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Group 5 Pulmonary Hypertension:

The Orphan's Orphan Disease

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INTRODUCTION

PH is a complex disorder with multiple etiologies; as such, the World Health Organization classification system divides PH patients into 5 groups based on the underlying cause and mechanism. This classification system is designed to help organize diagnostic evaluations and direct treatment. Group 5 PH is an important heterogeneous group of diseases that encompass PH secondary to multifactorial mechanisms. For many of the diseases, the true incidence, etiology, and treatment remain uncertain.[1,2] Increased vascular resistance can occur secondary to hypoxic vasoconstriction, inflammation, proliferative arteriopathy shunting, chronic anemia, veno-occlusive disease, left ventricular dysfunction, and valvular heart disease. This article reviews the epidemiology, pathogenesis, and management of many of the various group 5 PH disease states.

GROUP 5.1: HEMATOLOGIC DISORDERS

Chronic Myeloproliferative Diseases—Chronic myeloproliferative diseases (CMPDs) are a heterogeneous group of diseases with different genetic bases. Myeloproliferative diseases, including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, have been associated with PH.

Prevalence/etiology: The true prevalence of PH in CMPD using hemodynamic criteria by RHC is unknown. Small case reports have reported a prevalence of PH (as defined by

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estimated RV systolic pressure ≥35 using transthoracic echo) in 36% to 48% of cohorts.[3,4] The etiology of PH in myeloproliferative diseases is multifactorial and has been associated with chronic thromboembolic PH (CTEPH), vascular remodeling, pulmonary veno-occlusive disease, tumor microembolism, and drug-induced PH.[5] CMPDs, in particular polycythemia vera and essential thrombocythemia, are characterized by a thrombophilic state, which may lead to arterial and venous thrombosis.[6] CMPD patients treated with the tyrosine kinase inhibitor dasatinib have also developed PAH.[7]

Treatment: There is no known effective treatment of PH associated with CMPDs. There is minimal evidence to support the use of cytoreductive (hydroxyurea and antiplatelet agents) therapy, which is effective in treating risk of thrombosis and vascular events in CMPD and may be effective in treating CMPD-PH.[5,8] There are few data to guide the role of pulmonary vasodilators in patients with CMPD-associated PH.[9,10] Standard-of-care clinical follow-up, however, with biomarkers, imaging, and cardiac catheterization should be done if these therapeutics are used.

Postsplenectomy

Incidence: Splenectomy may be a risk factor for PH.[11] After splenectomy, thrombotic and thromboembolic complications can occur. One retrospective study found a 10% incidence of pulmonary thromboembolic disease in 150 patients post-splenectomy.[12] Splenectomy has been associated with chronic thromboembolic pulmonary hypertension (CTEPH) as well as idiopathic PAH.[11,13]

Etiology: The etiology of thromboembolism postsplenectomy is not well understood. Splenectomy is associated with thrombocytosis; however, this has not been shown associated with increased thromboembolic risk.[14] There are minimal data on the presence of a hypercoagulable state postsplenectomy. The loss of the spleen's filtering function allows abnormal red cells to remain in the peripheral circulation after splenectomy, which may lead to facilitation of the coagulation process, which has been demonstrated in vivo.[15]

Treatment: Patients who present with PAH postsplenectomy without evidence of CTEPH may be treated with PAH-specific therapies and follow PAH group 1 guidelines.[4] If possible, splenectomy-associated proximal CTEPH should be treated with surgical pulmonary endarterectomy.[16]

If pulmonary endarterectomy is not possible due to anatomic distribution of the disease or comorbidities, then medical treatment consists of anticoagulation and diuretics with consideration of specific PAH therapy or lung transplantation. Two randomized placebo-controlled studies, one with bosentan, an endothelin receptor antagonist, and the other with riociguat, a guanylate cyclase stimulator, with inoperable or persistent CTEPH after thromboendarterectomy, improved exercise capacity and hemodynamics.[17,18]

The role for anticoagulation prophylactics to prevent CTEPH after splenectomy is unclear. A case-based approach evaluating each patient's risk of thromboembolic disease is likely warranted. Patients with asplenia in whom PH is suspected should undergo thorough

assessment for thromboembolic disease with ventilation perfusion scanning and CT angiography.

Chronic Hemolytic Anemia – Sickle Cell Disease

Incidence: PH associated with chronic hemolytic anemia secondary to hemoglobinopathies recently moved from group 1 PAH to group 5.[1] This switch occurred due to its mixed etiology PH presentations. Sickle cell anemia results from a genetic mutation leading to the production of hemoglobin S, which is less soluble when deoxygenated than the normal hemoglobin molecule, hemoglobin A.[19] Deoxygenated hemoglobin S polymerizes and aggregates, leading to microvascular occlusion and chronic hemolytic anemia. Three recent studies using RHC data to evaluate the incidence of PH among patients with sickle cell disease (SCD) found a prevalence of 6% to 10.5% and that the presence of PH was a major risk factor for death.[20–22]

Etiology: RHC data has revealed both precapillary PH as well as pulmonary venous hypertension secondary to left ventricular dysfunction in patients with SCD and PH.[20–22] PH has not been associated with the number of vasoocculsive episodes or acute chest syndrome, only with abnormalities in hemolytic anemia markers. Screening studies of patients with SCD have shown an association between the degree of hemolysis and the development of PH.[22] Some investigators propose that plasma-free hemoglobin that is released during hemolysis leads to decreased nitric oxide bioavailability, potentially mechanistically linking hemolysis with PH.[23] The high cardiac output state secondary to chronic hemolysis and resultant anemia might also lead to an increased pulmonary artery pressure. Many adult SCD patients have mildly restrictive abnormalities on pulmonary function testing; however, these abnormalities are rarely severe enough to lead to group 3 PH.[24] Among SCD-PH patients, CTEPH has been identified in approximately 5%.[25]

Treatment: There are few data to guide the management for patients with chronic hemolytic anemia and PH. A reasonable approach is to attempt to treat the underlying disease to minimize hemolysis and associated cardiopulmonary conditions. Treatment with PAH therapies have not been successful. The Walk-PHaSST study (sildenafil therapy for PH and SCD) was a multicenter National Institutes of Health double-blind placebo-controlled trial of sildenafil in patients with SCD that was stopped early because of a higher incidence of serious adverse events in the sildenafil arm. This was primarily caused by increased hospitalization for vasoocclusive pain crisis with no suggestion of improvement.[26] The ASSET-1 and ASSET-2 studies aimed to assess the efficacy and safety of bosentan therapy in patients with SCD and PAH; however, the studies were terminated due to lack of overt efficacy, slow site activation, and withdrawal of sponsor support.[27] Although epoprostenol acutely improves hemodynamics in these patients, there have been no studies of chronic long-term therapy.[28] Despite anecdotal experience of benefit with oral and continuous infusion in a select group of SCD patients, PAH therapy is not recommended for routine use in PH-SCD patients.[4]

Chronic Hemolytic Anemia – Thalassemia—Thalassemia is caused by a spectrum of diseases with reduced or absent production of 1 or more α-globin or β-globin chains,

leading to hemolytic anemia and ineffective erythropoiesis. Small studies using echocardiographically defined PH found a prevalence of 60% in cases with thalassemia intermedia and 75% in patients with thalassemia major; however, the true prevalence is unknown. The etiology is unknown but likely multi-factorial with contributions from hemolysis, hypoxia, hypercoagulability, and high CO.[29,30] As part of the National Institutes of Health Thalassemia Clinical Research Network, patients with β-thalassemia and echocardiographically defined PH received sildenafil. Although no safety concerns arose and the tricuspid regurgitant jet velocity decreased, there was no statistical significant improvement in functional class or the 6-minute walk distance test.[31] No large-scale randomized studies have been done, with only cardiac catheterization reports demonstrating exercise capacity and hemodynamic improvements with PAH therapies.[32]

GROUP 5.2: SYSTEMIC DISORDERS

Sarcoid-Associated Pulmonary Hypertension

Incidence: The incidence of sarcoidosis and PH has been estimated to be between 5% and 28% but may be as high as 75% in patients awaiting lung transplantation.[33,34] In these studies, the presence of PH was associated with increased morbidity and mortality. The presence of lung disease, a low diffusing capacity, and hypoxia on 6-minute walk test are strong risk factors for the presence of PH.[35] Symptoms are often nonspecific and may overlap with symptoms associated with their lung disease leading to underdiagnosis. There is a high variability in presentation: patients may present with dyspnea, right-sided heart failure symptoms, syncope, or sudden death.[4,36]

Etiology: The etiology of sarcoid-associated pulmonary hypertension (SAPH) is often multifactorial. Mechanisms include fibrotic lung involvement leading to the destruction of the pulmonary vascular bed, extrinsic compression of pulmonary vessels leading to altered vascular mechanics, intrinsic vasculopathy, vasculitis involving the pulmonary vasculature, pulmonary veno-occlusion, porto-PH, and left ventricular dysfunction.[37] One series of 40 autopsy studies revealed that granulomatous vascular involvement was common in all levels from large pulmonary arteries to venules. This led to destruction of elastic fibers with eventual replacement of fibrous tissue in the vessel walls.[38] This type of active inflammation and fibrosis led to occlusive vasculopathy. The granulomatous vascular involvement occurs heterogeneously but more frequently involves the venules, leading to a phenotype similar to pulmonary veno-occlusive disease.[38]

Myocardial granulomatous inflammation and fibrosis involvement can lead to systolic and diastolic dysfunction as well as mitral valve pathology. Overall survival in patients with SAPH secondary to left ventricular dysfunction is better than in patients with SAPH secondary to other causes.[39]

Treatment: SAPH studies with PAH-specific therapies are not conclusive.[40,41] One small case series suggested a favorable hemodynamic response to short-term treatment with inhaled nitric oxide[40] A recent case series of 26 patients with SAPH, of whom 13 received treatment with long-term IV or subcutaneous prostacyclin therapy, revealed that prostacyclin therapy was well tolerated with signs of both hemodynamic (RHC: cardiac output and

pulmonary vascular resistance) and clinical improvement.[42] Vasodilatory testing is not recommended to determine if calcium channel blockers will be a successful monotherapy but may be used to help differentiate the different etiologies for PH (PH groups 1, 2, and 3).[4] Because the development of SAPH can be caused by multiple different pathophysiologic mechanisms, it is likely that the degree of vasoresponsiveness may be related to the underlying pathology. Those patients with extensive fibrosis and destruction of pulmonary vessels may be less responsive to vasodilator therapy. More investigational studies are needed to evaluate vasodilator therapies.

Pulmonary Langerhans Cell Histiocytosis–Pulmonary Hypertension— Pulmonary Langerhans cell histiocytosis (PLCH) is a rare disease characterized by lung nodules and cystic lesions that is strongly associated with cigarette smoking. The true incidence of PH is unknown, but studies suggest that it is common and associated with high morbidity and mortality.[43,44] The etiology of PLCH-PH is unknown, but some studies suggest pulmonary vascular pathology leading to precapillary PH. Up to one-third of patients have a positive vasodilator response, and a French registry suggested a trend toward improved survival with PAH therapy; however, there are few data to support specific treatment of PLCH-PH.[43,44]

GROUP 5.3: METABOLIC DISORDERS

Thyroid Disease

Incidence: PH patients have a high prevalence of thyroid disease[45,46] of approximately 20%.[47] One small observational study of 63 patients with PAH found that approximately half of these patients had concomitant autoimmune thyroid disease.[46] One case report noted a prevalence of 6.7% of thyroid-stimulating immunoglobulin-negative thyrotoxicosis in patients with preexisting PAH being treated with epoprostenol.[48]

Etiology: A common autoimmune process may be the underlying pathology for PH and associated thyroid disease. Patients with PAH have an increased prevalence of both antithyroglobulin and antithyroperoxidase antibodies.[46] Left ventricular dysfunction can also be seen in the setting of thyroid disease and may contribute to the development of PH.[45] Thyroid disease may also have a direct effect on pulmonary vasculature. Possible mechanisms include enhanced catecholamine sensitivity, increased metabolism of intrinsic pulmonary vasodilators, and decreased metabolism of vasoconstrictors.[49] A high cardiac output state in the setting of hyperthyroidism may also contribute to the development of PH.

Treatment: The development of thyroid disease can lead to arrhythmias and worsening right heart failure and requires immediate attention. Case reports support that the treatment of hyperthyroidism by antithyroid medications, radioactive iodine, surgery or a combination is associated with decreased pulmonary artery pressure.[47] The potential effects of calcium blockers, endothelin receptor blockers, phosphodiesterase 5 inhibitors, or prostacyclins in patients with PH and thyroid disease are not known.

Glycogen Storage Disease–Pulmonary Hypertension—Glycogen storage diseases (GSDs) are characterized by enzymatic deficiencies that lead to defective glycogen synthesis

or breakdown leading to abnormal glycogen deposition primarily in muscles and liver. There are 11 different types of GSD, and PH has primarily been described in GSD type 1 (von Gierke disease). The incidence of PH in GSD type 1 is unknown, but it is associated with increased morbidity and mortality and is usually diagnosed in patients in their second or third decade.[50] The etiology of GSD-PH is unknown; however, it has been postulated that abnormalities in serotonin metabolism may contribute.[50] There is no known treatment of GSD-PH.

Gaucher Disease–Pulmonary Hypertension—Gaucher disease (GD) is the most common lysosomal storage disease and is a genetic disorder caused by a deficiency of the enzyme glucocerebrosidase that leads to glucocerebroside accumulation in macrophages and subsequent organ infiltration. Type 1 GD has been associated with PH and has been described as occurring in up to 30% of untreated patients using echocardiographically defined PH. The etiology is unknown but may be secondary to direct pulmonary capillary infiltration as well as bone marrow microemboli leading to vasculopathy.[51] Splenectomy (described previously) has also been postulated as contributing to the development of PH.[52] GD-PH usually improves with enzyme replacement therapy and some severe cases have been treated with pulmonary vasodilators.[52]

GROUP 5.4: OTHER DISORDERS

Group 5.4 (other disorders) encompasses PH caused by chronic renal failure (CRF), fibrosing mediastinitis, tumor emboli, and mechanical vascular obstruction. Only PH associated with CRF is discussed.

Chronic Renal Failure on Dialysis

Incidence/etiology: The true incidence of PH CRF on dialysis is not known; however, prior studies relying on echocardiographically defined PH have reported that PH is common and associated with increased mortality. The etiology is multifactorial, including pulmonary venous hypertension secondary to left ventricular dysfunction, hypervolemia, and high-output secondary to anemia or shunting from an arteriovenous fistula.[53] CRF may also have a direct effect on the pulmonary vasculature due to systemic imbalances in vasoconstrictors and vasodilators, endothelial dysfunction, and vascular calcification.[53–55]

Treatment: The evaluation of PH in patients with CRF on dialysis depends on symptoms and clinical circumstances. Patients with more than mild PH (pulmonary arterial systolic pressure >50 mm Hg), with significant RV dysfunction on echocardiography, with systemic hypotension limiting fluid removal via hemodialysis, and who are considered for kidney transplantation should undergo RHC to understand etiology and guide treatment. Management consists of treating left ventricular systolic or diastolic dysfunction, optimizing fluid balance to achieve euvolemia, iron/erythropoietin supplementation to avoid anemia, and phosphate binders to limit vascular calcification. Clinical investigation of PAH therapies in CRF is needed.

SUMMARY

Group 5 PH consists of a complex group of disorders that are associated with PH. The cause is often multifactorial and can be secondary to increased precapillary and postcapillary pressure as well as direct effects on pulmonary vasculature. The true incidence of PH in these disorders is often unknown; however, studies suggest PH can be common and its presence is often associated with increased morbidity and mortality. Studies investigating the treatment of group 5 PH are rare and involve a limited number of patients; thus, management is guided by small case reports and series. In general, treatment is directed toward treating the underlying disorder. The etiology of PH should be thoroughly assessed in these patients, and treatment should be individually tailored to each patient. PAH therapies may have a role in some specific disease states on a case-by-case basis; however, patients must be carefully and fully assessed for the cause of their PH because the benefits of PAH therapies remain unclear and require further investigation.

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KEY POINTS

- Group 5 pulmonary hypertension (PH) contains a variety of diseases that can be subcategorized into hematologic disorders, systemic disorders, and metabolic disorders.
- The true prevalence of PH defined using the gold standard of right heart catheterization (RHC) is unknown in most of these disorders and the cause is multifactorial.
- Evidence-based pathogenesis and management are mostly guided by case reports or small case series. In general, treatment of group 5 PH is directed toward treating the underlying condition, with consideration of pulmonary arterial hypertension (PAH) therapies based on clinical characteristics on a case-by-case basis.