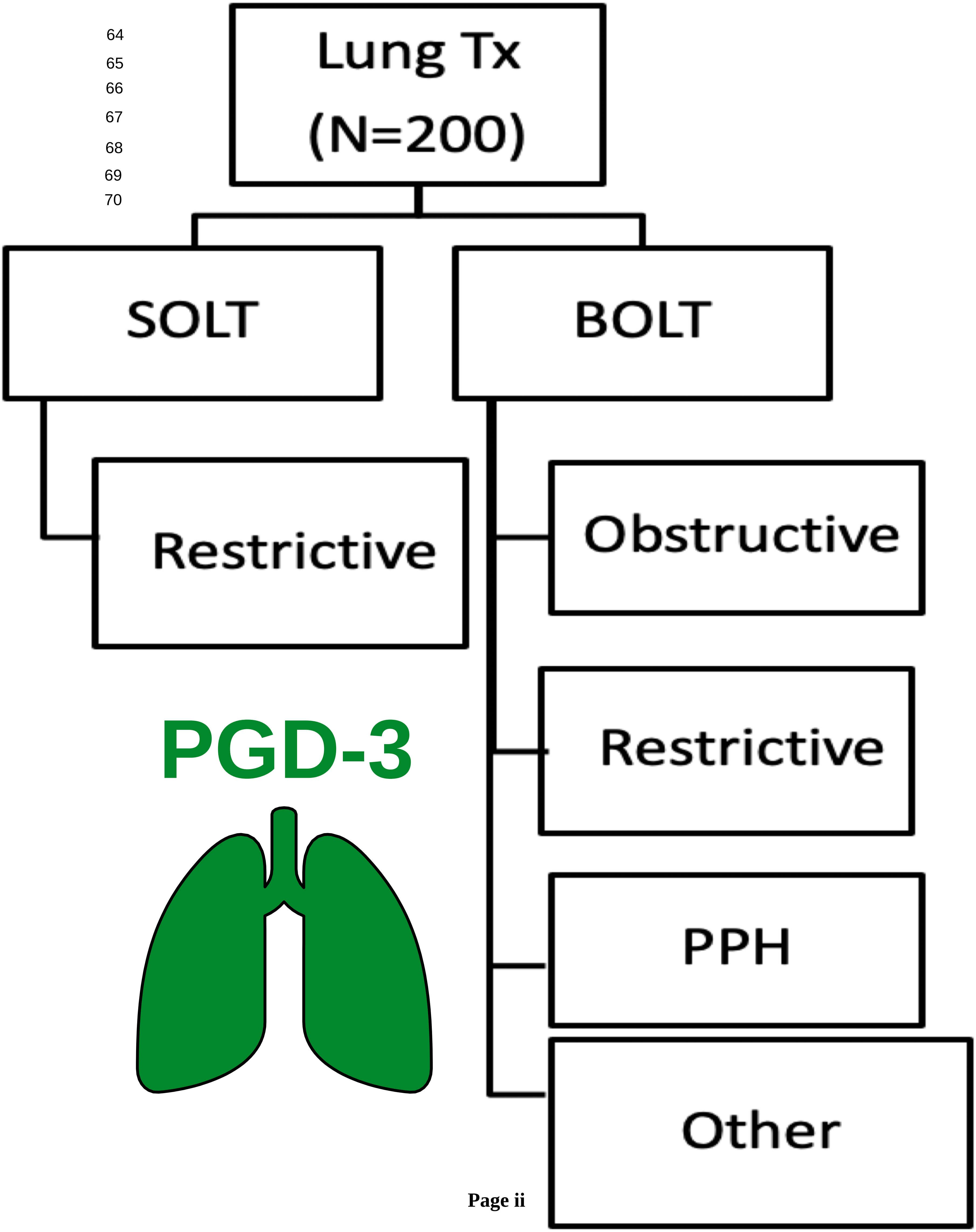
# Original iPVD Trial Protocol and Protocols for Lung Transplant Participants

**Table of Contents** **Page(s)**


Lung Tx
(N=200)
SOLT
BOLT
Restrictive
Obstructive
Restrictive
PPH
Other
PGD-3

**1. Protocol Title:** Inhaled Pulmonary Vasodilator Therapy in Left Ventricular Assist Device (LVAD) Implantation, Heart Transplantation, and Lung Transplantation: Prospective, Randomized, Double-Blinded Study

**2. Purpose of the Study:**

*1. Aim I – Clinical Trial Investigation.* In order to utilize Inhaled Epoprostrenol (iEPO, Veletri®, Actelion Pharmaceuticals, South San Francisco, CA, USA) as an acceptable alternative to Nitric Oxide (iNO, INOMAX®, Mallinkrodt Pharmaceuticals, St. Louis, MO, USA) in adult patients, we propose a randomized, prospective, double-blinded trial in the cardiothoracic surgical population, which will evaluate the primary hypothesis that these two medications will have similar efficacy in pulmonary vasodilation and a similar impact on clinical outcomes in end-stage lung disease patients undergoing lung transplantation and end-stage heart failure patients under durable LVAD implantation or heart transplantation (Table 1).

*2. Aim II – Cost-Capture Analysis.* There will be a parallel prospective cost-capture analysis designed to precisely acquire the expenses that each drug incurs per patient averaged across all patients randomized to that drug.

**Table 1. Study Summary**

| | |
|---|---|
| **§Sample Size** | N = 424 (50/50 by randomization strata) |
| **Population** | 1. Lung transplantation (N = 200)<br>2. Heart Transplantation / LVAD implantation (N = 224) |
| **Rationale** | • Comparison of iNO and iEpo impact on outcomes – evaluate for equivalency<br>• PVD therapy indications:<br>1. Lung Transplant: Improvement of ventilaton and perfusion matching after lung allograft implantation by vasodilation of ventilated pulmonary capillaries<br>2. Heart Transplant/LVAD Implantation: Improvement of RV contractility after cardiac allograft implantation or LVAD implantation by PVR reduction |
| **Study Design** | Prospective, Randomized, Double-Blinded |
| **Primary Outcomes** | 1. Lung Transplant: Severe PGD (grade 3)<br>2a. Heart Transplant: RVAD insertion<br>b. LVAD: INTERMACS Moderate or Severe RVF |
| **Secondary Outcomes** | All populations:<br>• ICU LOS (days)<br>• Hospital LOS (days)<br>• Mechanical ventilator duration (hours)<br>• Postoperative AKI<br>• In-hospital mortality<br>• Mortality 30-day, 90-day, 1-year |
| **Study length*** | 24-36 months |

§Sample size powered for primary outcomes
*Study length is determined through sample size divided by annual operations at Duke Universtiy Hospital; AKI = Acute kidney injury; iEpo = inhaled epoprostenol; iNO = Inhaled nitric oxide; ICU = Intensive care unit; LOS = Length of stay; LVAD = Left ventricular assist device; PGD = Primary graft dysfunction; PVD = Pulmonary vasodilators; PVR = Pulmonary vascular resistance; RVF = Right ventricular failure

***3.* Background & Significance:**

*Introduction.* Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator (PVD) with FDA-approval in the neonatal population alone. In adult patients, iNO is used off-label to treat pulmonary hypertension, right ventricular (RV) failure, and ventilation-to-perfusion mismatch. Adult patients who undergo durable LVAD implantation (e.g. Heartware®, Heartmate 2®, or Heartmate 3®) or cardiac transplantation for end-stage heart failure or those that have endured lung transplantation as a result of end-stage lung disease, compose the largest subpopulation which receives PVD therapy at Duke University Hospital. Intravenous Epoprostenol is FDA approved for adult patients with pulmonary hypertension and is the only agent which has displayed mortality benefit in these patients. The inhaled formulation of Epoprostenol (iEPO) was developed in order to maintain efficacy and avoid the systemic side effects of vasodilation and thrombocytopenia. Inhaled iEPO is used off-label in our cardiothoracic surgical patients for new-onset perioperative pulmonary arterial hypertension (PAH), known preoperative PAH, RV dysfunction with LVEF > 35-40%, and promotion of ventilation to perfusion matching through alveolar deposition of the prostanoid compound and vasodilation of the intimately associated intra-acinar pulmonary arteries. This vasodilation can decrease pulmonary vascular resistance and can improve oxygenation while avoiding systemic effects commonly seen in the intravenous formulation. iEPO has been introduced in the cardiothoracic operating rooms (OR) and ICU as a cost-conscious alternative medication to iNO. iEPO may display an equivalent efficacy profile to iNO for pulmonary vasodilation and oxygenation and have a similar impact on clinical outcomes. For the purposes of this writing, thoracic transplantation will refer to both heart and lung transplantation.

*Pharmacology.* There are 3 major pathways that affect pulmonary vascular tone: 1)Nitric oxide (vasodilatory), 2)Prostaglandin (vasodilatory), and 3)Endothelin (vasoconstrictive) pathways. During cardiothoracic operations, particularly transplantation and LVAD surgery, there is an appreciable imbalance in these pathways, which favors vasoconstriction. iNO administration, exerts its mechanism of pulmonary vasodilation and ventilation-to-perfusion matching through exogenous NO delivery and iEPO applies a similar mechanism via exogenous prostacyclin delivery. Both agents are delivered through mechanical ventilation to ventilated alveoli in order to promote gas exchange at the capillary bed. Both inhaled medications are desirable in this population due to pulmonary selectivity, absence of systemic vasodilation, as well as fast onset (5-10 seconds for iNO and 30-60 seconds for iEPO) and quick titration owing to short-half lives (10-20 seconds for iNO and 1-2 minutes for iEPO). There is no decision tree involved in the use of iNO vs iEPO except for that patient's known drug allergies which may preclude use of one inhaled agent in favor of the other. Of note, endothelin antagonists (e.g. bosentan), which are not part of our perioperative standard practice, are PO medications which require reliable gastrointestinal absorption that may not be present during high-dose inotropic support, and are not readily titrated to effect as are the inhaled PVD, iNO and iEPO.

*Contraindications and Adverse Effects.* Absolute indications for iNO in favor of iEPO are due to prostaglandin allergy leading to anaphylaxis (extremely rare) or if the patient is pregnant due to risk for labor induction as a result of prostacyclin agonism. Routine pregnancy testing is performed in the preoperative setting in line with established preoperative anesthesia testing criteria. Parturients rarely present for thoracic transplantation or LVAD implantation. There are no absolute contraindications to iNO therapy in adult patients but the iNO delivery device system routinely measures the toxic metabolite of iNO, nitrogen dioxide ($NO_2$), which can lead to hypoxemia during metabolite accumulation. Additionally, methemoglobinemia (MetHb) is another rare adverse occurrence of prolonged iNO administration and MetHb levels are measured during arterial blood gas analysis.

*Preliminary retrospective study supporting noninferiority hypothesis.* In a retrospective study of 51 adult cardiothoracic surgical patients (all-comers, including thoracic transplantation, durable LVAD implantation, and non-transplant and non-LVAD cardiac surgical patients), requiring pulmonary vasodilation, our group illustrated similar efficacy between the use of iEPO and iNO with respect to optimizing RV hemodynamic variables, including pulmonary vasodilation and mixed venous oxygenation (Table 2). During this investigation, iNO was initiated in the operating room (OR) and continued during transport and into the ICU. While in the ICU, postoperative hemodynamic stability was achieved within 2 hours and iNO was transitioned to iEPO over 30 minutes in order to provide continuous inhaled pulmonary vasodilation and allow the patient to self-control during medication cross-over between iNO and iEPO. Clinical variables were followed at 5-minute intervals for 1 hour after transition to iEPO. No statistically significant differences were seen in hemodynamic variables during this transition (Table 2). The small sample size and retrospective design, however, incorporated several confounding variables that could not be controlled and *prospective data was deemed necessary to achieve reliable conclusions by evaluating clinical outcomes in order to change clinician practice patterns*. Other investigations have demonstrated equivalence in hemodynamic variables, mixed venous oxygenation, and ventilation-to-perfusion matching when delivery of iNO was compared with iEPO. These studies were, however, also retrospective or inadequately powered to rely on conclusions related to outcome measures.

**Table 2. Hemodynamic values in CT surgical patients comparing inhaled Nitric Oxide and Epoprostenol**

| N= 51 | *HR | ¶MAP | ¶PAPs | ¶PAPd | ¶PAPm | ¶CVP | ¥CI | PI | §LVAD flow | SVO2 (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| [a]iNO | 98 | 78 | 37.9 | 18.6 | 25.3 | 12.5 | 2.61 | 5.36 | 4.66 | 71 |
| [a]iEpo | 100 | 80 | 39.1 | 19.0 | 26.8 | 12.2 | 2.67 | 4.93 | 4.82 | 70 |
| *P*-value | 0.41 | 0.40 | 0.48 | 0.58 | 0.24 | 0.74 | 0.63 | 0.52 | 0.65 | 0.52 |

a = reported as mean values; * units = beats per minute; ¶ units = mm Hg; ¥ units = $L/min/m^2$
CI = Cardiac Index, CVP = Central Venous Pressure, HR = Heart Rate, iNO = Inhaled nitric oxide, iEpo = Inhaled epoprostenol, LVAD = Left Ventricular Assist Device, MAP = Mean Arterial Pressure, PAPs = Systolic Pulmonary Artery Pressure, PAPm = Mean Pulmonary Artery Pressure, PAPd = Diastolic Pulmonary Artery Pressure, PI = Pulsatility Index, $SvO_2$ = Mixed Venous Oxygen Saturation

The large cost differential between these two agents remains an important concern for the health system: iNO is approximately 8-fold more expensive than iEPO, according to preliminary estimates based on PVD usage. Previous reports have estimated the cost of iNO administration to be between $95.00 – $115.00 per hour during medication delivery. The cost, however, has not precisely captured the time required to assemble the iNO delivery system as well as resources utilized to breakdown this setup into individual components following termination of delivery. The cost of iEPO delivery is captured at $14.83 per hour, which includes solution compounding by pharmacy as well as processing for delivery and nebulization by respiratory care services. Additionally, the iEPO delivery-system setup is a one-time, fixed cost for the duration of administration. Similar secondary resource utilization capture for iEPO is required for accurate cost comparison between these two agents.

## *4.* Design & Procedures:

*<u>Aim I – Development of a Definitive Clinical Trial Investigation</u>.*

*1. Randomization and Double-Blinding.* The clinical research unit (CRU) will receive preoperative notification of lung and heart transplantation patients by reviewing the transplant waitlist. Preoperative notification of LVAD implantation will be done by the review of the cardiothoracic surgical schedule. Using a 50% randomization process utilized and established by the CRU at Duke University Hospital, each eligible patient will be randomized to receive either iNO or iEPO. The primary endpoint data will be collected and documented in an electronic data capture system during the period of time the patient, clinical care team, and study team are blinded. Primary endpoint data collection will be complete prior to the subjects' discharge from the ICU, at which point the unblinding will occur. Since primary endpoint data collection will occur during the blinded period, the potential for bias will be substantially minimized.

*2. Measured Outcomes.* The primary endpoint for the comparison of efficacy in the Lung Transplant population will be the incidence of Grade 3 Primary Graft Dysfunction (PGD). This is defined by the International Society of Heart and Lung Transplantation (ISHLT) as severe hypoxemia with a $PaO_2$-to-$FiO_2$ ratio < 200 or the presence of venovenous extracorporeal membrane oxygenation (VV ECMO) at an time-point within the first 72 hours after lung transplantation. The primary endpoint for the comparison of efficacy in LVAD patients will be incidence of moderate or severe RV failure according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scoring. The primary endpoint for the comparison of efficacy in the heart transplant subset will be the incidence rate of RVAD insertion. Secondary endpoints related to clinical outcomes for all populations will be duration of postoperative mechanical ventilation, , ICU Length of Stay (LOS), hospital LOS, incidence of acute kidney injury, incidence of in-hospital mortality, as well as postoperative mortality at 30-days, 90-days, and 1-year after operation (Table 1).

*Aim II –Cost-Capture Analysis.*

In parallel with the design & procedures of *Aim I*, the cost capture analysis component will be essential in order to better gauge the cost due to duration of administration (variable cost) according to each inhaled PVD. Established clinical criteria specific to each group (lung transplantation vs. heart transplantation/LVAD implantation) have been developed to determine the inception of protocolized PVD weaning. Weaning medications according to established protocols will allow for accurate interpretation of the comparative length of therapy between iNO and iEPO and help prevent erroneous PVD usage without criteria for discontinuation. Secondary resource utilization will be documented by respiratory care services and itemized cost sheets will be developed.

Subject Groups

Inhaled PVD therapy is administered to every patient undergoing thoracic transplantation and LVAD implantation at our institution and each patient is eligible for enrollment. Over a 3-year period (1 year for follow-up) we will prospectively enroll 200 lung transplant subjects and 224 heart transplant or LVAD implantation patients who will be informed and consented prior to their scheduled procedure. Potential subjects will be under the care of 1 or more investigators in this study. Consented subjects will be randomly assigned to 1 of 2 groups, iNO vs iEPO, to be initiated in the OR on the day of the operation based on accepted standard of practice and study protocol. Medication administration will be double-blinded, such that neither the surgical nor anesthesiology teams will be notified of the inhaled agent to which the patient has been randomized. Ability to unblind the delivery system will be made available to both teams if required to preserve optimal patient care. As per our standard practice, respiratory care services will manage the initiation and maintenance of inhaled PVDs in the OR and ICU, and these personnel will be the only practitioners notified of the actual delivered medication during study blinding.

Exclusion Criteria

- Combined Organ Transplantation (Heart-Lung, Heart-Liver, Heart-Kidney)
- Age < 18 years old
- Pregnancy (females of child bearing potential will receive pregnancy testing prior to cardiothoracic surgery as a standard of care)
- Known allergy to prostaglandin (rare)
- Subject is enrolled in another study protocol, which does not allow randomization of PVD therapy
- Heart transplant or durable LVAD recipients with adult congenital heart disease (CHD)
- Caveat: Does NOT meet exclusion criteria if the scheduled heart transplant or LVAD implantation is due to heart failure from *a previous heart transplantation* related to CHD, performed more than 90 days previous to the date of trial enrollment
- Patient is scheduled to undergo lung transplantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo durable LVAD implantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo heart transplantation but has undergone lung transplantation in the previous 90 days
- Patients with preoperative VV ECMO as a bridge to lung transplantation
  - ○

Stopping Criteria – In the event the following criteria are met and the clinical team is in agreement, subjects will be weaned off of their iPVD per instutional standard iPVD weaning practice. If adverse events are encountered, the drug will be immediately stopped without weaning.

- Venoarterial (VA) ECMO insertion remains at end of operation
- VA ECMO insertion is performed postoperatively in the ICU
- LVEF < 30% on echocardiogram at the end of the operation for heart and lung transplant subjects
- LVEF < 30% for heart and lung transplant subjects on echocardiogram noted postoperative in the ICU

- Inhaled pulmonary vasodilation is halted for reasons other than standard weaning ordered by the clinical care team
- Adverse events related to the INO or EPO that affect the subject's welfare

<u>Data Collection</u>

*Secondary measures will be hemodynamic variables* (similar to those measured in Table 2) such as transesophageal echocardiographic (TEE) evaluation of RV function based on stand-of-practice protocol, intravenous administration of inotropes, serial measures of postoperative serum creatinine and GFR, resolution of elevated liver function tests (heart failure patients, illustrates improvement in RV function), incidence of thrombocytopenia (platelet count < 150 x $10^9$/L) and trajectory of resolution, as well as ventilation-to-perfusion matching (arterial oxygen tension, $PaO_2$; arterial carbon dioxide tension, $PaCO_2$; and fraction of inspired oxygen, $FiO_2$). Variables will be recorded at designated time points during the entire duration of administration – from initiation in the operating room to cessation in the ICU. These time points include: Intraoperative before surgical incision, time = 0 (initiation of PVD), 30 minutes, 2 hours, 6 hours, 12 hours, 18 hours, 24 hours, and every 6 hours up through 72 hours after initiation. These secondary measures will be obtained up through 72 hours after initiation regardless of cessation or continuation of the inhaled PVD. After 72 hours, increments of every 12 hours thereafter will be assessed if PVD administration continues. Ventilation and perfusion nuclear scans will be obtained and recorded per standard clinical practice for each group of lung transplant recipients. Established protocols with criteria for initiation of medication weaning have been created according to each medication based on individual pharmacokinetic properties. Once established criteria are met, weaning of each inhaled PVD will begin and continue until the medication is terminated according to standardized weaning protocols established for lung transplant patients and heart transplant/LVAD patients.

*Subject follow up.* Subject will be contacted by phone by a member of the research team and be asked a short series of questions to assess their current medical condition and any changes since surgery at 30-days (± 3 days), 90-days (± 5 days), and 1-year (± 7 days) after surgery completion date. The phone follow-up should take approximately 5 minutes of the subject's time. If subjects have been admitted to a hospital outside of Duke Health after surgery they will be asked to sign an authorization of release to provide us permission to obtain medical information related to their hospitalization.

<u>Blood Sampling</u>

Blood samples will be drawn for analysis as a part of this study. One 9 ml sample of blood will be obtained from each patient prior to the initiation of PVD therapy and stored at 4°C prior to processing. This sample will be stored for Genomic DNA analysis at the completion of this study in order to assess patients who are responders to inhaled pulmonary vasodilaton through upregulation and down regulation of notable vasoactive substances (e.g. endothelin, thromboxane, nitric oxide, prostaglandin, etc.). In addition, each subject will also be asked to sign the Genomic and Proteomic Database Repository (IRB Pro00015651) consent form, thus allowing the banking of their plasma and DNA samples as well as data to be used for future research. Participation in IRB Pro00015651 is voluntary and optional to all subjects consented in this parent study. Blood samples (7 ml each) will be drawn at 3 separate time points: 1) directly after insertion of the invasive blood pressure monitoring (arterial) line, 2) POD 1, and 3) POD 7. In each 7ml blood sample, 3.5ml will be collected in Sodium Citrate tubes for coagulation analysis and another 3.5ml will be collected in EDTA tubes for metabolomic and proteomic analysis. Plasma will be separated from these samples and banked at -80°C for analyses of proteomic and metabolomic signatures. Up to 30ml of blood will be collected during the 12 month study participation period.

**6. Subject Identification, Recruitment, & Compensation:** Subjects will be recruited either during the outpatient or inpatient evaluation phase, or contacted by phone. Recruitment may also occur on the day of the operation given the complexities of the transplant process, which may provide obstacles to earlier enrollment. After obtaining permission from the operating surgeon, surgical subjects will be screened by the study coordinator by reviewing the transplant pre-list. Prior to asking any patient for consent to participate, the patient or Legally Authorized Representative (LAR) will be approached first by the surgeon or one of the members of the surgical care team to determine if the patient or LAR is willing to consider enrollment in the study. If so, the subject or LAR will either be seen during an inpatient or outpatient visit, or be contacted by phone and informed about the study by a member of the research team. If the individual or LAR is willing to consider enrollment and does not meet exclusion criteria, then the research coordinator will present the research protocol in its entirety. During this time, the study coordinator will answer any and all questions as they arise. If the subject or LAR agrees to participate, the coordinator will ask the them to sign and date the appropriate consent form. A copy of this consent form will be given to the subject and a copy of the consent form will be added to the subject's medical record. The subject or LAR will be given the option to sign a separate consent form to allow us to store portions of the collected blood specimens and any data collected under this research study and maintain these samples and data in a database/repository (PRO00015651) for possible use in future research studies relating to surgical outcomes. In the event a LAR provides consent at the time of enrollment, the subject will be approached once they regain the ability to provide an informed consent.

Recruitment will not routinely occur on the day of the operation and most patients will be enrolled at least 12 hours in advance and provided at least the allowable time to review the study consent form and discuss their options with the PI and study personnel. There will be no direct compensation to the patient for recruitment.

If a subject is enrolled and randomized in this study for their LVAD implantation procedure and is later planned to receive a heart transplant, that previously enrolled subject is eligible to be re-enrolled. The following caveats apply to this subpopulation of LVAD patients:

A)Durable LVAD implantation may occur as a bridge to heart transplantation.

B)If LVAD implantation is followed by heart transplantation WITHIN 1 year following LVAD implantation, then data collected up through the time of heart transplantation will be recorded and valid as a patient in the LVAD group.

C)Data collected on or after the date of LVAD explantation/heart transplantation for such a patient will be considered as part of the heart transplant group.

D)If LVAD implantation is followed by heart transplantation AFTER 1 year following LVAD implantation, then the 1year follow-up period is complete and the patient may re-enter the trial as a heart transplant patient.

If a subject is enrolled and randomized in this study for their durable LVAD implantation procedure and is scheduled to receive a new durable LVAD via an LVAD exchange operation, the subject is eligible to be re-enrolled.

**7. Subject's Capacity to Give Legally Effective Consent:** Explicit (written) consent will be obtained from the patient or the patient's legal decision maker.

**8. Study Interventions:** Using a 50% randomization process utilized and established by the CRU, each eligible patient will be randomized to receive either iNO or iEPO, to be initiated in the OR based on accepted standard of practice at Duke University Hospital, during the clinical care of these patients.

**9. Risk/Benefit Assessment:** There is no direct benefit of this study to the enrolled subjects. Data gathered from this study may benefit future patients. Up to 30 ml of blood will be drawn during the 12 month study participation period. Blood sampling will be obtained, in the majority of subjects, from indwelling arterial or central venous lines inserted at the beginning of the intraoperative period as part of standard practice for these operations and there will be no additional risk to the patient for obtaining such vascular access. On rare occasion, blood sampling may be obtained from additional venipuncture sites during the postoperative period. Risks of blood sampling if obtained through venipuncture are pain, swelling, possible infection at the site of venipuncture. While these risks are minimal, the additional blood volume is highly unlikely to contribute to the patient's need for blood transfusion. To minimize any potential risk to the patient from genetic data, investigators and patients will be blinded to the individual patient's genotype. This information will not be included in the patient chart, will remain absolutely confidential, and will not be given to the patient or their family. DNA samples will be identified only by a coded number whose relation to the patient's name and other identifiers is available only to the data manager. The identity of the patient will remain anonymous in any publications which may result from this investigation.

There will be no additional risks to the subjects as a result of this study. Prior to June of 2015, iNO was the sole option for inhaled pulmonary vasodilation in this patient population and therefore utilized in each operation for this indication. As of June 2015, iEPO was introduced for the same indications as iNO in order to serve as a cost-conscious alternative to iNO and to potentially explore a different, equally impactful pathway for clinically evident pulmonary vasodilation (as measured by Swan-Ganz catheter data and determined by transesophageal echocardiography). There are no additional risks to the patient aside from the rare adverse effects such as allergic reaction, as previously discussed. The most common side effect of iNO is hypotension. The side effects common to intravenous iEPO are nausea, vomiting, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, difficulty breathing, abdominal pain, musculoskeletal pain and tachycardia.

**10. Costs to the Subject:** There will be no additional costs to the subjects as a result of this study.

**11. Data Analysis & Statistical Considerations:** Summary statistics will be computed for demographic, clinical, and outcome variables in the form of frequencies (percentage) for categorical variables and mean (standard deviation) for continuous variables for each arm. Univariate analysis will be performed to compare the difference of each variable between treatment groups by chi-square or Fisher exact tests for categorical variables, and t-tests or Wilcoxon Rank-Sum tests for continuous variables depending on data normality. The univariate results for the outcome variables will provide information on iNO treatment effect in comparison to iEPO without taking into account other potential confounding factors. All non-outcome variables meeting $p< 0.15$ association with treatment group will be considered for variable selection to build a multivariable regression model. For each outcome of interest, we will start with a regression model (logistic regression for binary outcomes or generalized linear model for continuous outcomes) with all variables selected from univariate analysis described above. Based on stepwise variable selection, we will determine the final set of covariates to be included in the final multivariable model to test the treatment group effect. Based on the analysis results, we will be able to understand if iNO is equivalent to iEPO (no significant difference) or significantly better or worse than iEPO (significant treatment effect) to address the efficacy of iNO for Aim 1. Several of secondary measures will be obtained over time. We will apply generalized mixed model to take into account the repeated measures over time to test for treatment effect. In the case of patients have switched to the other arm due to clinical decision, we will conduct the primary analysis based on the intent to treat (ITT) without reclassifying treatment assignment. In addition, protocol analysis, where only patients follow the protocol assignment are included will also be conducted to verify ITT results. For Aim 2 to compare cost capture analysis, the comparison of cost measures between two groups will be tested by two sample t-test.

Based on recent *annual* operations, approximately 120 LVAD implantations, 60 heart transplantations, and 110 Lung transplantations were performed at Duke University Hospital during FY 2014 – 2015. This study has been individually powered to primary endpoints for each arm (Table 1) and the duration of study enrollment has been determined according to annual operations and sample-size calculations. We estimated sample size based on equivalence test of the incidence rates of a binary outcome (e.g. PGD grade 3 (PGD-3)) of two treatment groups as an illustration. Assuming the incidence rate of PGD-3 under iEPO treatment is 0.35 and acceptable margin of the equivalence is ± 0.19, we will need 224 patients to have 80% power to detect an actual difference at 0.05 between two treatment group under this margin. This implies that the acceptable range of incidence rate for iNO treatment is from 0.21 to 0.59. Based on this estimate, we propose to enroll 200 lung transplant patients and 224 LVAD and heart transplant patients (n = 424) over a period of 24 to 36 months; the exact time point for trial culmination between 24 and 36 months will be dependent on enrollment rate. There will be a 50% randomization rate for each inhaled agent such that 212 patients will receive iEPO and 212 patients will receive iNO.

**12. Data & Safety Monitoring:** The proposal is not introducing a new medication that has not been utilized by our group and safety has been established for this patient population through clinical practice and medication usage. Safety will, however, be determined by assessing reported, rare, adverse effects of iNO (systemic hypotension, methemoglobinemia, and rebound pulmonary hypertension after appropriate weaning) and iEPO (systemic hypotension, non-surgical bleeding related to thrombocytopenia, flushing, and rebound pulmonary hypertension after appropriate weaning) in order to accurately monitor adverse events (AE) during this study. The PI will review and sign off on AE's as they occur and perform a quarterly review and determine if AE's are related to the study or otherwise. AE's will be reported to the IRB per HRPP policies.

*Stopping Rule:* Subjects who meet the stopping criteria in section 4 will continue to be enrolled and followed for primary outcome analysis.

**13. Privacy, Data Storage & Confidentiality:** All data collected in the case report forms (CRF) will be collected by review of the subjects routine medical record documentation or during the intraoperative portion of the study. All subjects will be given a study ID in an order to maintain their identity and subject's identity will be protected and confidentially maintained. Barcodes will be affixed to each study sample collected according to the protocol. For future review, the study number and barcode will be the only identifying information associated with the subject. All paper data will be stored in a locked cabinet in the research teams office as outlined in the research data security plan. Any computerized data will be stored within the Duke University Medical Center's Database, which is password protected, and located behind Duke Computing firewalls. Only the PI and the statisticians will have access to the data obtained from these cases.

ClinicalTrials.gov

Try our beta test site



Trial record **1 of 4** for: ghadimi

Previous Study | Return to List | Next Study

# Inhaled Pulmonary Vasodilator Therapy in Left Ventricular Assist Device (LVAD) Implantation, Heart Transplantation, and Lung Transplantation: Prospective, Randomized, Double-Blinded Study (iNO vs iEPO)

**This study is not yet open for participant recruitment. (see Contacts and Locations)**

*Verified March 2017 by Duke University*

**Sponsor:**
Duke University

**Information provided by (Responsible Party):**
Duke University

**ClinicalTrials.gov Identifier:**
NCT03081052

First received: March 8, 2017
Last updated: March 14, 2017
Last verified: March 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

## Purpose

The primary purposes of this study has 2 aims. First, to conduct a clinical investigation to determine if iEPO, Veletri® will have similar efficacy in pulmonary vasodilation and have a similar impact when compared to iNO, INOMAX® in adult patient who undergo a heart transplantation, lung transplantation or implantation of a left ventricular assist device . Second, to conduct a cost-capture analysis on the expense each drug incurs per patient.

| Condition | Intervention | Phase |
|---|---|---|
| Heart Transplant Surgery<br>Lung Transplant Surgery | Drug: iNO<br>Drug: iEPO | Phase 4 |

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Participant, Care Provider, Investigator
Primary Purpose: Other

Official Title: Inhaled Pulmonary Vasodilator Therapy in Left Ventricular Assist Device (LVAD) Implantation, Heart Transplantation, and Lung Transplantation: Prospective, Randomized, Double-Blinded Study

**Resource links provided by NLM:**

MedlinePlus related topics: Heart Transplantation Lung Transplantation

Drug Information available for: Nitric oxide

U.S. FDA Resources

**Further study details as provided by Duke University:**

Primary Outcome Measures:

- Incidence of Grade 3 Primary Graft Dysfunction (PGD) for Lung Transplant subjects. [ Time Frame: Up to 72 hours ]

This is defined by the International Society of Heart and Lung Transplantation (ISHLT) as severe hypoxemia with a PaO2-to-FiO2 ratio < 200 or the presence of venovenous extracorporeal membrane oxygenation (VV ECMO) at an time-point within the first 72 hours after lung transplantation.

- Incidence of moderate or severe RV failure for the LVAD implantation subjects. [ Time Frame: up to approximately 21 days after LVAD placement ]

  This is defined by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scoring.

- Incidence of severe RV failure for Heart Transplantation subjects. [ Time Frame: up to approximately 30 days after heart transplantation ]

  This is defined by the incidence of an RVAD placement

Secondary Outcome Measures:

- Duration of postoperative mechanical ventilation [ Time Frame: up to approximately 90 days ]

  Length of time from intubation until patient is extubated

- Per patient cost [ Time Frame: up to approximately 30 days ]

  Cost associated with the duration of PVD administration

- Length of ICU stay [ Time Frame: up to approximately 90 days ]

  Length of time from ICU admission from surgery until ICU discharge

- Length of hospital stay [ Time Frame: up to approximately 1 year ]

  Length of time from surgery to hospital discharge

- Incidence of Acute Kidney Injury [ Time Frame: up to approximately 14 days ]

  defined by KDIGO-AKI criteria

- Incidence of in-hospital mortality [ Time Frame: up to approximately 1 year ]

  Death that occurs during the hospital stay

- Incidence of postoperative mortality within 30 days [ Time Frame: up to approximately 30 days ]

  From the day of surgery to 30 days (+/- 3 days)

- Incidence of post-operative mortality within 90 days [ Time Frame: up to approximately 90 days ]

  From the day of surgery to 90 days (+/- 5 days)

- Incidence of post-operative mortality within 1 year [ Time Frame: up to approximately 1 year ]

  From the day of surgery to 1 year (+/- 7 days)

Estimated Enrollment: 424
Anticipated Study Start Date: April 2017
Estimated Study Completion Date: April 2021
Estimated Primary Completion Date: April 2021 (Final data collection date for primary outcome measure)

| Arms | Assigned Interventions |
|---|---|
| Active Comparator: Lung transplant with iNO | Drug: iNO<br>Subject will receive inhaled Nitric Oxide in this intervention<br>Other Name: Inhaled Nitric Oxide |
| Active Comparator: Lung transplant with iEPO | Drug: iEPO<br>Subject will receive inhaled Epoprostrenol in this intervention<br>Other Name: Inhaled Epoprostrenol |
| Active Comparator: Heart transplant & LVAD implantation with iNO | Drug: iNO |

| | |
|---|---|
| | Subject will receive inhaled Nitric Oxide in this intervention<br>Other Name: Inhaled Nitric Oxide |
| Active Comparator: Heart transplant & LVAD implantation with iEPO | Drug: iEPO<br>Subject will receive inhaled Epoprostrenol in this intervention<br>Other Name: Inhaled Epoprostrenol |

**Detailed Description:**

Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator (PVD) with FDA-approval in the neonatal population alone. In adult patients, iNO is used off-label to treat pulmonary hypertension, right ventricular (RV) failure, and ventilation-to-perfusion mismatch. Adult patients who undergo durable LVAD implantation (e.g. Heartware®, Heartmate 2®, or Heartmate 3®) or cardiac transplantation for end-stage heart failure or those that have endured lung transplantation as a result of end-stage lung disease, compose the largest subpopulation which receives PVD therapy at Duke University Hospital. Inhaled Epoprostenol (iEPO) has been introduced in the cardiothoracic operating rooms (OR) and ICU as a cost-conscious alternative medication to iNO. iEPO may display an equivalent efficacy profile to iNO for pulmonary vasodilation and oxygenation and have a similar impact on clinical outcomes.

424 informed and consented subjects undergoing thoracic transplantation or left ventricular assist device (LVAD) implantation under the care of one or more investigators will be prospectively enrolled over a three-year period (one-year for follow-up). Patients will be randomly assigned 50/50 according to randomization strata to one of two standard of care pulmonary vasodilation therapy, iNO vs iEPO. Additional study procedures will involve data collection and blood sampling.

## Eligibility

| | |
|---|---|
| Ages Eligible for Study: | 18 Years and older (Adult, Senior) |
| Sexes Eligible for Study: | All |
| Accepts Healthy Volunteers: | No |

**Criteria**

Inclusion Criteria:

- Thoracic (heart or lung) transplantation patients
- LVAD implantation patients

Exclusion Criteria:

- Combined Organ Transplantation (Heart-Lung, Heart-Liver, Heart-Kidney)
- Age < 18 years old
- Pregnancy
- Known allergy to prostaglandin (rare)
- Subject is enrolled in another study protocol, which does not allow randomization of PVD therapy
- Heart transplant or durable LVAD recipients with adult congenital heart disease (CHD) o Caveat: Does NOT meet exclusion criteria if the scheduled heart transplant or LVAD implantation is due to heart failure from a previous heart transplantation related to CHD, performed more than 90 days previous to the date of trial enrollment
- Patient is scheduled to undergo lung transplantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo durable LVAD implantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo heart transplantation but has undergone lung transplantation in the previous 90 days
- Patients with preoperative Venovenous ECMO as a bridge to lung transplantation

## Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT03081052

**Contacts**

Contact: Tiffany L Bisanar, RN, BSN 919-681-0866 tiffany.bisanar@duke.edu

Contact: Kamrouz **Ghadimi**, MD 919-681-6532 kamrouz.**ghadimi**@duke.edu

**Sponsors and Collaborators**

Duke University

**Investigators**

Principal Investigator: Kamrouz **Ghadimi**, MD Duke Health

## More Information

| | |
|---|---|
| Responsible Party: | Duke University |
| ClinicalTrials.gov Identifier: | NCT03081052 History of Changes |
| Other Study ID Numbers: | Pro00078035 |
| Study First Received: | March 8, 2017 |
| Last Updated: | March 14, 2017 |
| Individual Participant Data Plan to Share IPD: | No |

| | |
|---|---|
| Studies a U.S. FDA-regulated Drug Product: | Yes |
| Studies a U.S. FDA-regulated Device Product: | No |
| Product Manufactured in and Exported from the U.S.: | No |

Keywords provided by Duke University:
Heart and Lung transplantation surgery
Pulmonary vasodilation therapy

Additional relevant MeSH terms:
Nitric Oxide
Vasodilator Agents
Bronchodilator Agents
Autonomic Agents
Peripheral Nervous System Agents
Physiological Effects of Drugs
Anti-Asthmatic Agents
Respiratory System Agents
Free Radical Scavengers
Antioxidants
Molecular Mechanisms of Pharmacological Action
Neurotransmitter Agents
Endothelium-Dependent Relaxing Factors
Gasotransmitters
Protective Agents

ClinicalTrials.gov processed this record on May 05, 2017

Adult Mechanical Ventilation Protocol for Routine Post-Op Cardiothoracic Surgery and Lung Transplant Patients

**Purpose:** To provide consistent clinical practice and timely interventions in the management of cardiothoracic surgical (CTICU) patients who require mechanical ventilation.

**Protocol Initiation:**

The Mechanical Ventilation Protocol will be initiated upon receipt of a provider’s order e.g. "CTICU Mechanical Ventilation Protocol".

Upon receipt of a provider’s order, the respiratory care practitioner will:

- Based upon the patient’s diagnosis and surgical procedure, select the appropriate arm of the protocol from the following choices:
    - Ventilation Protocol - Cardiothoracic Surgery Patients (Section IV)
    - Ventilation Protocol - Lung Transplant Surgery Patients (Section V)
- Determine initial ventilator settings and initiate mechanical ventilation.

- Assess the patient's response to the level of mechanical ventilation support provided.
- Communicate the initial mechanical ventilation settings and all subsequent changes to other members of the patient care team.
- Document all interventions in the medical record.

**Ventilation Protocol – Cardiothoracic Surgery Patients**

Goals

- To maintain the patient's arterial pH between 7.35 and 7.45
- To maintain the patient's PaO2 between 60 and 85 mm Hg
- To maintain the patient's PaCO2 < 50 mm Hg
- To maintain the patient's SpO2 > 90%
- To maintain an ETCO2 < 45 mm Hg and PaCO2 < 50 mm Hg (during re-warming and shivering)
- To provide an inspiratory pressure plateau of no greater than 30 cm H2O

Initial Mode and Setting Selection

- Mode: The initial mode may be one of the following:
  - Pressure Assist-Control (PAC)
  - Pressure Support (PSV)
- Inspiratory Pressure (Tidal Volume) - Adjusted to achieve targeted tidal volume and comfort
  - Inspiratory pressure will be set to achieve an exhaled VT of 4-8 mL/kg of the patient's ideal bodyweight
  - Total pressure will not exceed 30 cm H2O.
- Respiratory Rate (f) - 14 (then adjusted to control PaCO2)
- Inspiratory Time will be set to optimize patient comfort, avoid or minimize air trapping, and produce an I:E ratio of less than 1:1
- FiO2 and PEEP
  - FiO2 - 0.6 (unless otherwise ordered by anesthesiologist)
  - PEEP - 5 cm H2O
- Pulmonary Vasodilator Therapy: Per provider order.
- Non-invasive Monitoring (Continuous):
  - Pulse Oximetry
  - Capnography
    - Continuously from admission to unit until extubation or for up to 24 hours post admission.
    - Patients receiving trach collar trials.
    - 24 hours post reintubation
    - On the order of a provider

Subsequent Adjustments/Weaning

- Obtain an ABG within 30 minutes after admission:

        - Assess the $PaCO_2$ – $ETCO_2$ gradient. If < 10 mm Hg, patient stable, no acidosis, use $ETCO_2$ to adjust respiratory rate unless otherwise stated.
- Management during re-warming and shivering
    - Adjust respiratory rate to keep $ETCO_2$ < 45 mm Hg, $PaCO_2$ < 50 mm Hg
- Oxygenation adjustments
    - Wean $FiO_2$
        - If $SpO_2$ > 90% ($PaO_2$ > 60 mm Hg) to a $FiO_2$ goal of 0.4
        - Notify MD if $SpO_2$ < 90%, $PaO_2$ < 60 mm Hg or if unable to obtain a $FiO_2$ of 0.4 within 4 hours.
    - Increase $FiO_2$/PEEP if indicated (see Appendix A)
        - For a patient with a VAD: Keep PEEP at 5 cm $H_2O$ unless directed otherwise by provider order.
- Respiratory rate adjustments
    - Patient must be hemodynamically stable without shivering or bleeding requiring treatment, temperature > 36°C, responsive and breathing spontaneously (RN will begin weaning sedation when patient begins to waken.)
    - Assess ABG to ensure $PaO_2$ > 60 mm Hg, $PaCO_2$ < 50 mm Hg, pH 7.35-7.45
- Elevate HOB 30° unless otherwise ordered or contraindicated (i.e. intra-aortic balloon pump)
- Change to PSV 10 cm $H_2O$ (40%, 5 PEEP) from PAC when $ETCO_2$ < 45 mm Hg and reliable, spontaneous respiratory drive present.
- Extubation – Refer to the following...
    - Appendix D: Daily Spontaneous Breathing Assessment and Trial (SBT) and
    - Appendix F: Extubation Criteria
- Weaning from Mechanical Ventilation – Trach Collar Trials
    - Appendix E. Trach Collar Trial Weaning

**Ventilation Protocol - Lung Transplant Surgery Patients**

Goals: The goals of the Lung Transplant Surgery Protocol include all of the following:

- To maintain the patient's arterial pH between 7.35 and 7.45
- To maintain the patient's $PaO_2$ between 60 and 85 mm Hg
- To maintain the patient's $SpO_2$ > 90%
- To maintain the patient's $PaCO_2$ < 50 mm Hg
- To maintain an $ETCO_2$ < 45 mm Hg and $PaCO_2$ < 50 mm Hg (during re-warming and shivering)
- Respiratory rate ≤ 16
- To provide an inspiratory pressure plateau of no greater than 30 cm $H_2O$

Initial Mode and Setting Selection upon Admission to CTICU

- Mode: The initial mode will be Pressure Assist-Control (PAC)
- Inspiratory Pressure (Tidal Volume)
    - Inspiratory pressure will be set to achieve an exhaled VT of 4-8 mL/kg of the patient's ideal body weight.
        - Total pressure will not exceed 30 cm $H_2O$.

- Respiratory Rate (f) = 10 (then adjusted to control PaCO2)
- FiO2 and PEEP
  - Start with a FiO2 of 0.21 to achieve a PaO2 > 65
  - PEEP = 8 cm H2O
- Inspiratory Time (Ti) will be set between 1.4-1.6 seconds on sedated patients.
- Pulmonary Vasodilator Therapy: Per provider order.
- Non-invasive Monitoring (Continuous):
  - Pulse Oximetry
  - Capnography
    - Continuously from admission to unit until extubation or for up to 24 hours post admission.
    - Patients receiving trach collar trials.
    - 24 hours post reintubation
    - On the order of a provider.

Subsequent Adjustments and Weaning

- Obtain an arterial blood gas within 30 minutes after admission:
  - Assess the PaCO2 – ETCO2 gradient. If < 10 mm Hg, patient stable, no acidosis, use ETCO2 to adjust respiratory rate unless otherwise stated.

- Oxygenation: : Appendix A: FiO2/PEEP Table

- Management during re-warming and shivering
  - Adjust respiratory rate to keep ETCO2 < 45 mm Hg, PaCO2 < 50 mm Hg
  - Treat shivering (nursing)
- Elevate HOB 30° unless otherwise ordered

- Weaning
  - Patient must be hemodynamically stable.
  - Assess ABG to ensure PaO2 > 65 mm Hg, PaCO2 < 50 mm Hg, pH 7.35-7.45
  - Change to PSV 10 cm H2O (40%, 5 PEEP) from PAC when ETCO2 < 45 mm Hg, and reliable, spontaneous respiratory drive present.

Extubation – Refer to the following...

- Appendix D: Daily Spontaneous Breathing Assessment and Trial (SBT) and
- Appendix F: Extubation Criteria

Weaning from Mechanical Ventilation – Trach Collar Trials

- Appendix E. Trach Trial Weaning

**Patient Assessment and Ventilator Monitoring** – Patient assessment and ventilator monitoring will be performed to determine the patient’s clinical status and progress toward goals.

- The RCP will assess the patient and monitor the ventilator…
  - Immediately after initiating mechanical ventilation
  - At 6-hour intervals (approximately) thereafter
  - Whenever there is a change in the level of support (mode) provided or a change in settings that effects minute ventilation or mean airway pressure.
  - Whenever there is an acute change in the patient's condition signaled by a rapid deterioration in vital signs or oxygenation or a change in ventilation.
- Patient assessment and ventilator monitoring will consist of…
  - An evaluation of the performance of the mechanical ventilator to include:
    - Settings and monitored data
    - Graphics – waveforms and loops (if available)
  - An evaluation of the patient's response to ventilation support (to include but not limited to):
    - Breath sounds, vital signs, and physical appearance
    - Arterial blood gases (if available)
    - Data from non-invasive monitors, e.g. SpO2 and ETCO2
    - Chest radiograph (if available)

**Action to be taken in the event of an acute deterioration in the patient's clinical condition.**

In the event of an acute deterioration in the patient's condition during the course of mechanical ventilation as evidenced by acute oxygen desaturation (SpO2 < 80%), acute hypotension (mean BP drop of > 20 mmHg), an acute increase in airway pressure or an acute decrease in tidal volume the respiratory care practitioner will…

- Immediately notify the nurse and provider.
- Manually ventilate the patient with a manual resuscitator set to deliver a FiO2 of 1.0.
- Assess the patient to rule out one of the following conditions:
  - Acute airway obstruction
  - Bronchospasm
  - Pneumothorax
  - Flash pulmonary edema
  - Aspiration
  - Airway misplacement – e.g. accidental extubation or decannulation, intubation of the right-mainstem bronchus.
  - Equipment failure
  - System leak/disconnect
- Recommend to the provider that an arterial blood gas sample be obtained if the acute decompensation has resulted in profound hypoxemia or acute hypotension.
- Recommend to the provider that a "stat" chest radiograph be obtained.

## Appendix A: FiO2/PEEP Table

Oxygenation Goals:

- 60 mm Hg ≤ PaO2 ≤ 85 mm Hg (
- SaO2 > 90%
- SpO2 > 90%

Clinical Application of Standard: If not at goal, move up one step, if above goal(s) move down one step – PEEP adjustments within each step are based on clinical assessment.

| FiO2 | PEEP |
|---|---|
| <.40 | 5 |
| 0.40-0.60 | 5-8 |
| > 0.60 | 8-15 |

## Appendix B: Arterial Blood Gases

An arterial blood gas sample should be obtained within 30 minutes following the initiation of mechanical ventilation.

Subsequent arterial blood gas samples should be obtained…

- Upon receipt of a provider's order
- Following a ventilator setting change that is intended to stabilize or achieve ventilation and/or acid-base goals.
- Following a ventilator change that is intended to stabilize or achieve oxygenation goals for the patient receiving total mechanical ventilation support (when non-invasive monitoring is unavailable to insufficient to provide reliable data).
- To assess the oxygenation, ventilation, and acid-base effects resulting from the changeover to partial mechanical ventilation support from total mechanical ventilation support.
- To assess the oxygenation, ventilation, and acid-base effects resulting from a ventilator setting change that leads to a significant change in respiratory rate, tidal volume and/or minute volume for patients in either total or partial mechanical ventilation support.

## Appendix C: Tolerance Criteria

Patient may be considered intolerant of the partial support settings or a SBT if any of the following exists:

- Development of rapid, shallow breathing: f ≥ 35 or an increase of ≥ 10 breaths per minute over previous respiratory rate.
- Intolerable dyspnea, diaphoresis, excessive use of accessory muscles, or development of paradoxical respirations.
- Heart rate > 120 or a change in heart rate of ≥ 20 that cannot be attributed to another cause.
- Diastolic blood pressure change of 20 mm Hg that cannot be attributed to another cause.
- Development of cardiac arrhythmia, deterioration of mental state, or deterioration of arterial blood gases.

**Appendix D. Daily Spontaneous Breathing Trial**

The patient requiring mechanical ventilation should be assessed daily to determine readiness for extubation and discontinuation of mechanical ventilation support with a Spontaneous Breathing Trial (SBT). In patients requiring mechanical ventilation for more than 21 days, SBTs should be considered when on PSV.

- The RCP will conduct a SBT on patients who meet the following indications:
    - $FiO_2 \leq 0.4$
    - PEEP ≤ 8 cm $H_2O$
    - A reliable, spontaneous respiratory drive regardless of mode or level of support provided.
    - Tolerance criteria outlined in Appendix C is met.
    - The patient's overall condition is stable or improving.
- A SBT is not indicated for patients…
    - receiving neuromuscular blockade
    - on HFOV
    - with an inspiratory to expiratory ratio ≥ 1:1
    - with a pH ≤ 7.20
    - with an impending MI
    - with a BP systolic of < 80; MAP < 60, or HR > 120 and/or the need for vasopressor therapy (dopamine or dobutamine) ≥ 10 ∝g/kg/min, or more than one vasopressor to maintain hemodynamic stability
- The SBT will be performed with a low level of CPAP (5-8 cm $H_2O$), PSV 5 with 5-8 cm $H_2O$ PEEP, or automatic tube/airway compensation (ATC/AAC) while maintaining the ventilator's $FiO_2$.
- The head of the bed should be elevated to 30 degrees.
- The RCP will monitor the patient closely for the first five minutes of the SBT to assess tolerance and, if tolerated the SBT will continue for at least 30 minutes but not greater than 120 minutes. Patients who tolerate the SBT will be considered for extubation (see Tolerance Criteria in Appendix C).
- At the completion of the trial, the following will be documented in the medical record:
    - Mode (e.g., PS-SBT, CPAP-SBT or ATC/AAC)
    - Respiratory rate
    - Minute volume
    - Tidal volume

- f/VT
- Patients who fail the SBT trial will be returned to mechanical ventilation at previously tolerated settings.
- A note will be entered into the medical record to indicate the reason for failure (e.g., high f/VT).
- A note will be entered into the medical record to indicate the reason a SBT was not indicated in patients not receiving an SBT despite meeting criteria above
- Extubation
    - The RCP will recommend extubation or discontinuing mechanical ventilation support when the patient meets the extubation criteria listed in Appendix F.
    - The RCP will extubate the patient upon receipt of a provider's order.

**Appendix E. Spontaneous Breathing Trials in tracheotomized patients**

- Spontaneous breathing trials for tracheotomized patients combine periods of spontaneous breathing, generally of increasing duration, with periods of mechanical ventilation support for patients who meet criteria in Appendix D.
- The decision to initiate and conduct these trials will be made by the medical care team as part of the daily plan of care. A provider's order is required to initiate a spontaneous breathing trial for tracheotomized patients.
- The patient will be removed from mechanical ventilation support and placed on a High Flow device. Flow and FiO2 will be adjusted to meet SpO2 goal.
- The patient will be placed on a continuous end tidal CO2 monitor with alarms set 10mmHG above and below their established baseline end tidal CO2.
    - *ETCO2 will not be monitored during Passey-Muir Valve use.
    - *ETCO2 may be discontinued once the patient is successfully liberated from mechanical ventilation > 48 hours.
- Patient tolerance will be assessed (Appendix C).
- The RCP will return the patient to mechanical ventilation support…
    - If the patient fails to meet tolerance criteria, or
    - According to the time interval determined by the medical team (plan of care), or
    - To "rest" the patient overnight with the intention of continuing trial the following morning.

**Appendix F: Extubation Criteria**

A patient should be considered for extubation when the following criteria are met:

- Patient is able to tolerate a Spontaneous Breathing Trial.
- Adequate airway protection, a reliable respiratory drive, and airway suctioning no more frequently than every two hours.
- Successful 'cuff leak test' in patients suspected of possible upper airway abnormalities.
- NIFM ≥ -25 (Lung Transplant Patients)
- Diaphragm unclamped (Lung Transplant Patients)

899

## REFERENCES

Epoprostenol: Adult Inhaled Pulmonary Vasodilator Protocol

**PATIENT POPULATION:**

Patients receiving Nitric Oxide (iNO) for pulmonary vasodilator therapy are eligible for continuous aerosolized or inhaled epoprostenol .

**DESCRIPTION:**

Veletri is a naturally occurring prostaglandin that serves as a potent vasodilator and is an effective inhibitor of platelet aggregation. Aerosolized Veletri is used as a selective pulmonary vasodilator when administered by inhalation, it has been shown to improve oxygenation, reduce pulmonary shunt, lower pulmonary artery pressure and pulmonary vascular resistance.

**INDICATIONS:**

Post-cardiothoracic surgery patients located on 7 West for management of pulmonary hypertension, right ventricular dysfunction, or refractory hypoxemia.

**PREPARATION/STORAGE/DISPENSING:**

- Veletri syringes shall be prepared by the pharmacy sterile preparation cleanroom (SPC). Standard concentration of syringe is 1.5 mg/50 mL (30,000 ng/mL).
- Prepared Veletri syringes shall be given a 7 days refrigerated beyond use dating.
- A non-patient specific supply of syringes will be stored in the Omnicell controlled refrigerator in the "B" medication room on 7W. Only Respiratory Medications will be stored in this refrigerator.

- To assure ongoing appropriate inventory management, respiratory therapists shall access the Veletri syringes by logging into the Omnicell cabinet and selecting the drug for removal each time.

**ADMINISTRATION GUIDELINES:**

1. Patient will present with Veletri from the operation room at a dosage rate of 50 ng/kg/min.
2. The usual dosage range is 15-50 ng/kg/min based on ideal body weight (IBW).
3. The usual starting dose of aerosolized Veletri is 50 ng/kg/min.
4. The dose of 50ng/kg/min is at the upper end of the dose range used in most clinical studies.
5. In order to increase the likelihood of a timely response it is preferable to start at 50 ng/kg/min and then, if needed, titrate dose down once a favorable response has been confirmed and the patient is stable.
6. Dosage adjustments should be made in increments/decrements of 5ng/kg/min.
7. Any variation from the standard concentration for **inhaled use** will require approval from RT and pharmacy administration.
8. Syringe must be changed at a minimum of every 24 hours; nebulizer and connecting tubing changed every 7 days.
9. Veletri is administered using a special nebulizer set-up as described below.
10. Veletri can be administered during invasive or noninvasive ventilation, and via facemask or High Flow nasal cannula.

**ASSESSMENT OF RESPONSE:**

The desired response to inhaled Veletri is a decrease in pulmonary artery pressure, improved hemodynamics, and/or improved arterial oxygenation.

**PRECAUTIONS AND SIDE EFFECTS:**

1. Inhaled Veletri has fewer adverse effects than intravenous administration.
2. Systemic effects such as hypotension, nausea, flushing, headache, and dizziness are rare except at very high doses. If hypotension should occur when initiated, stop the drug, reinitiate iNO and contact the ICU team.
3. Veletri has an alkaline pH, it can be an irritant when inhaled, causing severe coughing.
4. Abrupt withdrawal of inhaled Veletri can cause rebound pulmonary vasoconstriction and hypoxemia, but this is rare.

**EQUIPMENT:**

1. Medfusion 3500 Infusion pump
2. Aeroneb Pro-xcontrol unit, Aeroneb Pro-x nebulizer with T adapter, Aerogen Tubing Set
3. 50 mL Veletri syringe prepared by pharmacy
4. Hydroscopic filters to be placed between expiratory limb and ventilator exhalation filter) with Q4H change and PRN (for invasive ventilation)
5. Small syringe containing sterile saline solution


**PRACTITIONER ROLES:**

**Nursing/Respiratory Therapy Considerations**

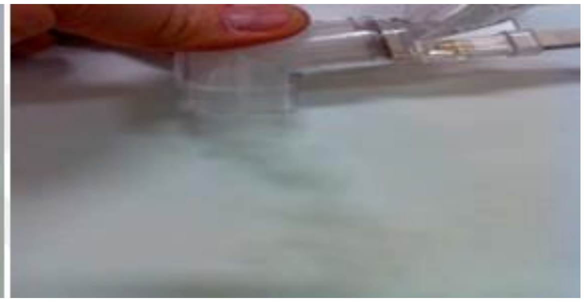
1. Any questions about the dose should be clarified with the pharmacist.
2. This therapy demands close collaboration between the respiratory therapist, nurse, and pharmacist.
3. Drug administration is documented in E-MAR, Respiratory Medication Administration flowsheet and noted in the shift note by the respiratory therapist.
4. Continuous oxygen saturation monitoring is required.
5. Standard unit-specific vital signs assessment is followed.
6. Aerosol delivery into the ventilator circuit or mask must be confirmed visually.
7. If the patient is receiving Veletri by face mask, assure that the mask is fitted comfortably and is only removed for short periods; monitor oxygen saturation closely when the mask is removed.
8. Care should be taken to avoid direct exposure to the aerosol emitted from the nebulizer.
9. Masks are not required when entering the room or when involved in usual caregiver activities in the room. However, N95 masks will be available for those who choose to use them.
10. Although evidence is lacking for exposure during pregnancy, it is recommended that women who are pregnant do not enter the room during treatment.

**EQUIPMENT SET-UP:**

1. Assure Aeroneb control unit is plugged into Uninterruptible Power Source (UPS).
2. Assure that UPS and infusion pump are plugged into 110 volt AC power source.
3. Place additional expiratory filter between expiratory limb and ventilator expiratory filter.(Q4H and prn change)
4. Confirm the dose in the E-MAR. A dose greater than 50 ng/kg/min will not be used. If there are concerns about spillover systemic hypotension, a lower starting dose (e.g., 30 ng/kg/min) should be used.
5. Scan the patient's ID band, scan barcode on syringe label, and look for Maestro Medication Administration window to appear.
6. Perform functional check of nebulizer.
   - Inject 1 mL of sterile saline into nebulizer cup and t-piece assembly.
   - Press and hold the On/Off power button for 3 seconds.

- Verify that Continuous Mode indicator illuminates and aerosol is produced.
- Allow nebulizer cup to empty.

7. Attach Aerogen tubing set to syringe containing Veletri solution. Attach the other end of the tubing to the luer connector for the nebulizer; this connector should be separate from the nebulizer assembly at this time.

**Program Medfusion 3500 Infusion pump.**

- ☐ Power pump on


- ☐ Select Respiratory Folder

- ☐ Select Epoprostenol Folder

- ☐ Verify that the concentration printed on the syringe label is 1.5 mg/50mL and press "Yes".


- Choose B-D syringe.
- Place 60 mL syringe containing 50 mL Epoprostenol (Veletri) solution into infusion pump and press "Enter".
- Enter patient's ideal body weight (ideal body weight) in KG

- Enter starting dose 50 ng/kg/min as ordered

- Prime the tubing by press and holding BOLUS until tubing is primed, (approximate priming volume 3.7 ccs')
- Confirm no "air" is in Aerogen tubing

- The dose set on the pump will be confirmed by a second clinician (respiratory therapist or nurse).
- Attach tubing from Veletri syringe to nebulizer.
- Place Aeroneb nebulizer unit into T-piece.
- Attach cable between Aeroneb control unit and nebulizer
- Press START (green button) on pump to begin dose after nebulizer is in circuit. Observe nebulizer for aerosol production.

- Response to therapy should be assessed after 30-60 minutes. Determination of criteria for response should be established by the clinical team before therapy is initiated. A general guideline is that there should be a 20% improvement in oxygenation or hemodynamics to continue therapy after 1 hour.
- Maximum dose is 50ng/kg/min. A lack of response at this dose level should prompt discontinuation of therapy
- If hypotension occurs, dose should be reduced.
- Dosage adjustments should be made in increments/decrements of 5 ng/kg/min.
- After 4 hours of clinical stability, consideration should be given to dose reduction.

**Changing Dose:**

- Select Change dose (ng/kg/min)
- Enter new dose, press start.

**Syringe Change:**

- The Veletri syringe is changed at least every 24 hrs or whenever the remaining volume in the syringe reaches 5 mL
- The connecting tubing and nebulizer only need to be changed every 7 days.
  - (The syringe will need to be changed in less than 24 hrs when the infusion rate is greater than 1.8 mL/hr).

1. To change syringe press STOP
2. Remove tubing from nebulizer and close port
3. Remove syringe
4. Remove tubing from syringe and attach to new syringe
5. Place new syringe in pump and Prime tubing
6. Reattach tubing to nebulizer
7. Press START
8. Oberve for delivery and aerosol production

**Invasive ventilator assembly:**

1. Connect T-piece into circuit at humidifer inlet (dry side); be certain that nebulizer cup is upright.
2. Place disposable bacterial/viral filter before exhalation valve assembly.
   - Change the filter every 4 hrs and PRN if resistance to expiratory flow is noted.

3. An active humidification system must be used. Do not use a Heat-Moisture Exchanger (HME) during administration of inhaled Veletri.


**Transport Ventilator Assembly:**

1. Place filter on ventilator outlet port
2. Connect T-piece/aerogen assembly into filter outlet.
3. Insert Expiratory filter on limb
4. Be certain that nebulizer cup is upright.
5. Do not use a Heat-Moisture Exchanger (HME) during administration of inhaled Veletri.

**Noninvasive Ventilator Assembly:**

1. Use a non-vented mask.
2. Place the nebulizer between the leak port and the mask.
3. Be careful to position the mask so that the nebulizer cup remains in a vertical position.


**Mask Assembly:**

1. Attach Aerogen "Mask Adapter" to Aerosol Mask inlet

2. Connect small bore O2 tubing to bottom inlet port of adapter
3. Place Aerogen nebulizer in Aerogen adapter


**High flow Nasal Cannula Assembly:**

1. Connect T piece to humidifier inlet with the nebulizer cup in an upright, vertical position.
2. Connect high flow nasal cannula to the other end of T piece.
3. Adjust oxygen flow meter to desired flow rate (liters/minute)

**Manual Ventilation Assembly:**

1. For patients with an artificial airway, place the T piece between the manual ventilator (AMBU) outlet and the endotracheal or tracheostomy tube. Be certain that the nebulizer cup is in a vertical position.
2. If a non-intubated patient requires emergency ventilation, immediately initiate manual bag-valve-mask ventilation.
3. If emergency ventilation is needed, the first priority is adequate ventilation and oxygenation and the secondary priority is administration of aerosolized Veletri.

**Equipment Maintenance**

1. Disposable hydroscopic filters are to be changed <u>Q4h and prn</u>.

2. Aeroneb nebulizer to be changed Q7 days and prn.
3. Syringe line tubing to be changed Q7 days and prn.

**RECOMMENDED DOSING STRATEGIES:**

1. The usual dosage range is 5-50 ng/kg/min based on ideal body weight. Do not use a dose greater than 50ng/kg/min.
2. The usual starting dose of aerosolized Veletri is 50ng/kg/min.
3. Dosage adjustments should be made in increments/decrements of 5ng/kg/min.
4. The initial dose of 50ng/kg/min is at the upper end of the dose range used in most clinical studies.
5. Assess the response to therapy within 30-60 minutes of initiation.
6. After 4 hours of clinical stability, consideration should be given to dose reduction.
7. At high doses, there is a potential for systemic effects, which results in systemic hypotension. There is a potential for rebound pulmonary vasoconstriction and hypoxemia when Veletri is abruptly discontinued, but it is probably less than that for inhaled nitric oxide.
8. Be prepared to increase the FIO2 and support hemodynamics during discontinuation. If rebound occurs, it may be helpful to wean the dose slowly before discontinuation.

**WEANING**

**GENERAL COMMENTS**: Right Heart hemodynamics include: $SVO_2$, CO, CI, $PA_{sys/dia}$, CVp. There is a potential for rebound increase in pulmonary vasoconstriction and hypoxemia when Veletri is abruptly discontinued. Weaning of Epoprostenol will commence following communication and consent of the Provider team. Prior to each dosing change, Right Heart hemodynamics will be assessed and documented in the comment section of the MAR for Epoprostenol by inhalation. In general, the Right Heart parameters should meet the following criteria before weaning or discontinuation: SvO2 > 65, CVP < 15,="" ci=""> 2.2, and adequate oxygenation. Pulmonary arterial pressure values will vary but should remain stable during weaning and trial off.

**WEANING PROCEDURE:**

1. Obtain consent for weaning commencement from provider team**.**

2. The following decrement strategy will be used:

| Dose | Action |
|---|---|
| 50 | Dosage rate at start of wean |
| 45 | Observe Right Heart hemodynamics and decrease dose to 45ng/kg/min only and allow stabilizing for 1 hour. |
| 35 | Observe Right Heart hemodynamics and decrease dose to 35ng/kg/min only and allow stabilizing for 1 hour. |
| 25 | Observe Right Heart hemodynamics and decrease dose to 25ng/kg/min only and allow stabilizing for 1 hour. |
| 15 | Observe Right Heart hemodynamics and decrease dose to 15ng/kg/min only and allow stabilizing for 1 hour. |
| Off | If Right Heart hemodynamics are stable, notify Provider for Discontinue of Epoprostenol and observe for 1 hour before taking down setup |

3. If rebound worsening of pulmonary hypertension, reduced SvO2 < 65, increased cvp by more than 5 mm Hg or cvp value is > 15 mm Hg, reduced CI < 2.2, or hypoxemia occurs during any dosing decrease, return to last dose, and notify provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.

**DISCONTINUATION:**

1. Once weaning protocol has been completed, notify the provider team of hemodynamic stability with Epoprostenol off after 1 hour.
2. If rebound worsening of pulmonary hypertension, reduced SvO2 < 65, increased cvp by more than 5 mm Hg or cvp value is > 15 mm Hg, reduced CI < 2.2, or hypoxemia occurs during any dosing decrease, return to last dose, and notify provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.

**DOCUMENTATION**

1. MAR documentation: Scan patient and scan medication. Enter dose and rate as delivered.
2. Respiratory Medication administration – Documet continuous nebulizer on Respiratory Medication Administration flowsheet. Use this comment section for care notes.

**CAREGIVER PROTECTION CONCERNS**:

1. **Toxicity:** Veletri has no known toxic effects or toxic metabolites.

2. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although the instability of Veletri makes the significance of these tests uncertain. Fertility was not impaired in rats given Veletri by subcutaneous injection at doses up to 2.5 times the recommended human dose.
3. **Pregnancy:** Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 2.5 times the recommended human dose and have revealed no evidence of impaired fertility or harm **to the fetus d**ue to Veletri. There are, however, no adequate and well-controlled studies in pregnant women.
4. **Recommendations:**
    - The patient should be in a single patient room, but it does not need to be a negative pr**essure room** and the door does not need to remain closed.
    - A sign will be placed on the door to indicate that ***inhaled Veletri is being administered.***
    - Care should be taken to avoid direct exposure to the aerosol emitted from the nebulizer.
    - Masks are not required when entering the room or when involved in usual caregiver activities in the room, but N95 masks will be available for those who choose to use them.
    - Women who are pregnant should not enter the room during treatment.

**Storage and Cleaning of System**

1. Disposable equipment, (nebulizer, t-piece, syringe, syringe tubing) will be removed and discarded in the patient room upon termination of use.
2. The administration system will be disinfected with “Sani-wipes” prior to removal from the patients’ room and placed in a designated RCS Equipment storage room for 7W.
3. Administration systems will be plugged in to electrical outlets while in storage to maintain full battery charge.

**REFERENCES:**


1. Dahlem P, van Aalderen WM, de Neef M, Dijkgraaf MG, Bos AP. Randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury. Crit Care Med 2004; 32(4):1055-60.
2. Domenighetti G, Stricker H, Waldispuehl B. Nebulized prostacyclin (PGI2) in acute respiratory distress syndrome: impact of primary (pulmonary injury) and secondary (extrapulmonary injury) disease on gas exchange response. Crit Care Med 2001; 29(1):57-62.
3. Lowson SM. Inhaled alternatives to nitric oxide. Crit Care Med 2005; 33(3 Suppl):S188-95.
4. Meyer J, Theilmeier G, Van Aken H, Bone HG, Busse H, Waurick R, Hinder F, Booke M. Inhaled prostaglandin E1 for treatment of acute lung injury in severe multiple organ failure. Anesth Analg 1998; 86(4):753-8.
5. Meyer J, Theilmeier G, Van Aken H, Bone HG, Busse H, Waurick R, Hinder F, Booke M. Inhaled prostaglandin E1 for treatment of acute lung injury in severe multiple organ failure. Anesth Analg 1998; 86(4):753-8.

6. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 1999; 160(2):600-7.
7. Putensen C, Hormann C, Kleinsasser A, Putensen-Himmer G. Cardiopulmonary effects of aerosolized prostaglandin E1 and nitric oxide inhalation in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1998; 157(6 Pt 1):1743-7.
8. Siobal M. Aerosolized prostacyclins. Respir Care 2004; 49(6):640-52.
9. Siobal MS, Kallet RH, Pittet JF, Warnecke EL, Kraemer RW, Venkayya RV, Tang JF. Description and evaluation of a delivery system for aerosolized prostacyclin. Respir Care 2003; 48(8):742-53.
10. van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. Chest 2000; 117(3):819-27.
11. Afshari A, Brok J, Moller AM, Wetterslev J. Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev 2010; (8): CD007733.
12. Siobal MS, Hess DR. Are inhaled vasodilators useful in acute lung injury and acute respiratory distress syndrome? Respir Care 2010;55(2): 144-57; discussion 157-61.
13. Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart and lung transplant recipients. J Thorac Cardiovasc Surg 2009; 138(6): 1417-24.

## REFERENCES

Transport of the Mechanically Ventilated CardioThoracic Patient on inhaled Nitric Oxide or inhaled Epoprostenol

- This policy sets forth the standards for transporting the mechanically ventilated cardiothoracic patient on inhaled nitric oxide (iNO) or inhaled Epoprostenol (iEPO) within Duke University Hospital by respiratory care practitioners.
- Patient transport includes patient preparation, movement to and from the ICU, a diagnostic suite, Operating room, and time spent at the destination.
- For transport, a mechanical ventilator designed for transport and the Pulmonary Vasodilator system in use (iEpo, iNO), will be utilized.
- ETCO2 will be monitored during all transports of mechanically ventilated patients.
- All mechanically ventilated patients will be accompanied during transit by a respiratory care practitioner (RCP).
- If the patient is scheduled to undergo a procedure in the operating suite, the RCP may return to his/her assigned area after verbal hand off with the Attending Anesthesiologist.

**Description**

- Mechanically ventilated patients on inhaled pulmonary vasodilators are transported within the hospital for diagnostic or therapeutic procedures that cannot be performed in an in-patient unit. To insure patient safety, respiratory care practitioners will make every effort to provide and maintain an appropriate and constant level of ventilation, oxygenation, and pulmonary vasodilator delivery during transport.
- The RCP will assess the patient’s airway, ventilation and oxygen status prior to the transport. If the patient is hemodynamically unstable or if difficulty maintaining the patient’s ventilation or oxygenation status is anticipated during transport, the RCP will voice these concerns to the medical team.

**Indications**

- Transport of all patients using Respiratory Care owned equipment must be accompanied by a Respiratory Care Practitioner.

**Hazards and Complications**

- Hyperventilation during manual ventilation may lead to respiratory alkalosis, cardiac dysrhythmia, hypotension, and decreased cerebral perfusion.
- Loss of PEEP/CPAP may result in hypoxemia and decreased oxygen delivery.
- Disruption of inhaled pulmonary vasodilator may cause rebound pulmonary hypertension and/or hypoxemia.
- Position changes may result in hypotension, hypercarbia, hypoxemia and loss of the airway.
  - Movement may cause disconnection from ventilator support.
  - Movement may result in accidental extubation.
- Tachycardia and other dysrhythmias have been associated with transport.
- Equipment failure can result in inaccurate data or loss of monitoring capabilities.
- Loss of oxygen supply may lead to hypoxemia.

**Contraindications**

- Inability to provide adequate oxygenation and ventilation during transport either by manual ventilation or mechanical ventilation.
- Inability to maintain acceptable hemodynamic performance during transport.
- Inability to adequately monitor the patient's cardiopulmonary status during transport.
- Inability to maintain airway control during transport.
- Transport should not be undertaken unless all the necessary members of the transport team are present.

**Respiratory Care Resources**

A manual resuscitator with in-line pressure manometer, PEEP valve, and mask must accompany the patient during transport.

iNOMAX DSir

Medfusion 3500

Aerogen Aeroneb

Portable oxygen supply ['e' cylinder(s)] of adequate volume.

Viasys Vela Transport ventilator and patient circuit.

**Procedure**

- The RCP will gather all required respiratory care resources and bring the equipment to the bedside.

- The RCP will set-up and test the transport ventilator according to department procedure.
  * May use Vela Pole mount system or Stand Alone pole on wheels for Aerogen/Medfusion system.
- The RCP will place in line the Pulmonary Vasodilator system in use per department guidelines.
  - iNO Transport
    - Ensure adequate supply of gas (>1000 psi)
    - No HME in line
    - Injector Module and sampling line inserted per departmental guidelines
  - iEpo
    - Ensure adequate supply of Epoprostenol (minimum 30 cc's)
    - No HME in line
    - Nebulizer placed post filter on inspiratory limb
    - Expiratory filter in place
    - * May use Vela Pole mount system or Stand Alone system on wheels.
- The RCP will adjust the transport ventilator to provide an adequate level of ventilatory support
  - The RCP should duplicate the patient's existing ventilator settings whenever possible.
  - The RCP will insure that an appropriate respiratory rate is set (minute ventilation) whenever sedation may be administered during the transport procedure to avoid hypoventilation, hypercapnia, and hypoxemia.
- The RCP will ensure the airway is secure and in proper position before leaving the unit.
  - The RCP will monitor the patient during transport to insure artificial airway stability and patency.
- Prior to leaving the unit the RCP will assess the transport ventilator's ability to provide an adequate level of ventilation support by observing the monitored
  - Exhaled tidal volume
  - Minute volume
  - Respiratory rate.
  - $SpO_2$
  - $ETCO_2$
- On arrival to destination, the RCP will review all above monitored parameters and verify stability of values and system.
- If the patient is scheduled to undergo a procedure in the operating suite, the RCP may return to his/her assigned area after verbal hand off with the Attending Anesthesiologist.
  - Hand off will include a review of the pulmonary vasodilator system in use, the mechanical ventilator, and the procedure for ordering inhaled epoprostenol from OR pharmacy.
  - The RCP will provide the Anesthesiology team with his/her pager/phone number so that he/she may be contacted.

- Documentation of transport will be done in the EMAR per department standards.

## REFERENCES

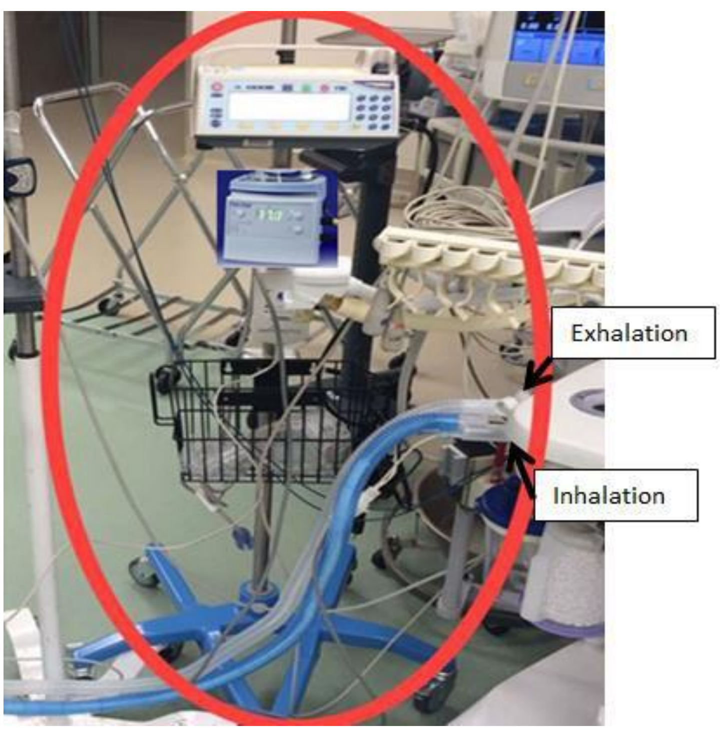
1. AARC Clinical Practice Guideline: In-Hospital Transport of the Mechanically Ventilated Patient – 2002 Revision and Update. Resp Care 2002; 47(7):721-723

# OR Support for Epoprostenol

The use of inhaled Epoprostenol is moving forward into the OR. We have supported 5 cases thus far and an additional 2 cases that were on inhaled epoprostenol and required to return to the OR. To continue this support, please note the following and contact a supervisor or J Cappiello when inhaled epoprostenol in the OR is requested.

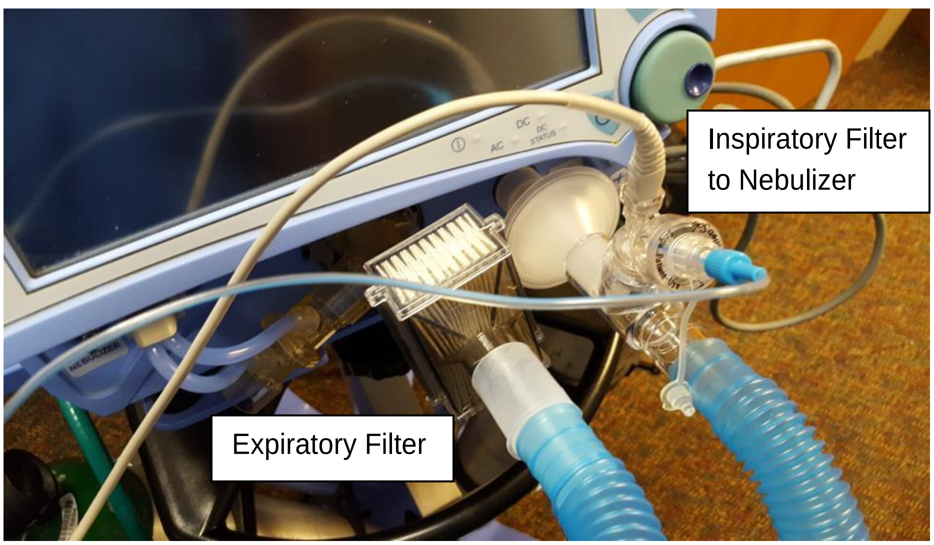
**New OR Case requiring Epoprostenol**

1. Contact Supervisor/J Cappiello to obtain F&P heater
2. Obtain Medfusion/Aerogen delivery unit, 3 Aerogen nebulizers, circuit tee and infusion tubing, heated wire circuit, and 1 L sterile water for humidification.
3. Proceed to OR requesting unit.
4. Place Unit between OR bed and anesthesia machine and set up circuit from anesthesia inspiratory port, to humidifier, to patient and return to exhalation port, (as in the PB840).
5. Inform Anesthesia to place order for Epoprostenol Inhalation
6. If Epoprostenol available, set up syringe pump assembly. If Epoprostenol not available, instruct anesthesia to call when Epo is available.
7. Review circuit, delivery system, how to monitor neb, troubleshooting and dosing (IBW) with Anesthesia.
8. HME may be used until Epo and Humidity is initiated.
9. Provide Anesthesia with RCS contact phone number and request to be called for Epo initiation
10. Transport of this patient from the OR will occur with a transport ventilator



## **Return to OR from CTICU on Epoprostenol**

1. Contact Supervisor/J Cappiello
2. Consult with Anesthesia for duration of case and intra-operative ventilation plans
3. Place patient on transport ventilator with inhaled epo as per policy. No HME
4. Place two additional nebulizers in delivery unit basket
5. Ensure Epoprostenol volume is 40 cc or greater
6. Transport patient to OR on transport ventilator
7. Review delivery system, how to monitor, trouble shooting and dosing (IBW) with Anesthesia team
8. If transport ventilator will be used for the case, review ventilator with Anesthesia team. No HME.
9. Provide Anesthesia with RCS contact phone number
10. Transport of this patient from the OR will occur with a transport ventilator



Inhaled Nitric Oxide Protocol for the Adult Lung Transplant Patient in the Cardiothoracic Intensive Care Unit

This protocol sets forth the standards for the use of inhaled nitric oxide (iNO) for the Lung Transplant Patient in the Adult Cardiothoracic Intensive Care Unit (CTICU) by Respiratory Care Practitioners.

**PATIENT POPULATION:**

Lung Transplant patients receiving inhaled Nitric Oxide (iNO) for pulmonary vasodilator therapy.

**DESCRIPTION:**

INO (nitric oxide gas) is an odorless, colorless gas administered by inhalation. Nitric oxide, the active substance in INO, is a vasodilator and when inhaled, vasodilation is limited to the pulmonary vasculature.

**INDICATIONS:**

Lung transplant patients located on 7 West for the management of pulmonary hypertension, right ventricular dysfunction, or refractory hypoxemia.

**ASSESSMENT OF RESPONSE:**

The desired response to iNO is a decrease in pulmonary artery pressure, improved hemodynamics, and/or improved arterial oxygenation.

**PRECAUTIONS AND SIDE EFFECTS:**

Hypoxemia secondary to Methemoglobinemia

Airway inflammation due to elevated $NO_2$ >1.5PPM. $NO_2$ is a nitric oxide byproduct - not to be mistaken with nitrous oxide ($N_2O$), an anesthetic gas).

**EQUIPMENT:**

INOmax DS IR

**PROCEDURE and DOSING STRATEGIES**

- The RCP will follow established departmental standards per INOmax DS IR policy for set up and administration.
- INO therapy will be administered on provider order.
- The dose range is 0.5-20 PPM with the usual starting dose of 20 PPM.
- INO therapy will be administered by the INOmax® DS IR system with the following equipment:
    - Viasys Avea
    - Puritan Bennett 840
    - Viasys Vela
    - SensorMedics 3100B
    - Optiflo Humidification System
    - Nasal cannula
- Incremental dose adjustments should be done by doubling current dose (not to exceed 20 PPM). Decrements should be done by halving the current dose.
- The following parameters will be monitored to assess dose response: $PA_{sys}$, $PA_{dias}$, $PA_{mean}$, CVP, CI, POx, $SVO_2$
- iNO can be administered during invasive or noninvasive ventilation, Nasal Cannula, and High Flow Humidity delivery.

**DOCUMENTATION**

- Performed twice a shift and at each dosing change to include:
    - NO Dose set
    - NO Dose monitored
    - NO2 monitored
    - Right Heart hemodynamic parameters, SVO2, Pulse Oximetry
    - Tank pressure
- Weaning will follow below guidelines.

## WEANING

**GENERAL COMMENTS**: Right Heart hemodynamics include: $SVO_2$,CI, PA $_{sys/dia}$, CVP. There is a potential for rebound increase in pulmonary vasoconstriction and hypoxemia when iNO is abruptly discontinued. Weaning of iNO will commence following communication and consent of the Provider team. Prior to each dosing change, Right Heart hemodynamics will be assessed and documented in the comment sectionof the Nitric Flowsheet. In general, the Right Heart parameters should meet the following criteria before weaning or discontinuation: SvO2 > 60, CVP < 15, CI > 2.0, and adequate oxygenation. Pulmonary arterial pressure values will vary but should remain stable during weaning and trial off.

1. Obtain consent for weaning commencement from provider team.
2. Initiate weaning if non-ECMO, stable 2 hours post-op and no bleeding (chest tube output < 100 cc/hr) and hemodynamically stable. Reassess every 2 hours.
3. After initiation of weaning, one or more of the following conditions warrant a return to the last dose and notification of the provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.
    - PF ratio 200 or less
    - PaO2 <70mmHg
    - FiO2>0.40
    - pulmonary hypertension (MPAP > 30 mmHg)
    - reduced SvO2 < 60 %
    - increased CVP by more than 5 mm Hg or CVP value is > 15 mm Hg
    - reduced CI < 2.0 during any dosing decrease

| Set Dose | Action |
|---|---|
| 20 | Dosage rate at start of wean |
| 10 | Observe Right Heart hemodynamics/oxygenation and decrease dose to 10 ppm only and allow stabilizing for 60 min. |
| 5 | Observe Right Heart hemodynamics/oxygenation and decrease dose to 5 ppm only and allow stabilizing for 60 min. |
| 1 | Observe Right Heart hemodynamics/oxygenation and decrease dose to 1 ppm only and allow stabilizing for 60 min. |
| 0.5 | Observe Right Heart hemodynamics/oxygenation and decrease dose to 0.5 ppm only and allow stabilizing for 60 min. |
| Off | If Right Heart hemodynamics/oxygenation are stable, notify Provider for Discontinue of iNO and observe for 60 min before taking down setup |

**DISCONTINUATION:**

1. Once weaning protocol has been completed, notify the provider team of hemodynamic stability with iNO off after 1 hour.

2. If rebound worsening of pulmonary hypertension, reduced SvO2 < 60, increased CVP by more than 5mmHg or CVP value is > 15 mmHg, reduced CI < 2.0, or hypoxemia occurs during any dosing decrease, return to last administered dose, and notify provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.

## REFERENCES

Inhaled Epoprostenol Protocol for the Adult Lung Transplant Patient in the Cardiothoracic Intensive Care Unit

This protocol sets forth the standards for the use of inhaled epoprostenol (iEPO) for the Lung Transplant Patient in the Adult Cardiothoracic Intensive Care Unit (CTICU) by Respiratory Care Practitioners.

**PATIENT POPULATION:**

Lung Transplant patients receiving inhaled epoprostenol (iEPO) for pulmonary vasodilator therapy.

**DESCRIPTION:**

Epoprostenol (Veletri) is a naturally occurring prostaglandin that serves as a potent vasodilator and is an effective inhibitor of platelet aggregation. Aerosolized epoprostenol is used as a selective pulmonary vasodilator when administered by inhalation, it has been shown to improve oxygenation, reduce pulmonary shunt, lower pulmonary artery pressure and pulmonary vascular resistance.

**INDICATIONS:**

Lung transplant patients located on 7 West for the management of pulmonary hypertension, right ventricular dysfunction, or refractory hypoxemia.

**ASSESSMENT OF RESPONSE:**

The desired response to iEPO is a decrease in pulmonary artery pressure, improved hemodynamics, and/or improved arterial oxygenation.

**PRECAUTIONS AND SIDE EFFECTS:**

- IEPO has fewer adverse effects than intravenous administration.
- Systemic effects such as hypotension, nausea, flushing, headache, and dizziness are rare except at very high doses. If hypotension should occur when initiated, immediately change to a lower dose.
- IEPO has an alkaline pH, it can be an irritant when inhaled, causing severe coughing.
- Abrupt withdrawal of iEPO can cause rebound pulmonary vasoconstriction and hypoxemia, but this is rare.

**EQUIPMENT:**

- Medfusion 3500 Infusion pump
- Aeroneb Pro-xcontrol unit, Aeroneb Pro-x nebulizer with T adapter, Aerogen Tubing Set
- 50 mL Epoprostenol syringe prepared by pharmacy
- Hydroscopic filters to be placed between expiratory limb and ventilator exhalation filter with Q4H and PRN change (for invasive ventilation)

**PROCEDURE and DOSING STRATEGIES**

- The RCP will follow established departmental standards per Epoprostenol policy for set up and administration.
- The usual dosage range is 5-50 ng/kg/min based on ideal body weight. Do not use a dose greater than 50ng/kg/min.
- The usual starting dose of iEPO is 50ng/kg/min.
- Dosage adjustments should be made in increments/decrements according to the weaning protocol outlined below.
- The initial dose of 50ng/kg/min is at the upper end of the dose range used in most clinical studies.
- Assess the response to therapy within 30-60 minutes of initiation.
- After 4 hours of clinical stability, consideration should be given to dose reduction.
- At high doses, there is a potential for systemic effects, which results in systemic hypotension. If this is suspected, the dose should be lowered.
- There is a potential for rebound pulmonary vasoconstriction and hypoxemia when iEPO is abruptly discontinued, but it is probably less than that for inhaled nitric oxide.
- Be prepared to increase the FIO2 and support hemodynamics during discontinuation. If rebound occurs, it may be helpful to wean the dose slowly before discontinuation.
- IEPO therapy can be administered through the following equipment:
    - Viasys Avea
    - Puritan Bennett 840
    - Viasys Vela
    - V60
    - Optiflo Humidification System
    - Nasal cannula

    - Venturi Mask

- The following parameters will be monitored to assess dose response: $PA_{sys}$, $PA_{dias}$, $PA_{mean}$, CVP, CI, POx, $SVO_2$

## DOCUMENTATION

- A Respiratory Care Assessment and type of medication administration will be documented twice a shift
- eMAR documentation will occur at each syringe change and at each dosing change.
    - Right Heart hemodynamic parameters, SVO2, Pulse Oximetry will be entered into the comment section

## WEANING

**GENERAL COMMENTS**: Right Heart hemodynamics include: $SVO_2$,CI, PA $_{sys/dia}$, CVP. There is a potential for rebound increase in pulmonary vasoconstriction and hypoxemia when iEPO is abruptly discontinued. Weaning of iEPO will commence following communication and consent of the Provider team. Prior to each dosing change, Right Heart hemodynamics will be assessed and documented in the comment sectionof the eMAR. In general, the Right Heart parameters should meet the following criteria before weaning or discontinuation: SvO2 > 60, CVP < 15, CI > 2.0, and adequate oxygenation. Pulmonary arterial pressure values will vary but should remain stable during weaning and trial off.

1. Obtain consent for weaning commencement from provider team.
2. Initiate weaning if non-ECMO, stable 2 hours post-op and no bleeding (chest tube output < 100 cc/hr) and hemodynamically stable. Reassess every 2 hours.
3. After initiation of weaning, one or more of the following conditions warrant a return to the <u>last dose</u> and notification of the provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.
    - PF ratio 200 or less
    - PaO2 <70mmHg
    - FiO2>0.40
    - pulmonary hypertension (MPAP > 30 mmHg)
    - reduced SvO2 < 60 %
    - increased CVP by more than 5 mm Hg or CVP value is > 15 mm Hg
    - reduced CI < 2.0 during any dosing decrease

| Set Dose | Action |
| --- | --- |
| 50 | Dosage rate at start of wean |
| 45 | Observe Right Heart hemodynamics and decrease dose to 45ng/kg/min only and allow stabilizing for 1 hour. |
| 35 | Observe Right Heart hemodynamics and decrease dose to 35ng/kg/min only and allow stabilizing for 1 hour. |
| 25 | Observe Right Heart hemodynamics and decrease dose to 25ng/kg/min only and allow stabilizing for 1 hour. |
| 15 | Observe Right Heart hemodynamics and decrease dose to 15ng/kg/min only and allow stabilizing for 1 hour. |
| Off | If Right Heart hemodynamics are stable, notify Provider for Discontinue of Epoprostenol and observe for 1 hour before taking down setup |

**DISCONTINUATION:**

1. Once weaning protocol has been completed, notify the provider team of hemodynamic stability with iEPO off after 1 hour.

2. If rebound worsening of pulmonary hypertension, reduced $SvO_2 < 60$, increased CVP by more than 5mmHg or CVP value is > 15 mmHg, reduced CI < 2.0, or hypoxemia occurs during any dosing decrease, return to last administered dose, and notify provider team. Provider may choose to resume wean in 1 hour or halt weaning at current dose until further discussion.

## <u>REFERENCES</u>

**Primary study objectives**

Evaluate iNO and iEPO in order to determine if they have similar impact on clinical outcomes in end-stage lung disease patients undergoing lung transplantation and end-stage heart failure patients undergoing LVAD implantation or heart transplantation.

Perform a cost analysis to evaluate the average per-patient cost to use each drug.

Sub-Study

The purpose of this sub-study is to understand the role of RV muscle bioenergetics using targeted metabolite profiling, which include acylcarnitines, amino acids, and ceramides, in order to (i) identify the pathway through which iPVD therapy improves outcomes and affects RV mitochondrial fatty acid utilization, and (ii) identify plasma metabolites that predict responsiveness to iPVD therapy.

Secondary study objectives

Sub-Study

1.Circulating metabolic biomarkers will identify heterogeneity of response to iPVD therapy, by reporting on this underlying RV muscle's mitochondrial fatty acid utilization for energy production.

Standard Research Summary

**Purpose of the Study**

Objectives & hypotheses to be tested

1. Aim I – Clinical Trial Investigation. In order to utilize Inhaled Epoprostrenol (iEPO, Veletri®, Actelion Pharmaceuticals, South San Francisco, CA, USA) as an acceptable alternative to Nitric Oxide (iNO, INOMAX®, Mallinkrodt Pharmaceuticals, St. Louis, MO, USA) in adult patients, we propose a randomized, prospective, double-blinded trial in the cardiothoracic surgical population, which will evaluate the primary hypothesis that these two medications will have similar efficacy in pulmonary vasodilation and a similar impact on clinical outcomes in end-stage lung disease patients undergoing lung transplantation and end-stage heart failure patients under durable LVAD implantation or heart transplantation (Table 1).

2. Aim II – Cost-Capture Analysis. There will be a parallel prospective cost-capture analysis designed to precisely acquire the expenses that each drug incurs per patient averaged across all patients randomized to that drug.

*Sub-Study*

Central hypothesis - Patients who are refractory to changes in pulmonary vascular tone after iPVD therapy will also display reduced right ventricular (RV) mitochondrial fatty acid utilization through increased lipid infiltration of right heart muscle.

2. Secondary Hypothesis - Circulating metabolic biomarkers will identify heterogeneity of response to iPVD therapy, by reporting on this underlying RV mitochondrial fatty acid utilization.

**Background & Significance**

*Introduction.* Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator (PVD) with FDA-approval in the neonatal population alone. In adult patients, iNO is used off-label to treat pulmonary hypertension, right ventricular (RV) failure, and ventilation-to-perfusion mismatch. Adult patients who undergo durable LVAD implantation (e.g. Heartware®, Heartmate 2®, or Heartmate 3®) or cardiac transplantation for end-stage heart failure or those that have endured lung transplantation as a result of end-stage lung disease, compose the largest subpopulation which receives PVD therapy at Duke University Hospital. Intravenous Epoprostenol is FDA approved for adult patients with pulmonary hypertension and is the only agent which has displayed mortality benefit in these patients. The inhaled formulation of Epoprostenol (iEPO) was developed in order to maintain efficacy and avoid the systemic side effects of vasodilation and thrombocytopenia. Inhaled iEPO is used off-label in our cardiothoracic surgical patients for new-onset perioperative pulmonary arterial hypertension (PAH), known preoperative PAH, RV dysfunction with LVEF > 35-40%, and promotion of ventilation to perfusion matching through alveolar deposition of the prostanoid compound and vasodilation of the intimately associated intra-acinar pulmonary arteries. This vasodilation can decrease pulmonary vascular resistance and can improve oxygenation while avoiding systemic effects commonly seen in the intravenous formulation. iEPO has been introduced in the cardiothoracic operating rooms (OR) and ICU as a cost-conscious alternative medication to iNO. iEPO may display an equivalent efficacy profile to iNO for pulmonary vasodilation and oxygenation and have a similar impact on clinical outcomes. For the purposes of this writing, thoracic transplantation will refer to both heart and lung transplantation.

*Pharmacology.* There are 3 major pathways that affect pulmonary vascular tone: 1) Nitric oxide (vasodilatory), 2) Prostaglandin (vasodilatory), and 3) Endothelin (vasoconstrictive) pathways. During cardiothoracic operations, particularly transplantation and LVAD surgery, there is an appreciable imbalance in these pathways, which favors vasoconstriction. iNO administration, exerts its mechanism of pulmonary vasodilation and ventilation-to-perfusion matching through exogenous NO delivery and iEPO applies a similar mechanism via exogenous prostacyclin delivery. Both agents are delivered through mechanical ventilation to ventilated alveoli in order to promote gas exchange at the capillary bed. Both inhaled medications are desirable in this population due to pulmonary selectivity, absence of systemic vasodilation, as well as fast onset (5-10 seconds for iNO and 30-60 seconds for iEPO) and quick titration owing to short-half lives (10-20 seconds for iNO and 1-2 minutes for iEPO). There is no decision tree involved in the use of iNO vs iEPO except for that patient's known drug allergies which may preclude use of one inhaled agent in favor of the other. Of note, endothelin antagonists (e.g. bosentan), which are not part of our perioperative standard practice, are PO medications which require reliable gastrointestinal absorption that may not be present during high-dose inotropic support, and are not readily titrated to effect as are the inhaled PVD, iNO and iEPO.

*Contraindications and Adverse Effects*. Absolute indications for iNO in favor of iEPO are due to prostaglandin allergy leading to anaphylaxis (extremely rare) or if the patient is pregnant due to risk for labor induction as a result of prostacyclin agonism. Routine pregnancy testing is performed in the preoperative setting in line with established preoperative anesthesia testing criteria. Parturients rarely present for thoracic transplantation or LVAD implantation. There are no absolute contraindications to iNO therapy in adult patients but the iNO delivery device system routinely measures the toxic metabolite of iNO, nitrogen dioxide (NO2), which can lead to hypoxemia during metabolite accumulation. Additionally, methemoglobinemia (MetHb) is another rare adverse occurrence of prolonged iNO administration and MetHb levels are measured during arterial blood gas analysis.

*Preliminary retrospective study supporting noninferiority hypothesis*. In a retrospective study of 51 adult cardiothoracic surgical patients (all-comers, including thoracic transplantation, durable LVAD implantation, and non-transplant and non-LVAD cardiac surgical patients), requiring pulmonary vasodilation, our group illustrated similar efficacy between the use of iEPO and iNO with respect to optimizing RV hemodynamic variables, including pulmonary vasodilation and mixed venous oxygenation (Table 2). During this investigation, iNO was initiated in the operating room (OR) and continued during transport and into the ICU. While in the ICU, postoperative hemodynamic stability was achieved within 2 hours and iNO was transitioned to iEPO over 30 minutes in order to provide continuous inhaled pulmonary vasodilation and allow the patient to self-control during medication cross-over between iNO and iEPO. Clinical variables were followed at 5-minute intervals for 1 hour after transition to iEPO. No statistically significant differences were seen in hemodynamic variables during this transition (Table 2). The small sample size and retrospective design, however, incorporated several confounding variables that could not be controlled and prospective data was deemed necessary to achieve reliable conclusions by evaluating clinical outcomes in order to change clinician practice patterns. Other investigations have demonstrated equivalence in hemodynamic variables, mixed venous oxygenation, and ventilation-to-perfusion matching when delivery of iNO was compared with iEPO. These studies were, however, also retrospective or inadequately powered to rely on conclusions related to outcome measures.

*The large cost differential between these two agents remains an important concern for the health system:* iNO is approximately 8-fold more expensive than iEPO, according to preliminary estimates based on PVD usage. Previous reports have estimated the cost of iNO administration to be between $95.00 – $115.00 per hour during medication delivery. The cost, however, has not precisely captured the time required to assemble the iNO delivery system as well as resources utilized to breakdown this setup into individual components following termination of delivery. The cost of iEPO delivery is captured at $14.83 per hour, which includes solution compounding by pharmacy as well as processing for delivery and nebulization by respiratory care services. Additionally, the iEPO delivery-system setup is a one-time, fixed cost for the duration of administration. Similar secondary resource utilization capture for iEPO is required for accurate cost comparison between these two agents.

*Sub Study*

Acute right-sided heart failure (aRHF) strongly predicts the incidence of early death after left ventricular assist device placement (Soliman Oll) or heart transplantation (Taghavi S) for the surgical treatment of advanced left-sided heart failure. Although inhaled pulmonary vasodilator (iPVD) therapy is the mainstay for vascular afterload reduction in aRHF, more than 40% of patients may be refractory to treatment and display persistently elevated pulmonary vascular tone without improvement in right ventricular (RV) muscle contractility. Healthy RV muscle contraction utilizes long-chain fatty acids, delivered to mitochondria by acylcarnitine molecules, for efficient energy production. Prior work in patients with aRHF and pulmonary hypertension has identified derangements in fatty acid transport into mitochondria by acylcarnitines. Notably, lipid infiltration in RV muscle occurs during aRHF with overexpression of ceramide metabolites (biomarkers of lipotoxicity). (Brittain EL) In circulating plasma, long-chain fatty acid acylcarnitine (LC FA AC) metabolites are displaced from RV muscle cells and serve as biomarkers for aRHF.(Brittain and Luo) Reduced levels of LC FA AC are illustrated in such patients who respond to vasodilators by lowering pulmonary vascular tone and this response is associated with improved survival.(Rhodes CJ) Members of my mentorship committee have shown that plasma LC FA AC levels decrease to pre-left HF values after left ventricular assist device placement. (Ahmad T) However, the molecular pathways underlying aRHF after surgery remain unknown and the clinical utility of complimentary plasma biomarkers in guiding therapy has not been defined. Therefore, there is a critical need to identify the underlying metabolic aberrancies in RV muscle of cardiac surgical patients with postoperative aRHF refractory to iPVD therapy. Without such information, novel personalized therapeutic targets for aRHF after surgery will remain limited

**Design & Procedures**

Aim I – Development of a Definitive Clinical Trial Investigation.

*1. Randomization and Double-Blinding*. The clinical research unit (CRU) will receive preoperative notification of lung and heart transplantation patients by reviewing the transplant waitlist. Preoperative notification of LVAD implantation will be done by the review of the cardiothoracic surgical schedule. Using a 50% randomization process utilized and established by the CRU at Duke University Hospital, each eligible patient will be randomized to receive either iNO or iEPO. The primary endpoint data will be collected and documented in an electronic data capture system during the period of time the patient, clinical care team, and study team are blinded. Primary endpoint data collection will be complete prior to the subjects' discharge from the ICU, at which point the unblinding will occur. Since primary endpoint data collection will occur during the blinded period, the potential for bias will be substantially minimized.

*2. Measured Outcomes.* The primary endpoint for the comparison of efficacy in the Lung Transplant population will be the incidence of Grade 3 Primary Graft Dysfunction (PGD). This is defined by the International Society of Heart and Lung Transplantation (ISHLT) as severe hypoxemia with a PaO2-to-FiO2 ratio < 200 or the presence of venovenous extracorporeal membrane oxygenation (VV ECMO) at an time-point within the first 72 hours after lung transplantation. The primary endpoint for the comparison of efficacy in LVAD patients will be incidence of moderate or severe RV failure according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scoring. The primary endpoint for the comparison of efficacy in the heart transplant subset will be the incidence rate of RVAD insertion. Secondary endpoints related to clinical outcomes for all populations will be duration of postoperative mechanical ventilation, , ICU Length of Stay (LOS), hospital LOS, incidence of acute kidney injury, incidence of in-hospital mortality, as well as postoperative mortality at 30-days, 90-days, and 1-year after operation (Table 1).

Aim II –Cost-Capture Analysis.

In parallel with the design & procedures of Aim I, the cost capture analysis component will be essential in order to better gauge the cost due to duration of administration (variable cost) according to each inhaled PVD. Established clinical criteria specific to each group (lung transplantation vs. heart transplantation/LVAD implantation) have been developed to determine the inception of protocolized PVD weaning. Weaning medications according to established protocols will allow for accurate interpretation of the comparative length of therapy between iNO and iEPO and help prevent erroneous PVD usage without criteria for discontinuation. Secondary resource utilization will be documented by respiratory care services and itemized cost sheets will be developed.

*Sub-Study*

This sub study will leverage the target enrollment of 224 patients undergoing left ventricular assist device placement or heart transplantation in the parent study. Furthermore, cardiac tissue is collected in collaboration with the Duke Human Heart Repository (IRB PRO#00005621) and data will be used to test the causal relationship between RV myocardial fatty infiltration and plasma elevation of LC FA acylcarnitines in patients refractory to iPVD who develop acute RHF. This tissue and plasma is already being collected. In patients receiving a heart transplant, one RV tissue core sample will be obtained during routine, standard-of-care, post-operative endomyocardial biopsy. Core samples are the size of 2mm pellets.

**Selection of Subjects**

Subject Groups

Inhaled PVD therapy is administered to every patient undergoing thoracic transplantation and LVAD implantation at our institution and each patient is eligible for enrollment. Over a 3-year period (1 year for follow-up) we will prospectively enroll 200 lung transplant subjects and 224 heart transplant or LVAD implantation patients who will be informed and consented prior to their scheduled procedure. Potential subjects will be under the care of 1 or more investigators in this study. Consented subjects will be randomly assigned to 1 of 2 groups, iNO vs iEPO, to be initiated in the OR on the day of the operation based on accepted standard of practice and study protocol. Medication administration will be double-blinded, such that neither the surgical nor anesthesiology teams will be notified of the inhaled agent to which the patient has been randomized. Ability to unblind the delivery system will be made available to both teams if required to preserve optimal patient care. As per our standard practice, respiratory care services will manage the initiation and maintenance of inhaled PVDs in the OR and ICU, and these personnel will be the only practitioners notified of the actual delivered medication during study blinding.

Exclusion Criteria

- Combined Organ Transplantation (e.g., Heart-Lung, Heart-Liver, Heart-Kidney, Lung-Liver, etc.)
- Age < 18 years old
- Pregnancy (females of child bearing potential will receive pregnancy testing prior to cardiothoracic surgery as a standard of care)
- Known allergy to prostaglandin (rare)
- Refusal of blood products due to personal or religious preference.
- Subject is enrolled in another study protocol, which does not allow randomization of PVD therapy

- Heart transplant or durable LVAD recipients with adult congenital heart disease (CHD)
- Caveat: Does NOT meet exclusion criteria if the scheduled heart transplant or LVAD implantation is due to heart failure from a previous heart transplantation related to CHD, performed more than 90 days previous to the date of trial enrollment
- Patient is scheduled to undergo lung transplantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo durable LVAD implantation but has undergone heart transplantation in the previous 90 days
- Patient is scheduled to undergo heart transplantation but has undergone lung transplantation in the previous 90 days
- Patients with preoperative VV ECMO as a bridge to lung transplantation

Stopping Criteria – In the event the following criteria are met and the clinical team is in agreement, subjects will be weaned off of their iPVD per instutional standard iPVD weaning practice. If adverse events are encountered, the drug will be immediately stopped without weaning.

Venoarterial (VA) ECMO insertion remains at end of operation

VA ECMO insertion is performed postoperatively in the ICU

LVEF < 30% on echocardiogram at the end of the operation for heart and lung transplant subjects

LVEF < 30% for heart and lung transplant subjects on echocardiogram noted postoperative in the ICU

Inhaled pulmonary vasodilation is halted for reasons other than standard weaning ordered by the clinical care team

Adverse events related to the INO or EPO that affect the subject's welfare

Data Collection

Secondary measures will be hemodynamic variables (similar to those measured in Table 2) such as transesophageal echocardiographic (TEE) evaluation of RV function based on stand-of-practice protocol, intravenous administration of inotropes, serial measures of postoperative serum creatinine and GFR, resolution of elevated liver function tests (heart failure patients, illustrates improvement in RV function), incidence of thrombocytopenia (platelet count < 150 x 109/L) and trajectory of resolution, as well as ventilation-to-perfusion matching (arterial oxygen tension, PaO2; arterial carbon dioxide tension, PaCO2; and fraction of inspired oxygen, FiO2). Variables will be recorded at designated time points during the entire duration of administration – from initiation in the operating room to cessation in the ICU. These time points include: Intraoperative before surgical incision, time = 0 (initiation of PVD), 30 minutes, 2 hours, 6 hours, 12 hours, 18 hours, 24 hours, and every 6 hours up through 72 hours after initiation. These secondary measures will be obtained up through 72 hours after initiation regardless of cessation or continuation of the inhaled PVD. After 72 hours, increments of every 12 hours thereafter will be assessed if PVD administration continues. Ventilation and perfusion nuclear scans will be obtained and recorded per standard clinical practice for each group of lung transplant recipients. Established protocols with criteria for initiation of medication weaning have been created according to each medication based on individual pharmacokinetic properties. Once established criteria are met, weaning of each inhaled PVD will begin and continue until the medication is terminated according to standardized weaning protocols established for lung transplant patients and heart transplant/LVAD patients.

Subject follow up. Subject will be contacted by phone by a member of the research team and be asked a short series of questions to assess their current medical condition and any changes since surgery at 30-days (± 3 days), 90-days (± 5 days), and 1-year (± 7 days) after surgery completion date. The phone follow-up should take approximately 5 minutes of the subject's time. If subjects have been admitted to a hospital outside of Duke Health after surgery they will be asked to sign an authorization of release to provide us permission to obtain medical information related to their hospitalization.

Blood Sampling

Blood samples will be drawn for analysis as a part of this study. One 9 ml sample of blood will be obtained from each patient prior to the initiation of PVD therapy and stored at 4°C prior to processing. This sample will be stored for Genomic DNA analysis at the completion of this study in order to assess patients who are responders to inhaled pulmonary vasodilaton through upregulation and down regulation of notable vasoactive substances (e.g. endothelin, thromboxane, nitric oxide, prostaglandin, etc.). In addition, each subject will also be asked to sign the Genomic and Proteomic Database Repository (IRB Pro00015651) consent form, thus allowing the banking of their plasma and DNA samples as well as data to be used for future research. Participation in IRB Pro00015651 is voluntary and optional to all subjects consented in this parent study. Blood samples (7 ml each) will be drawn at 3 separate time points: 1) directly after insertion of the invasive blood pressure monitoring (arterial) line, 2) POD 1 (8 to 24 hours after completion of surgery), and 3) POD 7 (6 days from POD 1). In each 7ml blood sample, 3.5ml will be collected in Sodium Citrate tubes for coagulation analysis and another 3.5ml will be collected in EDTA tubes for metabolomic and proteomic analysis. Plasma will be separated from these samples and banked at -80°C for analyses of proteomic and metabolomic signatures. Up to 30ml of blood will be collected during the 12 month study participation period.

*Sub-Study*

This sub-study only pertains to LVAD and heart transplant patients who meet inclusion criteria and have consented to participate in the parent study. For heart transplant patients, the POD 7 sample collection will occur on the day of the biopsy procedure regardless of post operative day.

**Subject Recruitment and Compensation**

Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a)(3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Subjects will be recruited either during the outpatient or inpatient evaluation phase, or contacted by phone. Recruitment may also occur on the day of the operation given the complexities of the transplant process, which may provide obstacles to earlier enrollment. After obtaining permission from the operating surgeon, surgical subjects will be screened by the study coordinator by reviewing the transplant pre-list. Prior to asking any patient for consent to participate, the patient or Legally Authorized Representative (LAR) will be approached first by the surgeon or one of the members of the surgical care team to determine if the patient or LAR is willing to consider enrollment in the study. If so, the subject or LAR will either be seen during an inpatient or outpatient visit, or be contacted by phone and informed about the study by a member of the research team. If the individual or LAR is willing to consider enrollment and does not meet exclusion criteria, then the research coordinator will present the research protocol in its entirety. During this time, the study coordinator will answer any and all questions as they arise. If the subject or LAR agrees to participate, the coordinator will ask the them to sign and date the appropriate consent form. A copy of this consent form will be given to the subject and a copy of the consent form will be added to the subject's medical record. The subject or LAR will be given the option to sign a separate consent form to allow us to store portions of the collected blood specimens and any data collected under this research study and maintain these samples and data in a database/repository (PRO00015651) for possible use in future research studies relating to surgical outcomes. In the event a LAR provides consent at the time of enrollment, the subject will be approached once they regain the ability to provide an informed consent.

Recruitment will not routinely occur on the day of the operation and most patients will be enrolled at least 12 hours in advance and provided at least the allowable time to review the study consent form and discuss their options with the PI and study personnel. There will be no direct compensation to the patient for recruitment.

If a subject is enrolled and randomized in this study for their LVAD implantation procedure and is later planned to receive a heart transplant, that previously enrolled subject is eligible to be re-enrolled. The following caveats apply to this subpopulation of LVAD patients:

A)Durable LVAD implantation may occur as a bridge to heart transplantation.

B)If LVAD implantation is followed by heart transplantation WITHIN 1 year following LVAD implantation, then data collected up through the time of heart transplantation will be recorded and valid as a patient in the LVAD group.

C)Data collected on or after the date of LVAD explantation/heart transplantation for such a patient will be considered as part of the heart transplant group.

D)If LVAD implantation is followed by heart transplantation AFTER 1 year following LVAD implantation, then the 1 year follow-up period is complete and the patient may re-enter the trial as a heart transplant patient.

If a subject is enrolled and randomized in this study for their durable LVAD implantation procedure and is scheduled to receive a new durable LVAD via an LVAD exchange operation, the subject is eligible to be re-enrolled.

*Sub-Study*

Only subjects consented in the parent study will be asked to participate in the substudy and they will have opt in/out ability.

**Consent Process**

Subject’s Capacity to Give Legally Effective Consent

If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Explicit (written) consent will be obtained from the patient or the patient’s legal decision maker.

**Study Interventions**

Using a 50% randomization process utilized and established by the CRU, each eligible patient will be randomized to receive either iNO or iEPO, to be initiated in the OR based on accepted standard of practice at Duke University Hospital, during the clinical care of these patients.

**Risk/Benefit Assessment**

Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

There is no direct benefit of this study to the enrolled subjects. Data gathered from this study may benefit future patients. Up to 30 ml of blood will be drawn during the 12 month study participation period. Blood sampling will be obtained, in the majority of subjects, from indwelling arterial or central venous lines inserted at the beginning of the intraoperative period as part of standard practice for these operations and there will be no additional risk to the patient for obtaining such vascular access. On rare occasion, blood sampling may be obtained from additional venipuncture sites during the postoperative period. Risks of blood sampling if obtained through venipuncture are pain, swelling, possible infection at the site of venipuncture. While these risks are minimal, the additional blood volume is highly unlikely to contribute to the patient's need for blood transfusion. To minimize any potential risk to the patient from genetic data, investigators and patients will be blinded to the individual patient's genotype. This information will not be included in the patient chart, will remain absolutely confidential, and will not be given to the patient or their family. DNA samples will be identified only by a coded number whose relation to the patient’s name and other identifiers is available only to the data manager. The identity of the patient will remain anonymous in any publications which may result from this investigation.

There will be no additional risks to the subjects as a result of this study. Prior to June of 2015, iNO was the sole option for inhaled pulmonary vasodilation in this patient population and therefore utilized in each operation for this indication. As of June 2015, iEPO was introduced for the same indications as iNO in order to serve as a cost-conscious alternative to iNO and to potentially explore a different, equally impactful pathway for clinically evident pulmonary vasodilation (as measured by Swan-Ganz catheter data and determined by transesophageal echocardiography). There are no additional risks to the patient aside from the rare adverse effects such as allergic reaction, as previously discussed. The most common side effect of iNO is hypotension. The side effects common to intravenous iEPO are nausea, vomiting, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, difficulty breathing, abdominal pain, musculoskeletal pain and tachycardia

**Costs to the Subject**

There will be no additional costs to the subjects as a result of this study

**Data Analysis & Statistical Considerations**

Summary statistics will be computed for demographic, clinical, and outcome variables in the form of frequencies (percentage) for categorical variables and mean (standard deviation) for continuous variables for each arm. Univariate analysis will be performed to compare the difference of each variable between treatment groups by chi-square or Fisher exact tests for categorical variables, and t-tests or Wilcoxon Rank-Sum tests for continuous variables depending on data normality. The univariate results for the outcome variables will provide information on iNO treatment effect in comparison to iEPO without taking into account other potential confounding factors. All non-outcome variables meeting $p< 0.15$ association with treatment group will be considered for variable selection to build a multivariable regression model. For each outcome of interest, we will start with a regression model (logistic regression for binary outcomes or generalized linear model for continuous outcomes) with all variables selected from univariate analysis described above. Based on stepwise variable selection, we will determine the final set of covariates to be included in the final multivariable model to test the treatment group effect. Based on the analysis results, we will be able to understand if iNO is equivalent to iEPO (no significant difference) or significantly better or worse than iEPO (significant treatment effect) to address the efficacy of iNO for Aim 1. Several of secondary measures will be obtained over time. We will apply generalized mixed model to take into account the repeated measures over time to test for treatment effect. In the case of patients have switched to the other arm due to clinical decision, we will conduct the primary analysis based on the intent to treat (ITT) without reclassifying treatment assignment. In addition, protocol analysis, where only patients follow the protocol assignment are included will also be conducted to verify ITT results. For Aim 2 to compare cost capture analysis, the comparison of cost measures between two groups will be tested by two sample t-test.

Based on recent annual operations, approximately 120 LVAD implantations, 60 heart transplantations, and 110 Lung transplantations were performed at Duke University Hospital during FY 2014 – 2015. This study has been individually powered to primary endpoints for each arm (Table 1) and the duration of study enrollment has been determined according to annual operations and sample-size calculations. We estimated sample size based on equivalence test of the incidence rates of a binary outcome (e.g. PGD grade 3 (PGD-3)) of two treatment groups as an illustration. Assuming the incidence rate of PGD-3 under iEPO treatment is 0.35 and acceptable margin of the equivalence is ±0.19, we will need 224 patients to have 80% power to detect an actual difference at 0.05 between two treatment group under this margin. This implies that the acceptable range of incidence rate for iNO treatment is from 0.21 to 0.59. Based on this estimate, we propose to enroll 200 lung transplant patients and 224 LVAD and heart transplant patients (n = 424) over a period of 24 to 36 months; the exact time point for trial culmination between 24 and 36 months will be dependent on enrollment rate. There will be a 50% randomization rate for each inhaled agent such that 212 patients will receive iEPO and 212 patients will receive iNO.

**Data & Safety Monitoring**

The proposal is not introducing a new medication that has not been utilized by our group and safety has been established for this patient population through clinical practice and medication usage. Safety will, however, be determined by assessing reported, rare, adverse effects of iNO (systemic hypotension, methemoglobinemia, and rebound pulmonary hypertension after appropriate weaning) and iEPO (systemic hypotension, non-surgical bleeding related to thrombocytopenia, flushing, and rebound pulmonary hypertension after appropriate weaning) in order to accurately monitor adverse events (AE) during this study. The PI will review and sign off on AE's as they occur and perform a quarterly review and determine if AE's are related to the study or otherwise. AE's will be reported to the IRB per HRPP policies.

Stopping Rule: Subjects who meet the stopping criteria in section 4 continued to be enrolled and followed for primary outcome analysis.

**Describe Role of External Personnel:**

All data collected in the case report forms (CRF) will be collected by review of the subjects routine medical record documentation or during the intraoperative portion of the study. All subjects will be given a study ID in an order to maintain their identity and subject's identity will be protected and confidentially maintained. Barcodes will be affixed to each study sample collected according to the protocol. For future review, the study number and barcode will be the only identifying information associated with the subject. All paper data will be stored in a locked cabinet in the research teams office as outlined in the research data security plan. Any computerized data will be stored within the Duke University Medical Center's Database, which is password protected, and located behind Duke Computing firewalls. Only the PI and the statisticians will have access to the data obtained from these cases.