Group 5 Pulmonary Hypertension
The Orphan's Orphan Disease

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KEYWORDS

• Pulmonary hypertension • Multifactorial • Chronic thromboembolic pulmonary hypertension

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.

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.

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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 estimated RV systolic pressure $\geq$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