An Update on Pulmonary Arterial Hypertension

Joanna Wapner, MSN, RN, and Lea Ann Matura, PhD, RN

Pulmonary arterial hypertension (PAH) is a progressive disease that ultimately leads to right heart failure and death. PAH is defined as a mean pulmonary arterial pressure $\geq$ 25 mmHg with a pulmonary capillary wedge pressure $\leq$ 15 mmHg at rest. The diagnosis of PAH is one of exclusion; diagnostics include an extensive history, serology, chest radiograph, pulmonary function tests, ventilation/perfusion scan, transthoracic echocardiogram, and right heart catheterization. Treatment and care of patients with PAH can be complex. Therefore, the nurse practitioner is an integral member of the health care team caring for PAH patients, helping to ensure seamless care and support.

Keywords: diagnosis, pathophysiology, pulmonary arterial hypertension, treatment

Pulmonary arterial hypertension (PAH) is a progressive disease that ultimately leads to right heart failure and death. It is hemodynamically defined as a mean pulmonary arterial pressure (PAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure $\leq$ 15 mmHg at rest, resulting in increased pulmonary vascular resistance.[1] PAH is predominantly found in women (80%) with a mean age at diagnosis of 53 years.[1] Patients with PAH may initially report dyspnea, especially on exertion, along with fatigue. These symptoms can be severe,[2] impairing their ability to function and their health-related quality of life (HRQOL).[2] Symptoms continue to worsen until patients are diagnosed and therapies are initiated. Diagnosis may be delayed because of the symptoms mimicking other cardiopulmonary disease resulting in worsening right ventricular modeling and increasing mortality.[3] The purpose of this review is to provide an overview and update on the pathophysiology, classification, diagnosis, and treatment of PAH.

American Association of Nurse Practitioners (AANP) members may receive 1.0 continuing education contact hours and 0.33 pharmacology credit, approved by AANP, by reading this article and completing the online posttest and evaluation at cecenter.aanp.org/program?area=JNP.

EPIDEMIOLOGY AND CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is an umbrella term that contains several groups.[1] Historically, PH was classified into 2 categories (ie, primary PH and secondary PH) based on the presence of identified risk factors. During the Second World Symposium on PH in 1998, a clinical classification was developed to categorize forms of PH sharing similar pathologic findings, hemodynamic characteristics, and treatment management strategies. Five PH etiology groups were identified: PAH (group 1), PH caused by left-sided heart disease (group 2), PH because of lung diseases and/or hypoxia (group 3), chronic thromboembolic pulmonary hypertension (CTEPH, group 4), and PH with unclear multifactorial mechanisms (group 5).[4] In 2013, a symposium was convened to determine if any changes were needed to the current PH classifications. Consensus determined to maintain most of the previous classifications with some changes in group 1 (Table 1).[1]

The Registry to Evaluate Early and Long-term PAH Disease Management was a US-based registry, multicenter observational study to assess the clinical course and disease management of patients with PAH. Enrollment included 3,515 patients with PAH

Table 1. Updated Classification of Pulmonary Hypertension[a]

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, **SMAD9, CAV1, KCNK3**
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. **Persistent pulmonary hypertension of the newborn (PPHN)**

2. Pulmonary hypertension caused by left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 **Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

3. Pulmonary hypertension caused by lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

Alk-l, activin receptor-like kinase 1; BMPR2, bone morphogenetic protein receptor type II; CAV-1, caveolin I; Eng, endoglin; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.
[a] 5th World Symposium on Pulmonary Hypertension Nice 2013. Main modifications to the previous Dana Point classification are in bold.

who were enrolled between 2006 and 2009 in order to establish updated characteristics of patients with PAH and to improve diagnosis, treatment, and management.[5] Estimated incidence and prevalence are 2.0 and 10.6 cases per million.[6] Registry to Evaluate Early and Long-term PAH Disease Management data show there is a 4.1:1 female-to-male ratio among patients with idiopathic pulmonary arterial hypertension (IPAH) and a 3.8:1 ratio among those patients with associated pulmonary PAH (Table 1).

IPAH is diagnosed in approximately 50% of all patients with PAH. In addition, there are heritable forms of PAH that include the following mutations: bone morphogenetic protein receptor type II, activin receptor like kinase 1, endoglin, and caveolin-1 (Table 1). Disorders associated with PAH include connective tissue disease, human immunodeficiency virus, portal hypertension, congenital heart disease, and schistosomiasis. Toxins and drugs have been implicated in the PAH etiology. Definitive causes include anorexigens (aminorex, fenfluramine, dexfenfluramine, and benfluorex) along with toxic rapeseed oil. Selective serotonin reuptake inhibitors are considered a risk factor for the development of persistent PH in the newborn in pregnant women exposed to selective serotonin reuptake inhibitors, especially after 20 weeks of gestation. Other likely causes of PAH include amphetamines, methamphetamines, and dasatinib, which is a tyrosine kinase inhibitor used for cancer treatment. Other possible causes include cocaine, St. John's wort, interferon-α and -β, and other chemotherapeutic drugs. Although PAH is more prevalent in women, oral contraceptives and estrogen are unlikely causes of PAH.[1]

PATHOPHYSIOLOGY

PAH results from restricted blood flow through the pulmonary arterial circulation that leads to increases in pulmonary vascular resistance (PVR) and, ultimately, right heart failure. PAH is characterized by a variety of arterial abnormalities including intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, inflammation, and