LEARNING OBJECTIVES: As the result of this educational program the learner will be able to:
1. Assess the preoperative status PAH patient
2. Choose an appropriate anesthetic and monitoring plan for the PAH patient
3. Predict and treat perioperative complications of the PAH patient

CASE
The perioperative care for a patient with PAH is very challenging and patients are considered to be a high surgical risk.

57 year old male with an 8 year history of primary PAH develops a left upper lobe lung mass, presumed to be non-small call lung cancer. History of 60 pack years, quit 10 years ago, type 2 diabetes. Medications: Rx: bosentan, epoprostanol and warfarin.

INTRODUCTION
See Background at end of syllabus

PREOPERATIVE ASSESSMENT
The goal of the pre-op evaluation is to determine if the severity of the PAH, existence of concurrent and assessment of therapeutic optimization.

Clinical Assessment: The clinical signs of PH are vague, including dyspnea from that with exertion to dyspnea at rest, chest pain, fatigue, and syncope. A history of syncope is a poor sign.

Chest radiograph: The classic chest radiograph shows enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in oligemic lung field. Right ventricular enlargement (diminished retrosternal space) and right atrial dilatation (prominent right heart border) may also be seen. Occasionally, the underlying cause of the PH is apparent on the chest radiograph (interstitial lung disease).

ECG: The electrocardiogram (ECG) may demonstrate signs of right ventricular hypertrophy or strain, including right axis deviation, an R/S ratio greater than one in lead V1, incomplete or complete right bundle branch block, or increased P wave
amplitude in lead II (P pulmonale) due to right atrial enlargement. Most ECG signs are specific but not sensitive for the detection of right ventricular disease.

**Echocardiography:** Echocardiography is performed to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function. In addition, echocardiography can evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts.

**Pulmonary function tests:** Pulmonary function tests (PFTs) are performed to identify and characterize underlying lung disease that may be contributing to PH. An obstructive pattern is suggestive of COPD, while restrictive disease suggests interstitial lung disease, neuromuscular weakness, or chest wall disease. A preoperative ABG is recommended.

**Polysomnography:** Polysomnography is the gold standard diagnostic test for sleep related breathing disorders, such as obstructive sleep apnea (OSA).

**V/Q scan:** Ventilation-perfusion (V/Q) scanning is used to evaluate patients for thromboembolic disease.

**Laboratory tests:**
- Routine CBC, metabolic panel, coagulation status (per institutional policy/surgical need).
- Liver function tests to screen for portopulmonary hypertension
- Antinuclear antibody (ANA), rheumatoid factor (RF), and antineutrophil cytoplasmic antibody (ANCA) titers to screen for PH due to the connective tissue diseases

**Exercise testing:** Exercise testing is most commonly performed using the six-minute walk test or cardiopulmonary exercise testing. The latter can be performed with gas exchange measurements, echocardiography, and/or right heart catheterization.

**Right heart catheterization:** Right heart catheterization is necessary to confirm the diagnosis of PH and accurately determine the severity of the hemodynamic derangements. Right heart catheterization is also helpful in distinguishing patients who have group 2 PH. Such patients have a mean pulmonary capillary wedge pressure (PCWP) ≥15 mmHg, as measured by right heart catheterization. An additional benefit of right heart catheterization is that the presence and/or severity of a congenital or acquired left-to-right shunt can be confirmed when noninvasive studies are not definitive.

**Medications:** PAH medications should be continued including the day of surgery. Anticoagulated patients should be bridged with low molecular weight heparin or unfractionated heparin. The last dose of LMWH should be 12 hours prior to surgery and should be ½ of the usual dose. UH should be discontinued 6-8 hours prior to
surgery.

**INTRAOPERATIVE CONSIDERATIONS**

*Choice of Anesthetic:* The choice of anesthetic is less important than the need for increased monitoring and vigilance in this fragile population. If appropriate for the surgical procedure and the coagulation status is normal, regional anesthesia is a popular choice. However, one must prevent large changes in SVR and preload related to an anesthetic choice such as a spinal anesthetic. For thoracic surgery, even thoracic epidural anesthesia (TEA) is controversial: Although TEA may contribute to the attenuation of the surgical stimulus (and thus limit increases in PAH), it is also postulated that, TEA could block cardiac sympathetic nerves and thus profoundly alter cardiac function.

*Maintain preoperative medications:* Many patients will present with indwelling catheters with continual infusions. It is crucial to both continue these medications as brief interruptions can cause abrupt changes in PAH. Further, the anesthesiologist should be prepared to escalate therapy and/or introduce additional therapies as needed.

*Monitoring:* Arterial lines are indicated for most procedures and central venous access is often desirable, but catheter placement must be cautious to avoid inducing arrhythmias. A PA catheter may be desired to guide anesthetic and hemodynamic drug choices. Further, immediate information about changes in pulmonary artery pressures due to conditions induced by the anesthesia and/or surgery may be useful. Extreme caution should be used in the placement and management of these catheters. TEE monitoring can be extremely useful and may carry a lower risk than PA catheter placement while providing similar information. One must pay close attention the acid-base balance and K/Mg status of the PAH patients as acidosis and arrhythmias should be prevented if at all possible.

*Hemodynamic Goals:* Avoid elevations in PVR due to hypoxemia, hypercarbia, acidosis and pain. Hypercarbia is especially important to consider with line placement in a sedated patient. Maintain normal SVR, preload and a sinus rhythm as the PAH patient has few compensatory mechanisms for changes in these parameters and due to a relatively fixed PVR. Clearly myocardial depressants should be avoided with the goal of maintaining normal myocardial contractility.

Specific drug considerations: Assess the need for dobutamine or milrinone for inotropic support – as both agents are “inodilators”, one should prevent decreases in SVR with phenylephrine, vasopressin or norepinephrine. Inhaled nitric oxide
(NO) is a potent pulmonary vasodilator with little systemic effects. Inhaled prostacyclin has also been used intra-operatively either as continuous inhalational therapy or as an hourly inhaled boluses. Drug interactions should be avoided as possible - this is especially important to consider for patient taking PDE5 inhibitors (such as Sildenafil) as the addition of veno or arterial dilators may result in severe hypotension.

responses on PVR, but may be needed in the setting of persistent systemic hypotension.

**Induction and Maintenance of Anesthesia**
The specific drug choice is less important than slow administration and titration. Also longer acting sedatives may need to be held to avoid the effects of hypercarbia in the postoperative period. An induction that limits hemodynamic changes is ideal. Inhaled and/or intravenous anesthetics are appropriate for maintenance of anesthesia. One should attempt to maintain euvoolemia so as not to induce or aggravate RV dysfunction – therapy can be guided by urinary catheter output, TEE and/or PA catheter readings.

**Ventilator Management:** Avoidance of hypoxia and hypercarbia are critical. As importantly, one must avoid over-distention of the lungs and ventilator settings that result in large inspiratory pressures. One can cautiously use PEEP but be aware that either excessive or inadequate PEEP can dramatically alter PVR in PAH patients. A lung protective ventilation strategy using low tidal volumes and low PEEP (adjusting RR to prevent hypercarbia) may be useful.

**One Lung Ventilation (OLV)**
OLV is especially dangerous in the PAH patient due to the induction of hypoxic pulmonary vasoconstriction (HPV) which could lead to catastrophic increases in PVR. Inhaled pulmonary vasodilators may be especially useful in this situation as inhaled agents may enhance V/Q matching as the vasodilation effect occurs in the well-ventilated lung units. In contrast, intravenous vasodilators may interfere with HPV in both lungs, resulting in an increased pulmonary shunt and systemic hypoxemia. However, this phenomenon has not been adequately studied with conflicting literature. Even more concerning is the introduction of OLV to patients receiving chronic vasodilator therapy as they may also inhibit bilateral HPV, also resulting in increased pulmonary shunt and hypoxemia. Extreme caution should be used with the introduction of OLV; this should be discussed with the surgical team before surgery with the plan to ventilate both lungs as needed during the procedure.

**Intraoperative Complications.**
PAH patients are fragile and may suddenly experience acute deterioration from a variety of causes. For example, atrial arrhythmias should be treated early with cardioversion is desirable to avoid rapid CV decline. Impending RV failure is the most feared complication; it leads to a spiral of hemodynamic compromise from reduced pulmonary blood flow leading to hypoxia, which subsequently increases
the pulmonary vascular resistance. An elevated PVR in turn further increases the strain on the RV. With decreased RV function, blood flow from the right heart to the left heart is compromised, LV cardiac output falls and coronary blood flow to the RV and LV may decrease. An already failing and hypertrophied RV may be unable to compensate leading to cardiac arrest.

**POSTOPERATIVE CONSIDERATIONS**
The post-operative period is high-risk time PH patients; one should strongly consider monitoring the postoperative PAH patient in an intensive care setting immediately after surgery. Major concerns include respiratory compromise and right ventricular failure. Further, sudden changes in the medications used during surgery (such as NO) may precipitate hemodynamic compromise – changes and withdrawal of those medications should be made slowly under controlled circumstances. As soon as is feasible, PAH patients should be transitioned back to their usual oral anticoagulation post-operatively.

As pain may be a primary driver of increased PVR, adequate analgesia must be provided that does not induce excessive sedation. Thus, patients may benefit from regional analgesia postoperatively.

**BACKGROUND**

*Definition:* The definition of PAH is based upon right heart catheterization measurements. PAH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest. A mean pulmonary artery pressure of 8 to 20 mmHg at rest is considered normal, while a mean pulmonary artery pressure of 21 to 24 mmHg at rest has uncertain clinical implications. PAH is associated with reduced nitric oxide and prostacyclin synthesis as well as with increased thromboxane production. Histologic features include medial thickening and intimal fibrosis.

*Symptoms:* Most patients with PAH initially experience exertional dyspnea, lethargy, and fatigue, which are due to an inability to increase cardiac output with exercise. As the PAH progresses and right ventricular failure develops, exertional chest pain, exertional syncope, and peripheral edema may develop. In most circumstances, angina is due to subendocardial hypoperfusion caused by increased right ventricular wall stress and myocardial oxygen demand. However, angina is occasionally caused by dynamic compression of the left main coronary artery by an enlarged pulmonary artery; this risk is greatest for patients with a pulmonary artery trunk at least 40 mm in diameter. Passive hepatic congestion may cause anorexia and abdominal pain in the right upper quadrant. Less common symptoms of PAH include cough, hemoptysis, and hoarseness.

*Survival:* Symptomatic patients with idiopathic PAH who do not receive treatment have a median survival of approximately 3 years. Symptomatic patients with PAH that is associated with another disease such as liver disease, systemic sclerosis
generally have a worse prognosis than patients with idiopathic PAH (IPAH). However, patients with PAH associated with Eisenmenger syndrome are an exception because they have a better prognosis than patients with IPAH.

Patients with severe PAH or right heart failure die sooner, usually within one year without treatment. As an example, patients with IPAH and a mean right atrial pressure ≥20 mmHg have a median survival of approximately one month. Factors that may indicate a poor prognosis include age at presentation greater than 45 years, World Health Organization (WHO) functional class III or IV, failure to improve to a lower WHO functional class during treatment, pericardial effusion, large right atrial size, elevated right atrial pressure, septal shift during diastole, decreased pulmonary arterial capacitance increased N-terminal brain natriuretic peptide level, and perhaps hypocapnia. Patients with PAH who experience cardiac arrest rarely survive. In a retrospective study of more than 3000 patients with PAH who required CPR, only 6 percent survived for 90 days.

**Classification:** The current WHO classification of PAH:

**Group 1:** Pulmonary hypertension: idiopathic and other

This group consists of sporadic IPAH, heritable IPAH, and PAH due to diseases that localize to small pulmonary muscular arterioles. These include connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, persistent pulmonary hypertension of the newborn, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis.

Drug- and toxin-induced PAH is also considered Group 1 PAH. Exposure to the following drugs are considered definite risk factors for PAH: aminorex, fenfluramine, dexfenfluramine, and toxic rapeseed oil.

**Group 2:** Pulmonary hypertension due to left heart disease.

PAH due to systolic dysfunction, diastolic dysfunction, or valvular heart disease is included in this group.

**Group 3:** Pulmonary hypertension due to lung diseases or hypoxemia.

This group includes PAH due to chronic obstructive pulmonary disease, interstitial lung disease, and other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing, alveolar hypoventilation disorders, and other causes of hypoxemia.

**Group 4:** Chronic thromboembolic pulmonary hypertension.

This group includes patients with PAH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature.

**Group 5 PAH:** Pulmonary hypertension with unclear multifactorial
mechanisms.

These patients have PAH caused by hematologic disorders (e.g., myeloproliferative disorders), systemic disorders (e.g., sarcoidosis), metabolic disorders (e.g., glycogen storage disease), or miscellaneous causes.

**Chronic Therapy**

*Diuretics:* Diuretics are used to treat fluid retention due to PAH because diuresis will diminish hepatic congestion and peripheral edema.

*Oxygen therapy:* Continuous oxygen administration remains the cornerstone of therapy in patients with group 3 PAH. It is inferred that oxygen may benefit other groups of patients either with resting, exercise-induced, or nocturnal hypoxemia.

*Anticoagulation:* Patients with PAH are at increased risk for intrapulmonary thrombosis and thromboembolism, due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis, and a sedentary lifestyle. Even a small thrombus can produce hemodynamic deterioration in a patient with a compromised pulmonary vascular bed that is unable to dilate or recruit unused vasculature.

*Exercise:* Exercise training appears to be beneficial for patients with PAH.

*Advanced Therapy:* Patients with PAH who are selected for advanced therapy should undergo an invasive hemodynamic assessment prior to the initiation of advanced therapy. It is recommended that patients with Group 1 PAH also undergo a vasoreactivity test with intravenous adenosine, intravenous epoprostenol or inhaled nitric oxide. Patients with a positive vasoreactivity test can be given a trial of oral calcium channel blocker therapy with a dihydropyridine or diltiazem. In contrast, patients with a negative vasoreactivity test require advanced therapy with a prostanoid, endothelin receptor antagonist, or phosphodiesterase 5 inhibitor. Combination advanced therapy may be appropriate in refractory cases, although data are limited. Some patients are refractory to all medical interventions. In such cases, lung transplantation or creation of a right to left shunt by atrial septostomy may be considered.

*Calcium channel blockers:* Some patients who are vasoreactive and receive CCB therapy with a dihydropyridine or diltiazem can achieve prolonged survival, sustained functional improvement, and hemodynamic improvement.

*Prostanoids:*

*Epoprostenol:* Intravenous epoprostenol (Flolan) is the advanced therapy that has been best studied. It improves hemodynamic parameters, functional
capacity, and survival in patients with IPAH. It is delivered continuously through a permanently implanted central venous catheter using a portable infusion pump. It is usually initiated at doses of 1 to 2 ng/kg per min and increased by 1 to 2 ng/kg per min every one to two days as tolerated. A maximal dose has not been established. Patients who have been receiving therapy for many years may receive doses as high as 150 to 200 ng/kg per min with sustained clinical and hemodynamic benefit.

**Treprostinil**: Treprostinil (Remodulin) can be given intravenously or subcutaneously, although subcutaneous administration is uncommon due to severe pain at the injection site. Inhaled treprostinil (Tyvaso) has more recently been approved; specifically for patients with group 1 PAH who are WHO functional class III. It improves hemodynamic parameters, symptoms, exercise capacity, and possibly survival in patients with group 1 PAH. It has not been evaluated in patients with other types of PAH.

**Iloprost**: Inhaled iloprost (Ventavis) has theoretical advantages in targeting the lung vasculature and does not require intravenous administration. The main disadvantage is the need for frequent administration (six to nine times per day).

**Endothelin receptor antagonists**:

**Bosentan**: Bosentan (Tracleer), a nonselective endothelin receptor antagonist, improves hemodynamics and exercise capacity in patients with group 1 PAH and delays clinical worsening. The mortality of bosentan-treated IPAH patients appears favorable compared to historical controls. The major advantage of bosentan is its oral administration.

**Ambrisentan** (Letaris) and **sitaxsentan** (Thelin) are selective type A endothelin-1 receptor antagonists that are administered orally. The evidence suggests that ambrisentan and sitaxsentan improve exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PAH. Only ambrisentan is currently available.

The main adverse effect of some endothelin receptor antagonists is hepatotoxicity, which appears to be more severe at higher doses. Liver function tests should be monitored monthly during treatment with bosentan. The monitoring of liver function tests is no longer required for patients treated with ambrisentan.

Peripheral edema is the most common side effect that requires attention. Mild cases can be managed with diuretics, but more severe cases warrant discontinuation of the medication.

Endothelin receptor antagonists are also potent teratogens, requiring meticulous contraception if used by women who have childbearing potential.
**PDE\textsubscript{5} inhibitors:**

*Sildenafil:* It improves pulmonary hemodynamics and exercise capacity in patients with group 1 PAH.  
*Tadalafil* and *vardenafil* also appear to improve outcomes in patients with group 1 PAH.

*Combination therapy:* It has been proposed that combining pharmacologic agents with different mechanisms of action may produce an additive effect or may induce the same effect at lower doses of each agent.

**Special considerations for each group of pulmonary hypertension:**

**Group 1 PAH:** Advanced therapy is often needed for patients with group 1 PAH because there are no effective primary therapies.

**Group 2 PAH:** For most patients in this group, advanced therapy should be avoided because it may be harmful.

**Group 3 PAH:** Advanced therapy is not approved by FDA for patients with group 3 PAH and several guideline panels recommend against its use in this population, except in the context of a clinical trial.

**Group 4 PAH:** Advanced therapy can be considered for patients with group 4 PAH who remain WHO functional class III or IV even after anticoagulation or thromboendarterectomy.

**Group 5 PAH:** Small studies have addressed the role of advanced therapy for patients with PAH related to sarcoidosis.

**Special considerations in different functional classes (Table 1)**

**WHO functional class II:** Preferred agents include ambrisentan, bosentan, or sildenafil. An acceptable alternative includes tadalafil.

**WHO functional class III:** Preferred agents include ambrisentan, bosentan, intravenous epoprostenol, intravenous or subcutaneous treprostinil, inhaled iloprost or sildenafil. An acceptable alternative includes tadalafil.

**WHO functional class IV:** Patients with severe PAH who are WHO functional class IV should be treated with an intravenous prostanoid. Most clinicians consider intravenous epoprostenol to be the preferred agent. Intravenous treprostinil is considered a reasonable alternative by some. Inhaled iloprost can be considered for patients who refuse or cannot receive intravenous therapy.
Atrial septostomy: Creation of a right-to-left shunt by atrial septostomy has been performed in some patients with syncope or severe right heart failure in an attempt to increase systemic blood flow by bypassing the pulmonary vascular obstruction.

Transplantation: Transplantation has been performed in patients with IPAH and is considered by some to be the final effective treatment for selected patients with IPAH. Bilateral lung or heart-lung transplantation is the procedure of choice.

The timing of transplantation is critical, since survival from severe IPAH refractory to medical therapy is poor and the availability of suitable organs for transplantation is limited. The three-year survival of patients who had a lung or heart-lung transplant for IPAH is approximately 50 percent.

Table 1: World Health Organization (WHO) functional classification for pulmonary hypertension

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<tr>
<th>Class</th>
<th>WHO functional classification</th>
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<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitations of Physical activity. Ordinary Physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of Physical activity. They are comfortable at rest. Ordinary Physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.</td>
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<tr>
<td>III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of Physical activity. They are comfortable at rest. Less than ordinary Physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.</td>
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IV

Patients with pulmonary hypertension resulting in inability to carry on any Physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by Physical activity.


References:

1. Minai OA Perioperative Risk and Management in Patients with Pulmonary Hypertension PVRI REVIEW Apr - Jun 2009 • Volume 1 • Issue 2


