withdrawal

Patients may be withdrawn from the study for any of the following reasons:

- Pregnancy
- Lung transplantation
- Unacceptable side effects or toxicity, as deemed by the principal investigator
- Patient non-adherence or inability to communicate with the patient
- More than three dose reductions of medications required
- Patient request to withdraw from the study

I. Data Monitoring

a. Quality Control

Data will be monitored for quality control by the study coordinator, statistician and principal investigator. Within the study database, conventional limits will be set on each data entry cell to minimize entry of erroneous values.

b. Recruitment

Problems with recruitment will be assessed after 12 months of enrollment of the first patient. If less than a fourth of the sample size has been recruited for the study, additional recruitment strategies will be addressed and implemented.

c. Benefit/Risk and Subject Safety

This study will be submitted to the Institutional Review Board for review of the benefits and risks of the proposed trial. We plan to comprise a Data and Safety Monitoring committee to oversight

the trial. Overall, we believe the potential benefits of carvedilol for PAH outweigh the potential risks of the study.

Potential Benefits

A potential direct benefit to the subjects includes possible improvement in clinical symptoms for those randomized to carvedilol treatment. This study may also be beneficial for future patients because the results of this investigation will enhance our mechanistic understanding of the pathophysiology of PAH, how β blockers affect patients with pulmonary arterial hypertension, and may therefore lead to the development of new treatments for PAH and heart failure in general.

Potential Risk Associated with Carvedilol Therapy

Common side effects associated include hypotension, dizziness, fatigue, hyperglycemia, diarrhea, weight gain, and weakness. Less common side effects include bradycardia, syncope, peripheral edema, angina, AV block, palpitation, cerebrovascular accident, hypertension, headache, depression, hypercholesterolemia, gout, hyperkalemia, hyponatremia, nausea, vomiting, abdominal pain, weight loss, melena, impotence, anemia, thrombocytopenia, back pain, arthralgia, paresthesia, blurry vision, renal insufficiency, cough, pulmonary edema, and dyspnea. Rare adverse reactions may include anaphylaxis, alopecia, aplastic anemia, asthma, bronchospasm, bundle branch block, cholestatic jaundice, erythema multiforme, exfoliative dermatitis, GI bleed, hearing loss, hyperbilirubinemia, hypokalemia, interstitial pneumonitis, leukopenia, migraine, MI, pancytopenia, rash, seizure, Stevens-Johnson syndrome, toxic epidermal necrolysis, urinary incontinence, and xerostomia. Subjects will be closely monitored for side effects throughout the study period and withdrawn from the study should unacceptable toxicity or side effects develop.

Risk Associated with PET/CT Scans

The radiation associated with the cardiac PET/CT scans is a potential risk to human subjects. For each scan, the injection of ^{18}F -FDG (10 mCi) results in an effective dose equivalent of 7.3 mSv. The CT portion of the study is performed at a very low dose for the purpose of PET data correction and results in an effective dose equivalent of 0.2 mSv. For this study, each subject may be exposed to a total of 14.6 mSv over the course of two PET/CT scans, which is considered to be in the acceptable range for diagnostic imaging studies. For comparison, the typical annual exposure to background radiation (radon, other terrestrial sources, and cosmic rays) is about 3 mSv, which means that the radiation exposure from this study is similar to that of seven years of typical exposure to background sources.

Risks Associated with Blood Draws and Genetic Risks

Risks associated with blood draws include brief pain resembling a bee sting, light bruising, bleeding, swelling, lightheadedness, and very rarely, infection. Although not a part of the longitudinal trial, in anticipation of future analyses of relationships of outcome parameters to hereditary PAH, DNA will be extracted from blood cells for genetic analyses of mutations in the genes associated with PAH, such as BMPR2. Work with the DNA will be performed at Cleveland Clinic by our collaborator Dr. M. Aldred. Genetic samples will only be identified by an ID number (not the patient name), and no genetic analyses will be performed other than that associated with PAH. Any identifying data will be kept in a locked drawer. The laboratory processing the DNA is a research facility. Genetic information about the patient or other information obtained from the blood sample will not be given to the patient, family or the patient's doctor. The patient may withdraw consent to use of the blood at any time by contacting the PI of the study.

Data and Safety Monitoring

This is a small, single-center trial, mechanistic study but will be registered on ClinicalTrials.gov. An internal Data Safety Monitoring committee will be comprised of Cleveland Clinic physicians who are experts in heart failure, β -blocker therapy, functional assessment of the heart, and

pulmonary hypertension: Dr. David Taylor, Chair of the DSM committee, and members including Dr. Jim Thomas, and Dr. Raed Dweik. Jeff Hammel, biostatistician will also serve on the committee for purposes of data analyses and quality control. Participant safety will be protected and monitored by weekly phone calls to the patients and biweekly review of the safety and tolerability outcome measures by the study coordinator. These safety and tolerability outcomes and any other adverse events that occur will be recorded in the patient's electronic medical record. Any adverse events that occur will be investigated to identify possible etiology and relationship to study procedures and reported to the IRB and the DSM committee within 10 working days of their discovery, with the exception of any deaths, which will be reported within 5 working days of their discovery.

d. Early Termination

Because this study requires a small sample size, there are no mid-study analyses scheduled, and thus a plan for early termination is not necessary.

G. Data Analysis/Reporting

a. Analysis Plan

Baseline characteristics will be reported, including age range and the proportions that are female, postmenopausal, and Caucasian. Means and standard deviations or medians and interquartile range will be reported for all continuous data, and non-continuous data will be reported as percentages. A log transformation may be utilized for any data that is not normally distributed. The three randomized study groups will be compared, based on the intent-to-treat principle, with respect to changes from baseline. Repeated measures analysis of variance will be used to compare groups using data from all time points together, though T-tests will also be used to compare pairs of groups with respect to differences between pairs of time points. Using actual administered doses, relationships between dose and changes over time will also be explored using appropriate linear or non-linear models to estimate dose-response relationships. Reports of blinded group summaries of adverse events will be regularly produced for safety monitoring.

b. Confidentiality

To maintain patient confidentiality, all study data will be de-identified. Each subject, upon enrolling in the study, will be assigned a three-digit subject number. Case report forms and the study database will identify each subject only by subject number and will contain no patient identifiers. De-identified case report forms will be kept within study binders, kept in a locked filing cabinet in a locked room. Completely de-identified study data will be stored in a data table maintained on a password-protected computer and stored on the Cleveland Clinic network, which is regularly backed up. The code identifying which patient belongs to each subject number will be kept in a separate locked filing cabinet in a locked room. Only the study coordinator and investigators will have access to this code.

REFERENCES

1. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.