STUDY PROTOCOL 3/11/2016

OUTPATENT ***V***ASODILATOR ***A***SSESSMEN***T*** USING **I**LOPROST IN PULM***ON***ARY HYPERTENSION (The **OVATION** Study)

A. Specific Aims

Iloprost was the first inhaled prostacyclin analogue to be FDA-approved for the treatment of pulmonary arterial hypertension in 2004.[1-3] Iloprost aerosol has been shown to significantly improve pulmonary hemodynamics in patients with idiopathic pulmonary hypertension (PH), with an effect greater than nitric oxide and sildenafil.[4] It was also shown to be more effective than nitric oxide in reducing PH intraoperatively, and more effective at reducing pulmonary arterial pressure (PAP) than prostacyclin infusion when used in the cardiac catheterization laboratory.[5, 6] Because of its administration through inhalational means, iloprost has the advantage of selective action on the pulmonary vasculature with avoidance of the systemic side effects that plague many of the other treatments for PH.[7,8] We intend to compare the efficacy of inhaled iloprost in reducing pulmonary artery pressure to the gold standard of nitric oxide in patients with pulmonary hypertension.

Without an established noninvasive algorithm to identify beneficial hemodynamic response to vasodilators, patients with pulmonary hypertension (PH) are routinely subjected to expensive and invasive testing. Doppler echocardiography is routinely used to facilitate a diagnosis of PH.[9,10] Doppler-derived estimates of pulmonary artery pressures correlate well with direct measurements obtained by right heart catheterization, though they may be imprecise in determining the actual pressures.[9-16] A few echocardiographically-derived estimates have even been shown to correlate with vasodilator responsiveness and survival.[17-20]

Dynamic, real time changes in echocardiographic parameters have not been previously evaluated as a predictor of vasodilator responsiveness or of clinical outcome. We hypothesize that echocardiographic changes in response to inhaled iloprost could predict invasively derived vasodilator responsiveness and help assess prognosis in patients with pulmonary hypertension, possibly even obviating the need for invasive testing.

Specific aims include the following:

Specific Aim 1: To compare the clinical efficacy of iloprost as an invasive, selective vasodilator in the cardiac catheterization laboratory in patients with PH to the gold standard of inhaled nitric oxide.

Specific Aim 2: To test the hypothesis that echocardiographic estimates of response to inhaled iloprost can predict responsiveness to invasive vasodilator testing (using iloprost or inhaled nitric oxide) in patients with PH.

Specific Aim 3: To build a model of dynamic echocardiographic parameters that can predict responsiveness to vasodilator testing and eventually clinical outcomes in patients with PH.

B. Background

1-Echocardiographic parameters to evaluate the right ventricle:

Noninvasive quantification of the right ventricular function is limited by the complex geometry of the right ventricle (RV) and with the load dependency of traditional echocardiographic indices.[19,21] Several echocardiographic techniques for estimating pulmonary artery pressures and RV function have been proposed, including RV ejection fraction, RV acceleration time, RV myocardial performance index (RVMPI), pulmonary and tricuspid valve velocity measurements, eccentricity index, strain imaging and tissue Doppler imaging. Most of these echocardiographic variables show correlation with pulmonary vascular resistance; though they may be imprecise in determining actual pressures.[9-16] Models consisting of several variables have been built to increase the sensitivity and specificity of these tests.

New RV function parameters are also being evaluated. Tricuspid annular displacement (tricuspid annular plane systolic excursion; TAPSE), for example, is a parameter that correlates closely with RV ejection fraction and was found to be associated with mortality in patients with PH.[17,19] Tissue Doppler-derived measurements also have been used to assess RV systolic and diastolic properties.[22-27]

To our knowledge, most of these variables were studied for follow-up purposes in patients treated chronically for PH. One study retrospectively reviewed echocardiographic correlates of vasodilator responsiveness in patients with primary pulmonary hypertension and found only Doppler pulmonic peak flow velocity to be an independent index of responsiveness.[28] Furthermore, none of these tests previously mentioned have involved real time echocardiographic monitoring of changes during a vasodilator challenge. The study proposes the use of changes in echocardiographic

parameters during a vasodilator challenge for prediction of responsiveness and assessment of clinical outcome in PH.

2-Vasodilator challenge:

Iloprost is one of two inhaled prostacyclin analogues that are FDA-approved for the treatment of pulmonary arterial hypertension.[1-3] The unique iloprost delivery system produces aerosol particles of appropriate size (with an optimal mass median diameter of 3.0 micrometers) to ensure alveolar deposition, thereby improving pulmonary selectivity.[29] Its clinical efficacy for both long-term (to 5 years) and short term (12 weeks) use has been studied.[30-32] The aerosol does not have systemic adverse effects, nor does it negatively alter pulmonary function tests or gas exchange.[33] Furthermore, while intravenous prostacyclin can cause significant increases in heart rate and decreases in blood pressure, inhaled iloprost does not affect either of these parameters.[6]

Inhaled iloprost has been shown to positively affect both invasively and non-invasively obtained measures of hemodynamics and cardiac performance.[4,34] An iloprost challenge also can be utilized to identify which patients are likely to respond to oral vasodilators.[35]

A few studies have compared the hemodynamic response to inhaled iloprost versus inhaled nitric oxide and oxygen. In patients with idiopathic pulmonary hypertension or HIV-related pulmonary hypertension, inhaled iloprost was more effective at lowering pulmonary vascular resistance (PVR) than the combination of inhaled nitric oxide and oxygen.[4,36] Iloprost aerosol also caused a greater decrease in PVR than oral sildenafil, though the difference was not statistically significant.4 Of note, during the latter study (10 patients), the PVR response rate was higher with inhaled iloprost (70%) compared with sildenafil and nitric oxide (each 40%). In addition 57% of the iloprost responders responded to sildenafil and nitric oxide (all responders to sildenafil and nitric oxide responded to iloprost).

The pharmacodynamic and pharmacokinetic studies have shown that inhaled iloprost has a serum level half-life of 6.5 to 7.7 minutes but a pharmacodynamic effect (decrease in PVR) half-life ranging from 21 to 25 minutes.[37] The peak hemodynamic effect (decrease in PVR and mean PAP) was reached by the end of the inhalation (five micrograms inhaled over ten minutes), and the effect lingered for about twenty minutes (especially the decrease in mean PAP) and leveled off after 120 minutes.[Figure 1]

Inhaled iloprost is the most appropriate vasodilator to use in conjunction with echocardiography for noninvasive assessment of responsiveness because of its convenient administration, potency, selectivity for the pulmonary vasculature, low systemic side effect profile, and short half-life. From a cost effectiveness standpoint,

also, inhaled iloprost is among the least expensive of the prostanoid therapies, while being more effective than some of the other available prostanoids, particularly subcutaneous trepostinil.[38]

The optimal evaluation would be to measure the echocardiographic parameters at the following time points:

- Baseline: performed before the initiation of inhalation

- Maximum effect: initiated up to 3 minutes before the completion of the inhalation and lasting up to 20 minutes after completion of the 10 minute inhalation.

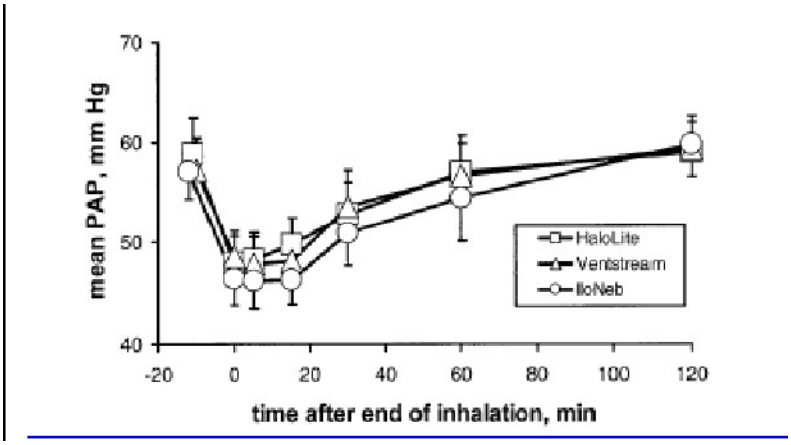

Figure 1. Time course of pulmonary arterial pressure in response to iloprost inhalation.

C. Study Plan

1-Patient population:

Prospective participants will be recruited from the outpatient pulmonary and adult congenital heart disease clinics at their routine pulmonary hypertension visits.

2-Inclusion criteria:

- Adult patients no younger than 18 years of age

- Recently diagnosed pulmonary hypertension (defined by RV systolic pressure of ≥ 40 mmHg as measured by echocardiography), going for invasive hemodynamic assessment for pulmonary hypertension

- Normal left ventricular function defined as a left ventricular ejection fraction (LVEF) greater than or equal to 50%

3-Exclusion criteria:

- Heart failure (LVEF < 50%, diastolic dysfunction > stage 1, history or symptoms of left heart failure)

- 2+ or higher MR or AI

- Inadequate echocardiographic windows

- Pregnancy

- Systolic blood pressure ≤ 90 mmHg

4-Study design:

Patients who present with the above inclusion criteria typically are sent for echocardiography and then referred for vasodilator responsiveness invasive testing, which includes a right heart catheterization with vasodilator challenge as part of their usual management. Patients who agree to participate in the study first will undergo an initial assessment, including a history, physical exam, and blood work (CBC, CMP), per the standard of care. An echocardiogram with iloprost aerosol challenge will be performed within the 24 hours prior to the right heart catheterization. Patients then will be routinely followed by the Pulmonary Department every 3 months according to standard of care. At each of these visits, all patients undergo a variety of tests, including the 6 minute walk test, echocardiogram, and blood work (CBC, metabolic panel, BNP). Data from the 3 and 12 month follow-up visits will be used in this study.

Echocardiography:

All echocardiographic measurements will be performed by an echocardiography research technician blinded to the initial presentation and invasive results of the patients, using state of the art echocardiographic imaging equipment. Parameters listed in Appendix A will be gathered prior to iloprost inhalation challenge and sometime between 3 minutes before the completion of the inhalation and 20 minutes after completion of the 10 minute inhalation. The vasodilator challenge echocardiographic test will be done within 24 hours of right-heart catheterization.

Iloprost will be administered by the I-neb ultrasonic nebulizer (Respironics, Cedar Grove, New Jersey) with a disposable attachment that allows for administration to a supine patient at a concentration of 10 µg/ml with a 10 minute dose of 2.5 µg and then repeated to a cumulative dose of 5.0 µg if tolerated. Systemic blood pressure will be checked before, at the end, and at 10, 20, 40 and 60 minutes after the iloprost challenge using a General Electric DASH 4000 automatic monitoring system with complete ECG and pulse oximetry. The challenge will also be done using standard electrocardiographic, hemodynamic, and oxygen saturation monitoring.

Right heart catheterization:

Right-heart catheterization (RHC) will be performed in the catheterization lab at Duke Medical Center according to standard protocol. A Swan-Ganz catheter will be inserted either through the internal jugular vein or the femoral vein into the right heart cavities under fluoroscopic guidance. An arterial line will also be inserted into the right radial or femoral artery to continuously monitor the blood pressure. This procedure and all testing procedures will be done in a controlled environment with continuous electrocardiographic, hemodynamic and oxygen saturation monitoring. Inhaled nitric oxide will be administered at the dose of 40 ppm using a specialized delivery system (INOvent Delivery System, Ohmeda Inc., Madison, WI). Hemodynamic parameters will be measured before and five minutes after the nitric oxide challenge, including systolic, diastolic, and mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and cardiac index (CI) measured using the Fick method and pulmonary and systemic vascular resistance indices (PVRI and SVRI).

A second vasodilator challenge with iloprost will be performed 10 minutes after stabilization of hemodynamic parameters and return to baseline (as defined by the above hemodynamic parameters). Iloprost will be administered by the I-neb ultrasonic nebulizer (Respironics, Cedar Grove, New Jersey) with a disposable attachment that allows for administration to a supine patient, at a concentration of 10 µg/ml with a 10 minute dose of 5.0 µg if previously tolerated during the echocardiographic challenge (if not 2.5 µg will be used). The same hemodynamic parameters will be measured as noted above for inhaled nitric oxide.

We are aware that having patients undergo a challenge with iloprost directly after a challenge with NO may theoretically influence the iloprost data due to carryover effects. It is however not feasible to randomize the patients into a group receiving iloprost first and a group receiving NO first as the effective half-life of inhaled NO is between 2 and 6 seconds[39] and the effective half-life of inhaled iloprost is between 21 and 25 minutes.[37] Therefore administering iloprost as the first drug to some patients would cause up to a 40 minute delay to the cath lab and would lengthen both the procedure and sedation time for the patient. Other studies that have investigated multiple vasodilators (including

iloprost) in this setting, acknowledge the constraints of contrasting pharmacological properties on the sequence of vasodilator administration. In such cases the investigators have chosen not to randomize the order of vasodilators but instead ensure adequate wash-out times by waiting for normalization of hemodynamics.[6]

5-Endpoints:

Primary endpoint:

To compare the percent change in the invasively measured PAP after challenge with NO compared to the percent change in invasively measured PAP after challenge with iloprost.

Secondary endpoints:

- To compare the percent change in echocardiographic parameters measured after vasodilator challenge with the percent change of invasively measured vasodilator response.

- To dichotomize the vasodilator response into responders and nonresponders, based on a 10 mm Hg drop in PA pressure and a mean pressure <40 mm Hg determined invasively. Receiver operating characteristic (ROC) curves will evaluate the echocardiographic parameters for prediction of vasodilator response.

- To measure the clinical response to vasodilator challenge during echocardiography, by tracking the changes of echo parameters (such as RVSP) before and after iloprost challenge, as well as through the 3 and 12 month follow-up visits.

- To observe the association of the percent change of echocardiographically estimated pressures after iloprost challenge with mid-term clinical outcomes (all cause mortality and all-cause mortality +/- hospitalization). These data will be collected at 3 months and at 12 months. Data from all hospitalizations will be collected, though we will make special note of those related to pulmonary hypertension.

Power study and sample size:

Based on combined data from the Duke University Medical Center and the Cleveland Clinic catheterization laboratories, the response to NO has been 13.6 ± 6% compared to the published response to inhaled iloprost of 17.2 ± 6%,[43] resulting in an expected difference of 3.6%. In order to detect this difference using a two-sided one-sample

t-test, alpha of 0.05, a power of 90% (β=0.1), and assuming a correlation between responders to NO and responders to iloprost, the study will need 32 patients. Given our clinical load it is reasonable for us to reach up to a 50 patient sample. This will allow us to compensate for anticipated attrition as patients may eventually need to be excluded if invasive parameters show insufficient pulmonary pressure elevation or elevated pulmonary capillary wedge pressure, the discovery of criterion for exclusion on the vasodilator challenge echocardiography, and assuming that up to 20% of patients may be lost to follow-up.

Statistical analysis:

The percent change in pulmonary blood pressure during the nitric oxide invasive test and the iloprost invasive test will be compared using paired t-testing. The percentage change estimated from the echocardiographic iloprost challenge, and the iloprost invasive test will be compared using Bland and Altman plots to assess the level of agreement between the 2 methods and the limits of agreement will be calculated. After dichotomizing the invasive response data to responders and nonresponders, ROC curves will evaluate the predictive value of the change in the different echocardiographic parameters collected during the iloprost challenge (Appendix A). The changes in echo parameters before and after iloprost challenge (and at 3 and 12 months) will be compared with a repeated measures ANOVA or paired t-testing as indicated. Statistical tests will be two-sided and results with p-values ≤ 0.05 will be considered statistically significant.

6-Ethical Aspects of Proposed Research:

The subject population sampled will be inclusive of the adult population of patients with suspected pulmonary hypertension seen at Duke Medical Center, without restriction to gender, race, age (other than being ≥18 years of age), socioeconomic status, or location of care. This research work will be performed at the Cardiac Catheterization Laboratory and the Echocardiography Laboratory at Duke Medical Center. As already mentioned, the right heart catheterization is part of the standard of care of the pulmonary hypertension patient: patients will not get the right heart catheterization only for the purposes of this study but as part of their evaluation and management outside the scope of this study. The echocardiogram also will be part of their standard evaluation prior to initiation of medical therapy. Enrollment of research subjects into the study will follow the strict guidelines stipulated by the Duke University Institutional Review Board who have approved the protocol and consent form. All subjects will be informed of their rights, the risks, benefits, and alternatives to participation in the study and all subjects will sign an informed consent if they are willing to undergo the study.

The materials and data will be obtained specifically for research purposes, and no use will be made of existing specimens, records, or data other than those mentioned in the informed consent.

D. Significance of Research

Right heart catheterization is an invasive, expensive, and time consuming procedure that has a considerable side effect profile. To our knowledge, real time changes in echocardiographic parameters have never been used to assess vasodilator responsiveness. If echocardiographic parameter changes after inhaled iloprost challenge can predict the vasodilatory results obtained during a right heart catheterization, this could potentially obviate the need for invasive testing in patients with pulmonary hypertension. Moreover, the associated reductions in invasive testing and inhaled nitric oxide challenges in this patient population would result in significant cost savings.

E. Facilities at the Sponsoring Institution

The echocardiogram and iloprost challenge will be conducted by an experienced research echocardiography technician. The Cardiac Imaging Core Laboratory will provide technical expertise in echocardiography. The catheterization will be performed in the Duke Cardiac Catheterization Laboratory as per the standard of care for this patient population.

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