Pulmonary Hypertension

Increased pulmonary vascular resistance with pathophysiologic consequences including cor pulmonale and RV failure. Requires optimization prior to anesthesia when possible and avoidance of the precipitants of pulmonary HTN during anesthesia.
Definition: Mean PAP > 25mmHg at rest & > 30mmHg with exercise (Normal ~ 15mmHg)
PVR = (Mean PAP – PAOP) x 80 = 50-150 dynes/sec/cm^{-5} (Normal range) & > 300 dynes/sec/cm^{-5}= PAH
CO

ANESTHETIC CONSIDERATIONS:

- **Life-threatening risk of RV failure**
- **Risk of arrhythmias 2^0 to SA and AV node ischemia**
- **Co-morbid disease :**
  - COPD, obesity, OSA, collagen vascular ds, HIV, sarcoidosis, thromboembolic, left heart disease etc.
- **Anesthetic effects**:
  - Potential to increase PVR & RHF, need to **avoid precipitants** (hypoxia, hypercarbia, acidosis etc)
  - Decreased myocardial contractility (need for maintenance of right heart supply / demand balance)
- **Type of surgery**
  - Laparoscopic surgery: decreased venous return, increased risk acidosis (CO_2 reabsorption)
  - Major surgery: i.e. blood loss, fluid shifts (maintain RV preload)
- **Medication Management -** maintain pulmonary vasodilator infusions/meds perioperatively at usual dose
  - Pt may be anticoagulated (warfarin) for increased risk thrombosis/thromboembolism
  - Other meds may include: CCB (nifedipine, diltiazem, amlodipine), diuretic, phosphodiesterase inhibitors (sildenafil), prostacyclins (epoprostenol, treprostinil, iloprost), endothelin receptor antagonist (bosentan)
- **Consider invasive monitoring** (art line +/- PAC) or **need for inhaled NO** (20 - 40 ppm)
- **Potential for paradoxical emboli**

ANESTHETIC GOALS:

- **Avoid Increases in PVR**
  - hypoxia, hypercarbia, acidosis, hypothermia, SNS stimulation (pain, anxiety), hyperinflation of the lungs (high airway pressures & PEEP)
  - alpha-adrenergic drugs, ketamine, nitrous oxide

- **C: Optimise RV contractility** (inotropy, decreased pulmonary afterload – milrinone)
- **R: Avoid tachycardia** – maintain coronary perfusion time
- **R: Maintain NSR** – facilitate diastolic filling of noncompliant right ventricle – need atrial 'kick'
- **A: Maintain high normal SVR -** maximize coronary perfusion – norepinephrine, vasopressin
- **P: Adequate RV preload** – avoid overdistention – poorly tolerated & may result in RV ischemia d/t increased myocardial wall tension & RVEDP (may need echo to guide fluid therapy)

HISTORY

- Standard anaesthetic history (AMPLE) with additional attention to:
- Cardiopulmonary function and reserve:
  - Dyspnea – earliest most common symptom
  - Fatigue
  - Functional capacity – decreased exercise tolerance
  - Features of ischemia (exertional dyspnea, tachypnea, chest pain, light-headedness = ↑ RV work)
- Others: Pre-syncope/syncope, palpitations, orthopnea, PND, pedal edema, ascites, hemoptysis, hoarseness, cyanosis
- Angina & Syncope are serious prognostic indicators
- Hemoptysis (seen in pulmonary venous hypertension)
- Hoarseness: Ortner's sign (compression of Left RLN by enlarged proximal pulmonary arteries)
- Conditions assoc with PAH (cocaine use, HIV, appetite supressants) or diseases (COPD, OSA, ILD)
- Medications, adherence, and side effects (esp. PAH meds)
- Raynaud's: ~10% of patients (usually women)

PHYSICAL

- **GENERAL**
  - Vitals
- **HEENT**
  - Ease of intubation
- **RESP**
  - Standard respiratory exam including auscultation for crackles if LV failure, cyanosis, clubbing
- **CVS**
  - JVD (distention with giant A wave & systolic V wave)
  - Precordial exam (parasternal lift / heave)
  - Auscultation:
    - prominent P2 heart sound (if heard at 4th left intercostal space)
    - TR murmur – may ↑ during inspiration as RV dilates
    - PR/PI murmur LUSB – (diastolic decrescendo) aka ***Graham Steell*** murmur
      - Due to dilation of pulmonary valve annulus
    - S3 gallop, or S4
- **GI**
  - Hepatosplenomegaly, ascites, peripheral edema, anasarca indicative of critical impairment RV fx

INVESTIGATIONS

- **Labs**
  - CBC/d, Lytes, Cr, BUN, PT, PTT
  - +/- ABGs – pulmonary ds
  - +/- LFTs (if liver congestion or on Bosentan)
  - +/- serologic tests for collagen vascular ds etc (RF, ANA, ANCA, HIV etc)
  - +/- crossmatch depending on surgical indication
- **Imaging**
  - **EKG**:
    - RVH, RAD, R/S ratio > 1 in V1 & V2, S > 3 mm in V5, V6, RBBB
    - P pulmonale: P wave > 2.5 mm in amplitude in leads II, III, aVF, & V1
    - RV strain – inverted T waves & ST depression in V1-V3
  - **CXR**
    - globular heart (RA dilation), prominent/engorged central PA with attenuation peripheral vessels (oligemic lung fields), loss retrosternal air space – RV enlargement
  - **Echo**
    - Assess chamber size and function, TR / PI, EF, any R to L shunts, effusions, presence of paradoxical bulging of septum into LV, and pulmonary artery systolic pressure
- **Special**
  - **V/Q scan** if thromboembolic disease (safe despite reports of fatalities)
  - **PFTs** (for baseline and deterioration) – DLCO is usually decreased in PAH
  - **Sleep study** if suspect OSA
  - ****Angiography** **– (right side) "gold standard" – elevated PAP and correlation with PCWP
  - **Six Minute Walk Test –** determines WHO functional class which guides therapy & establishes baseline to measure response to therapy.

OPTIMIZATION

- If evidence of **significant RV dysfunction, reevaluate the need for surgery**
- **Reduce PAP if possible;** (more likely to succeed prior to surgery)
  - O2, bronchodilators, antibiotics and steroids if lung disease
  - vasodilators and inotropes if cardiac disease
- Optimization of **RV preload** should be considered if CVP is < 10 mmHg (however, if have RV infarction this can make symptoms of R-sided failure worse)
- If **newly diagnosed in an urgent / emergent surgery**, start **sildenafil 50-100 mg OD and L-arginine 15 g OD immediately**
- **Heparinize** patient if indicated (replace coumadin with heparin) NB: GOAL INR on coumadin 2-2.5
- **PGI_2** (prostacylin) stimulates adenylate cyclase to ↑ cAMP causing vasodilation. Used as a continuous intravenous infusion for the treatment of severe pulmonary hypertension and may be particularly useful as a bridge to transplantation: IV – epoprostenol/Flolan, IH – Iloprost/Ventavis, PO – Beraprost
  - **MUST CONTINUE INFUSION IF ON PGI_2** as the T½ is very short (3-5 min) & can get significant rebound hypertension.
- **Start or continue chronic therapy for pulmonary arterial HTN**
  - Refer to medication table that follows under pathophysiology/treatment section
- **Supplemental O_2** therapy can prolong life in hypoxemic patients with chronic obstructive pulmonary disease, although its hemodynamic effects are variable and frequently not dramatic (usually given if PaO_2 55 mmHg when breathing ambient air or a PaO_2 60 mmHg with P-pulmonale, a hematocrit greater than 55%, or edema)
  - Cor pulmonale:
    - Change in structure and function of the right ventricle of the heart as a result of a respiratory disorder (the cause must originate in the pulmonary circulation)
    - RVH (right ventricular hypertrophy) is the predominant change in chronic cor pulmonale, however in acute cases dilation dominates, both d/t increased right ventricular pressure
    - Left untreated, cor pulmonale can lead to right-heart failure and death
- Isovolumic **phlebotomy** is recommended if the hematocrit exceeds 50%, because at this level, the decrease in oxygen carrying capacity produced by phlebotomy is offset by the increases in cardiac output and systemic oxygen delivery, which occur when the viscosity of blood is returned to normal
- SBE prophylaxis if appropriate

ANESTHETIC OPTIONS

- Depends on the type of surgery; cardiac, non-cardiac, obstetric
- Maintaining anesthetic goals more important than the technique
- Similar considerations to the pt with AS plus changes in PVR
- Generally high perioperative morbidity and mortality
- Regional techniques good when appropriate
- Epidurals used as can have slow stable block onset and titration, some use more opiates and less local anesthetic to reduce hemodynamic changes from SNS block
- Single shot spinals generally contraindicated due to risk of acutely decreased SVR with fixed CO
- Avoid excess sedation with regional as hypoventilation → hypoxemia & hypercarbia → ↑ PVR
- GA for major surgery
  - IH; may ↓ SVR and contractility, Sevo best as no tachycardia
  - High dose opiate & O2, best hemodynamic stability & pulm vasodilation (anticipate neonatal depression – NICU)
  - Or consider etomidate – minimal negative inotrope & SVR effects
- GA Advantage: easy to administer inhaled prostacyclin/NO & use TEE while intubated

ANESTHETIC SETUP

- **Drugs**
  - Pulmonary vasodilators
    - Nitroglycerin, nitroprusside, hydralazine
    - Nitric oxide
    - Alpha-blockers: phentolamine
    - B-agonists: isoproterenol

        - CCB: nifedipine, diltiazem
        - Prostaglandins: PGE_1 (misoprostol), prostacyclin (PGI_2) (epoprostanil IV, iloprost IH)
        - Adenosine
        - Acetylcholine (causes nitric oxide release)
    - Inotropes / pressors
        - Dobutamine
        - Phosphodiesterase III inhibitors: Milrinone (5mg ETT or IH), or Amrinone
        - Norepinephrine
        - Phenylephrine
        - Vasopressin
        - Consider avoiding epinephrine (can worsen pHTN in higher doses, loses its B_2-effect)
- **Equipment**
    - CAS monitors, temp probe
    - Arterial line; both for BP and frequent ABG
    - Equipment for in-line nitric oxide
    - CVP and PAC:
        - In severe pHTN the CO is limited by RV function so CVP is best estimate
        - In moderate pHTN CO varies with both RV and LV function so need to assess both CVP and PCWP
        - PAC good for CVP / PCWP, CO and calculations of PVR / SVR, PAP and MVO_2
        - PAC risks arrhythmias, PA rupture, venous air embolism and thromboembolism
        - CO measurements may also be inaccurate with shunts or significant TR (overestimates)
    - TEE – in skilled hands may obviate need for PA catheterization

MANAGEMENT OF ANESTHESIA

- **Induction**
    - Risk of hypotension and cardiovascular collapse
    - Patient with R to L shunts (Eisenmenger's) have ↑ response to IV agents & delayed response to IH agents
    - Etomidate has stable pulmonary & systemic hemodynamics
    - STP and propofol ↓ SVR, PVR, venous return & contractility
    - Ketamine – avoid as ↑ PVR
    - Opioids +/- Lido to blunt response to intubation
    - Hyperventilate to decrease pulmonary response to stimuli
    - Muscle relaxants are safe
- **Maintenance**
    - Inhalational , opiate based or TIVA as long as hemodynamic goals applied
    - Pulmonary vasodilators, inotropes and vasopressors as required
    - Titrate volatiles carefully (myocardial depressants)
        - ISO at 1-1.2 MAC best as shown to ↓ PAP, ↓ PVR, ↑ CO with no inhibition HPV
    - Watch tachycardia with DES
    - Avoid N_2O as it ↑PVR & attenuates HPV
    - Recruitment maneuvers to improve ventilation / perfusion mismatch but avoid hyperinflation/high Peak press/PEEP as ↑ PVR
    -
- **Emergence**
    - If OSA patient continue CPAP postoperatively
    - Avoid hypoxia and hypercapnia (very judicious use of opioids)
    - Manage stress and anxiety & pain
    - Avoid shivering and hypothermia

DISPOSITION & MONITORING

- ICU for several days post-op
- Most patients who die perioperatively do so several days postoperatively
- Need to continue all pre- / intraoperative vasodilator therapy

COMPLICATIONS

- Intraoperative pHTN / worsening of pHTN
- Intraoperative causes include:

Table 3. Occurrence of Pulmonary Hypertension During Anesthesia (36)

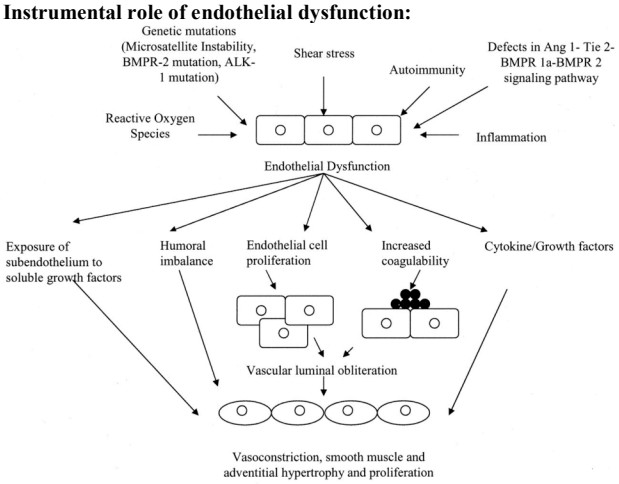
• Thromboembolism	Thrombectomy of deep veins, pregnancy, childbirth
• CO_2 embolism	Laparoscopy
• Air embolism	Surgery with patient in sitting position (e.g., neurosurgery)
• Bone cement (Pallacos©)	Orthopedics
• Protamine	Cardiac surgery
• Extracorporeal circulation	Cardiac surgery
• Ischemia-reperfusion syndrome	Clamping/declamping of the aorta (e.g., liver transplantation)
• Loss of lung vessels	Pneumectomy

- For patient failing consider RVAD esp. if waiting for transplant
- IABP if unable to increase CO or SVR
- ECMO

PATHOPHYSIOLOGY

- Prolonged or intense pulmonary vasoconstriction leads to a remodeling of the pulmonary circulation, which includes:
  - A loss of distal vasculature
  - Extension of smooth muscle into small, non-muscularized pulmonary arterioles
  - Intimal fibrosis
  - Eventually, more severe degrees of vascular obstruction and obliteration
- The major stimulus for remodeling is hypoxia and HPV
- Mediated by vascular growth factors, may be responsible for the progression of pulmonary hypertension in chronic hypoxic lung diseases and primary pulmonary hypertension
- In conditions such as chronic pulmonary thromboembolism, obstruction of a large component of the vascular surface area is the primary cause of the increased pulmonary artery pressure

Instrumental role of endothelial dysfunction:



Classification (J Am Coll Cardiol 2009)

- **Group I** – Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Familial (FPAH)
  - Drug/toxin induced
    - Appetite suppressants - fenfluramine and dexfenfluramine
    - Cocaine and methamphetamine use
  - Associated with other diseases (APAH):
    - Connective tissue ds (scleroderma, SLE, RA)
    - HIV
    - Portal hypertension
    - Congenital heart disease (shunts) – Eisenmengers in most severe form
    - Schistosomiasis
    - Chronic hemolytic anemia
  - Persistent pulmonary hypertension of the newborn
  - Pulmonary veno-occlusive ds (PVOD), pulmonary capillary hemangiomatosis (PCH)
- **Group II** – PH assoc. with left heart disease (Pulm Venous HTN)
  - Atrial or ventricular disease (systolic/diastolic dysfx)
  - Valvular disease (AS,MS etc)
- **Group III** – PH assoc. with lung ds and/or hypoxemia
  - COPD, ILD
  - Sleep-disordered breathing (OSA), alveolar hypoventilation
  - Chronic exposure to high altitude
  - Developmental lung abnormalities
- **Group IV** – Chronic thromboembolic PH (CTEPH)
  - Pulmonary embolism in the proximal or distal pulmonary arteries
  - Embolization of other matter, such as tumor cells or parasites
- **Group V** – Miscellaneous multifactorial mechanisms
  - Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, neurofibromatosis, vaculitis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)
  - Myeloproliferative disorders, splenectomy, CRF on dialysis

Characteristics of medications used in the treatment of pulmonary hypertension

Drug	Route	Dose range, adult	Half-life
Epoprostenol*	Continuous IV	1 to 20 ng/kg/min	3-5 min
Treprostinil*	Continuous SC/IV	0.625 to 1.25 ng/kg/min	4-5 hr

Iloprost	Inhaled	2.5 to 5 mcg, 6-9 times/day	1-2 hr
Treprostinil	Inhaled	6-18 mcg, 4 times daily	4 hrs
Bosentan	Oral	62.5 to 125 mg, 2 times/day	5 hr
Ambrisentan	Oral	5 to 10 mg/day	9 hr
Sitaxsentan•	Oral	100 mg/day	10 hr
Sildenafil	Oral	20 mg, 3 times/day	4 hr
Tadalafil	Oral	40 mg/day	35 hr
NifedipineΔ	Oral	30 to 240 mg/day	2-5 hr
DiltiazemΔ	Oral	120 to 900 mg/day	2-4.5 hr
Amlodipine	Oral	2.5-20 mg/day	30-50 hr

* The dose range shown is for a short-term infusion; higher doses are required for long-term infusions (range often exceeds 100 to 150 ng per kg per minute).
• Not available in United States.
Δ The half-life shown refers to immediate-release preparations; however sustained-release preparations that can be administered once daily are available and preferred for maintenance.

UpToDate.

IMPLICATIONS IN PREGNANCY

- Maternal Mortality as high as 30-50%, may counsel to terminate pregnancy if PAH severe enough
- High incidence of IUGR, fetal loss & preterm delivery.
- Pain during labour especially detrimental because further ↑ PVR & ↓venous return
- Pre-delivery assessment of effects of vasodilators, inotropes, oxytocin, and fluids may be of value
- Drug Therapy tolerated in pregnancy:
  - CCB, digoxin, prostacyclin, nitric oxide, PDE5 (sildenafil/Viagra)
  - Prostaglandin E (misoprostol) causes pulmonary vasodilation
- Drugs to watch out for:
  - Endothelin-1-Receptor competitive anatgonists (bosentan/Tracleer) are potent teratogens
  - Prostaglandin F2alpha (Haemabate) causes pulmonary vasoconstriction.
  - Methylergonovine should be used cautiously has potential to produce severe systemic HTN
  - Very low concentrations of oxytocin seem to be tolerated in labour; postpartum changes in hemodynamics requires a very slow infusion
- Continuous neuraxial block preferred for labor & delivery
  - Careful titration of epidural critical. Treat hypotension initially with IV fluids
  - epidural or CSE with low dose spinal have been used successfully - **single shot spinal is relatively contraindicated (↓ SVR with fixed CO in RVF)**
  - Effective labour analgesia could include inthrathecal opioid for the first stage followed by epidural or if the patient is anticoagulated then a remifentanil infusion/PCA.
- GA possible but hazards include:
  - ↑ PAP during laryngoscopy/intubation
  - PPV ↓ venous return
  - Negative inotropic effects of anesthetic agents
- Avoid precipitants: Prevent Pain, hypoxemia, acidosis, hypercarbia, hypothermia etc
- Give supplemental O_2
- Hemodynamic goals:
  C – Maintain contractility – avoid myocardial depression (narcotic based GA)
  R – Avoid tachycardia
  R – Maintain sinus rhythm
  A – Maintain PAP as low as possible
  Keep systemic P within 15% above and below basal level
  (and always higher than PAP)
  P – Maintain preload and venous return (avoid aortocaval compression & replace blood loss)
- Must also be careful with fluid overload re: autotransfusion with 300 mL blood per contraction
  - most deaths due to CHF that occurs during labour and early post-partum period
- ↑ CO poorly tolerated since it ↑ PAP /RVP with volume overload. RV dilation & TR may occur with impact on LV function and further impairment CO
- Intensive post-op monitoring important and should continue for one week d/t high incidence sudden death during this period.
  - Possible etiologies include:
    - progressive increase in pulmonary vascular tone
    - acute pulmonary vasospasm
    - pulmonary thromboembolism
    - cardiac arrhythmia

    - heightened sympathetic tone
    - fluid shifts
- 43% of deaths often occur secondary to thromboembolic phenomenon in pregnant patients with Eisenmenger's (up to 4-6 weeks post-partum).

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