Pulmonary Hypertension and Pulmonary Resection

Tamas Seres, MD, PhD
Katherine Grichnik, MD, MS

Learning Objectives:

1. Recite the signs and symptoms of pulmonary hypertension
2. List the chronic medications that pulmonary hypertension patients are treated with
3. Describe the impact of pulmonary hypertension on the intraoperative and postoperative management of patients
4. Discuss the anticipated perioperative morbidity and mortality rates with an explanation of why.

A 64-year-old female with a 9-year history of primary pulmonary hypertension developed a solid pulmonary tumor. Partial resection of the lung for suspicious primary lung cancer was planned.

Questions:

1. What is the definition of pulmonary hypertension?
2. What are the symptoms of pulmonary hypertension?
3. What is the classification of pulmonary hypertension?
4. What are the preoperative diagnostic procedures, which help to evaluate the patients?
5. What is the treatment of pulmonary hypertension?

Diagnostic procedures 6 years ago:

A. Chest X-ray: prominent pulmonary arteries.
B. Electrocardiogram: increasing R wave, a negative T wave of V1-2, and a deep S wave of V5-6, (findings consistent with right ventricular hypertrophy).
C. Lung perfusion scintigraphy showed no segmental defect.
D. Room air arterial blood gas: PaO₂ = 74.6 mmHg, SpO₂ 95.2%.
E. Right cardiac catheterization: revealed that pulmonary arterial pressure (PAP), pulmonary vascular resistance, and pulmonary capillary wedge pressure were 53/28(38) mmHg, 594 dyn·sec·cm⁻⁵, and 12 mmHg.
F. Diagnosis was: primary pulmonary hypertension (PPH), Rx: bosentan, beraprost, and warfarin.

Diagnostic procedures Preoperatively:
A. Computed tomography showed a solid lung tumor measuring 13x12 mm under the pleura, in segment 1 of the right upper lobe.

B. Primary lung cancer was suspected, and video-assisted partial lung resection was planned.

C. The preoperative right cardiac catheterization showed that mean PAP, cardiac output, and cardiac index were 40 mmHg, 3.50 l/min, and 2.41 l/min/m², respectively.

Questions:
1. What is the mechanism of action of the pharmaceutical agents for PPH?
2. What is your anesthetic plan?
3. What additional agents would you plan to control the PPH?
4. Would you use invasive monitors?
5. How would you optimize the PA pressure?

After intubation with a double-lumen endotracheal tube, a pulmonary arterial catheter was inserted and PAP was monitored. Intravenous prostacyclin (PGI₂) was initiated at a rate of 2 ng/kg/min; the PAP was 70/30 mmHg. Before the operation, one-lung ventilation was tested with the patient in the supine position. Six minutes later, it was discontinued because PAP rose to 105/40 mmHg, and the systolic systemic arterial pressure fell to 90 mmHg, from 130.

Under two-lung ventilation, the patient was then placed in the left lateral decubitus position. Her PAP rose to 110/42 mmHg, from 70/30. After the administration rate of PGI₂ was increased to 6 ng/kg/min, PAP fell to 60/35 mmHg. A mini-thoracotomy was begun under two-lung ventilation.

One-lung ventilation was started for the purpose of lung resection after PGI₂ was increased to 8 ng/kg/min. However, it was discontinued six minutes later because her PAP rose to 110/45 mmHg and systemic arterial pressure decreased.

Questions:
1. What medications are appropriate to increase the systemic pressure?
2. What are the options to decrease the pulmonary artery pressure?
3. During one lung ventilation the mean PAP fell from 60 to 40 mmHg and CVP was changing from 10 to 30 mmHg and CO was 3 L/min. What is going on? What would you do in this situation?

Partial lung resection with linear staples was performed while the right lung was ventilated and held with forceps. A portion of the suture line broke, and a hemorrhage from the
pulmonary artery occurred. The surgery was converted to a standard thoracotomy and the bleeding was controlled. When the operation ended, PGI₂ was administered at a rate of 6 ng/kg/min, and PAP was 50/20 mmHg.

Questions:

1. How would you manage the patient in the recovery room?
2. What is your approach for pain management?
3. CVP is 8 mmHg mean PAP 40 mmHg CO is 3 L/min. What would you do in this situation?

Oral intake of bosentan and beraprost was resumed on the first postoperative day, and PGI₂ dosage was gradually tapered. The mean PAP was within 35-40 mmHg until the pulmonary arterial catheter was removed on postoperative day 4. Oxygen administration via nasal cannula was discontinued on postoperative day 10 when the room air SpO₂ was 95%.

The patient was discharged home without postoperative complications on postoperative day 15. The pathological examination revealed a bronchioloalveolar carcinoma, Noguchi classification type B. The surgical margin was free, and the background lung tissue showed no significant pathological changes, such as proliferation of capillary vessels involving the alveolar septa.

Discussion

1. What is the definition of pulmonary hypertension?

The definition of pulmonary hypertension (PH) is based upon right heart catheterization measurements. PH 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.

2. What are the symptoms of pulmonary hypertension?

Most patients with PH initially experience exertional dyspnea, lethargy, and fatigue, which are due to an inability to increase cardiac output with exercise. As the PH 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 PH include cough, hemoptysis, and hoarseness.
Symptomatic patients with IPAH 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 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 idiopathic pulmonary hypertension (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 cardiopulmonary resuscitation (CPR), only 6 percent survived for 90 days.

3. What is the classification of pulmonary hypertension?

The current WHO classification of PH:

**Group 1:** Pulmonary arterial hypertension (PAH).

This group consists of sporadic idiopathic 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.

PH 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 PH due to chronic obstructive pulmonary disease, interstitial lung disease, 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 PH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature.

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

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

4. What are the preoperative diagnostic procedures, which help to evaluate the patients?

**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.

**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:**

- HIV serology to screen for HIV-associated PH
- 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.

5. **What is the treatment of pulmonary hypertension?**

**Therapies should be considered in all patients with PH:**

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

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

**Anticoagulation:** Patients with PH 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 PH.

**Advanced therapy:**

Patients with PH 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 PH.

**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.

**Selective agents**: 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.

**Adverse effects**: 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.

**PDE5 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 PH: For most patients in this group, advanced therapy should be avoided because it may be harmful.
• Group 3 PH: Advanced therapy is not approved by FDA for patients with group 3 PH and several guideline panels recommend against its use in this population, except in the context of a clinical trial.
• Group 4 PH: Advanced therapy can be considered for patients with group 4 PH who remain WHO functional class III or IV even after anticoagulation or thromboendarterectomy.
• Group 5 PH: Small studies have addressed the role of advanced therapy for patients with PH related to sarcoidosis.

Special considerations in different functional classes:

• 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 PH 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

<table>
<thead>
<tr>
<th>Class</th>
<th>WHO functional classification</th>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>IV</td>
<td>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.</td>
</tr>
</tbody>
</table>