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.
Pulmonary hypertension is an increasingly recognized complication of chronic hereditary and acquired hemolytic anemias, including sickle cell disease, thalassemia (in particular thalassemia intermedia and inadequately transfused and chelated patients with thalassemia major), paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis and stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, red cell alloimmune mediated hemolytic anemia and unstable hemoglobin variants. This observation suggests the existence of a syndrome of hemolysis associated pulmonary hypertension that develops with the aging of patients suffering from chronic hereditary or acquired hemolytic anemia.

Echocardiographic studies have reported that approximately 30% of screened adult patients with sickle cell disease develop mild-to-severe pulmonary hypertension in adulthood (defined by systolic pulmonary artery pressures (sPAP) ≥ 35 mm Hg). In 9–20% of patients the pulmonary hypertension is more severe (defined by sPAP ≥ 45 mm Hg). Recent autopsy studies suggest that up to 75% of sickle cell patients have histological evidence of pulmonary arterial hypertension at the time of death. Similarly, retrospective studies have demonstrated that 40–50% of patients with thalassemia intermedia, and 10–75% of patients with thalassemia major have echocardiographic evidence of pulmonary hypertension.

**Importance of Screening for PH**

Patients with sickle cell disease and pulmonary hypertension have a significantly increased mortality rate compared with patients without pulmonary hypertension. In the NIH screening study a measured tricuspid regurgitant jet velocity (TRV) of at least 2.5 m/sec, as compared to a velocity of less than 2.5 m/sec, was associated with a marked increased risk of death (RR 10.1; 95% CI, 2.2–47; P < 0.001) and remained so after adjustment for other possible risk factors in proportional hazards regression analysis. The 18-month mortality was 16% for patients with a TRV of greater than or equal to 2.5 m/sec and was less than 2% in patients without pulmonary hypertension. Further updated follow-up data from this cohort continues to demonstrate that pulmonary hypertension is a strong independent risk factor for mortality (RR 7.4, 95% CI 2.4–22.6, P < 0.001) with 40-month mortality rate of approximately 40%. Furthermore, these updated follow-up data show that survival can be stratified by pulmonary pressure severity with the highest risk of death with a TRV 3.0 m/sec and an intermediate risk in those with TRV 2.5–2.9 m/sec. Ataga and colleagues at UNC have also found a high mortality rate in the patients with TRV 2.5 m/sec with a relative risk for death of 9.24 (95% confidence interval: 1.2–73.3; P = 0.01). Taken together, the retrospective and prospective studies suggest that pulmonary hypertension is the greatest risk factor for death facing the aging population of patients with sickle cell disease and possibly other patients with chronic high-grade intravascular hemolysis.

Doppler echocardiography provides essential information such as non-invasive estimation of pulmonary artery systolic pressure (via calculation of the TRV), valvular function and right and left ventricular systolic and diastolic function. The use of echocardiography to estimate pulmonary artery systolic pressures has been validated in patients with sickle cell disease, and non-invasive assessment correlates well with the measurement of pulmonary arterial systolic pressures by right heart catheterization. The velocity of regurgitant blood across the tricuspid valve during systole is measured, and the pulmonary artery systolic pressure is calculated using the modified Bernoulli’s equation (4 * TRV^2 plus central venous pressure estimates). To avoid the more subjective estimation of central venous pressures, pulmonary hypertension can be defined by a specific tricuspid regurgitant jet velocity value (TRV) 2.5 m/sec and moderate-to-severe pulmonary hypertension defined by a TRV 3.0 m/sec. More severe disease is also suggested by evidence of right ventricular failure, such as paradoxical septal motion, a flattened interventricular septum, a dilated right ventricle and atrium, and a pericardial effusion.

Because the differential diagnosis for an elevated TRV includes left heart failure, it is important to evaluate by echocardiogram indications of left ventricular systolic dysfunction (observed in 2% of patients in the NIH cohort) and diastolic dysfunction (observed in 18% of patients in the NIH cohort of patients with sickle cell disease), either of which may be found alone or in combination with pulmonary arterial hypertension. Diastolic dysfunction produces elevations in end-diastolic filling pressures which increase pulmonary venous and
pulmonary artery pressures. The presence of diastolic dysfunction can be assessed by echocardiography (tissue Doppler or conventional assessment of the E/A ratio) and a combination of both pulmonary hypertension estimated by high TRV and diastolic dysfunction is present in 11% of sickle cell patients evaluated at the NIH. The presence of both pulmonary hypertension and diastolic dysfunction is a particularly poor prognostic sign, associated with a relative risk of death of 12.0 (95% confidence interval 3.8 to 38.1; p<0.01).

In addition to the above measures, patients with TRV ≥ 3 m/s should undergo:

• Right heart catheterization to assess left ventricular diastolic and systolic function.

• A CT-pulmonary angiogram, V/Q scan, and or pulmonary angiogram to exclude chronic thromboembolic pulmonary hypertension.

• Consider systemic anticoagulation if no contraindications (improves outcomes in patients with primary pulmonary hypertension and in situ thrombosis but no data available in patients with sickle cell disease). This decision should occur with consultation between hematologist and cardiologist/pulmonologist.

• Consider specific therapy with selective pulmonary vasodilator and remodeling drugs, particularly if the patient has symptomatic dyspnea on exertion which has progressed in recent months or years. While these drugs have not been studied in phase III trials sickle cell patients, hemoglobinopathy is listed as a cause of PAH and insurance companies will cover these medications for patients with SCD and catheterization documented PAH. A multicenter trial of sildenafil for hemolysis-associated pulmonary hypertension was initiated by the NHLBI, based on encouraging phase I-II data. However this trial was stopped prematurely, secondary to an unexpected increase in episodes of vaso-occlusive crisis in patients on the active treatment. A smaller study of endothelin receptor blockade does not show evidence of similar adverse effects but also lacked appropriate power to detect a treatment effect. The current recommendation of experts is that patients identified with PH be aggressively treated with therapies known to improve outcomes in sickle cell disease patients, such as hydroxyurea, iron chelation, transfusion, and therapies for established thromboembolism and diastolic dysfunction initiated if appropriate. Patients with classic Group I PAH hemodynamics can be considered for pulmonary hypertension specific therapy based on the direction of PAH specialists. Appropriate consultation and right heart catheterization is recommended at baseline and repeated annually for patients on such therapy. More detailed management recommendations are available in recently published reviews.
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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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 sickle cell disease, visit the Sickle Cell Disease Association of America at www.sicklecelldisease.org

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