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Reviews

Pulmonary Hypertension: Newer Concepts in Diagnosis and Management

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Summary: Pulmonary hypertension comprises a family of disorders occurring as a primary disease or as a complication of a large number of respiratory and cardiac diseases. Pulmonary hypertension is present when pulmonary artery pressure or mean pressure exceeds 30 mmHg or 20 mmHg, respectively. Underlying the hemodynamic changes that result in pulmonary hypertension, whether from hypoxia, acidosis, increased pulmonary blood flow, increased shear stress, or idiopathic causes, is a dysfunctional vascular endothelium. In this review, the role of the history and physical examination in the initial assessment is emphasized. Newer diagnostic modalities, such as subselective pulmonary angiography and ultrafast computed tomography scanning, are reviewed. Low-flow oxygen, anticoagulation, and calcium-channel blockade are presented as accepted therapeutic modalities. Inhaled nitric oxide and prostacyclin infusion are presented as newer therapies that may be useful given the limited availability of donor organs for heart-lung transplantation. Future therapeutic strategies are likely to develop from advances in vascular biology.

Key words: endothelial cell, nitric oxide, anticoagulation

Introduction

Pulmonary hypertension comprises a family of disorders occurring as a primary disease or as a complication of a large number of respiratory and cardiac diseases. In this article we review new developments in the pathophysiology, diagnosis and treatment of this disorder.

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Definition

The normal pulmonary artery pressure in an individual living at sea level has a peak systolic value of 18–25 mmHg and a mean value ranging from 12–16 mmHg. Pulmonary hypertension is present when pulmonary artery systolic pressure or mean pressure exceeds 30 mmHg or 20 mmHg, respectively.

Pathophysiology

The pulmonary circulation is normally a low-pressure, high-capacity circuit with a remarkably low resistance (about 1/10 systemic vascular resistance). Through vascular recruitment and owing to its distensibility, the normal pulmonary circulation can accommodate large increases in cardiac output with only slight increases in pulmonary arterial pressure. Increased pulmonary artery pressures are only important in terms of the effect they have on the performance of the right ventricle. The right ventricle can develop systolic pressures of up to 50 mmHg acutely prior to failing. However, right ventricular failure can occur at lower pressures in the myopathic right ventricle. Hypertrophied ventricles can generate significantly higher pressures that approach or rarely exceed systemic pressures. The familiar equation relating the pressure drop across the pulmonary circulation to the resulting pulmonary blood flow is analogous to Ohm's Law:

$$PVR = (\overline{PAP} - \overline{PCWP}) / CO$$

where PVR is the pulmonary vascular resistance, $\overline{PAP}$ represents the mean pulmonary arterial pressure, $\overline{PCWP}$ is the mean pulmonary capillary wedge pressure, and CO represents the cardiac output. This formula is an adaptation based on linear flow of a Newtonian fluid through rigid tubes. The normal pulmonary vascular bed, however, is composed of distensible vessels in which the flow is pulsatile and turbulent. This formula, however, can be applied to the pulmonary circulation in pulmonary hypertension as the vessels become more rigid with advanced disease.

Pulmonary arterial hypertension is a consequence of multiple determinants that increase pulmonary vascular resistance. The potential causes of an increase in resistance are listed categorically in Table I.

Cross-Sectional Area of Pulmonary Resistance Vessels

The pulmonary circulation has a large reserve capacity such that up to 50% of the pulmonary bed can be occluded or resected before a rise in pulmonary artery pressure is observed. Once this reserve capacity is lost, further reductions cause a precipitous rise in pulmonary artery pressure.

Pulmonary Blood Flow

During states of increased cardiac output, for example, with exercise, there is a small rise in pulmonary artery pressure. At sea level, even during vigorous exercise, pulmonary artery pressure rarely exceeds 30 mmHg. In the presence of vessels with reduced compliance, flow-related, precipitous rises in pulmonary artery pressure occur. Early in the course of pulmonary hypertension, the pulmonary artery pressure increases abnormally only during exercise when pulmonary blood flow may increase up to five times basal values.

Perivascular Pressure

Pulmonary vascular resistance is affected by alveolar and pleural pressures. During exercise, pleural pressure becomes negative, decreasing the resistance in extra-alveolar vessels. In patients with air space disease, by contrast, pleural and alveolar pressures are increased, elevating the pulmonary vascular resistance.

Blood Viscosity

When the hematocrit exceeds 55% in patients with pre-existing pulmonary hypertension, there is further elevation in pulmonary vascular resistance. Several other factors affect the pulmonary vascular resistance. Chronic exposure to hypoxia results in pulmonary vascular remodeling and the development of persistent pulmonary hypertension in humans and animals. These changes are observed in individuals living at high altitudes[1, 2] and with hypoxic lung diseases such as chronic bronchitis and cystic fibrosis. Continuous exposure to hypoxia for as little as 1 to 2 weeks results in persistent pulmonary hypertension, right ventricular hypertrophy, and vascular remodeling in several mammals, including rats, guinea pigs, and neonatal cows.[3–5] Acidosis, changes in temperature, and various exogenous substances, for example, cocaine, aminorex fumarate, fenfluramine, and rape seed oil, affect pulmonary vascular resistance as well.[6–8]

Endothelial Dysfunction

Underlying the hemodynamic changes resulting in pulmonary hypertension, whether from hypoxia, acidosis, increased pulmonary blood flow, shear stress, or unknown causes, is a dysfunctional pulmonary vascular endothelium.[9] As in other vascular beds, the endothelium of the pulmonary vasculature plays an important role in the maintenance of normal vascular structure and function. Endothelial cells release growth factors and cytokines that modulate the tone of vascular smooth muscle cells and control proliferation and migration of smooth muscle cells. Endothelial cells also play a central role in vasodilation and in determining the propensity of the blood to clot by elaborating substances that promote vasodilation and by inhibiting platelet activation and thrombin generation, respectively. By contrast, dysfunctional endothelial cells manifest an altered phenotype that supports vasoconstriction and thrombus formation. Thus, endothelial dysfunction due to an external stimulus or to the disease process itself (primary pulmonary hypertension) is likely to be an important factor in determining the development and progression of pulmonary hypertension.

TABLE 1 Determinants of pulmonary vascular resistance

1. Total cross-sectional area of pulmonary resistance vessels
2. Rate of blood flow through pulmonary vessels
3. Alveolar and pleural pressures constituting transmural pressure
4. Blood viscosity
5. Miscellaneous factors: hypoxia, acidosis, chemical and hormonal factors, exogenous substances, e.g., rapeseed oil, L-tryptophan, pyrrolizidine alkaloids, aminorex fumarate, fenfluramine, human immunodeficiency virus infection

Evidence of endothelial cell dysfunction in pulmonary hypertension has been demonstrated in numerous studies.[10, 11] Endothelial cell injury occurs early after administering monocrotaline to rats; follow-up studies show progression in this model to frank pulmonary hypertension.[10] Altered endothelial cell metabolism and synthetic function have been suggested in patients with pulmonary hypertension secondary to congenital heart disease by demonstrating intense immunofluorescent staining for von Willenbrand factor in the pulmonary arterial endothelium of these individuals.[11] Dinh-Xuan *et al.* have found that the endothelium-dependent relaxation response to acetylcholine and adenosine 5' diphosphate is impaired in patients with pulmonary hypertension.[12] The impairment in relaxation was reversed with the addition of sodium nitroprusside, an endothelium-independent nitric oxide donor.

Decreased elaboration of prostacyclin, increased release of endothelin, and decreased production of endothelium-derived relaxing factor (EDRF) (believed to be similar if not identical to nitric oxide) all promote pulmonary vasoconstriction; decreased elaboration of prostacyclin and EDRF serve to promote platelet activation in the vasculature. Elevated fibrinopeptide A levels, indicating thrombin formation, increased levels of Factor VIIIc and von Willebrand factor, and an imbalance of the fibrinolytic system because of increased plasminogen activator inhibitor type 1 have been described, as well.[13]

The pathogenesis of pulmonary hypertension is multifactorial. Primary pulmonary hypertension may be due to such factors as genetic determinants, drugs, toxins, autoimmune disorders, and endothelium-derived vasoconstrictors. Mechanical factors such as blood flow, shear stress, and hypoxia may underlie secondary pulmonary hypertension.

Pathology

In secondary pulmonary hypertension, the pathologic changes that occur in the vascular tree are similar irrespective of etiology. Light microscopic examination of the lungs shows distended pulmonary capillaries, thickening and rupture of the basement membrane of the endothelium, and transudation of erythrocytes into the alveoli.[14] The latter results in pulmonary hemosiderosis which can lead to fibrosis. Rarely, particularly in mitral valve disease, may the entity of pulmonary alveolar ossification occur.[15] The anatomical changes that take place in the pulmonary arteries depend on whether or not pulmonary venous hypertension is a result of congenital or acquired disease. In the former, the elastic tissue in the large vessels consists of long, unbranched fibers, whereas in the latter the elastic fibers are short, irregular, and branched. In the smaller arteries and arterioles in both congenital and acquired disease, intimal fibrosis and medial hypertrophy occur. The pathology in primary pulmonary hypertension will be described below in greater detail.

Symptoms and Signs

The earliest symptoms in pulmonary hypertension are exertional dyspnea and fatigue. Syncope or presyncope is another common symptom that occurs in patients with high pulmonary arterial pressures at rest.[16] In patients with advanced pulmonary hypertension, angina-like pains occur that are believed to be due to subendocardial ischemia of the right ventricle.[17] Hemoptysis, probably due to alveolar capillary aneurysm or distended bronchial submucosal vein rupture, has also been described. Ortner's syndrome occurs from compression of the left recurrent laryngeal nerve between the aorta and a dilated left pulmonary artery, the cardinal symptom of which is hoarseness.

The physical signs of pulmonary hypertension are similar irrespective of the etiology. Early on, a prominent 'a' wave is seen; as progression occurs, a 'v' wave predominates in the jugular venous pulse owing to ensuing right ventricular failure and tricuspid insufficiency. Palpation of the anterior chest wall may reveal pulmonary arterial valve closure at the second left intercostal space, the right ventricle near the left sternal border, and a prominent subxiphoid impulse. Auscultation shows an accentuated P2, which is a closely split component of S2. A murmur of tricuspid insufficiency may also be appreciated. Rarely, particularly in chronic thromboembolic disease, soft bruits may be heard on auscultation.

Diagnostic Assessment

Detection of early pulmonary hypertension remains elusive to noninvasive techniques. The importance of a carefully obtained history and physical examination cannot be overemphasized. The history should specifically search for possible etiologic causes or exacerbating factors for pulmonary hypertension. Laboratory studies at the initial evaluation should include a complete blood count, coagulation profile, liver function tests, and a collagen vascular screen. These studies may reveal an underlying contributing cause, for example, polycythemia vera, cirrhosis, an hypercoagulable state, or a connective tissue disorder. Human immunodeficiency virus (HIV) testing should be discussed with the patient if suggested by the clinical presentation or risk factors. If pulmonary disease is suspected, arterial blood gases, chest radiograph, and pulmonary function tests should be performed. A ventilation- perfusion scan should be performed to aid in the identification of thromboembolic pulmonary vascular disease. Further evaluation for underlying pulmonary embolism is reserved for patients with a moderate to high clinical suspicion by history or on lung scan. In an effort to improve safety, several alternatives to pulmonary angiography of the main and branch vessels, including superselective injection beyond an occlusion balloon and delayed filming of the pulmonary vasculature after peripheral venous injection, are now routinely practiced. More recently, techniques such as ultrafast computed tomography scanning and magnetic resonance angiography have begun to emerge as alternatives to invasive evaluation, particularly for central pulmonary thromboembolism.[18]

Echocardiography is essential in the evaluation of structural cardiac abnormalities and of right and left chamber dimensions and function. Right heart catheterization is considered the standard of reference for establishing pulmonary hypertension and for excluding intracardiac shunts. An approach to assessment of these patients is depicted in Figure 1.

Secondary Pulmonary Hypertension

Pulmonary hypertension that results from identifiable causes is far more common than primary (idiopathic or unexplained) pulmonary hypertension. A classification based on hemodynamic causes (Table II) shows predominantly that cardiac disorders produce pulmonary hypertension by increasing pulmonary venous pressure or pulmonary blood flow, whereas pulmonary disorders cause obliteration of the pulmonary vascular bed.

Increased resistance to pulmonary venous drainage may result from ischemic heart disease, hypertension, cardiomyopathy, or left-sided valvular disorders. Left ventricular failure is a common cause of pulmonary hypertension. The degree of pulmonary hypertension, however, is not usually sufficient to account for the severity of right heart failure in these patients, a discrepancy which remains largely unexplained. However, involvement of the right ventricle, particularly the interventricular septum, with the same pathologic process that affects the left ventricle may, in part, explain these findings in some patients. Mitral and aortic valve disorders also commonly cause pulmonary hypertension. Less commonly, constrictive pericarditis, cor triatriatum, and pulmonary venocclusive disease are accompanied by elevated pulmonary artery pressures. All these disorders cause pulmonary hypertension by increasing pulmonary venous pressure. In some patients, a subsequent elevation in pulmonary vascular resistance with associated pul-

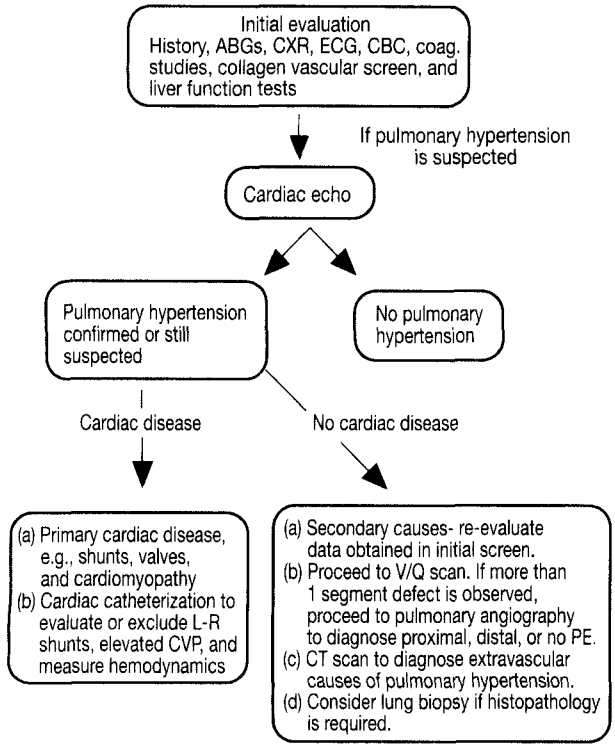

FIG. 1 A guide to the evaluation of suspected pulmonary hypertension. CXR = chest x-ray, PE = pulmonary emboli, ABG = arterial blood gases, ECG = electrocardiogram, CBC = complete blood count, L-R = left-to-right, CVP = central venous pressure, CT = computed tomography.

TABLE II Causes of pulmonary hypertension

1. Increased resistance to pulmonary venous drainage or postcapillary obstruction
   (a) Increased left ventricular diastolic pressure, e.g., left ventricular failure
   (b) Increased left atrial pressure, e.g., mitral valve disorders
   (c) Increased pulmonary venous resistance, e.g., atrial tumors, adenopathy, fibrosing mediastinitis
2. Obliterative causes resulting in increased resistance through the pulmonary vascular bed
   (a) Pulmonary parenchymal disease
   (b) Pulmonary arteritis
   (c) Eisenmenger's syndrome
   (d) Miscellaneous factors, e.g., crotalaria alkaloids, aminorex fumarate, fenfluramine, rape seed oil
3. Obstruction resulting in increased resistance through the medium and large-sized pulmonary arteries
   (a) Pulmonary thromboembolism
   (b) In situ thrombosis, e.g., sickle cell disease
4. Hypoxia causing increased resistance by vasoconstriction, e.g., obesity-hypoventilation syndrome, neuromuscular disorders, high altitude pulmonary edema

monary vasoconstriction and structural changes (dubbed the "second stenosis" in mitral stenosis) occurs.[15, 16] Surgical relief of mechanical causes of pulmonary venous hypertension leads to reversal of the structural changes and a decrease in pulmonary pressure.

Pulmonary hypertension may also result from various pulmonary disorders that cause increased resistance to flow through the pulmonary vascular bed (Table II). The most common etiology of hypertension in this category is chronic obstructive pulmonary disease (COPD), which has been traditionally thought to be solely a consequence of the mechanical changes that accompany destruction of the vascular bed. However, numerous studies have documented a poor correlation between right ventricular mass and the severity of the COPD.[17] Most authors argue that the degree of hypoxia-induced vasoconstriction is the main correlate for the severity of pulmonary hypertension. Decreases in local pH act synergistically with hypoxia-induced vasoconstriction to produce elevated pulmonary vascular pressures. In addition to hypoxia and local pH, other factors, such as an increased propensity to thrombosis and increased whole blood viscosity due to an elevated red cell mass, may also play a role.

Long-term studies have shown that continuous oxygen therapy can decrease the degree of pulmonary hypertension and the incidence of cor pulmonale.[19] Patients with the lowest pulmonary vascular resistances have the greatest benefit in terms of symptomatic improvement and survival. Arterial hypoxia, bronchospasm, and infection when vigorously treated generally result in both symptomatic and hemodynamic improvement. Alveolar hypoventilation can result in ventilation-perfusion abnormalities leading to alveolar hypoxia, arterial hypoxemia, and hypercapnea. The alveolar hypoventilation results from either an inadequate ventilatory drive or an ineffective respiratory muscle effort, for example, severe obesity, sleep apnea, myasthenia gravis, kyphosis, and impairment of central ventilatory drive. There have been significant advances in our understanding and treatment of the sleep-apnea syndrome, particularly with the use of continuous positive airway pressure and tracheostomy. For patients with neuromuscular disorders, advances have been achieved using negative pressure ventilatory systems. Collagen vascular disorders often have pulmonary vascular involvement as a result of either pulmonary vasculitis or interstitial disease. Treatment of the primary disorder with steroids and other immunosuppressives in systemic lupus erythematosus leads to partial reversal of the pulmonary hypertension.

Pulmonary hypertension as a result of decreased cross-sectional pulmonary vascular area characterizes the Eisenmenger's syndrome. Wood used this term to refer to patients who had shunts within the heart or between the greater vessels and who developed pulmonary hypertension.[20] The term "Eisenmenger complex" refers specifically to the development of pulmonary hypertension in the setting of a ventricular septal defect. It is clear that increased blood flow by itself (up to three times normal) does not cause pulmonary hypertension. This is clearly demonstrated in patients in whom acute left-to-right shunting is induced. Other factors contribute to the pulmonary

hypertension by increasing the pulmonary vascular resistance, including the duration of the hemodynamic changes, hypoxia, and reflex pulmonary vasoconstriction secondary to the pressure distending the pulmonary vessels and left atrium. The increased pulmonary vascular resistance may have a functional and a fixed component. According to the "Bayliss" or myogenic theory, the former is thought to be related to arteriolar vasoconstriction stimulated by distension of pulmonary arteries and arterioles, and the latter is a consequence of later changes leading to obliterative endarteropathy. This vasoconstriction leads to increased work of the vascular smooth muscle with resulting hypertrophy, which is believed to be reversible. Irreversibility is associated with the presence of the fixed component of necrotizing arteritis and plexiform lesions, as reflected in the Heath and Edwards classification.[21]

The Heath and Edwards classification implies sequential morphologic changes. In *Grade I*, hypertrophy of the media of the small muscular arteries is described. *Grade II* is characterized by the earlier intimal proliferation to which intimal cellular proliferation is added. In *Grade III*, concentric fibrosis complicates these changes, resulting in diffuse obliteration of many arterioles and small muscular pulmonary arteries. *Grade IV* changes are characterized by plexiform lesions of the small muscular pulmonary arteries and arterioles; these lesions may be recanalized thrombi. *Grade V* changes describe the presence of numerous thin-walled blood vessels with hyalinization of the intima, and *Grade VI* is characterized by a necrotizing arteritis.

Surgical reversal of shunts may lead to reversibility of pulmonary hypertension except in those patients with balanced or predominantly right-to-left shunts; in this latter group, closure of the communication merely increases the load on an already overburdened right ventricle.

Increased resistance to flow through the pulmonary vascular bed may be caused by impeding blood flow through major pulmonary arteries by pulmonary thromboembolism. Smaller pulmonary vessels may also be occluded, resulting in pulmonary hypertension. The latter may result from in situ thrombosis, whereas the former commonly results from multiple pulmonary emboli. In situ thrombosis secondary to dysfunctional endothelium results in thrombosis and recanalization of the smaller muscular pulmonary arteries. The perfusion scan reveals patchy inhomogeneity without subsegmental defects. Treatment consists of long-term anticoagulation. Chronic proximal pulmonary thromboembolism is a treatable cause of pulmonary hypertension. The obstruction is due either to multiple embolic showers or to a single embolus that subsequently propagates locally. Ventilation-perfusion scans demonstrate segmental defects, and selective angiography is essential to delineate the extent of the embolism, particularly if surgery is being contemplated. Thromboendarterectomy is considered for patients with pulmonary hypertension who have persistent thrombi in lobar or more proximal vessels despite 6 months of anticoagulation. Hemodynamic improvements after surgery can generally be anticipated.[22]

In the recent literature, there have been associations noted between HIV and pulmonary hypertension.[23] According to Petitpretz *et al.*,[23] the incidence of pulmonary hypertension in HIV-infected patients is 25 times higher than that in the general population. The clinical, hemodynamic, and pathologic similarities between HIV-infected patients and non-HIV infected patients with pulmonary hypertension suggest that HIV infection must be regarded as another common risk factor for the development of pulmonary hypertension.

Primary Pulmonary Hypertension

Pulmonary hypertension caused by pulmonary vascular disease was first described by Romberg in 1891 in a case report of a patient with unexplained pulmonary hypertension.[24] The clinical diagnosis is based on:

1. Clinical, radiographic, and electrographic manifestations of pulmonary hypertension
2. Demonstration of increased pulmonary vascular resistance, high pulmonary arterial pressures, and a normal mean capillary wedge pressure
3. No secondary cause in the heart or lungs, and no systemic disease to account for either (1) or (2).

Primary pulmonary hypertension (PPH) is an uncommon disorder. It affects both genders equally in childhood, but after puberty females predominate 5:1. In the U.S., this female-to-male preponderance is highest among African Americans. The mean age at diagnosis is in the mid 20s, and the mean interval from the onset of symptoms to diagnosis is 2 years.[25]

Based on data from the National Institutes of Health's PPH Registry, Pietra *et al.*[26] describe three histopathologic classes—pulmonary arteriopathy, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis. Primary pulmonary arteriopathy is divided into three subsets: medial hypertrophy (with minimal intimal hypertrophy), arteriopathy with plexiform lesions (associated predominantly with concentric laminar intimal proliferation), and microthrombotic lesions (associated predominantly with eccentric intimal proliferation and fibrosis). Veno-occlusive disease is an uncommon cause of pulmonary hypertension. The hallmark of this disease is the presence of organized and recanalized thrombi in pulmonary veins and venules. Histopathologic changes in the pulmonary arteries and arterioles are considered to be secondary to the venous obstruction. Patients with pulmonary arteriopathy and plexiform lesions or pulmonary veno-occlusive disease have a much poorer prognosis than do patients with thrombotic lesions. Pulmonary capillary hemangiomatosis represents a small subset of patients with PPH characterized by infiltrating thin-walled blood vessels that spread throughout the pulmonary parenychma.

Patients with PPH have a clinical course that proceeds in a steadwise fashion toward death. In the National Institutes of Health patient registry,[25] an inverse correlation was found between hemodynamic abnormalities and survival. Median survival for those patients with a mean pulmonary artery pressure < 55 mmHg was 48 months compared with 12 months

for those with a mean pulmonary artery pressure of 85 mmHg or more. The cause of death in these patients involved right ventricular failure, pneumonia, pulmonary embolism, and sudden death.

Management of Pulmonary Hypertension

The main aim in the management of patients with pulmonary hypertension is the recognition and treatment of underlying reversible or treatable causes. Left ventricular dysfunction can be improved by correcting systemic hypertension and using diuretics, digitalis, and afterload-reducing agents. In patients with pulmonary parenchymal disease, low-flow oxygen attenuates hypoxemia with a subsequent decrease in pulmonary vasoconstriction. In general, most patients with PPH do not have resting hypoxia and derive little benefit from supplemental oxygen. However, patients with symptoms or signs of right-sided failure or desaturation with exercise benefit from low-flow oxygen.

Patients with severe primary pulmonary hypertension are at increased risk for thrombotic events. A retrospective study from the Mayo clinic[27] points toward a survival benefit in patients who are anticoagulated. The recommended target International Normalized Ratio should be between 2 and 3. Rich *et al.* prospectively documented a survival benefit from anticoagulation, particularly in those patients with primary pulmonary hypertension who were not responsive to calcium-channel blockers.[28]

Vasodilator therapy has been tried in an effort to dilate the pulmonary resistance vessels and to arrest and reverse the pulmonary vascular changes. In that subset of patients whose pulmonary artery pressures are lowered by high-dose calcium-channel blockers, survival is higher than in those whose pressures are not lowered (5-year survival, 94 vs. 55%, $p<0.003$).[28] A recent study by Barst *et al.*[29] compared continuous intravenous infusion of prostacyclin with conventional therapy in patients with severe pulmonary hypertension (New York Heart Association class III or IV). Compared with conventional therapy, prostacyclin produced symptomatic and hemodynamic improvement and, more important, improved survival. It is interesting that the randomization for this study was performed independently of the short-term responses to epoprostenol, which implies that in addition to its direct vasodilator properties, benefits from the prostanoid may be a consequence of modulating vascular growth, altering vascular remodeling, or modifying platelet function. Endothelium-derived relaxing factor, as discussed above, relaxes vascular smooth muscle and inhibits platelet function. Given its short duration of action in the circulation, it may theoretically serve a relatively selective pulmonary vasodilator when given by inhalation.[30] Frostell *et al.* demonstrated that inhalation of nitric oxide at 5–80 ppm reversed pulmonary hypertension induced by either a thromboxane endoperoxide analogue or by hypoxia.[31]

In patients with PPH, it has been noted that those with a patent foramen ovale live longer than those without. Although this approach is considered experimental, several studies have shown symptomatic improvement in patients with advanced pulmonary hypertension and severe right-sided failure who have undergone blade balloon septostomy.[32]

Small numbers of patients with pulmonary hypertension have had successful heart and lung transplantation.[33] Significant progress has been made in improving surgical techniques and reducing the incidence of graft rejection. In general, following transplantation, pulmonary artery pressure falls and right ventricular function improves.

Patients with severe right-sided failure, hepatomegaly, hyperbilirubinemia, and ascites are usually not suitable transplant candidates. Transplantation is limited by the small pool of donors and by the number of centers involved with this procedure.

Future therapeutic strategies for pulmonary hypertension are likely to emanate from developments in vascular biology, for example, the use of novel nitric oxide donors, endothelin inhibitors or endothelin receptor antagonists, and smooth muscle cell growth inhibitors. However, until we understand better the underlying causes of pulmonary hypertension, treatments will be targeted at relief of symptoms rather than at cure.

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