Introduction

The pulmonary circulation is a high flow, low pressure system. Pulmonary hypertension (PH) exists when the mean pulmonary artery pressure (PAP) is >25mm Hg at rest, or >30mm Hg during exercise.

PH has been described as being either primary or secondary. It is termed primary in the absence of secondary causes, such as pulmonary disease (e.g., COPD, ARDS), cardiac disease (e.g., shunts, left ventricular failure), thromboembolic disease, or other pathologic processes. Primary pulmonary hypertension PPH is a rare disease (1 to 2 per million), occurs three times more frequently in women than in men, and has a poor prognosis. Patients with PPH typically have a mean PAP >60mm Hg. Secondary pulmonary hypertension is more common but elevations in PAP are generally less severe (rarely >40mm Hg).

The signs and symptoms of PH are nonspecific and subtle. Left untreated, patients will experience progressive symptoms of dyspnea and right heart failure culminating in markedly curtailed survival.

Causes and Classification

Traditionally, PH has been classified as either primary or secondary. In 1998, the World Health Organization sponsored the 2nd World Symposium on PH where a new more clinically useful classification system was adopted. In 2003, during the 3rd World Symposium on PH, a modified version of the same classification was accepted. This new classification divides PH into five distinct categories (see Table 1) Genetic studies will most likely further refine current classification schemes in the near future.
Pathophysiology

Pulmonary vascular tone is normally very low, even when the pulmonary vessels are exposed to hypoxia and vasoconstrictive agents. Several factors have been proposed as contributors to the pathogenesis of PH. One of the earliest factors discovered to play a role is the imbalance between vasoconstrictors (endothelin-1, thromboxane) and vasodilators (prostacyclin, nitric oxide), where vasoconstrictive substances are in excess. This chronic vasoconstriction can lead to smooth muscle hyperplasia, which may be the earliest change in PPH. As the disease progresses, the smooth muscle and endothelial cells of the pulmonary vessels undergo marked proliferation, likely due to both hypoxia and a mutation of an inhibitory receptor. This dysregulation is known as vascular remodeling and it causes thickening of the normally thin vessel walls which then increases pulmonary vascular resistance. Other contributors to PPH include increased levels of thrombogenic factors and down-regulation of K+ channels in smooth muscle cells leading to a build up of positive charge inside smooth muscle cells and thus, vasoconstriction.

Table 1
Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Idiopathic (i.e., primary)</td>
</tr>
<tr>
<td>- Familial</td>
</tr>
<tr>
<td>- Associated with: collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs/toxins, and/or other (thyroid disorders, gglcyogen storage disease, Gaucher disease, hereditary hemorrhagic talangiectasia, hemoglobinopathy, myeloproliferative disorders, splenectomy)</td>
</tr>
<tr>
<td>- Associated with significant venous or capillary involvement (pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis)</td>
</tr>
<tr>
<td>- Persistent pulmonary hypertension of the newborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary venous hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Left-sided atrial or ventricular heart disease</td>
</tr>
<tr>
<td>- Left-sided valvular heart disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary hypertension associated with lung disease and/or hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>- Interstitial lung disease</td>
</tr>
<tr>
<td>- Sleep-disordered breathing</td>
</tr>
<tr>
<td>- Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>- Chronic exposure to high altitudes</td>
</tr>
<tr>
<td>- Developmental abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary hypertension due to chronic thrombotic and/or embolic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Thromboembolic obstruction of proximal pulmonary arteries</td>
</tr>
<tr>
<td>- Thromboembolic obstruction of distal pulmonary arteries</td>
</tr>
<tr>
<td>- Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)</td>
</tr>
</tbody>
</table>

| Miscellaneous: | Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis) |

Adapted from Simonneau

Clinical Presentation

The most common presenting symptom in PH is dyspnea. Other symptoms may include angina, fatigue, weakness, and syncope. Early in the progression of PH, signs may consist of a loud pulmonic component of the second heart sound (S2), a narrowly split S2, a fourth heart sound, or an early diastolic murmur reflecting tricuspid regurgitation. Jugular venous distention, peripheral edema, cyanosis, a third heart sound, and ascites are all signs seen late in the progression of PH.

Evaluation and Diagnosis (see Table 2)

In the evaluation of a patient with PH, identifying the etiology is essential for appropriate management. The initial screening tool of choice is the echocardiogram. A contrast echocardiogram provides data involving ventricular and valvular function, estimates of PAP, and the presence of shunts. Findings on echocardiogram specific to PH might include right ventricular hypertrophy and/or dilation, left ventricular filling impairment, or paradoxical motion of the interventricular septum. An electrocardiogram of a patient with PH will commonly show right axis deviation, right ventricular hypertrophy (tall R waves in V1-V3), right ventricular strain (T-wave inversion in V1-V3), S wave in V6, and enlarged P waves in II, III, and aVF; though, an electrocardiogram cannot determine disease severity or prognosis. Chest radiograph findings include right ventricular prominence, enlarged hilar...
pulmonary artery trunk, and hyperlucent peripheral lung fields. Chest radiograph together with pulmonary function tests can demonstrate COPD, pulmonary fibrosis, or thoracic cage abnormalities as causes of PH. Patients who are overweight and have a history of snoring should undergo a sleep study to rule out obstructive sleep apnea, a potentially reversible cause of PH. A ventilation-perfusion (V/Q) scan should be done to rule out thromboembolic disease. If abnormal, the V/Q scan should be followed up with a pulmonary angiogram and spiral chest computed tomography. Multiple serological tests, including antinuclear antibody, rheumatoid factor, HIV, and liver function can be used in further diagnostic study. Right-sided heart catheterization remains the gold standard for diagnosis of PH as it provides confirmation of increased PAP. It also provides the ability to measure and follow hemodynamic abnormalities which can predict survival. In addition, right-sided heart catheterization is used to test for a response to vasodilator drugs.

### Table 2
**Evaluation of Patient with Pulmonary Hypertension**

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Diagnosis of Association Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiogram</td>
<td>Left ventricular dysfunction</td>
</tr>
<tr>
<td></td>
<td>Left sided valvular disease</td>
</tr>
<tr>
<td></td>
<td>Congenital heart disease with systemic-to-pulmonary shunt</td>
</tr>
<tr>
<td>Chest radiograph and Pulmonary function tests</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Thoracic cage abnormalities</td>
</tr>
<tr>
<td>Ventilation perfusion scan</td>
<td>Chronic thromboembolic disease</td>
</tr>
<tr>
<td>Pulmonary angiogram</td>
<td></td>
</tr>
<tr>
<td>Spiral computed tomogram</td>
<td></td>
</tr>
<tr>
<td>Sleep study</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Blood tests</td>
<td>Lupus, scleroderma, HIV infection</td>
</tr>
<tr>
<td>Serologic (ANA, HIV)*</td>
<td>Postpulmonary hypertension</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
</tr>
</tbody>
</table>

* ANA-antinuclear antibody; HIV-human immunodeficiency virus
Adapted from Gaine

### Treatment of PAP

**I. Oxygen.** In the 1960s, continuous oxygen administration was found to lower PAP in patients with pulmonary hypertension caused by COPD. Subsequent trials showed that supplemental oxygen improved exercise tolerance and consistently increased survival times. However, oxygen therapy does not appear to affect vascular remodeling. At least 15 hours of daily oxygen therapy is recommended as the benefits increase with longer duration. Oxygen works as a selective pulmonary vasodilator, although the exact mechanism by which it lowers mortality is not known.

**II. Anticoagulants.** In the case of a patient with PH secondary to thromboembolic disease, anticoagulants have an obvious and important role. Anticoagulants also increase survival in patients with primary PH as it has been shown that these patients have abnormalities in blood coagulation and increased thrombotic activity. Furthermore, patients with PH typically have an inactive lifestyle, venous insufficiency, and compromised pulmonary blood flow, which favors the use of anticoagulation. The drug most often used is warfarin, which prevents the formation of vitamin K dependent clotting factors. Heparin, which enhances the action of antithrombin III and inhibits platelet aggregation, is also used.

**III. Vasodilators.** Vasodilator therapy is very useful in the treatment of PH and represents a majority of options. Generally, vasodilators are most effective in the earlier stages of the disease, before vascular remodeling begins to outweigh vasoconstriction. The ideal vasodilator will decrease PAP, PVR, and cardiac output, without decreasing systemic vascular resistance.

#### A. Calcium channel blockers (CCBs). CCBs have been used in the treatment of PH since the early 1980s. Nifedipine and diltiazem are the CCBs most often used because they are less cardiac depressant than other drugs in this class. They act by blocking calcium channels on smooth muscle cells, thereby inhibiting calcium influx and preventing vasoconstriction. They are most effective in a state of increased vasomotor tone (which involves a high influx of calcium). As such, CCBs are especially useful in patients with PH, where the pulmonary vasculature has elevated vascular tone compared to its normal state. High doses of CCBs are necessary to achieve maximum benefit and as such, the drugs should be titrated to each individual’s optimal physiologic response.
CCBs appear to be most useful in the treatment of primary PH. One study showed a 94% survival rate over 5 years in patients with primary PH treated with high dose CCBs compared to a 38% survival rate over the same period in patients who were not treated with CCBs.

The effectiveness of CCBs in patients with secondary PH, especially those with PH due to COPD, is less clear and may depend on the initial PAP (the higher the initial PAP, the less effective the drug). It is important to confirm a patient’s response to vasodilators as non-responders may only develop systemic hypotension when given CCBs.

B. Prostacyclin. The vasodilator prostacyclin was first reported to reduce PAP in 1980. It is mainly produced by the vascular endothelium as a product of arachidonic acid metabolism and acts on receptors linked to adenylate cyclase. This increases levels of cyclic adenosine monophosphate (cAMP), causing vasodilation, increased cardiac output and heart rate, and decreased PAP and right atrial pressure. Prostacyclin is of special benefit to patients with PH because production of prostacyclin is impaired in these patients. Prostacyclin has the added benefit of inhibiting both thrombus formation and vascular remodeling. These added benefits are of major importance as prostacyclin has been shown to improve long term survival in patients with primary PH, even in those patients who do not have an initial acute response to the drug. Prostacyclin also lowers PAP in other causes of PH including adult respiratory distress syndrome, persistent pulmonary hypertension of the newborn, and PH secondary to connective tissue disease. However, like CCBs, it is not effective in patients with PH due to COPD. Prostacyclin is also similar to CCBs in that the patient should be maintained at the highest dose tolerated. One disadvantage of prostacyclin is that it has a very short half life in the circulation (2-3 minutes); therefore long term treatment requires a portable infusion pump. In addition, it is not selective for pulmonary vasculature, and thus it has side effects reflective of systemic vasodilation. Possible solutions include aerosolized and oral analogues of prostacyclin.

C. Inhaled nitric oxide (INO). Patients with PH were first administered INO in 1991. Like prostacyclin, INO is a vasodilator produced by the vascular endothelium. In addition to the endothelium, small amounts of NO are also produced in the nose. Hence, giving INO to patients who are intubated may substitute for the NO of nasal origin. It acts by directly activating guanylate cyclase which increases cyclic guanosine monophosphate (cGMP) thereby causing vasodilation. It is not inherently selective for pulmonary vasculature, but by virtue of its route of administration and rapid inactivation, INO does not typically reach the systemic circulation. NO is a major contributor to both the naturally low tone in the pulmonary vasculature and in the transition from fetal to adult pulmonary circulation. There are multiple causes of PH that respond to INO including COPD, congenital heart disease, ARDS, and especially persistent pulmonary hypertension of the newborn. NO is also very useful perioperatively for many types of heart and lung surgery including correction of congenital heart defects, heart and/or lung transplantation, and surgeries involving cardiopulmonary bypass. Disadvantages of INO include increased bleeding times due to inhibition of platelet aggregation, negative ionotropic effects, and the formation of potentially toxic products (including methemoglobin, which is of particular concern in preterm infants).

D. Alprostadil (PGE1). Alprostadil is a product of arachidonic acid metabolism and it increases cAMP to cause vasodilation, similar to prostacyclin. When inhaled, it has been shown to be effective in reducing PVR and improving arterial oxygenation in patients with ARDS. It is normally metabolized in the lung and therefore does not have systemic side effects. However, in patients with ARDS, metabolism can be impaired and systemic hypotension may occur. It has also been shown to be more effective than several other drugs for acute reversal of PH in congestive heart failure.

E. Adenosine. Adenosine acts at adenylate cyclase linked receptors on smooth muscle cells to cause vasodilation. It is administered as a continuous intravenous infusion as it has a very short half life (10 seconds) and therefore has limited use. However, adenosine has been shown to lower PAP and PVR in patients with primary PH and can be used to test the
pulmonary vasculature’s response to vasodilators in patients with PPH\textsuperscript{76}. Adenosine can also be of benefit when used as an adjunct to CCBs\textsuperscript{109} or to treat pulmonary hypertensive crises perioperatively\textsuperscript{77}. Fortunately, due to the small dosing schedule, arrhythmias are rarely observed\textsuperscript{78}.

F. PDE inhibitors. Phosphodiesterase (PDE) inhibitors work by inhibiting one or more enzymes responsible for the breakdown of cAMP and/or cGMP. This not only causes pulmonary vasodilation, but also increases left ventricular contractility and may potentiate INO\textsuperscript{16}. However, they are not selective for pulmonary vasculature and can cause systemic hypotension. Several different PDE inhibitors have been used with success in lowering PAP in patients with PH secondary to COPD\textsuperscript{79} and in patients with PH after cardiac surgery\textsuperscript{80,82}.

G. Magnesium. Magnesium is thought to cause vasodilation by blocking calcium channels\textsuperscript{83}. It is also thought to enhance nitric oxide synthase activity, activate adenylate cyclase, and release prostacyclin\textsuperscript{81}, which would all augment vasodilation. Magnesium has been used effectively in infants with PH to improve arterial oxygenation\textsuperscript{84,85} and thus could be useful when therapy of short duration and low cost is required\textsuperscript{86}.

H. ACE inhibitors. Angiotensin converting enzyme (ACE) inhibitors moderate the formation of angiotensin II and the breakdown of bradykinin. Angiotensin II is a potent vasoconstrictor and smooth muscle mitogen. ACE inhibitors are similar to prostacyclin in that both were more effective with long term treatment\textsuperscript{87} compared to short term treatment\textsuperscript{88}, emphasizing the importance of minimizing vascular remodeling\textsuperscript{89}.

IV. Transplant. Once the only method used to treat PH, transplant is now reserved for patients who do not respond to treatment with vasodilators. Various forms of PH have been treated successfully with transplantation\textsuperscript{80} and survival rates of 60-86% for one year and 44-72% for four years have been reported\textsuperscript{91}. The two major causes of death after transplantation are obliterative bronchiolitis (which is closely associated with rejection) and infection. As such, transbronchial biopsy is routinely done for early detection of rejection and prophylaxis with trimethoprim-sulfamethoxazole is standard\textsuperscript{80}.

Perioperative Management

I. Preoperative management. Surgery for patients with PH is associated with significant morbidity and mortality regardless of which anesthetic technique is utilized\textsuperscript{82-84}; therefore, medical optimization is critical. A thorough history and physical should be done with a focus on the signs and symptoms of PH. An electrocardiogram, chest radiograph, echocardiogram, and possible right heart catheterization should be strongly considered. Evidence of significant right ventricular dysfunction should prompt reevaluation of the need for surgery\textsuperscript{95}. All medications for treating the patient’s pulmonary hypertension should be continued until and after surgery, including CCBs, despite any possible interaction with the anesthetics on myocardium or vascular resistance\textsuperscript{96}. Warfarin should be changed to heparin before the procedure. If the patient has never been treated for pulmonary hypertension or has a new diagnosis, a PDE inhibitor (50-100 mg sildenafil daily) should be initiated\textsuperscript{97}.

II. Intraoperative management:

A. Monitoring. Proper operating room monitoring for patients with pulmonary hypertension is essential. Intra-arterial blood pressure monitoring is necessary for beat to beat blood pressure monitoring to ensure adequate myocardial perfusion pressures and for frequent blood gas analysis. A pulmonary artery catheter allows monitoring of pulmonary artery pressure, right atrial pressure, and assessment of left ventricle by way of pulmonary capillary wedge pressures. Additionally, PVR, SVR, and cardiac outputs can be measures and used as guides for volume, vasodilator, or ionotropic therapy. However, care should be taken in placing these catheters as these patients are at risk for rupture of the pulmonary artery during balloon inflation. In addition, these patients are reliant on atrial contraction for adequate cardiac output, and arrhythmias associated with catheter insertion may not be well tolerated. Finally, transesophageal echocardiography can be useful to assess the preload, contractility of both ventricles, and valvular function. Because of the risks inherent with placing pulmonary artery catheters, proficient use of transesophageal echocardiography can supplant the need for catheterization.

B. Anesthetic techniques. Because the right ventricle is a thin walled, compliant muscle not
intended for pressure work, chronic PH leads to right ventricular hypertrophy and failure. Additional acute increases in pulmonary vascular tone associated with the surgical stress response are poorly tolerated in this population. The goals of management are to optimize PAP, RV preload, avoid RV ischemia and failure. During anesthesia and surgery, there are significant alterations in all the above parameters and appropriate vigilance and monitoring is vital.

Various management techniques have been described with success including regional, general, and peripheral nerve blockade. The choice of technique is not as important as the ability to adhere to the goals mentioned above. In general, the anesthesiologist should strive to use basic physiology to his advantage such as using 100% oxygen for its pulmonary vasodilator effects, and aggressively treating hypercarbia, acidosis, and hypothermia as these all cause pulmonary vasoconstriction. Nitrous oxide has been associated with increases in PVR and should be used with caution. For major surgery, general anesthesia is still the method of choice as it allows for control of ventilation. IV anesthetics have minimal effects on pulmonary vascular tone and oxygenation. Propofol has been shown to reduce PAP, PVR and MAP. It has also been associated with higher PaO2 and lower shunt fraction values; however it may also diminish right ventricular function. Opioids, which have been shown to produce dose dependent vasodilator effects in a number of animal models, reduce the vasoconstriction associated with painful stimuli. Use of volatile anesthetics carries the risk of decreasing systemic vascular resistance, myocardial contractility and potential arrhythmias. A balanced technique utilizing high dose opioids to blunt the cardiovascular response to surgical stimulation and minimal volatile anesthetics can limit the adverse effects. Used in this way, isoflurane has been demonstrated to lower PAP and PVR, and improve CO and is therefore recommended in patients with PH. There is a paucity of data evaluating either desflurane or sevoflurane in pulmonary hypertensive patients.

C. Treating intraoperative PH. Intraoperative PH should first be managed by ensuring that oxygenation, ventilation, fluid volume, and acid/base status are optimized. IV vasodilators will cause dilation of both the pulmonary and systemic vascular beds and can be useful in the setting of combined pulmonary and systemic hypertension. For example, milrinone, a PDE inhibitor, has shown to reduce both pulmonary and systemic vascular resistance in addition to augmenting myocardial contractility. In cases of pulmonary hypertension with systemic hypotension, IV vasodilators may cause worsening of systemic blood pressure and subsequent RV hypoperfusion, ischemia and failure. In this situation, the patient may benefit from therapy selective for the pulmonary vasculature such as inhaled nitric oxide (INO). INO has the benefit of improving ventilation-perfusion matching by increasing perfusion to areas of the lung that are well ventilated. Also, INO has been shown to improve PH in cardiopulmonary bypass settings. Combination therapy with INO and prostacyclin has been shown to augment the effects compared to use of monotherapy. A disadvantage of both INO and inhaled prostacyclin is their cost, which can be prohibitive. In patients who are refractory to the above therapies, right ventricular assist device implantation should be considered.

III. Postoperative management. These patients warrant intensive care monitoring as there is a high mortality in the first postoperative days. As the effects of the anesthetics wear off, patients are at risk for an increase in pulmonary vascular tone, vasospasm, cardiac arrhythmia, increased sympathetic tone, and fluid shifts. Postoperative control of pain should be effective and all precautions should be taken to avoiding hypoxemia, hypotension, and hypovolemia; especially when weaning the patient from the ventilator, stopping or decreasing any vasodilator therapy, and during extubation.

Conclusion

Surgical patients with PH present challenging clinically scenarios and are at an increased risk of significant perioperative complications. Using all available diagnostic techniques to further detail each patient’s particular form of PH is of critical importance to treatment. Recent and ongoing progress in pharmacological treatment ensures that the future will unfold a variety of successful therapies for vasoconstriction, vascular remodeling, and improved
survival for patients with PH. The anesthesiologist’s knowledge of the existing treatment options, pathophysiology, and the implications of various anesthetic agents and techniques is required to ensure the highest level of patient safety and care.

References


112. ATZ AM, LEFFER AK, FAIRBROTHE LR, UBER WE, BRADLEY SM: Sildenafil augments the effect of inhaled nitric oxide for

