pulmonary hypertension [created by Paul Young 06/01/08]

definition

- Pulmonary hypertension is defined as a pulmonary artery mean pressure (PAPm) of 25mmHg or greater and may be precapillary or postcapillary in etiology.

aetiology

- The evaluation of patients with pulmonary artery hypertension (PAH) is directed at the detection of underlying contributing factors and associated conditions, such as:
(i) left-sided cardiac dysfunction,
(ii) underlying congenital heart disease,
(iii) pulmonary thromboembolic disease,
(iv) collagen vascular disease,
(v) parenchymal lung disease,
(vi) obstructive sleep apnea,
(vii) liver disease,
(viii) amphetamine or appetite suppressant use,
(ix) intravenous drug abuse, or
(x) human immunodeficiency virus (HIV) infection.

pre-capillary

- Precapillary pulmonary hypertension, or pulmonary arterial hypertension (PAH), can be idiopathic (IPAH-previously known as primary pulmonary hypertension [PPH]) or may occur in association with a variety of underlying disease processes such as collagen vascular disease, portal hypertension, congenital systemic to pulmonary shunts, drug or toxin exposure, or HIV infection.
- Initial therapy may be directed at an underlying cause or contributing factor, such as using continuous positive airway pressure (CPAP) and supplemental oxygen for PAH associated with obstructive sleep apnea.
- Following the identification and treatment of underlying associated disorders and contributing factors, specific therapy for PAH should be considered.
- IPAH/PPH carried a very poor prognosis (median survival approximately 2.8 years from the date of diagnosis) through the mid-1980s. Subsequently, a number of therapeutic options have been developed, and three have been approved by the U.S. Food and Drug Administration (FDA): epoprostenol, treprostinil, and bosentan . Other agents that are being studied for PAH include sitaxsenten, ambrisentan, sildenafil, and inhaled iloprost .

post-capillary

- Postcapillary causes include processes affecting the left side of the heart (e.g., left ventricular systolic or diastolic dysfunction, mitral stenosis or regurgitation, aortic valvular disease) or, more rarely, the pulmonary veins (pulmonary veno-occlusive disease).
- Management of postcapillary pulmonary hypertension typically involves treating the underlying left-sided cardiac process. Medications used to treat precapillary pulmonary hypertension are often not only ineffective for postcapillary pulmonary hypertension but may, in fact, be harmful, potentially leading to the development of pulmonary edema.

clinical features

- Because of the insidious onset of symptoms, PAH is often advanced at the time of diagnosis.
- Dyspnea on exertion is a common presenting symptom
- Chest pain, mimicking angina pectoris, may occur.
- Patients with advanced disease may present with syncope or signs and symptoms of right-sided heart failure, including lower extremity edema, jugular venous distention, and ascites.

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- Important clues to an underlying condition might include a previous history of a heart murmur, deep venous thrombosis or pulmonary embolism, Raynaud's phenomenon, arthritis, arthralgias, rash, heavy alcohol consumption, hepatitis, heavy snoring, daytime hypersomnolence, morning headache, and morbid obesity.
- Medication exposures, particularly to appetite suppressants and amphetamines, should be noted.

special situations in ICU

1. Procedures:
- Patients with severe PAH are particularly prone to vasovagal events, and when these occur they can lead to severe consequences, including syncope, cardiopulmonary arrest, and death.
- Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of pulmonary hypertension

2. Pregnancy:
- The changes induced by pregnancy impose a significant hemodynamic stress in women with IPAH/PPH, leading to an estimated 30% to 50% mortality rate.
- There have been case reports of successful treatment of pregnant IPAH/PPH patients with chronic intravenous epoprostenol, inhaled nitric oxide , and oral calcium channel blockers. In general, management includes early hospitalization for monitoring, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed.

3. Pulmonary Vascular Disease in Liver Disease
- Patients with chronic liver disease have an increased prevalence of pulmonary vascular disease. Two forms of pulmonary vascular disease can complicate chronic liver disease: the hepatopulmonary syndrome and portopulmonary hypertension. Both tend to occur in patients with chronic, late-stage liver disease, and each may increase the risk associated with liver transplantation.

investigation

Laboratory investigations:
- A collagen vascular screen, including antinuclear antibodies, rheumatoid factor, and erythrocyte sedimentation rate, is often helpful in detecting autoimmune disease, although some patients with IPAH/PPH will have a low titer positive antinuclear antibody test.
- Liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) may be elevated in patients with right ventricular failure and passive hepatic congestion but may also be associated with underlying liver disease. Liver disease with portal hypertension has been associated with the development of pulmonary hypertension.
- Thyroid disease may occur with increased frequency in patients with IPAH/PPH and should be excluded with thyroid function testing.
- HIV testing and hepatitis serologic studies should be considered in patients at risk.
- Routine laboratory studies such as the complete blood cell count, complete metabolic panel, prothrombin time, and partial thromboplastin time are recommended during the initial evaluation and as indicated to monitor the patient's long-term clinical status.

Echocardiography:
- Doppler echocardiography is useful in estimating the severity of pulmonary hypertension and detecting left-sided heart disease.
- Bubble contrast echocardiography may detect a right-to-left shunt, but exclusion of a left-to-right intracardiac shunt may require cardiac catheterization with an oximetry series.

Radiological investigation:
- Chest radiography may reveal enlargement of the central pulmonary vessels and evidence of right ventricular enlargement.
- Evidence of parenchymal lung disease may be apparent.
- When parenchymal lung disease is suspected, pulmonary function testing and high-resolution computed tomography (CT) of the chest may be indicated.
- Ventilation-perfusion lung-scanning should be performed in an attempt to exclude chronic-recurrent pulmonary thromboembolic disease, which is among the most preventable and treatable causes of pulmonary hypertension.
- Although contrast medium-enhanced CT has been popularized recently for the diagnosis of acute pulmonary thromboembolic disease, there is limited experience with this technique in chronic thromboembolic disease.

Pulmonary function testing
- Pulmonary function testing is indicated to detect underlying parenchymal lung disease.
- The diffusing capacity is often reduced in pulmonary vascular disease, consistent with impaired gas exchange.
- Oximetry testing of patients at rest, with exertion, and nocturnally, is useful in detecting hypoxemia and the need for supplemental oxygen.

Right heart catheterisation:
- Right-sided heart catheterization remains an important part of the evaluation. Left-sided heart dysfunction and intracardiac shunts can be excluded, the degree of pulmonary hypertension can be accurately quantified, and the cardiac output can be measured. PVR can then be calculated.
- Acute pulmonary vasoreactivity can be assessed using a short-acting agent such as prostacyclin (epoprostenol), inhaled nitric oxide , or intravenous adenosine. The European Society of Cardiology consensus definition of a positive acute vasodilator response in an IPAH/PPH patient is a fall of PAPm of at least 10 mm Hg to less than or equal to 40 mm Hg, with an increased or unchanged cardiac output.
- The primary objective of acute vasodilator testing in patients with IPAH/PPH is to identify patients who might be effectively treated with oral calcium channel blockers.

treatment

1. Warfarin, Oxygen, Diuretics, Digoxin , and Vaccination:
- Improved survival has been reported with oral anticoagulation in IPAH/PPH. The target International Normalized Ratio in these patients is 1.5 to 2.5. Anticoagulation of patients with PAH occurring in association with other underlying processes is controversial.
- Hypoxemia is a pulmonary vasoconstrictor and can contribute to the development or progression of PAH. It is generally considered important to maintain oxygen saturations at greater than 90% at all times.
- Diuretics are indicated in patients with evidence of right ventricular failure and volume overload (i.e., peripheral edema and/or ascites).
- Although not extensively studied in PAH, digitalis is sometimes utilized in refractory right ventricular failure or atrial dysrhythmias
- Because of the potentially devastating effects of respiratory infections in PAH, immunization against influenza and pneumococcal pneumonia is recommended.

2. Calcium Channel Blockers
- Patients with IPAH/PPH who respond to vasodilators and calcium channel blockers generally have improved survival. Unfortunately, this tends to represent a relatively small proportion of patients, comprising fewer than 20% of IPAH/PPH patients and even fewer patients with other causes of PAH.

3. Prostanoids
(i) Prostacyclin, (ii) Epoprostenol, (iii) Treprostinil, (iv) Inhaled Iloprost, (v) Beraprost

4. Endothelin Receptor Antagonists
- Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the pathogenesis of PAH. Endothelin-1 expression, production, and concentration in plasma and lung tissue are elevated in patients with PAH, and these levels are correlated with disease severity.
(i)Bosentan
- Bosentan is a dual endothelin receptor blocker that has been shown to improve pulmonary hemodynamics and exercise tolerance and delay the time to clinical worsening in PAH patients falling into NYHA Classes III and IV.

5. Phosphodiesterase Inhibitors
- Phosphodiesterases (PDEs) are enzymes that hydrolyze the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and limit their intracellular signaling. Drugs that selectively inhibit cGMP-specific PDEs (or type 5, PDE5 inhibitors) augment the pulmonary vascular response to endogenous or inhaled nitric oxide in models of pulmonary hypertension.
(i) Dipyridamole
- Early studies demonstrated that dipyridamole can lower pulmonary vascular resistance (PVR), attenuate hypoxic pulmonary vasoconstriction, decrease pulmonary hypertension, and, at least in some cases, augment or prolong the effects of inhaled nitric oxide in children with pulmonary hypertension.
(ii) Sildenafil
- Recent reports have shown that sildenafil blocks acute hypoxic pulmonary vasoconstriction in healthy adult volunteers and acutely reduces PAPm in patients with PAH.
- Several nonrandomized, single-center studies suggest promise in PAH with chronic sildenafil.

6. Inhaled Nitric Oxide
- Inhaled nitric oxide has been shown to have potent and selective pulmonary vasodilator effects during brief treatment of adults with IPAH/PPH.
- It is a potent pulmonary vasodilator in newborns with pulmonary hypertension (PPHN), children with congenital heart disease, and patients with postoperative pulmonary hypertension, acute respiratory distress syndrome, or undergoing lung transplantation. It is of substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation (ECMO).

7. Lung transplantation:
- Lung transplantation for PAH is generally reserved for patients whose condition is failing despite the best available medical therapy. The timing of transplantation in PAH is challenging. It is probably most useful in patients showing clear evidence of deterioration, such as decline in functional capacity and the development of right-sided heart failure, despite maximal medical therapy.