

Pulmonary Artery Hypertension

The diagnosis of primary pulmonary hypertension is established after ruling out secondary causes of pulmonary hypertension.

I. Acute Vasodilator Testing is done in the intensive care unit via a Swan-Ganz catheter. Anticoagulation should be stopped three to four days prior to Swan-Ganz catheter placement and prothrombin time checked. Keep arterial oxygen saturation = 89% at all times. The primary objective of acute vasodilator testing is to delineate the subset of patients who might be effectively treated with oral calcium channel blockers (CCBs). As such, unstable patients or those with severe right heart failure, who should not be treated with CCBs, need not undergo vasodilator testing.

I.A. Medications Used for Acute Vasodilator Testing:

1) Intravenous Adenosine:

Dose: Initial dose is 50-100 mcg/kg/min with increments of 50 mcg/kg/min every 2 minutes until a maximum dose of 350 mcg/kg/min is reached. Hemodynamics are recorded before adenosine and after each 2-minute interval. Once the desired dose is reached, the drip is reduced stepwise in a similar fashion.

Contraindications: Acute asthma exacerbation, Theophylline intake.

Adverse effects: Dyspnea, wheeze and chest discomfort

2) Intravenous Epoprostenol (Flolan®)

Dose: Initial dose is 2 ng/kg/min with increments of 2 ng/kg/min every 5-15 minutes until a maximum dose of 16 ng/kg/min is reached. Hemodynamics are recorded before

prostacyclin and after each interval. Once the desired dose is reached, the drip is reduced stepwise in a similar fashion.

Contraindications: Severe LV dysfunction and hypersensitivity to the drug or its components

Adverse effects: The most common adverse effects include nausea, vomiting, headache, hypotension and flushing but also include thoracic oppression, chest pain, dizziness, anxiety, bradycardia, tachycardia, dyspnea, abdominal pain and musculoskeletal complaints. Flu like symptoms can also occur (usually with chronic administration), as also jaw pain. Abrupt withdrawal can result in rebound pulmonary hypertension and even death. Some patients have developed pulmonary edema, which may be associated with veno-occlusive disease.

Drug interactions: Additional blood pressure reductions may occur with antihypertensives and diuretics. Epoprostenol may increase the risk of bleeding with anticoagulants

3) Inhaled Nitric Oxide

Dose: The dose is 20 ppm of NO in 100% oxygen via face mask obtained from the "Bagging Port" or back port of the iNOvent® machine. Hemodynamics are recorded before NO and after 15 minutes of gas breathing.

While this protocol suffers from increased cost and difficult access to the drug, it is believed to be the safest and simplest protocol and preferred by some authorities. (Although any observed vasodilation could be due to either O₂ or inhaled NO action, large amounts of significant vasodilation as defined in section I.B., if seen from either gas, will give the practical answer whether the subject has acute vasoreactivity or not.)

I.B. Desired dose response:

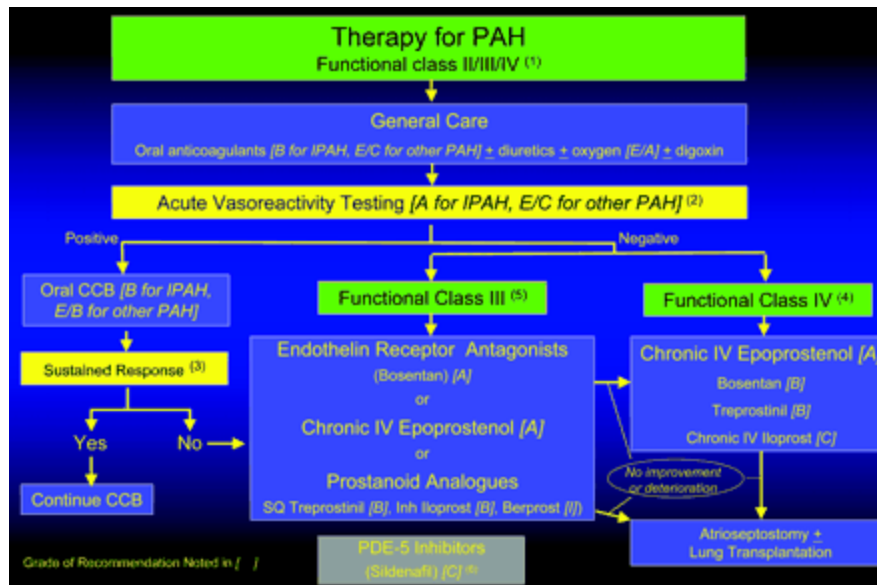
The dose of the above medications is titrated upwards till a positive response or symptomatic intolerance is reached. A positive response (reversibility) is considered a fall of mean PAP of at least 10 mm Hg to \leq 40 mm Hg with an increase or unchanged cardiac output.

Note: There is no consensus in the definition of acute vasoreactivity at right heart catheterization. Some pulmonary hypertension specialists define a positive vasodilator response as a 20% decrease in the mean pulmonary artery pressure and the pulmonary vascular resistance. The percentage of patients who demonstrate acute vasoreactivity is in the range of 10-15%. Symptomatic intolerance includes a decrease of more than 40% in systemic mean arterial pressure, an increase of more than 40% in heart rate, or signs and symptoms just sufficient to warrant discontinuation of the infusion.

Note: In event of borderline resting PA pressures and significant discrepancy between resting and exercise PA pressures, measure PA pressures after a standard period of exercise such as two minutes of lifting a one liter saline bag in both hands. Post-exercise PA pressures are then to be used for calculating both baseline pressures and for assessing dose response.

II. Chronic Vasodilator Use

Treatment Algorithm:



Note: A walking distance during 6 minutes of less than 332m correlates with decreased survival. Hemodynamic parameters obtained at right heart catheterization reflect overall right ventricular function and are major determinants of long-term prognosis. In particular, right atrial pressure greater than 15 mmHg and cardiac index less than 2L/min/m² are associated with increased mortality.

IIA. Medications Used

While the oral calcium channel blockers are used in those patients whose pulmonary vasculature demonstrates a vasoreactive effect on acute use, continuous prostacyclin therapy may be used with benefit even in those who fail to demonstrate a vasoreactive response.

1) Intravenous Epoprostenol (Flolan® by Glaxo Wellcome Telephone 800-366-8900; the specialized pharmacy in Springfield area is Accredo Therapeutics Inc at telephone 866-FIGHTPH at 866-344-4874; Please note that for some insurances, the specialized pharmacy may be TheraCom at 877-FLOLAN4 or 877-356-5264. Home care is provided by Gentiva Health Services at telephone 1-800-9-FLOLAN or 1800-935-6526 who maintain a 24 hours a day 7 days a week telephone number)

General: Chronic ambulatory epoprostenol use requires a permanent indwelling central venous catheter (usually a single lumen tunneled Hickman's catheter in the subclavian vein) and a portable infusion pump (CADD 1 Model 5100 HF, Pharmacia Deltec, St. Paul, Minn.) The patient should demonstrate commitment and understanding regarding sterile drug reconstitution, drug administration, and care of the pump and permanent catheter for life. Anticoagulation should be stopped three to four days prior to permanent central venous catheter placement and prothrombin time checked.

Dose: Chronic infusion is started at a dose 4 ng/kg/min less than the maximal dose determined during acute dose ranging (if Epoprostenol was used during acute dose ranging). If the maximal tolerated infusion rate is less than 5 ng/kg/min, the chronic infusion should be started at one-half the maximum tolerated infusion rate. If Epoprostenol was not used during acute dose ranging, the dose should be titrated upwards as during the acute dose-ranging process.

During outpatient follow-up, the dose should be further titrated upwards if a reduction in side effects permit (since tolerance may develop to some of the side effects) or in patient with minimal side effects, any time the patient has a return of symptoms that can be attributable to pulmonary hypertension. The goal is to have patients receive as high a dose of epoprostenol as possible.

Dose calculation formula: $\text{DOSE (ng/kg/min)} \times \text{WT (kg)} / \text{CONC (ng/ml)} \times 1440 \text{ (60 min} \times 24 \text{ hr)} = \text{RATE (ml/day)}$. For the current pumps, please note that if the daily pump rate falls below 45ml/24hr, concentration will be decreased and if the daily pump rate goes above 94ml/24hr the concentration will be increased. Usual concentration to begin Epoprostenol at is 10,000 ng/ml.

2) Calcium channel blockers

Nifedipine 20 mg orally or sublingually and hemodynamic measurements performed 30 minutes after ingestion of each dose. The dose is repeated every 30 minutes till a favorable response is achieved (defined as a = 20% reduction in pulmonary arterial pressure and pulmonary vascular resistance), unless systemic hypotension or other intolerable side effect precluded further testing. The daily dose is then determined for the patients who respond to treatment by halving the initially effective dose and readministering it every six to eight hours. Total oral dose of 30-240 mg/day is used and is preferred if there is resting bradycardia.

Diltiazem (short-acting) is preferred if there is resting tachycardia. Diltiazem 60 mg oral is given and repeated every 30 minutes. Total oral dose of 120-900 mg/day is used.

Amlodipine may also be used.

3) Oral Sildenafil (Pfizer):

Dose: Oral daily dose of 50 to 100 mg. Up to 400 mg has been used in patients with PAH who have failed or are not candidates for other available therapy.

Adverse effects: Headache, nasal congestion, and visual disturbances, although gas exchange may worsen due to impaired ventilation/perfusion matching.

4) Oral Bosentan (Tracleer® by Actelion Ltd. Telephone 650-624-6900):

Oral Bosentan is currently approved for WHO class III and IV patients only. For WHO class I and II patients, treatment should be individualized, but it should be strongly considered in cases of disease progression by symptoms and/or hemodynamics, in the absence of liver disease.

Dose: 62.5 mg BID for four weeks followed by 125 mg BID.

Adverse effects: Hypotension (7%), liver dysfunction (8%), flushing, palpitations, leg edema, nasopharyngitis

Caution: 1) Liver function tests prior to initiation of Bosentan and then monthly while on Bosentan. 2) Pregnancy should be excluded prior to therapy and pregnancy tests are required monthly while on therapy. Hormonal contraceptives should not be the sole method as induction of metabolism may render them ineffective.

5) Inhaled Iloprost (Ilomedin® by Schering, Ventavis® by Cotherix)

Ilomedin: For inhalation, iloprost is diluted with saline to a concentration of 10 µg per milliliter, and 2 ml was added to a nebulizer (HaloLite, MedicAid). This device delivered short pulses of aerosolized particles (geometric median [\pm SD] aerodynamic diameter of particles, 4.3 ± 0.05 µm) during the first part of each inspiration until a total inhaled dose of 2.5 µg had been dispensed. The inhalation is then stopped or repeated once, to achieve a total dose of 5.0 µg, depending on how well the patient tolerates the treatment. This maneuver is repeated six or nine times daily, with an overnight break. The frequency of inhalation and the dose is individually determined.

Ventavis: Use single ampoule per treatment 6 – 9 times per day with an overnight break. First inhalation 2.5 mcg and subsequent inhalations, if the first one is tolerated, is 5.0 mcg. This drug uses new Prodose® Adaptive Aerosol Delivery System, a dosimeter nebulizer system. Referral process is via Accredo Therapeutics at 1-877-4VENTAVIS or 877-483-6828. Not recommended for patients with SBP < 85 mm Hg. Side effects include hypotension, flushing, jaw pain.

6) Treprostinil (Remodulin® by United Therapeutic Corporation Telephone 301-608-9292) subcutaneous infusion.

Subcutaneous Treprostinil (Remodulin®) is approved for patients with WHO class II-IV symptoms. The clinical effect is dose-dependent.

General: The drug is administered by a catheter in the subcutaneous tissue of the abdominal wall via a positive pressure, small portable microinfusion pump system (miniMed, Sylmar, California). Home care teaching is recommended.

Dose: Initial dose is fixed at 1.25 ng/kg/min (If this does is not tolerated, start at 0.625 ng/kg/min instead) and then progressively increased according to signs and symptoms of PAH while minimizing the adverse effects of therapy. The infusion rate should be increased in increments of not > 1.25 ng/kg/min per week for the first 4 weeks and then not > 2.5 ng/kg/min/week afterwards. Dose range: 0.3-137 ng/kg/min though there is little experience with doses >40 ng/kg/min. Abrupt cessation of the infusion should be avoided.

Rapid escalation of dose has also been used, starting at a dose of 2.5 ng/kg/min and increasing the dose once or twice a week by 1.25-2.5 ng/kg/min.

When transitioning from IV Epoprostenol to SQ Trepostinil:

Initial dose is generally 5 ng/kg/min or less for the first six hours or equal to not more than one half of the current IV Epoprostenol dose for six hours. Dose of Epoprostenol is then gradually reduced, in no more than 2 ng/kg/min decrements, based on appearance of prostacyclin-related signs and symptoms. Trepostinil increased further, by no more than one half of the current dose, and maintained for at least six hours while Epoprostenol is further reduced based on prostacyclin-related events. This process is continued till Epoprostenol is discontinued.

Adverse Effects: Infusion site pain, infusion site reaction, diarrhea, nausea, headache, jaw pain, and flushing. Infusion site pain improves over months and generally not dose-limiting and manageable in majority of patients by relocating the infusion site, using of hot/cold compresses, OTC/prescription medications

Special populations: Hepatic insufficiency: initial dose should be decreased to 0.625 ng/kg/min and increased cautiously. Renal insufficiency: no studies performed.

7) Combination therapy

Combination therapy is often considered in patients with suboptimal response to monotherapy. This treatment approach is still considered experimental although this is currently studied in clinical trials

III. Long-term follow-up

Assess clinical state, drug side effects, functional class and six-minute walk test at least every three months and echocardiographic measurement of PA pressures every six months. Some authorities recommend right heart catheterization every six months. Continue coumadin and maintain INR between 1.5-2.5 (1.5-2.0 for portopulmonary

hypertension). Liver function tests and pregnancy tests should be checked monthly while on Bosentan.

Referral for lung transplantation: should be considered in all patients who do not improve clinically and hemodynamically after 3 - 6 months of intravenous epoprostenol therapy. Atrial septostomy may be used as a bridge to lung transplantation and should only be done in experienced centers.

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Nurse Checklist for elective admission for right heart catheterization:

1) Please fax the following reports to the hospital admitting office, along with the last clinic visit note:

- Six minute walk test _____
- Echocardiogram _____
- Electrocardiogram _____
- Chest X Ray _____
- Pulmonary Function Tests _____
- ABG _____
- Sleep Study _____
- VQ Scan _____
- CT Chest _____
- Autoantibody tests (ANA, RF, Anti-Scl 70, Anticentromere antibody, anti-U3 RNP antibody) _____
- HIV-1 test _____
- Liver function test _____
- Right heart catheterization _____

2) Please check the prothrombin time and platelet count within 48 hours of admission. If INR > 1.4 or platelet count < 100,000 inform the pulmonologist and the cardiologist, if any.

3) Please call up the hospital ICU nursing supervisor for a bed for placement of a right heart catheter (Jim at SJH, Valerie at MMC)

4) Inform the following of the admitting date:

- Pulmonologist
- Hospital admitting office
- Cardiologist, if any
- Hospital pharmacist for need for Epoprostenol
- Patient

5) The patient should be instructed to hold coumadin at least three days prior to the test and report NPO in the morning of the test to the hospital admitting office.

6) Hold anti-hypertensive medications the night before.

TABLE FOR DOSE TITRATION IN PULMONARY ARERY HYPERTENSION

1) Weight (in kgs.)

2) Definition of symptomatic intolerance

60% of baseline MAP calculated at: _____

140% of baseline HR calculated at: _____

3) Definition of positive response

80% of baseline mean pulmonary artery pressure calculated at: _____

80% of baseline pulmonary vascular resistance calculated at: _____

	Baseline	Dose #_____	Dose #_____	Dose #_____	Dose #_____
Time of starting the infusion at a particular dose					
Time of stopping the infusion at a particular dose					
Dose					
Mean systemic blood pressure					
Heart Rate					
Respiratory Rate					
Central venous pressure					
Mean pulmonary artery pressure					
Pulmonary Vascular Resistance					
Pulmonary capillary wedge pressure					
Cardiac output					
SpO2					
Venous oxygen saturation (if available)					
Adverse Effects					

Note: Please calculate pre and post exercise PA measurements at beginning and end of vasodilator test

Physician Checklist for presentation at the multi-disciplinary pulmonary vascular conference:

Name of patient:

Name of physician:

Date of presentation:

Question to be asked:

Tests	Date	Date	Date	Date
NYHA/WHO Classification				
Doppler echocardiogram: sPAP, RV				
Electrocardiogram				
Chest X Ray				
Pulmonary Function Tests				
ABG				
Sleep Study				
VQ Scan				
CT Chest				
Autoantibody tests				
HIV-1 test				
Liver function test				
Right heart catheterization:				
RAP				
mPAP				
PVR				
C.I.				
BNP level				
Six minute walk test				
Other				
Other				