

Pulmonary Hypertension In Pediatrics

- ▶ This talk will focus on the causes and treatment of the more common things we see in pediatrics. This includes:
 - ▶ Persistent Pulmonary Hypertension of the Newborn.
 - ▶ Pulmonary hypertension in the patient with chronic lung disease (bronchopulmonary dysplasia).
 - ▶ Single ventricle hearts.
 - ▶ Idiopathic pulmonary arterial hypertension.

Pulmonary Arterial Hypertension

- ▶ One subclass is pulmonary hypertension (PAH)
- ▶ Other subclasses include:
 - ▶ Pulmonary hypertension associated with left heart disease.
 - ▶ Pulmonary hypertension associated with lung disease/hypoxemia. Included in this category is developmental lung disease.
 - ▶ Pulmonary hypertension associated with thrombotic or embolic disease
 - ▶ Miscellaneous like sarcoidosis, tumor airway compression,

Updates to PAH Categories

- ▶ We all know that the premature infants with BPD are becoming a larger part of our patient population.
- ▶ In 2013 an update to the classification of PAH was done to include “developmental conditions.” (Simmoneau).
- ▶ This suggests to me that the BPD infants are a larger population of patients with pulmonary artery hypertension.

Pulmonary Hypertension (PH)

- ▶ Definition: a mean pulmonary artery pressure greater than 25 mmHg at rest.
- ▶ A subset of patients will have pulmonary arterial hypertension where:
 - ▶ The pulmonary capillary wedge pressure is less than 15 mmHg.
 - ▶ The pulmonary vascular resistance is greater than 3 wood units/meter squared.
 - ▶ Ratio of mean pulmonary artery pressure to mean systemic pressure is greater than .5

PAH survival

- ▶ In 1991 NIH registry study median survival for untreated children was 10 months, it was 2.8 years for adults (D'Alonzo).
- ▶ Recent study by Zijlstra suggested survival rates at 1,3,5, and 7 year transplant survival was 96%, 89%,81%,and 79%.

Single Ventricle and PAH

- ▶ In the patient with a single ventricle, after the final palliation, the pulmonary blood flow is dependent on the passive flow of blood from the SVC and IVC.
- ▶ The traditional definition of a MAP is too high for these patients.
- ▶ We use a MAP of less than or equal to 15 mmHg.

Pulmonary Vascular Resistance

PVR

- ▶ A calculation which represents the “stiffness” of the pulmonary arterial bed.
- ▶ The PVR may be compared to the systemic vascular resistance.
- ▶ The PVR in wood units is calculated with mean pulmonary artery pressure – LA (PCWP) divided by Q_p .
- ▶ LA is left atrium pressure, PCWP is pulmonary capillary wedge pressure, Q_p is pulmonary flow.

Clinical Assessment OI/ Saturation

- ▶ Oxygenation index (OI) is $\text{FIO}_2 \times \text{MAP} \times 100/\text{PAO}_2$
- ▶ A higher OI is bad. An $\text{OI} > 20$ bad, > 40 consider ECMO if other therapies did not work.
- ▶ Consider iNO with $\text{OI} > 15$
- ▶ Preductal saturation $20\% >$ then postductal saturation suggests PAH.

Echocardiogram in Pulmonary Hypertension

- ▶ Enlarged RV.
- ▶ Flattened IVS.
- ▶ Ductus with bidirectional flow.
- ▶ PFO with right-to-left or bidirectional flow.
- ▶ Tricuspid insufficiency with elevated RV-RA velocity (pressure gradient).

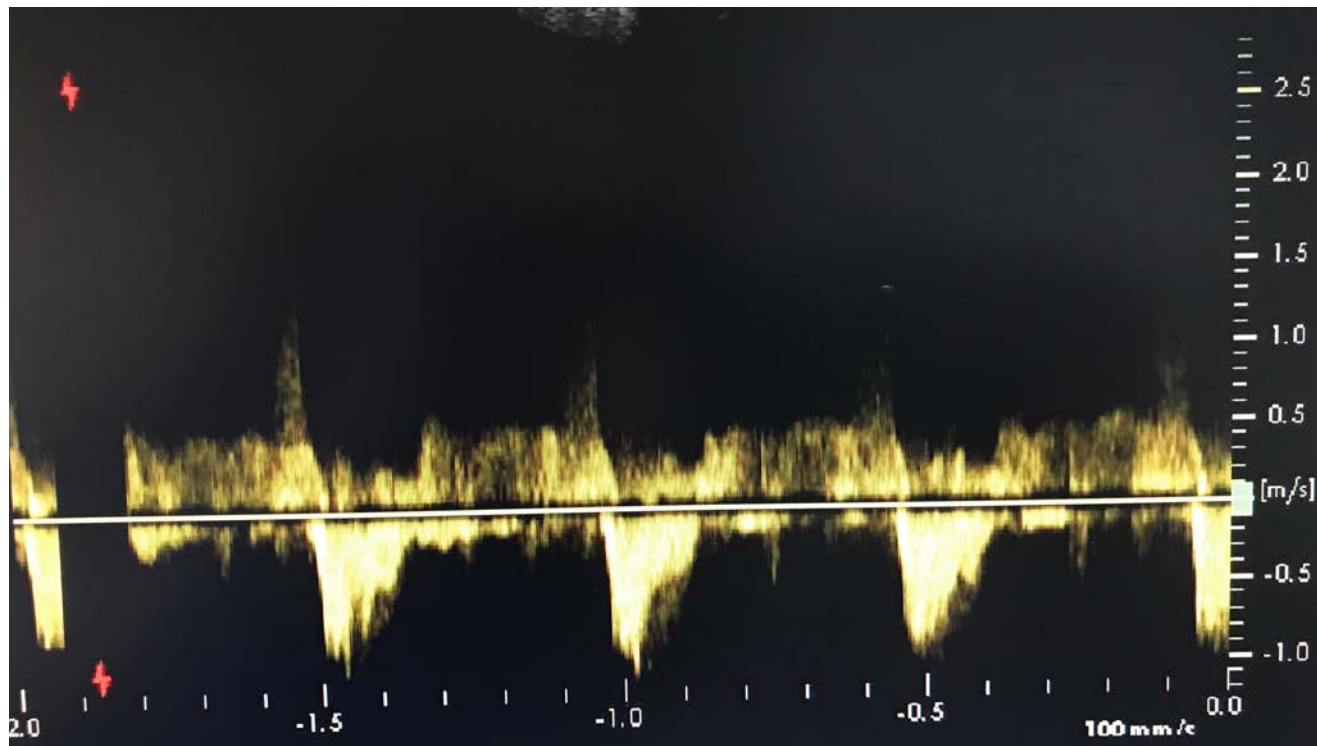
Left-to-right Ductus



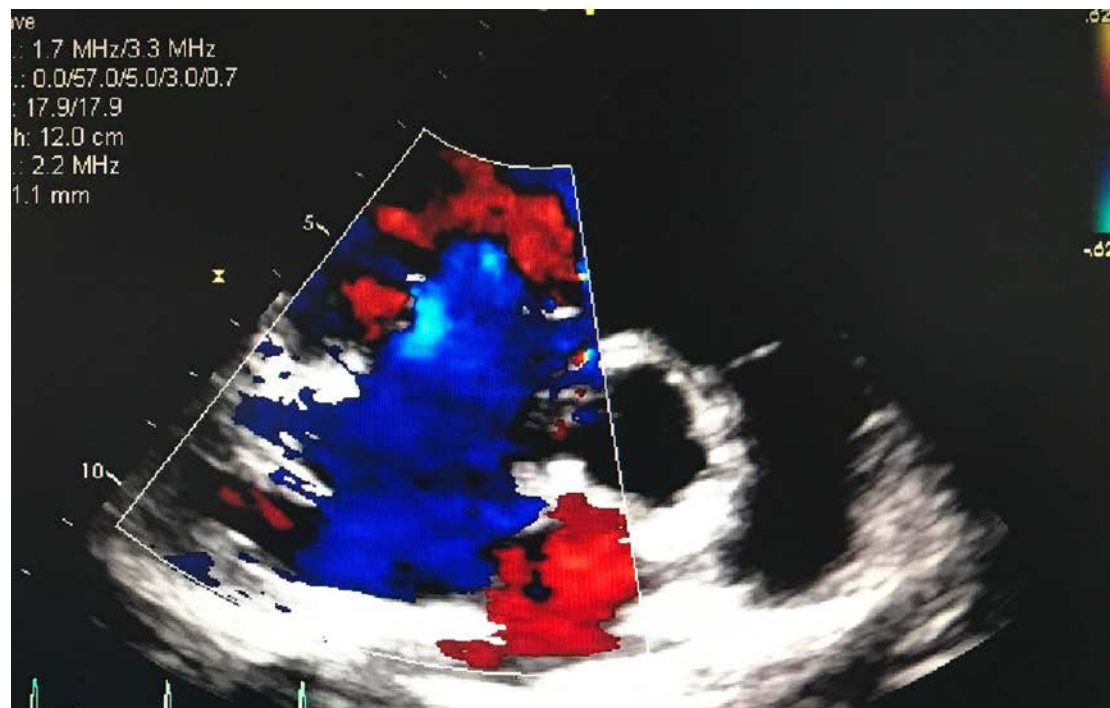
Right-to-left shunt at PDA



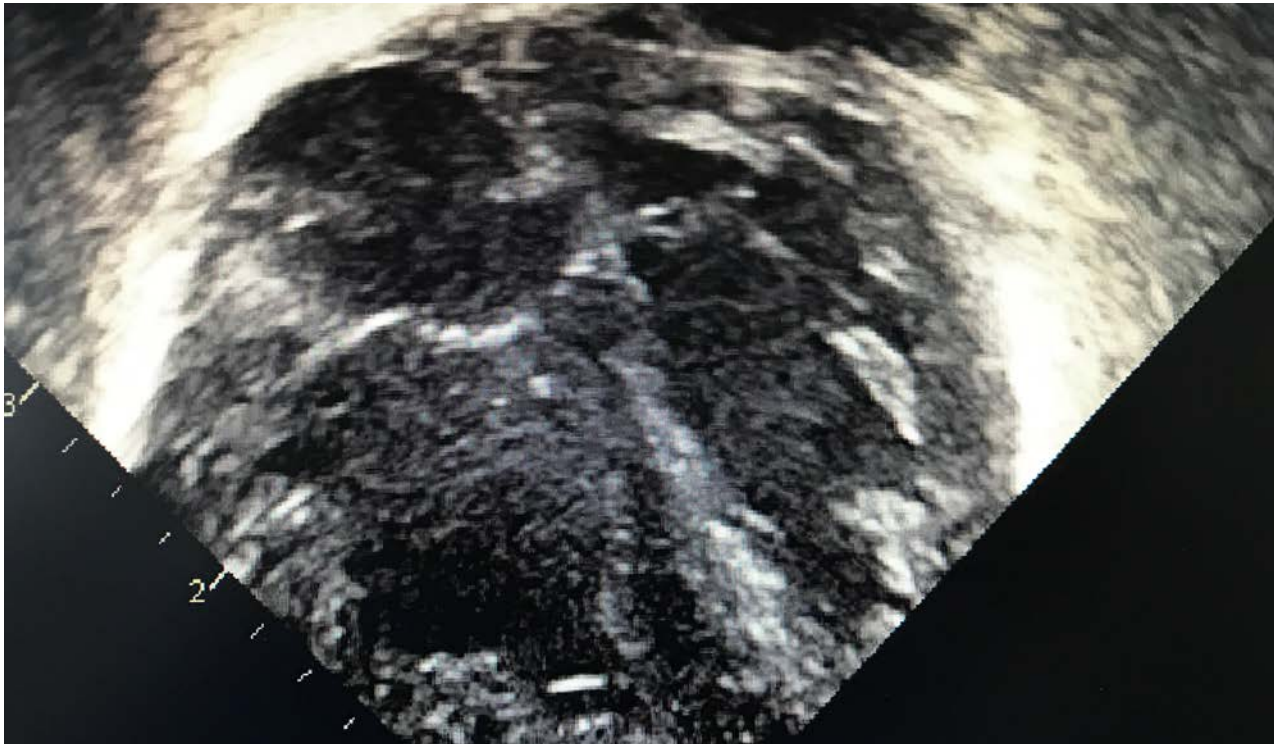
Bidirectional PDA



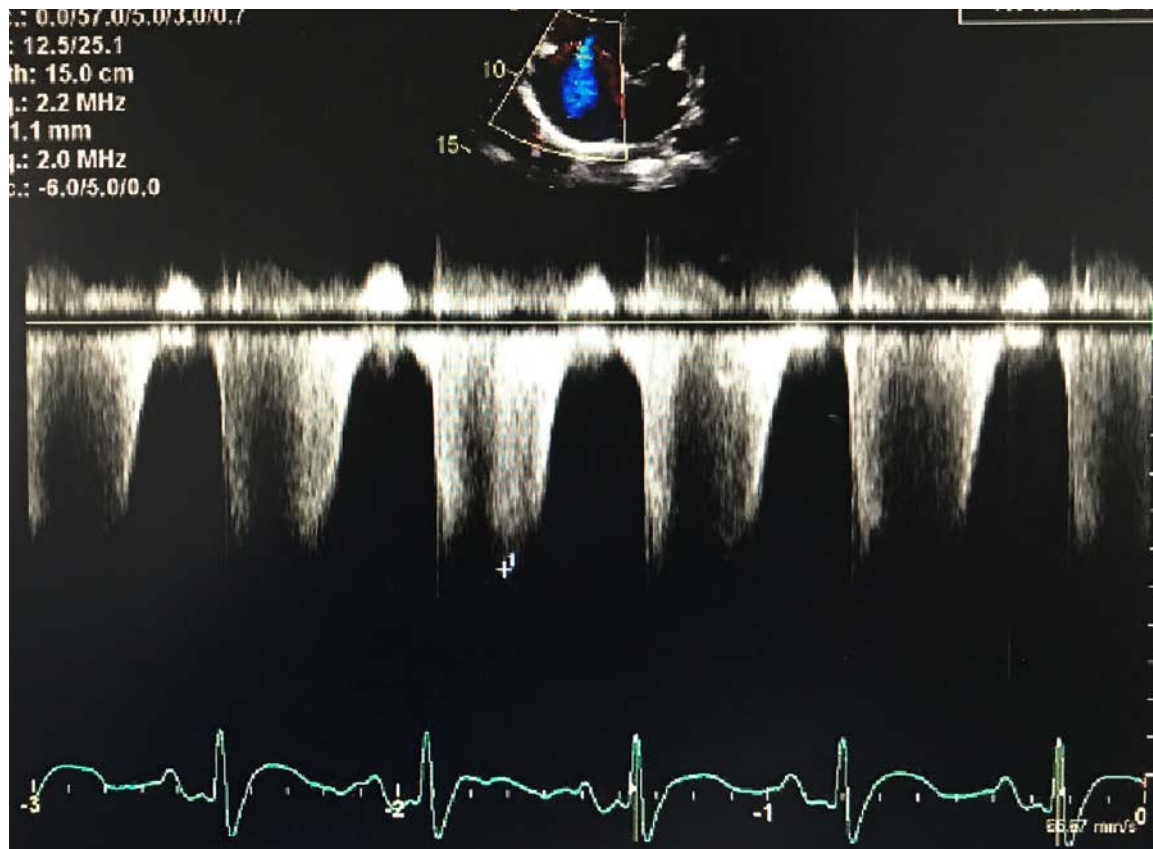
Tricuspid Insufficiency



Large Right Ventricle



Tricuspid Insufficiency



Assessment of Function Status

- ▶ 6 minute walk test in children greater than age 7 Years.
- ▶ A recent study showed that in children who can walk less then $6MWD < 352$ meters and desaturation were associated with a worse transplant free survival (Douwes).
- ▶ Other studies have not demonstrated the 6MWD to be a predictor for survival (Van Loon).
- ▶ For older children cardiopulmonary exercise testing can be helpful.

Assessment of Mortality Risk

- ▶ BNP is brain natriuretic peptide (BNP).
- ▶ Patients with BNP > 180pg/ml had worse survival.
- ▶ NT-proBNP is the N-terminal pro-brain natriuretic peptide.
- ▶ Patients who have a NT-proBNP >than 1200ng/L had a worse prognosis (Ploegstra et al).

Cardiac Catheterization

- ▶ Invasive testing with right heart and left heart catheterization.
- ▶ Measurements include: right atrial, right ventricular, pulmonary artery pressures as well as a Pulmonary capillary wedge pressure, LV pressure, aortic pressure.
- ▶ Vasoreactivity testing with 100% oxygen and 20-40 ppm iNO.
- ▶ Vasoreactivity testing positive if >20% drop in mean pulmonary artery pressure, preservation of cardiac index and improved PVR:SVR ratio.

Acute Responders

- ▶ Approximately 6-20% of individuals respond to iNO and oxygen.
- ▶ Survival better in pediatric patients who are acute responders (Douwes, JACC 2016).
- ▶ Acute responders may respond to calcium channel blockers.
- ▶ Calcium channel blockers cannot be used in patients with high right atrial pressure or low cardiac output.

Oxygen

- ▶ Oxygen is a very potent pulmonary vasodilator.
- ▶ However although hypoxia increases PVR, hyperoxia does not further decrease PVR then appropriate oxygen and instead results in free radical injury.
- ▶ The reactive oxygen species can inactivate NO, decrease eNOS and sGC activity and increase PDE5 activity. This will decrease cGMP and add to increased pulmonary artery vasoconstriction.

Calcium Channel Blockers (CCBs)

- ▶ CCBs work by relaxing the arteriolar muscles.
- ▶ Doses are higher than would be used for systemic hypertension.
- ▶ Examples of CCBs:
 - ▶ Nicardipine
 - ▶ Amlodipine
 - ▶ Diltiazem
 - ▶ Nifedipine

Pathways to treat PAH

- ▶ cGMP pathway. iNO increases cGMP. Sildenafil blocks degradation of cGMP.
- ▶ cAMP pathway. Prostaglandin I₂ (Prostacyclin) and analogs and PGE₁ increase production of cAMP. Milrinone blocks degradation of cAMP.
- ▶ Endothelin pathway has ETA (constricts) and ETB (dilates) receptors. Bosentan works on both.

Pulmonary Vasodilators

▶ cGMP Pathway

- ▶ Sildenafil
- ▶ tadalafil
- ▶ iNO
- ▶ riociguat

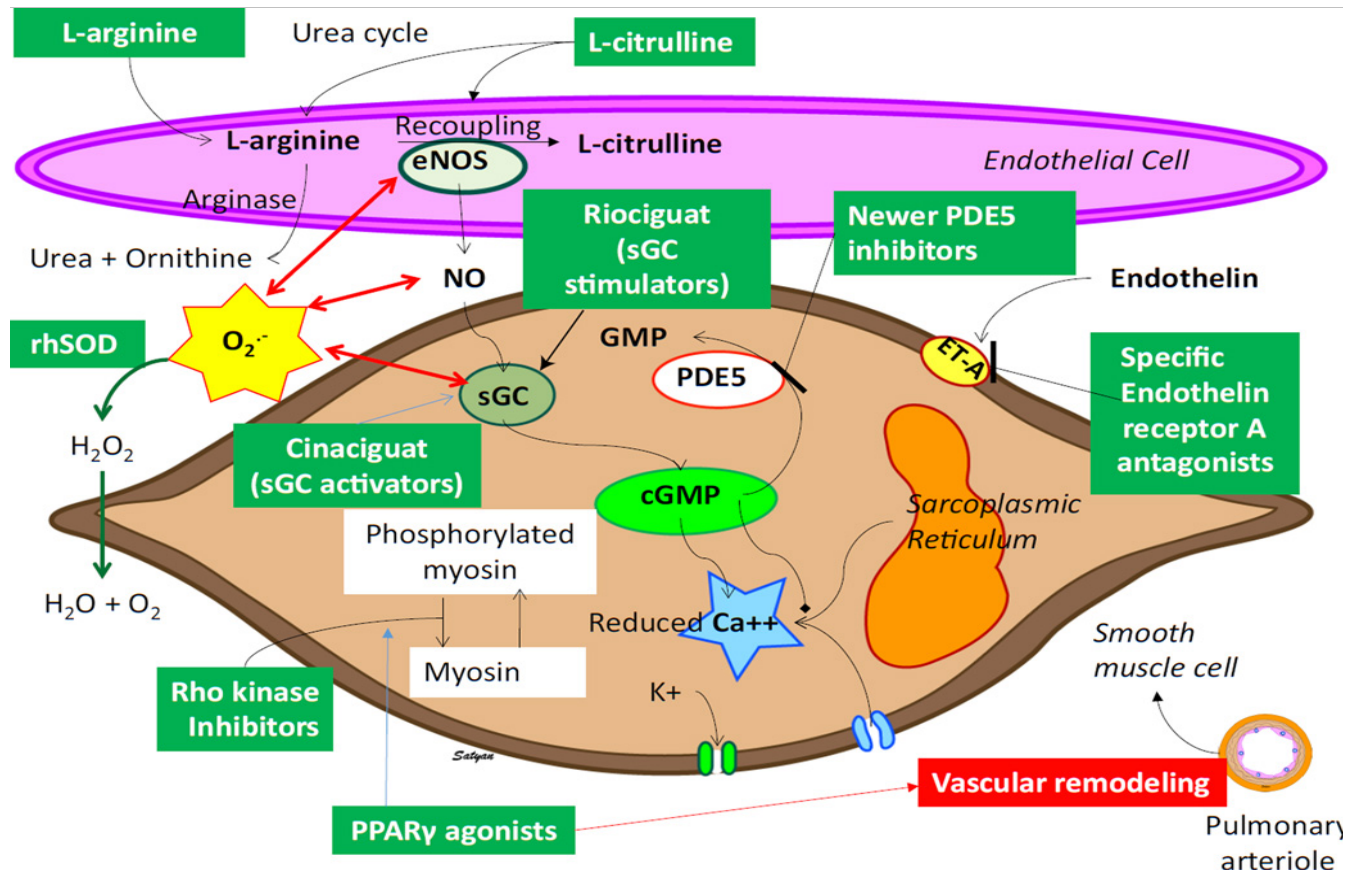
▶ Endothelin Pathway

- ▶ bosentan
- ▶ ambrisentan

▶ cAMP

- ▶ Milrinone
- ▶ Prostaglandin E1
- ▶ Prostacyclin I2
- ▶ Prostacyclin analogs:
Iloprost, Epoprostenol,
Trepstinil, Beraprost

Slide in Your Handout



iNO

- ▶ This is the only FDA approved specific pulmonary vasodilator therapy for infants.
- ▶ Common dose is 20ppm. Higher doses have not been shown to be effective.
- ▶ Up to 40% of infants could be non-responders. Younger premature infants more likely to be non-responders.
- ▶ Expensive and not available everywhere.

When iNO Does Not Work

- ▶ Try adding medications.
- ▶ Milrinone is usually easily available and has been shown to be helpful in iNO resistant pulmonary hypertension.
- ▶ Intravenous sildenafil also may help.
- ▶ Oral sildenafil has been used as well.
- ▶ Several studies used Iloprost as a second agent.

Sildenafil Intravenous

- ▶ Loading dose of .4/mg/kg over 3 hours.
- ▶ Maintenance dose of 1.6 mg/kg/day iv.
- ▶ Dosing above for > 34 weeks gestation and <72 hours old.

Sildenafil Enteric

- ▶ Dose is usually 1 mg/kg/dose q6 or q8 hours.
- ▶ Higher doses may result in higher mortality.
- ▶ Dosing same whether used in patients with acute PPHN or BPD associated PAH.

Sildenafil Warnings

- ▶ On 08/30/12 FDA recommended against using Sildenafil in children age 1-17 because of increased mortality in high dose treatment groups, from a study in 2012. None of the patients in the treatment group were neonates.
- ▶ On 03/31/14 FDA revised statement saying that health care professionals should use their discretion, but that high dose Sildenafil should be used with caution.

Sildenafil and Premature Babies

- ▶ Multiple studies have examined sildenafil in premature infants and have found improvement in their echocardiographic parameters of PH.
- ▶ However, sildenafil does not help prevent BPD.
- ▶ Multiple studies have also examined the effect of sildenafil on patients with BPD and found at least >20% drop in pulmonary artery pressures.
- ▶ Some of these studies used other drugs for pulmonary hypertension as well with improved success with more than one therapy.

Bosentan

- ▶ Based on several pediatric randomized demonstrated safety and efficacy of bosentan. As of 9/2017 it was approved for pediatric use.
- ▶ Usage is limited by oral formulation in the acute phase of PAH.
- ▶ Liver toxicity can occur.
- ▶ Dose is 1-2mg/kg/dose BID.
- ▶ Combination therapy with PDE-5 inhibitor and bosentan increases survival in iPAH and BPD.

Milrinone

- ▶ Milrinone is a phosphodiesterase III inhibitor. By inhibiting PDE3 less cAMP is broken down.
- ▶ Most studies used Milrinone as an adjuvant therapy in patients who were iNO non-responders (defined as an oxygenation index >25 despite 6 hours of iNO).
- ▶ Dosage is .33-.66 microgram/kg/min.
- ▶ Clinical improvement seen in PA pressures and cardiac output.

Prostaglandin I2 and E1 and Their Analogs

- ▶ Prostacyclin (PGI₂) and Iloprost can be given through the endotracheal tube even in the patient on a high-frequency ventilator.
- ▶ Iloprost, Epoprostenol can be given intravenously. Reports come from institutions where iNO not available.
- ▶ These medications increase cAMP.

Combination Therapy

- ▶ Two studies have shown in adults that combination therapy long term have improved survival.
- ▶ Therapies used were PDE-5 inhibitor and ET receptor antagonist.

CLD and PAH

- ▶ 1 out of 4 patients with moderate to severe CLD will develop pulmonary hypertension (Kim).
- ▶ Mortality in one study was 47% percent in that population at 2 years. This study however, is from 2007 (Khemani).
- ▶ As the survival in the extreme premature infants increases this population is likely to grow.

CLD/BPD Chronic Therapies

- ▶ Supplemental oxygen
- ▶ Diuretics
- ▶ Sildenafil
- ▶ Sildenafil has been shown to help in long term under the age of 2 (Mourani).

Cost of Pulmonary Vasodilators

- ▶ Riociguat: 30 day supply is 9270\$
- ▶ Bosentan: 30 day supply is 2,970\$.
- ▶ Treprostinil :30 day supply is 6,102.24\$
- ▶ Sildenafil: 30 day supply is approximately 55\$

Conclusion

- ▶ Pulmonary hypertension is a relatively common finding in the patients I treat.
- ▶ Many patients with a left to right shunt will have pulmonary artery hypertension because of the excess pulmonary blood flow, but most of them will improve after the shunt is removed.
- ▶ For the patients with PPHN oxygen, iNO are the mainstays of treatment with some patients (non – responders) improving with Intravenous sildenafil.

Conclusion

- ▶ Approximately .48-.7 cases per million per year of children are diagnosed with IPAH.
- ▶ Prognosis of patients with IPAH has improved but is still suboptimal.
- ▶ Patients who do not respond to medical therapy may be eligible for a lung transplant, atrial septostomy or Potts shunt (side by side anastomosis aorta to pulmonary arter).
- ▶ Median survival is 4.9 years after transplantation. Acute death is due to rejection, technical aspects. The late deaths are from bronchiolitis obliterans and infection.