Perioperative management solutions for Pulmonary Hypertension. An update and review.

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Pulmonary Hypertension (PH) creates a significant challenge for the anesthesiologist, placing patients for surgery in a high risk category. In addition to the elevated intraoperative risk, the limited available therapeutic options for treatment of PH complicate the perioperative care. This syllabus will attempt to outline the basic etiology of PH, discuss the pathophysiology, introduce considerations relating to these points regarding anesthetic management, and describe some of the outpatient medication therapies to supplement your background knowledge on these patients.

A. Etiology:

Pulmonary Hypertension is defined as a syndrome with elevated pulmonary artery pressures (mean PAP > 25mmHg at rest) (1-3). PH is associated with reduced nitric oxide and prostacyclin synthesis as well as with increased thromboxane production (4). Histologic features include medial thickening and intimal fibrosis (5). In 2008 the 4th world symposium on PH was convened in Dana Point, CA to update the classification system for pulmonary hypertension. PH is now classified into five different categories (1,3):

1. Isolated pulmonary arterial hypertension (PAH) (primary pulmonary hypertension, systemic to pulmonary shunts, collagen vascular disease etc.). PAH is defined as exclusion of secondary causes, elevated mPAP (>25mmHg) and elevated PVR of > 3 Woods units (3).

2. PH associated with diseases of the respiratory system and hypoxia (chronic obstructive pulmonary disease, obstructive sleep apnea).

3. Pulmonary venous hypertension (mitral valve disease, chronic left ventricle dysfunction).

4. PH associated with chronic embolic/thrombotic disease (chronic pulmonary embolism).

5. PH attributed to direct obstruction of the pulmonary vasculature (inflammatory pulmonary capillary hemangiomatosis)(1).

B. Pathophysiology

1. The major concern with Pulmonary Hypertension is the development of right heart failure – whether it occurs acutely or chronically depends on the underlying timeframe of disease progression.

2. Chronic PH: PH develops over time, allowing the RV to compensate for the increased work via hypertrophic changes. The RV has limited ability to compensate in this manner and will eventually dilate and fail. RV failure leads to a variety of events including(1,5):

   i) Reduced RV stroke volume, decreased preload to the left ventricle (LV), and resultant hypotension.

   ii) Intraventricular septum of the dilated RV shifts toward the left ventricle further decreasing LV output.

   iii) Reduced RV coronary blood flow secondary to disruption of the normal systolic and diastolic coronary blood flow pattern.
iv) Right-to-left shunt may develop in patients with a patent foramen ovale (~30% of adults) resulting in hypoxia.

3. Acute changes: The normal pulmonary vascular resistance is less than 90% of the systemic vascular resistance. Because the right ventricle (RV) is designed for a low pressure system, an acute increase in pulmonary pressure often results in rapid right ventricular failure (i.e., acute pulmonary embolus, acute severe MR) (1,5).

4. Prognosis: Pulmonary hypertension is a progressive disease with heterogeneous course and deterioration over months to years. The baseline survival data that is frequently quoted comes from the NIH registry that followed 194 patients with idiopathic PH from 1981-1988. The median survival was found to be 2.8 years.

   i) Caveat with this data is there were not any FDA approved therapies available at that time.

C. Medical Management (Outpatient):

1. Treat RV Failure: Diuretics, Digoxin, Sodium/Fluid Restriction

2. Calcium Channel Blockers: Nifedipine, diltiazem, or amlodipine are the mainstays. CCB therapy is used for responders to vasodilator testing on catheterization. Non-responders have worsened outcomes with CCB therapy. (6)

3. Warfarin: Improvement in long term outcome with anticoagulation therapy. (6)

4. Prostacyclins / Prostacyclin analogs: General class of agents with proven survival benefit.

   i) **Epoprostanol (Flolan):** must be continuously infused via a central venous catheter due to its very short half-life (<6 min); significant risk of rebound worsening with abrupt/inadvertent interruption of the infusion that can appear within 30 minutes; the drug is unstable at room temperature and should be kept cold prior to and during infusion (ice packs)

   ii) **Treprostinil (Remodulin):** equivalent efficacy to Flolan. Benefits include a 3-hour half-life, IV or SQ routes of administration, and room temperature stability. Pain and erythema at the infusion site is the major problem with remodulin – leading to IV formulation.

   iii) **Iloprost:** Main advantage is the inhaled route of administration; the hemodynamic effects of ventavis terminate within 30-90 minutes of administration, thus 6-9 nebulizer treatments per day are required (5-15 minutes per treatment). Studies question overall benefit of Iloprost.

5. **Endothelin Antagonists:** Endothelin-1 is a potent vasoconstrictor and a smooth-muscle mitogen that may contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH.

   i) **Bosentan** is an oral, nonspecific Endothelin-1 receptor antagonist with proven functional improvement (7). There are several notable potential toxicities associated with the use of bosentan: Asymptomatic Hepatic toxicity, Anemia, Teratogenicity – contraception required, ↓ OCP efficacy, Testicular atrophy.
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6. **Phosphodiesterase inhibitors**: NO directly increases cGMP production. cGMP subsequently causes vaso-relaxation. The effects of intracellular cGMP are short lived, however, due to the rapid degradation by phosphodiesterases. PDE-inhibitors thus interrupt this step.

   i) **Sildenafil (Viagra)**: Improvement in 6 minute walk test and able to ameliorate the rebound increase PVR and PAP after NO discontinuation

D. **Surgical Risk**: PH patients are high risk surgical candidates. Published series demonstrate a range of surgical mortalities from a low 4% to high of 24% depending on disease severity and surgical procedure (1). Surgical and anesthetic risk should be clearly stated to the patient, especially for an elective case.

1. **Hemodynamic Spiral**: Acute deterioration is possible as RV failure causes reduced pulmonary blood flow, leading to hypoxia which subsequently increases the pulmonary vascular resistance. The elevated PVR ultimately leads to increased strain on the RV. This initiates a catastrophic hemodynamic chain of events where the decreased RV stroke volume decreases LV output and coronary blood flow decreases to both the LV and RV. The already failing RV may not be able to recover from this resulting in cardiac arrest. This is always a potential in PH patients; the anesthesia provider should be aware of it and take steps to prevent it.

E. **Pre-operative Evaluation**

PH carries a perioperative morbidity of 42% for patients undergoing noncardiac surgery with respiratory failure and right ventricular failure as the most frequent complications. Patients with PH are high-risk patients who should be evaluated by a PH specialist before surgery, and should be started on appropriate medication as as outlined above. The goal of the pre-op evaluation is to determine if the patient suffers from PH, RV failure, or a combination of these, as management depends on this(5).

1. **Clinical findings**: The signs of PH are vague, but the most common sign is dyspnea with exertion, progressing to dyspnea at rest, chest pain, fatigue, and syncope. A history of syncope is an extremely poor prognostic sign(1).

2. Symptoms of low cardiac output and metabolic acidosis along with hypoxia, syncope and evidence of RV failure indicate severe disease state(1).

3. The **etiology** of the PH should be determined if possible, and a cardiac echocardiographic exam should be obtained (1,5).

4. Valvular structures, size and function of both RV and LV, and the presence of any intracardiac shunts should be evaluated. Echocardiography can measure mPAP, however this is often underestimated; therefore cardiac catheterization is the gold standard of measure.

5. Pulmonary vascular reactivity can also be determined at catheterization to test responsiveness to vasodilators.

6. **PH medications should be continued including taking it the day of surgery.** Common medications for the treatment of PH include calcium channel blockers, digoxin, diuretics, prostaglandin infusion, and sildenafil. Patients with PH are often taking coumadin, and they should be transitioned to low molecular weight heparin prior to their surgery.
7. A complete blood count, metabolic panel, and coagulation panel should be evaluated. Consider pre-operative blood gas analysis.

8. An EKG should be performed to evaluate signs of ischemia or right-sided ventricular strain.

F. Anesthetic Management

1. **Type of anesthetic:** Regional anesthesia is likely the best approach if the surgery can be performed in this manner (peripheral nerve block or epidural but not spinal anesthesia); data is limited and retrospective in nature. Martin et al showed that operative mortality in patients with Eisenmenger syndrome was 18% with general anesthesia vs. 5% with regional anesthesia (8). Conversely, Weiss et al conducted a review of obstetric outcomes over 18 years demonstrating similar outcomes using either general or regional anesthesia (9). For moderate – severe PH, spinal anesthesia is contraindicated due to chance for abrupt alterations in SVR and preload.

2. **Key Point: Management of either Regional or General Anesthesia with requires utmost vigilance in this population**

3. Maintain pre-operative medications and continue the prostaglandin infusion, as even brief infusion interruptions can cause rapid deterioration and death. For patients taking sildenafil, avoid nitroglycerin and nipride, which can cause severe hypotension. Outpatient therapy is typically titrated slowly and carefully, so do not disrupted for elective surgery.

4. **Monitoring:**
   i) **Arterial lines** are indicated for all but the lowest risk surgeries.
   ii) **Central Venous Access:** Caution during placement to avoid inducing arrhythmias. If atrial arrhythmias develop, cardioversion will avoid the rapid cardiovascular collapse.
   iii) **Pulmonary Artery Catheters (PAC):** The information gained by this monitor may provide critical information for ventilatory and inotropic management making it recommended for most intermediate and all high risk procedures. Caution must be used when inserting a PAC, which may be more difficult to place in a PH patient. **PAC should not be placed in patients with Eisenmenger’s physiology(4).**
   iv) **TEE** should be considered if available.

5. **General Anesthesia:** Anesthetic induction can be challenging due to the high resting

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Anesthetic and Hemodynamic goals for Pulmonary Hypertension:

1. **Avoid elevations in PVR:** Prevent hypoxemia, acidosis, hypercarbia and pain. Provide supplemental oxygen at all times.
2. **Maintain SVR:** Decreased SVR dramatically reduces CO due to “fixed” PVR.
3. **Avoid myocardial depressants and maintain myocardial contractility.**
4. **Maintain preload:**
5. **Maintain sinus rhythm.**
sympathetic tone and resultant deficiency of catecholamine levels (5). This can result in exaggerated hemodynamic compromise following induction and as such, induction should be titrated slowly to effect.

i) **Sedation:** Supplemental oxygen should be used and pre-operative sedation minimized to avoid hypoxia and hypercapnia.

ii) **Induction:** Should be carried out using a slow titration of narcotics, followed by an induction agent such as Etomidate (0.2-0.4 mg/kg) to limit hemodynamic changes. Lidocaine (1 mg/kg) may also help blunt response to intubation and should be considered.

iii) **Maintenance of anesthesia:** Combinations of inhaled agents along with IV narcotics / benzodiazepines should be titrated to effect.

iv) **Fluid Management:** Attempt to maintain euvolemia as close to baseline as possible. TEE / PAC measurements should guide fluid management with care taken not to overwhelm the RV function.

6. **Hemodynamic Management:** Determine if hypotension is due to RV failure or inadequate preload. Assuming euvolemia, inotropic therapy must be considered.

i) Consider Dobutamine (\(\beta_1\) agonist) or Milrinone (PDE III inhibitor) as IV inotropic therapy. Both agents should be considered “inodilators” and may result in systemic vasodilation and hypotension. This can usually be treated with phenylephrine or norepinephrine.

ii) Inhaled nitric oxide (NO) is a potent pulmonary vasodilator whose starting doses of 20-40 ppm do not affect the systemic circulation(10). However, NO requires special equipment to administer inline in the circuit, and not all hospitals have NO available. NO must be weaned slowly, so once started the patient will need to remain intubated as NO is weaned in the ICU. Inhaled prostacyclin has also been used intra-operatively either as continuous inhalational therapy (50 ng/kg/min) (11) or as an hourly inhaled bolus (50 mcg over 15 minutes) (12).

iii) Vasoconstrictors such as phenylephrine, norepinephrine and vasopressin may have variable responses on PVR, but may be needed in the setting of persistent systemic hypotension.

7. **Ventilator Management:** Avoidance of hypoxia and hypercapnia is critical, but must be balanced by avoidance of lung hyperinflation. Large alterations in lung volumes by positive pressure ventilation, along with either excessive or inadequate PEEP can dramatically alter PVR in PH patients (5).

i) Low Tidal Volume Ventilation with low PEEP levels may be the ideal strategy, adjusting respiratory rate to prevent hypercapnia. Hypercapnia dramatically elevates PVR, but is a risk with this ventilation strategy and must be monitored carefully.

G. **Post-Operative Management**

The post-operative period represents a high risk time for PH patients. PH patients should be monitored in an intensive care setting in the first few days following surgery as there is high risk for sudden death. Patients may benefit from epidural anesthesia for post-operative analgesia. Finally, the patients should be transitioned back to their usual oral anticoagulation post-operatively.
H. Considerations for Labor in PH and Eisenmenger’s Syndrome (ES)(2):
ES represents the most common cyanotic cardiac defect in adults. Chronic left to right shunting results in right ventricular hypertrophy, elevated PVR and significant ventricular and arterial remodeling on the right side. ES carries a maternal mortality ranging from 30 – 70% along with high incidence of fetal demise, so patients are usually counseled against pregnancy. Sudden death is common and may be due to stroke, arrhythmia, abscess, or heart failure. 25 year survival after diagnosis of ES is reported to be 42% in the absence of pregnancy. A significant number of complications occur 2-6 weeks post-partum. Mortality and morbidity is also high in PPH and many authors consider pregnancy contraindicated. Risk for maternal mortality is nearly 30% for PPH.

1. Pathophysiology: ES is defined by a PVR greater than 800 dyn·s/cm$^5$ along with right-to-left or bidirectional shunt flow. Correction of the shunt may resolve the pulmonary hypertension, but once pulmonary arteriolar remodeling (i.e., medial hypertrophy) develops the elevated PVR is irreversible, differentiating ES from primary pulmonary hypertension.
   i. Symptoms: Fatigue, dyspnea, cyanosis, edema, clubbing, and polycythemia.
   ii. The underlying right-to-left shunt, hyperviscosity from polycythemia, and the development of heart failure promote thrombus formation and may elevate stroke risk.

2. Peripartum Considerations: Patients with ES are often unable to accommodate the increased oxygen demands of pregnancy.
   i. Reduced SVR from pregnancy coupled with the irreversible elevated PVR of Eisenmenger’s increases right-to-left shunting and cyanosis.
   ii. Reduction in functional residual capacity adds to the hypoxemia, further reducing oxygen delivery to the fetus and increasing fetal demise.
   iii. Management of patients who desire to remain pregnant should be carried out utilizing a multidisciplinary approach among obstetricians, cardiologists and anesthesiologists trained in high risk deliveries.

3. Anesthetic Management for Labor: Historically, regional anesthesia was thought to be contraindicated and general anesthesia was the standard. A recent review of cases of non-cardiac surgery including labor and cesarean section in Eisenmenger’s syndrome indicates that regional anesthesia is indeed safe for these patients. Anesthetic delivery requires utmost vigilance to maintain the above hemodynamic goals with any type of anesthesia. Vaginal deliveries will often require an assisted second stage to reduce cardiac stress.

**Anesthetic and Hemodynamic goals for Eisenmenger’s syndrome:**

- **Avoid elevations in PVR:** Prevent hypoxemia, acidosis, hypercarbia and pain. Provide supplemental oxygen at all times.
- **Maintain SVR:** Reductions in SVR will increase right to left shunting.
- **Avoid myocardial depressants and maintain myocardial contractility.**
- **Maintain preload:** Avoid aortocaval compression.
- **Maintain sinus rhythm.**
4. **Labor**: Early and effective analgesia is critical to maintain the balance of SVR and PVR by avoiding catecholamine surges from pain. Intrathecal opioid administration (CSE) in first stage of labor is ideal, however if anticoagulation is a concern then a low-dose remifentanil infusion or patient controlled analgesia are good options.
   i. Slow titration of local anesthetic with aggressive treatment for any reduction in SVR (i.e., systemic hypotension) using phenylephrine will provide good results for second stage of labor as well as instrumental delivery.
   ii. Maintenance of intravascular volume status using careful fluid boluses along with use of phenylephrine for decreased SVR should be used to prevent onset or exacerbation of cyanosis.
   iii. Pudendal blockade may also be employed to avoid the risk of extending the epidural blockade (and decreasing SVR) to “cover” stage 2 of labor and for delivery.
   iv. Oxytocin, mepertine and prostaglandin should be used with extreme caution because of systemic and pulmonary vascular side effects.

5. **Anesthesia for Cesarean section**: Either epidural or general anesthesia is acceptable.
   i. Single shot spinal anesthesia is contraindicated.
   ii. Slow titrated doses of local anesthetic to obtain a surgical block can be safely used.
   iii. Tight hemodynamic monitoring and control is of utmost importance. Avoidance of elevations in PVR is critical.

6. **For general anesthesia**, slow titration of induction agents is preferred as rapid sequence inductions carry high risk of SVR alterations and subsequent hemodynamic collapse. This places the patient at increased risk of aspiration, so strict NPO guidelines, use of pharmacologic prophylaxis against aspiration (sodium citrate, H\textsubscript{2} blockade, etc), and mask ventilation using cricoid pressure are recommended. Propofol and thiopental should be avoided or used with extreme caution due to marked reductions in SVR, whereas ketamine and etomidate seem appropriate. Inhalational agents should be used with caution because of their propensity to decrease SVR. Nitrous oxide should be avoided because of its propensity to increase PVR. Maintenance of anesthesia may be accomplished using careful titration of intravenous agents such as nondepolarizing neuromuscular blockers, opioids, and sedative-hypnotic agents such as midazolam or ketamine, “topping off” with potent inhalational agents being used at concentrations of less than 0.5 MAC.

7. **Monitors**:
   i. **Pulse oximetry** may be the most important monitor as changes in saturation directly correlate with alterations in shunt flow.
   ii. **Intraarterial monitoring** is generally employed to closely follow blood pressure.
   iii. Central venous catheters are controversial. CVP catheter placement carries a risk of air embolus, thrombus and pneumothorax which can be devastating in these patients; although information regarding cardiac filling pressures can be useful.
   iv. **Pulmonary artery catheters are contraindicated** in obstetric patients with ES for a number of reasons. The anatomic abnormality causing ES typically renders “flow-directed flotation of PA catheters difficult or impossible, and the risk of arrhythmia, pulmonary artery rupture and thromboembolism are elevated. Cardiac output measurements will be inaccurate due to the large shunt.
   v. **PAC is generally employed for those patients with PH but not ES.**
vi. If general anesthesia is employed, TEE may provide the best real time monitor of cardiac preload and of the status of right-to-left shunting.

8. Anesthetic Management specifics for PH: Refer to the hemodynamic goals for ES, with one caveat: reduction in SVR will not alter the shunt fraction for PPH patients as there is no defect, but will cause a marked drop in cardiac output due to relatively fixed right-sided pressures. As a result of small numbers of cases, there is no consensus about ideal anesthetic management for labor and delivery.

i. Vaginal delivery is preferred using epidural anesthesia (or CSE), with assisted second stage labor (i.e., forceps delivery) to minimize stress on the right ventricle.

ii. Oxytocin has been used successfully both for induction of labor and to increase uterine tone post partum (11). Careful titration is required as it can decrease SVR and elevate PVR to decrease both coronary perfusion pressure and forward flow (11). Avoid carboprost and methergine because of pulmonary side effects and vasoconstrictive effects, respectively.

iii. Cesarean section has been associated with increased mortality; however patients with severe disease causing right heart failure may require operative delivery (39). The anesthetic should be tailored to each patient’s underlying cardiac function, as epidural and general anesthesia have similar outcomes.
References: