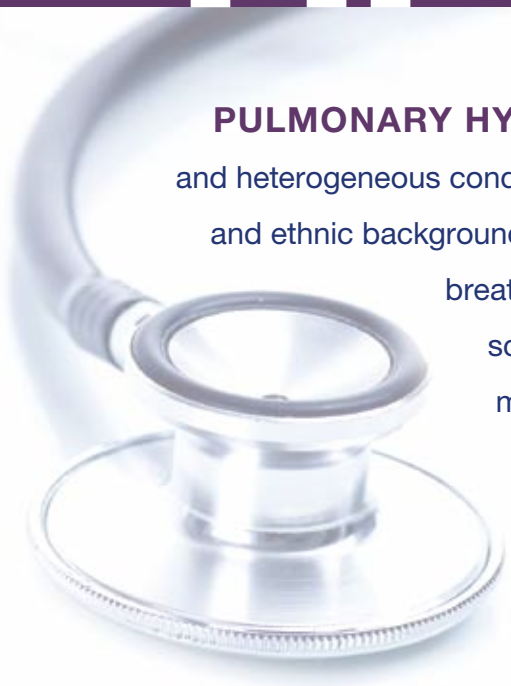
Hereditary Hemorrhagic Telangectasia (HHT)

& PH Pulmonary Hypertension



PULMONARY HYPERTENSION, OR PH, is a complex and heterogeneous condition. It is a disease that affects people of all ages and ethnic backgrounds. The primary symptoms include shortness of breath, fatigue, lightheadedness and loss of consciousness. While there is no cure yet, since the mid-1990s new and better treatments have become available that are extending and enhancing the lives of PH patients. Importantly, further advances appear to be on the horizon.

Pulmonary hypertension (PH) is defined by the presence of elevated pulmonary artery (PA) pressures, with a commonly employed threshold being a mean PA pressure greater than 25 mmHg. Many different types of patients can present with PH, including those with left-sided heart disease, chronic intrinsic lung disease and chronic thromboembolic disease. However, a much more discrete group of patients, said to have pulmonary *arterial* hypertension (PAH) has been found to share common pathophysiological features directly involving the pulmonary arterial tree, and to lack evidence of elevated left-heart filling pressures, intrinsic lung disease or thromboembolism. Such patients also tend to share a positive response to PAH-specific therapies. This group of patients includes those with idiopathic (IPAH) and familial (FPAH) forms of PAH, as well as those with PAH associated with connective tissue diseases, chronic hepatic or congenital heart disease, hemoglobin disorders, HIV infection and selected toxic exposures.

Pulmonary arterial structural and functional abnormalities frequently seen in PAH include vasoconstriction, medial hypertrophy, fibrosis, inflammation, cellular proliferation, *in situ* thrombosis and formation of plexiform lesions. These combine to increase pulmonary vascular resistance and right ventricular afterload. Without therapy, right heart failure and early morbidity and mortality are inevitable.

PAH remains relatively rare and its presenting signs and symptoms are notoriously non-specific. Accordingly, it is often confused with other diagnoses, and proper diagnosis and therapy are unacceptably delayed. It is the hope that increased awareness on the part of health professionals and the general public will help rectify this.

PH in Association with Hereditary Hemorrhagic Telangectasia (HHT)

HHT primarily develops from mutations in either the endoglin (ENG -*HHT1*) or activin receptor-like kinase 1 (ACVRL-1 or ALK-1 - *HHT2*) genes. Cardinal manifestations include small vessel telangectasias on mucocutaneous surfaces and visceral arterio-venous malformations, primarily in the lung, liver and central nervous system. Available data suggests that 15–20% of HHT patients will have at least mildly elevated pulmonary artery pressures (i.e. systolic pressure > 40 mm) by non-invasive assessment.

ALK-1 mutations, which occur in ~40% of HHT families, have been linked to a small vessel proliferative arteriopathy of the pulmonary circulation that is indistinguishable from other types of World Health Organization Group I PH (Pulmonary Arterial Hypertension—PAH). Like other conditions in Group I PH, HHT-associated PAH is characterized by an abnormal relationship between blood flow through the pulmonary circulation and the resultant pressures, which is represented as an *elevated pulmonary vascular resistance* (PVR). Interestingly, ALK-1 and bone morphogenetic protein receptor II—the causative gene in familial pulmonary arterial hypertension—are both members of the transforming growth factor β signaling pathway and influence proliferation and migration of endothelial cells through regulatory intra-cellular messengers, SMAD1 and SMAD5. While the true incidence of HHT-associated PAH is unknown, 15% of families with HHT2 are estimated to have an affected member. HHT-associated PAH appears to be much less common in HHT1 families.

Alternatively, PH can develop in HHT as a consequence of a high cardiac-output (HO) state, which is distinguished from PAH by a *normal* PVR. HO-state can result in HHT from three mechanisms. First, a significant burden of systemic telangectasias, particularly in the gastro-intestinal tract, can drastically lower systemic vascular resistance and secondarily elevate the cardiac output. Second, a large degree of blood flow through hepatic arterio-venous malformations can create a HO-state. Third, severe anemia from chronic blood loss, typically from the gastro-intestinal tract, can cause a HO-state. Differentiation between PH associated with a normal PVR (i.e., HO-state) and PH with an elevated PVR (i.e., PAH) is paramount, as treatments greatly differ.

Importance of Screening for PH

Symptoms of PAH, including dyspnea, poor exertional tolerance and fatigue, can be challenging to decipher in HHT patients, thanks to other potential maladies, including heart failure, anemia and liver dysfunction. As a result, an index of suspicion must be high in the appropriate setting, especially if more common causes are not present.

Trans-thoracic echocardiogram (TTE) is a standard screening test for the detection of intra-pulmonary shunts in HHT patients. TTE also provides an effective screening method for PH by estimating the pulmonary artery systolic pressure (sensitivity 80–100%, specificity 60–100%) and by qualitatively assessing right ventricular size and function. TTE can also quantify flow through the left ventricular outflow tract and possibly uncover an underlying HO-state. Finally, TTE can estimate left-sided filling pressures, which could be indicative of heart failure, including high-output heart failure (HOHF).

If PH is diagnosed by Echo or is clinically suspected in an HHT patient, right heart catheterization is crucial to confirm the elevated pulmonary artery pressures and to differentiate the types of PH (described above). Direct measurement of the pulmonary artery pressures, pulmonary artery occlusion or "wedge" pressure, and cardiac output, allow for calculation of the PVR.

Treatment of HHT-Associated PH

Patients with PH related to a HO-state are not candidates for PAH-specific treatments, as their underlying pathophysiology will not benefit from further attempts to increase cardiac output and lower the PVR. Therapy should be directed towards minimizing the cause of the HO-state (e.g., correct anemia, reduce burden of telangectasias). If HOHF is present, diuretics should be used to lower left-sided filling pressures. While conventional PAH treatments have been used in HHT-associated PAH, caution must be exercised to avoid aggravating other manifestations of HHT. Prostanoids have potent anti-platelet effects and can exacerbate bleeding from mucosal telangectasias. Similarly, phosphodiesterase 5 inhibitors have been associated with increased mucosal blood flow and epistaxis. Lastly, PAH-specific therapies have varying vasodilatory effects on the systemic circulation and can lower systemic vascular resistance, which may not be tolerated in patients with significant systemic shunts. Application of PAH-specific therapies in these complex patients is best accomplished in conjunction with a PH treatment center.

About the Pulmonary Hypertension Association

The mission of the Pulmonary Hypertension Association is to find ways to prevent and cure pulmonary hypertension, and to provide hope for the pulmonary hypertension community through support, education, advocacy and awareness. PHA's members stand as part of a community that is fighting back against this terrible illness.

Under the leadership of the Scientific Leadership Council (SLC), a group of approximately 30 global leaders in the field of pulmonary hypertension, PHA proactively facilitates the development of new knowledge about pulmonary hypertension, develops educational resources for medical and public audiences and advocates to raise awareness about pulmonary hypertension. PHA's professional membership bodies enhance the care and support of PH patients by enabling interaction among PH colleagues and providing opportunities for professional advancement. Just a few of the many benefits of membership available to clinicians and researchers include listing your practice in the Find A Doctor section of PHA's website, discounted registration fees for PHA's International PH Conference and Scientific Sessions and a free subscription to an online email group, offering peer-to-peer education and information sharing. To learn more about membership, visit **www.PHAssociation.org/MedicalProfessionals/PHANetworks.**

PHA's Medical Education fund was founded in 2009 and provides ongoing educational information on PAH by nationally recognized and experienced medical leadership. The fund currently supports three professional education initiatives: PHA Online University, 30-City Program and Preceptorship Program, and one for patients, *PHA on the Road*. To learn more and get involved today, visit **www.PHAssociation.org/MedicalEducationFund.**

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Murali Chakinala, MD, FCCP
Washington University School of Medicine, St. Louis, Mo.

Michael A. Mathier, MD, FACC
University of Pittsburgh School of Medicine, Pittsburgh, Pa.

PHA fulfills its mission through:

- Funding for research
- Quarterly medical journal *Advances in Pulmonary Hypertension* (www.phaonlineuniv.org/Journal)
- Professional membership sections:
  - PH Clinicians and Researchers (PHCR) — for physicians and doctorate-level researchers (www.PHAssociation.org/PHCR)
  - PH Resource Network — for nurses and allied health professionals (www.PHAssociation.org/PHResourceNetwork)
- PHA Online University offering free CME credits and the latest information on pulmonary hypertension (www.PHAOnlineUniv.org)
- Educational conferences and materials for medical professionals and patients
- 300+ page book Pulmonary Hypertension: *A Patient's Survival Guide*
- PH patient support groups
- Quarterly newsletter *Pathlight*
- Advocacy and awareness campaigns
- Toll-free Patient-to Patient Helpline (1-800-748-7274)
- PHA website with PH discussion boards, email groups and online support chats (www.PHAssociation.org/ConnectOnline)

For more information on hereditary hemorrhagic telangectasia (HHT), visit the **HHT Foundation International** at **www.hht.org**.

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PHA Pulmonary Hypertension Association
Empowered by hope

801 Roeder Rd, Suite 1000
Silver Spring, MD 20910

Phone: 301-565-3004
www.PHAonlineUniv.org

E-mail: pha@PHAssociation.org
www.PHAssociation.org