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Group 5 PH: A Myriad of Faces

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Pulmonary Hypertension Association
Matt Granato, LL.M., MBA, President and CEO

PHA OFFICE
Pulmonary Hypertension Association
8401 Colesville Road, Suite 200
Silver Spring, MD 20910
301-565-3004; 301-565-3994 (fax)
Advances@PHAssociation.org

PUBLISHING OPERATIONS
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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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EDITOR'S MEMO

Welcome back all. The summer of 2021 is commencing. As we all step into this new season with optimism and anticipation, it is a great time reflect back on this challenging last year. I would like to thank everyone at PHA, Allen Press, and every member of the editorial board, guest editor, author and panelist who have generously contributed their time, effort and expertise in creating outstanding issues of *Advances,* during a time when none of us *had* a lot of time. These issues have received some of the highest readerships we have seen. It is this enduring dedication by staff and faculty alike who make this unique journal so well-loved in our community. Thank you to all.

I would like to congratulate Drs. Oksana Shlobin and Anjali Vaidya, the co-guest editors of this edition of *Advances*. The topic is Group 5 PH, an ever changing and ever challenging topic for us all. Drs. Shlobin and Vaidya and their faculty have met the challenge of organizing this difficult group of conditions into a beautifully written resource which touches on the most important subgroups in Group 5. The group focused the round table and PHGR section on Sarcoidosis, a major topic in the 6th WSPH. Readers will turn to these documents when looking for expert viewpoints on this controversial topic.

I know you will enjoy this issue of *Advances.* This issue will serve as a great resource in 2021 and beyond, as this topic will continue to ebb and flow with more experience and knowledge.

Deborah Jo Levine, MD
Professor of Medicine, Pulmonary and Critical Care
Medical Director Lung Transplantation
Director of Pulmonary Hypertension
University of Texas Health Science Center San Antonio
San Antonio, TX

GUEST EDITOR'S MEMO

Group 5 Pulmonary Hypertension (PH), i.e. the Miscellaneous Group, is a heterogeneous group that includes a myriad of conditions that differ in etiology and pathophysiology. One can argue that Group 5 PH is the most complex group in the current classification of PH, as, in addition to variability of the underlying conditions, the mechanisms of superimposed PH differ vastly, making a proper diagnosis and management more nuanced and challenging.

In this issue of *Advances*, we are very excited to bring to the readers an array of topics, covered by the experts in the field with particular clinical and research interests in specific forms of Group 5 PH.

Drs. Melendres-Groves and Bostwick's article *The Story of Group 5 PH* offers the readers an overview of the historical context of the classification system and how Group 5 has morphed into its current classification. The paper further succinctly describes major subgroups of Group 5 PH including hematologic (chronic hemolytic anemias, myeloproliferative disorders), systemic and metabolic disorders (Pulmonary Langerhans Cell Histiocytosis, Gaucher disease, Glycogen storage disease, Neurofibromatosis, and Sarcoidosis), congenital heart diseases that do not fall into Group 1 PAH, and also covers chronic renal failure and fibrosing mediastinitis.

The Myriad Presentations of Sickle Cell Disease-Related Pulmonary Hypertension by Drs. Prohaska and Machado is a comprehensive review of the most common hemolytic anemia that fall in Group 5 PH: sickle cell disease. The authors offer an insight and guidance into the pathogenesis, diagnosis, prognosis and treatment of this complex group of patients.

In their article *Metabolic Disorders of Pulmonary Hypertension*, Dr. Oliveros and the guest co-editor of this issue Dr. Vaidya offer a deeper dive into the two metabolic diseases: Glycogen storage diseases and Gaucher's disease. In their paper, they also cover a topic of the complex relationships between PH and thyroid abnormalities.

Sarcoidosis associated pulmonary hypertension (SAPH) was a hot topic during the 6th World Symposium on Pulmonary Hypertension with a discussion centered on whether it should be "housed" in Group 3 rather than Group 5 category. While the supporters of the move made many persuading arguments that in majority of the cases, SAPH occurs in the setting of a significant parenchymal lung disease, at the end, it remained in Group 5, as there are a number of other etiologic processes that can lead to development of PH in this group of patients. Dr. Kristen Alman and authors offer the readers *An Interesting Case of Sarcoidosis Associated Pulmonary Hypertension* describing one of such situations in the PH grand Rounds Section. The topic of SAPH is further discussed in the roundtable with great insights from Drs. Roxana Sulica, Stacy Mandras, and Bob Baughman, and facilitated by the co-editors of this issue.

We hope that the readers will find this issue thought provoking, educational and practical. It is important for us as a PH community to continue the ongoing discussions regarding this complex agglomerate of distinct conditions. It is our hope that with the increased awareness of Pulmonary Hypertension in general, this often under-recognized and under-appreciated group will be on the forefront of research, as more guidance is needed to help clinicians caring for these complicated patients.

Oksana Shlobin, MD
Medical Director, Pulmonary Hypertension Program
Director of Education, Advanced Lung Disease and Transplant Program
Inova Fairfax Hospital
Falls Church, VA

Anjali Vaidya, MD
Associate Professor of Medicine
Co-Director, Pulmonary Hypertension, Right Heart Failure, and CTEPH Program
Associate Program Director, Cardiology Fellowship
Temple University Lewis Katz School of Medicine
Philadelphia, PA

REGULAR ARTICLE

Metabolic Disorders of Pulmonary Hypertension

Estefania Oliveros, MD, MSc
Department of Medicine
Division of Cardiovascular Disease
Pulmonary Hypertension, Right Heart Failure and CTEPH Program
Temple University Lewis Katz School of Medicine
Philadelphia, PA

Anjali Vaidya, MD
Associate Professor of Medicine
Co-Director, Pulmonary Hypertension, Right Heart Failure and CTEPH Program
Associate Program Director, Cardiology Fellowship
Temple University Lewis Katz School of Medicine
Philadelphia, PA

There is overlap between pulmonary hypertension and metabolic disorders. According to the 6th World Symposium on Pulmonary Hypertension, glycogen storage diseases and Gaucher disease are included in the heterogeneous group 5 pulmonary hypertension. This review highlights the known insights into the role of metabolic disorders and pulmonary hypertension, including epidemiology, pathogenesis, diagnosis, and treatment of pulmonary hypertension. Thyroid disorders have multiple mechanisms by which association with pulmonary hypertension have been described, and these will also be discussed. Pulmonary hypertension-specific targeted therapies and disease-specific therapies have been suggested, and the use alone or in combination has variable responses.

INTRODUCTION

The 6th World Symposium on Pulmonary Hypertension proposed to include pulmonary vascular resistance ≥3 Wood Units in the definition of all forms of precapillary pulmonary hypertension (PH) associated with mean pulmonary artery pressure >20 mmHg.[1] Since 1998, group 5 has undergone significant changes from "disorders directly affecting the pulmonary vasculature" to "miscellaneous" in 2003, until more recent updates wherein multiple pathophysiological processes are included in this group.

As part of this heterogenous group, metabolic disorders have been recognized to play a role in predominant pathophysiological mechanisms related to PH. Those include glycogen storage disease and Gaucher disease. Thyroid disorders, while not specifically included in the World Symposium classification, have multiple mechanisms by which PH association have been described, and thus will also be discussed in this review. We will describe the epidemiology, pathogenesis, and management of these metabolic associations of PH (Table 1).

Table 1. Epidemiology, Associations, and Management of Metabolic Disorders of PH

	Glycogen storage disease	Lysosomal storage disease
Prevalence of PH	25% in glycogen storage disease type 1	30% if Gaucher disease is untreated and 7% if the disorder is treated
Portocaval shunt	Yes	Yes
Splenectomy	No	Yes
Genetic association with PH risk	No	Yes
Screening of PH by echocardiogram recommended	Yes	Yes
PH specific therapy	Limited experience	Limited experience

Key Words—pulmonary hypertension, metabolic disorder, glycogen storage disease, Gaucher disease, thyroid
Correspondence: Estefania.oliveros@temple.edu

GLYCOGEN STORAGE DISEASE

Glycogen storage diseases are caused by genetic alterations of the glycogen metabolism leading to deposition of glycogen various organs, predominantly liver and kidney. There are 11 different types of glycogen storage disease, varying by enzyme deficiency and clinical manifestations. There are PH case reports related to glycogen storage disease type 1 (von Gierke disease) and 2 (Pompe disease). Among the varieties of glycogen storage disease, PH has predominantly been described in glycogen storage disease type 1.

Glycogen Storage Disease Type 1

In glycogen storage disease type 1, there is deficiency of the glucose 6-phosphatase enzyme (GSD 1a) or a deficiency in the microsomal transport proteins for glucose 6-phosphate (GSD 1b). This condition is usually diagnosed during infancy with hypoglycemia between feedings. About 25% of the patients with glycogen storage disease are thought to have type 1. The incidence of

Table 2. Reported Cases of Pulmonary Hypertension With Patients With Glycogen Storage Disease Type I

Author	GSD	Age of PH diagnosis (year)	Sex	Portocaval shunt	Pathology	Survival
Pizzo[5]	1	16	F	Yes	Intimal fibrosis, medial hypertrophy, plexiform lesions	No
Hamaoka[7]	1	12	F	No	Fibrous occlusion, plexiform lesions	No
	1	16	M	Yes	N/A	No
Ohura[8]	1	21	F	No	N/A	No
Bolz[9]	1	4	F	No	Intimal fibrosis	No
Kishnani[4]	1	24	F	No	N/A	No
Humbert[3]	1	25	M	Yes	N/A	No
Ueno[10]	1	17	M	No	N/A	Yes
Torok[11]	1	14	M	No	N/A	Yes

glycogen storage disease type 1a is 1 per 100 000.[2] To date, the incidence of PH is unknown in glycogen storage disease, and only 11 patients with glycogen storage disease 1 have been reported with PH (Table 2).[3-11] Of these, 5 had associated conditions that could also precipitate PH, including portocaval shunts, atrial septal defect, and hereditary hemorrhagic telangiectasia.

Some have hypothesized that patients with PH related to glycogen storage disease type 1 have similar characteristics to 6th World Symposium Group 1 PH (pulmonary arterial hypertension) because they have elevated serotonin levels, a vasoconstrictive amine that serves as pulmonary vasoconstrictor and growth factor for vascular smooth muscle cells stored in platelets.[2] Based on this hypothesis, Humbert et al[12] collected plasma serotonin in 13 patients with glycogen storage disease 1a, 1 patient with severe PH and glycogen storage disease 1a, and 16 patients with severe PH. Interestingly, plasma serotonin was dramatically elevated in the patient with glycogen storage disease 1a and PH (113.4 nmol/L), compared to cases with only severe PH (38.8 ± 7.3 nmol/L) or glycogen storage disease 1a (36.8 ± 11.5 nmol/L). This finding prompted the consideration for PH targeted therapy in this population. Ueno and colleagues[10] used sildenafil in a 17-year-old patient who developed syncope, was diagnosed low cardiac output right sided heart failure, and had improvement of hemodynamics and biomarkers after 3 weeks on single therapy treatment.

Screening for PH by periodic echocardiography has been suggested in these groups. The known reported cases of glycogen storage disease type 1 and PH were in children older than 10 years of age. Hence, screening can be timed and planned accordingly according to guidelines for glycogen storage disease for patients 10 years of age and older.[2,13]

Glycogen Storage Disease Type 2

Li and colleagues[14] described one case of PH with glycogen storage disease type 2 in a 16-year-old girl with severe respiratory muscle weakness, leading to impaired pulmonary function and respiratory failure. She was found to have PA systolic pressure 65 mm Hg and chronic respiratory acidosis with pH 7.3 and Pco_2 83 mm Hg. They speculated that severe muscle weakness leading to impaired pulmonary function and respiratory failure may have precipitated PH. Our group has previously described mechanisms by which hypercarbia can also directly contribute to pulmonary vasoconstriction and vascular remodeling, including via increased hydrogen ion concentration and sympathetic nervous systemic activation.[15]

LYSOSOMAL STORAGE DISORDER (GAUCHER DISEASE)

Gaucher disease is an autosomal recessive inherited disorder characterized by lysosomal storage disease in which there is a deficiency of the enzyme glucocerebrosidase. Consequently, there is glucocerebroside accumulation in the macrophage-monocyte system and organ infiltration, predominantly in the bone marrow, liver, and spleen. The adult or chronic form (type 1) comprises the majority of cases of Gaucher disease, compared to the less common infantile or acute form (type 2) (Table 3).

Table 3. Gaucher Disease

Gaucher disease	Type 1	Type 2	Type 3
Age at onset	Childhood or adulthood	Infancy	Childhood or adolescence
Pulmonary hypertension	Yes	Yes	Yes
Hepatosplenomegaly	Yes	Yes	Yes
Bone disease	Yes	No	Yes
Neurodegeneration	No	Yes	Yes
Age at death	Childhood or adulthood	Median 9 months	Childhood or early adulthood
Ethnic origin	Pan-ethnic or Ashkenazi Jews	Pan-ethnic	Pan-ethnic or Norrbottnian type from Sweden

The proposed mechanism of PH in Gaucher disease is accentuated basilar deposition of glucocerebroside in the interstitium (demonstrated as septal thickening), along with vasculopathy due to pulmonary alveolar capillary occlusions and fatal bone marrow microemboli.[16-18] Gaucher cells have been identified in the pulmonary parenchyma, intracapillary beds, patchy infiltrates in the lymphatic distribution, intra-alveolar infiltrates, and interstitial space (peri-bronchial, perivascular and septum).[18] The universal involvement of the pulmonary capillaries suggests the systemic nature of the disease. Interestingly, however, Gaucher disease type 1 has been associated with isolated PH, without Gaucher cells in the lung parenchyma.

Gaucher disease has indirect mechanisms by which it also contributes toward pulmonary vascular disease, as it is also associated with splenectomy and liver disease, both of which contribute to the development of PH. After splenectomy, thromboembolism may occur secondary to bone marrow infarction and enforcement of capillaries by megakaryocytes from extramedullary hematopoiesis. Furthermore, the presence of splenectomy in Gaucher disease is strongly associated with severe and life-threatening PH; in a study by Mistry et al[19] all patients with severe PH (right ventricular systolic pressure 50-130 mm Hg) were asplenic compared to only 31% of patients with right ventricular systolic pressure <50 mm Hg (odds ratio 28.8, 95% confidence interval 1.6-531.6, $P < .001$). Removal of the spleen, the primary reservoir of cell storage, will promote migration of mononuclear phagocytes toward other tissues, such as liver, skeletal muscle, and lung. Hence, there is perpetual remodeling of the vascular wall. Genetic associations of BMPR2 and ALK1 have not shown to be modifiers in Gaucher disease type 1.[20] Liver involvement is common in Gaucher disease, with its severity and clinical significance spanning a wide spectrum ranging from asymptomatic to cirrhosis. Portal hypertension can lead to pulmonary artery hypertension, while hyperdynamic circulation commonly seen in cirrhosis physiology can cause PH due to high increased right ventricular cardiac output.

The incidence of PH in untreated Gaucher disease type 1 is 30%, and it can be reduced to 7% in cases receiving enzyme replacement therapy.[19] Individuals can develop PH on the basis of elevated pulmonary vascular resistance and hepatopulmonary syndrome. Elstein et al[21] studied 134 adults with Gaucher disease type 1, and since 7% of the cases had PH, they recommended routine echocardiographic monitoring of all treated and untreated patients with enzyme replacement therapy. Risk factors for developing PH include female sex, splenectomy, angiotensin converting enzyme 1 gene polymorphism, acid beta-glucosidase gene mutation, poor compliance with enzyme replacement therapy, and positive family history (ie, sibling with Gaucher disease and PH).[19,20] The severity of Gaucher disease does not correlate with severity of PH.[22] Similar to the risk factors for developing PH, specific mutations (ie, non-N370S mutation of GBA gene), positive family history of similar phenotype, ACE 1 allele), and epigenetic modifiers such as female sex or a history of splenectomy predict severity of PH.

Enzyme replacement therapy is proven to be safe and effective in the treatment of Gaucher disease type 1, establishing imiglucerase as the current standard of care. In PH patients with Gaucher disease, the use of enzyme replacement therapy and use of PH-targeted therapy has been described.[16,19] The literature has few cases of Gaucher disease type 1 patients requiring lung transplant related to PH and parenchymal lung disease, all of them female with prior splenectomy. The first case with Gaucher disease type 1 that underwent lung transplant was a 10-year-old patient with extensive interstitial lung disease, with Gaucher cells by bronchoalveolar lavage.[23] Later on, Goobie and et al[24] and de Boer et al[25] described 2 cases of female patients with Gaucher disease type 1 with severe PH and splenectomy treated with enzyme replacement therapy with imiglucerase and PH-targeted therapy with bosentan, sildenafil, and epoprostenol. The patients underwent bilateral lung transplant, and the explanted lungs showed pulmonary vascular finding consistent with pulmonary artery hypertension, without Gaucher cells. The lack of Gaucher cells was thought to be related to the use of imiglucerase in the pretransplant period. On the contrary, other authors have shown possible, albeit slight, worsening of PH with the use of enzyme replacement therapy. Goitein et al[26] described their experience of symptomatic lung involvement in 8 patients with Gaucher disease who presented with prominent pulmonary symptoms, and from that cohort 2 adults treated with enzyme replacement therapy demonstrated new or worsening PH on the basis of Doppler estimated pressure on echocardiogram. The clinical significance of this is unknown, and likely minimal, as the increases in estimated pulmonary artery systolic pressure reported was not clear and seemingly ranged from approximately 5 mm Hg to 10 mm Hg. High resolution computed tomography and chest x-ray showed abnormal lung architecture despite the use of enzyme replacement therapy. Unfortunately, the underlying mechanism was unable to be elucidated in this report.

THYROID DISEASE

Thyroid disorders are not uncommon in patients with PH and may be often associated with sudden decompensation. The prevalence of thyroid disease in patients with PH is elevated, approximately 20% to 35%.[27-29] Correlations have been described between thyroid stimulant hormone and pulmonary artery pressure ($r = -0.82$; $P < .001$) and free thyroxine and pulmonary artery pressures ($r = 0.85$; $P < .001$).[28] The physiological effects of thyroid dysfunction have been associated with poorer outcomes in patients with PH.

Retrospective studies have suggested an association between thyroid disease and the diagnosis[30] or therapies[31,32] of PH, plus several case reports describe the associations between PH and thyroid disease. There are case series to suggest an association with PH and hyperthyroidism,[33-37] hypothyroidism,[27,29] or elevated antibodies. Zuhur and colleagues[36] described higher pulmonary vascular resistance in 35% of patients with Graves disease, 36% of patients with multinodular goiters, and 13.5% of patients with hypothyroidism.

Table 4. Mechanisms of Thyroid Disease in Pulmonary Hypertension

Hyperthyroidism	Hypothyroidism
Autoimmune phenomenon associated with endothelial damage or dysfunction	Autoimmune phenomenon associated with endothelial damage or dysfunction
Increase in catecholamine sensitivity, resulting in high cardiac output and endothelial damage	Vascular reactivity caused by a decrease in the levels of thyroid hormone
Increased metabolism of intrinsic pulmonary vasodilator (ie, prostacyclin and nitric oxide)	Decreased nitric oxide
Decrease metabolism of vasoconstrictors (serotonin, endothelin-1 and thromboxane)	Decreased arterial compliance and increased vascular resistance
Stimulation of sympathetic nervous system, causing pulmonary vasoconstriction	Inflammation (high C reactive protein and elevated interleukin 6)
Alteration of gene expression (inhibits calcium ATPase channels in the sarcoplasmic reticulum, increase adrenergic receptors)	Alteration of gene expression (decrease in adrenergic receptors)

A link between autoimmune processes and PH has been established, and interestingly thyroid disease can also be precipitated by autoimmune processes.[38] This has been shown in an observational study of 63 patients with PH who showed evidence of concomitant autoimmune thyroid disease in 49% of them,[39] and the authors found that in PH there was a higher prevalence of antithyroglobulin and antithyroperoxidase antibodies. There was no chronologic relationship between the diagnosis or treatment of PH and that of autoimmune thyroid disease. Importantly, 25% of the patient had first-degree family members with autoimmune thyroid disease. Yanai-Landau et al[40] also found 40 patients with PH in which 30% had antithyroglobulin antibodies. There is no clear explanation for this association. Additionally, bone morphogenetic protein receptor 2 mutations in adults and children with PH have been found patients with thyroid disease.[41]

Besides the autoimmune process, thyroid disease may also increase catecholamine sensitivity, enhance intrinsic pulmonary vasodilators, reduce pulmonary artery compliance, decrease vasoconstrictors, and generate high cardiac output states that can precipitate PH (Table 4). Some of these proposed mechanisms are supported by the reduction of pulmonary vascular resistance after euthyroid states are achieved.[42] Thyroid hormones affect growth and maturation of vascular cells and tissues, which affect the level of plasma membrane and endoplasmic reticulum influence over the calcium ATPase and transcellular membrane flux of cations and substrates, and consequently affect smooth muscle cells.[43] Specific thyroid regimens, like methimazole, induce immunoregulation by a direct inhibitory effect of thyrocytes, proportion of T help-like and T suppressor cells, that secrete vasoactive agents.[44]

Other than anecdotal reports, there is no clear evidence regarding the use of PH-targeted therapy for patients with PH and thyroid disease. The use of antithyroid medications, radioactive iodine, surgery, or combination of these therapies has demonstrated a reduction or normalization in pulmonary artery mean pressures.[28,34] An observational study revealed that 164 patients with mean pretherapy pulmonary arterial systolic pressure of 39 mm Hg could achieve mean posttreatment pressures of 30 mm Hg after antithyroid medications, radioactive iodine, and surgery.[27] The use of PH-targeted therapy has also been described in cases of thyroid dysfunction and PH. Menon et al[45] described 6 cases with hyperthyroidism and autoimmune goiter, in which 5 received intravenous prostacyclin (epoprostenol) and 1 received oral prostacyclin receptor agonist (selexipag). These authors concluded that targeting prostacyclin pathways was a potential risk factor for the development of symptomatic thyroid disease, since the patients developed Graves disease, Hashimoto disease, and thyrotoxicosis.

One of the less common side effects of prostacyclin-based PH medical therapy is hyperthyroidism, demonstrated with epoprostenol,[31] treprostinil, and selexipag.[46] In the event-driven, phase 3 trial, Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study, the use of selexipag was associated with hyperthyroidism in 8 patients in the treatment arm (N = 574), compared to 0 of the individuals in the placebo group (N = 582).[46] Others have reported a prevalence of 6.7% of thyroid stimulating immunoglobulin negative thyrotoxicosis in adults with preexisting PH treated with epoprostenol.[47]

CONCLUSION

The data currently available indicate that glycogen storage disease and Gaucher disease are important metabolic disorders that have demonstrated an increased risk of PH and are included as a group 5 in the 6th World Symposium on PH classification. Thyroid disorders, while not included in the group 5 classification, are more prevalent, and have been associated with PH via various mechanisms. The real incidence of PH in these disorders is often unknown, although studies suggest PH can be common. The management is guided by small case reports, series. and observational studies, but overall treatment is directed toward treating the underlying disorder.

References

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913.
2. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;16(11):e1.
3. Humbert M, Labrune P, Simonneau G. Severe pulmonary arterial hypertension in type 1 glycogen storage disease. *Eur J Pediatr*. 2002;161 Suppl 1:S93-S936.
4. Kishnani P, Bengur AR, Chen YT. Pulmonary hypertension in glycogen storage disease type I. *J Inherit Metab Dis*. 1996;19(2):213-216.
5. Pizzo CJ. Type I glycogen storage disease with focal nodular hyperplasia of the liver and vasoconstrictive pulmonary hypertension. *Pediatrics*. 1980;65(2):341-343.

6. Furukawa N, Kinugasa A, Inoue F, Imashuku S, Takamatsu T, Sawada T. Type I glycogen storage disease with vasoconstrictive pulmonary hypertension. *J Inherit Metab Dis*. 1990;13(1):102-107.
7. Hamaoka K, Nakagawa M, Furukawa N, Sawada T. Pulmonary hypertension in type I glycogen storage disease. *Pediatr Cardiol*. 1990;11(1):54-56.
8. Ohura T, Inoue CN, Abukawa D, et al. Progressive pulmonary hypertension: a fatal complication of type I glycogen storage disease. *J Inherit Metab Dis*. 1995;18(3):361-362.
9. Bolz D, Stocker F, Zimmermann A. Pulmonary vascular disease in a child with atrial septal defect of the secundum type and type I glycogen storage disease. *Pediatr Cardiol*. 1996;17(4):265-267.
10. Ueno M, Murakami T, Takeda A, Kubota M. Efficacy of oral sildenafil in a beraprost-treated patient with severe pulmonary hypertension secondary to type I glycogen storage disease. *Circ J*. 2009;73(10):1965-1968.
11. Torok RD, Austin SL, Britt LK, Abdenur JE, Kishnani PS, Wechsler SB. Pulmonary arterial hypertension in glycogen storage disease type I. *J Inborn Errors Metab Screen*. 2017;5:2326409817707773.
12. Humbert M, Labrune P, Sitbon O, et al. Pulmonary arterial hypertension and type-I glycogen-storage disease: the serotonin hypothesis. *Eur Respir J*. 2002;20(1):59-65.
13. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr*. 2002;161 Suppl 1:S20-S34.
14. Li H-P, Xie W-M, Huang X, et al. Pulmonary hypertension in glycogen storage disease type II. *Chin Med J (Engl)*. 2018;131(11):1375-1376.
15. Forfia PR, Vaidya A, Wiegers SE. Pulmonary heart disease: the heart-lung interaction and its impact on patient phenotypes. *Pulm Circ*. 2013;3(1):5-19.
16. Smith RL, Hutchins GM, Sack GH Jr, Ridolfi RL. Unusual cardiac, renal and pulmonary involvement in Gaucher's disease. Intersitial glucocerebroside accumulation, pulmonary hypertension and fatal bone marrow embolization. *Am J Med*. 1978;65(2):352-360.
17. Roberts WC, Fredrickson DS. Gaucher's disease of the lung causing severe pulmonary hypertension with associated acute recurrent pericarditis. *Circulation*. 1967;35(4):783-789.
18. Amir G, Ron N. Pulmonary pathology in Gaucher's disease. *Hum Pathol*. 1999;30(6):666-670.
19. Mistry PK, Sirrs S, Chan A, et al. Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy. *Mol Genet Metab*. 2002;77(1-2):91-98.
20. Lo SM, Liu J, Chen F, et al. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. *J Inherit Metab Dis*. 2011;34(3):643-650.
21. Elstein D, Klutstein MW, Lahad A, Abrahamov A, Hadas-Halpern I, Zimran A. Echocardiographic assessment of pulmonary hypertension in Gaucher's disease. *Lancet*. 1998;351(9115):1544-1546.
22. Mistry PK, Sirrs S, Chan A, et al. Pulmonary hypertension in type 1 Gaucher's disease: genetic and epigenetic determinants of phenotype and response to therapy. *Mol Genet Metab*. 2002;77(1):91-98.
23. Rao AR, Parakininkas D, Hintermeyer M, Segura AD, Rice TB. Bilateral lung transplant in Gauchers type-1 disease. *Pediatr Transplant*. 2005;9(2):239-243.
24. Goobie GC, Sirrs SM, Yee J, et al. Lessons from lung transplantation: cause for redefining the pathophysiology of pulmonary hypertension in gaucher disease. *Respir Med Case Rep*. 2019;28:100893.
25. de Boer GM, van Dussen L, van den Toorn LM, et al. Lung transplantation in Gaucher disease: a learning lesson in trying to avoid both Scylla and Charybdis. *Chest*. 2016;149(1):e1-e5.
26. Goitein O, Elstein D, Abrahamov A, et al. Lung involvement and enzyme replacement therapy in Gaucher's disease. *QJM*. 2001;94(8):407-415.
27. Vallabhajosula S, Radhi S, Alalawi R, Raj R, Nugent K, Cevik C. Hyperthyroidism and pulmonary hypertension: an important association. *Am J Med Sci*. 2011;342(6):507-512.
28. Marvisi M, Brianti M, Marani G, Del Borello R, Bortesi ML, Guariglia A. Hyperthyroidism and pulmonary hypertension. *Respir Med*. 2002;96(4):215-220.
29. Curnock AL, Dweik RA, Higgins BH, Saadi HF, Arroliga AC. High prevalence of hypothyroidism in patients with primary pulmonary hypertension. *Am J Med Sci*. 1999;318(5):289-292.
30. Badesch DB, Wynne KM, Bonvallet S, Voelkel NF, Ridgway C, Groves BM. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med*. 1993;119(1):44-46.
31. Ferris A, Jacobs T, Widlitz A, Barst RJ, Morse JH. Pulmonary arterial hypertension and thyroid disease. *Chest*. 2001;119(6):1980-1981.
32. Hegazi MO, El Sayed A, El Ghoussein H. Pulmonary hypertension responding to hyperthyroidism treatment. *Respirology*. 2008;13(6):923-925.
33. Thurnheer R, Jenni R, Russi EW, Greminger P, Speich R. Hyperthyroidism and pulmonary hypertension. *J Intern Med*. 1997;242(2):185-188.
34. Armigliato M, Paolini R, Aggio S, et al. Hyperthyroidism as a cause of pulmonary arterial hypertension: a prospective study. *Angiology*. 2006;57(5):600-606.
35. Hwang JY, Bae SH, Lee JM, et al. A case of pulmonary arterial hypertension associated with hyperthyroidism, persistent after euthyroidism was obtained. *Korean Circ J*. 2010;40(11):593-595.
36. Zuhur SS, Baykiz D, Kara SP, Sahin E, Kuzu I, Elbuken G. Relationship among pulmonary hypertension, autoimmunity, thyroid hormones and dyspnea in patients with hyperthyroidism. *Am J Med Sci*. 2017;353(4):374-380.
37. Siu CW, Zhang XH, Yung C, Kung AW, Lau CP, Tse HF. Hemodynamic changes in hyperthyroidism-related pulmonary hypertension: a prospective echocardiographic study. *J Clin Endocrinol Metab*. 2007;92(5):1736-1742.
38. Satoh M, Aso K, Nakayama T, et al. Autoimmune thyroid disease in children and adolescents with idiopathic pulmonary arterial hypertension. *Circ J*. 2010;74(2):371-374.
39. Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest*. 2002;122(5):1668-1673.
40. Yanai-Landau H, Amital H, Bar-Dayan Y, et al. Autoimmune aspects of primary pulmonary hypertension. *Pathobiology*. 1995;63(2):71-75.
41. Roberts KE, Barst RJ, McElroy JJ, et al. Bone morphogenetic protein receptor 2 mutations in adults and children with idiopathic pulmonary arterial hypertension: association with thyroid disease. *Chest*. 2005;128(6 Suppl):618S.
42. Nakchbandi IA, Wirth JA, Inzucchi SE. Pulmonary hypertension caused by Graves' thyrotoxicosis: normal pulmonary hemodynamics restored by (131)I treatment. *Chest*. 1999;116(5):1483-1485.
43. Hasunuma K, Rodman DM, McMurtry IF. Effects of K+ channel blockers on vascular tone in the perfused rat lung. *Am Rev Respir Dis*. 1991;144(4):884-887.
44. Totterman TH, Karlsson FA, Bengtsson M, Mendel-Hartvig I. Induction of circulating activated suppressor-like T cells by methimazole therapy for Graves' disease. *N Engl J Med*. 1987;316(1):15-22.
45. Menon AA, Sahay S, Braverman LE, Farber HW. Thyroid dysfunction in patients with pulmonary artery hypertension (PAH): the effect of therapies affecting the prostanoid pathway. *Lung*. 2019;197(6):761-768.
46. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373(26):2522-2533.
47. Chadha C, Pritzker M, Mariash CN. Effect of epoprostenol on the thyroid gland: enlargement and secretion of thyroid hormone. *Endocr Pract*. 2009;15(2):116-121.

REGULAR ARTICLE

The Story of Group 5 Pulmonary Hypertension

A. Doran Bostwick, MD
Division of Pulmonary, Critical Care and Sleep Medicine
Department of Internal Medicine
The University of New Mexico, Albuquerque, NM

Lana Melendres-Groves, MD
Division of Pulmonary, Critical Care and Sleep Medicine
Department of Internal Medicine
The University of New Mexico
Albuquerque, NM

Pulmonary hypertension (PH) has historically been categorized into 5 groups based on similar pathophysiological mechanisms, hemodynamic characteristics, and therapeutic management. Group 5 has evolved over time in concert with our understanding of PH. Currently, it is comprised of diseases leading to PH with unclear and/or multifactorial mechanisms. We will review the historical context of the classification system and how group 5 has morphed into its current classification. We will briefly review the diseases encompassed in group 5 and the current understanding of the associated pathophysiological mechanism leading to PH. We provide a brief review of the diseases of group 5 PH, including the proposed mechanism for PH and potential therapies. Group 5 is comprised of a varied group of diseases, and the mechanisms leading to PH in this group are complex, multifactorial, and often incompletely understood.

INTRODUCTION

The clinical classification system for pulmonary hypertension (PH) allows for the categorization of associated diseases with similar pathophysiological mechanisms, hemodynamic characteristics, and therapeutic management. However, classification systems are limited by the completeness of our understanding and the confines of our system. Group 5 allows for these limitations by grouping the heterogenous diagnoses which lack a clear and predominant pathophysiological mechanism for the development of PH. Included in this group are (1) hematologic disorders: chronic hemolytic anemia, including sickle cell disease and β-thalassemia, and myeloproliferative disease; (2) systemic and metabolic disorders: Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis, and pulmonary Langerhans cell histiocytosis (PLCH); (3) others: chronic renal failure and fibrosing mediastinitis; and (4) complex congenital heart disease.[1] We will review the history of the PH classification system and then briefly review the components of group 5.

Table 1. The Evian Clinical Classification

1. Pulmonary arterial hypertension
2. Pulmonary venous hypertension
3. Pulmonary hypertension (PH) associated with disorders of the respiratory system or hypoxemia
4. PH caused by chronic thrombotic or embolic disease
5. PH caused by disorders directly affecting the pulmonary vasculature

HISTORY OF THE PH CLASSIFICATION SYSTEM

Pulmonary arterial sclerosis was first described in 1891. It was not until 1951, in concert with the development of right heart catheterization (RHC), that hemodynamic variation was noted and an elevation in pulmonary pressures was coined "primary PH." Soon after, the concepts of vasoreactive PH and PH due to overflow of the pulmonary circulation from congenital heart disease were described.[2] In 1973, the World Health Organization met in Geneva to discuss PH for the first time. After this meeting, PH was subsequently classified into primary PH or secondary PH depending on the presence of an attributable cause.[3]

In 1981, a National Institutes of Health-funded national registry for PH began and allowed for the recognition of groups of patients with similar hemodynamic characteristics, survival, demographics, and associated diseases.[4] The Second World Health Symposium for PH was not held until 1998, where the first clinical classification system the Evian classification was proposed. Based on data from the PH registry, categories were developed which shared similarities in pathophysiological mechanisms, clinical presentation, and therapeutic options. The Evian classification system divided PH patients into 5 familiar categories with group 5 consisting of disorders directly affecting the pulmonary vasculature (Table 1). Group 5 was then subdivided into (1) inflammatory disorders including schistosomiasis and sarcoidosis and (2) mechanical obstruction including pulmonary capillary hemangiomatosis. After the Second Symposium, multiple case series were published indicating new risk factors for PH. For instance, splenectomy was found to be associated with PH as well as certain hemoglobinopathies and metabolic disorders. The Third World Symposium on PH in 2003

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Correspondence: ABostwick@salud.unm.edu
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Table 2. Current Group 5 Classification Scheme

Group 5 pulmonary hypertension (PH) with unclear and/or multifactorial mechanisms	
5.1 Hematological disorders	Chronic hemolytic anemia
	Myeloproliferative disorders
5.2 Systemic and metabolic disorders	Pulmonary Langerhans cell histiocytosis
	Gaucher disease
	Glycogen storage disease
	Neurofibromatosis
	Sarcoidosis
5.3 Others	Chronic renal failure
	Fibrosing mediastinitis
5.4 Complex congenital heart disease	Segmental PH
	Single ventricle physiology
	Scimitar syndrome

evaluated and revised the proposed Evian classification scheme incorporating newly associated diagnoses. One of the most notable revisions reclassified pulmonary capillary hemangiomatosis into group 1 with pulmonary veno-occlusive disease due to similar histological changes and clinical risk factors as group 1 PAH, despite primarily affecting the capillary and venous system. Group 5 was subsequently termed, "miscellaneous," and included sarcoidosis, histiocytosis X, lymphangiomatosis, and compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis).[5] Over the years, the diseases which occurred concurrently with PH continued to expand. At the Fourth World Symposium, the Dana Point classification scheme allowed for further delineation of group 5. Often due to the rarity of these diseases causing PH, this group provided more of a diagnostic differential when more common causes of PH had been ruled out. Group 5 became subdivided into hematologic disorders, systemic disorders, metabolic disorders, mechanical obstruction, and chronic renal failure.[6] The most recent updates to the clinical classification scheme occurred in 2018 at the Sixth World Symposium (Table 2).[1] Complex congenital heart disease such as segmental disorders, single ventricle physiology, and scimitar syndrome were added to group 5, as these anomalies are increasingly difficult to define and classify.[7]

Over the last 20 years, group 5 has undergone notable changes. From initially being a group of diseases directly affecting the pulmonary vasculature, it has morphed into the current category where the difficulty in classifying the mechanism of disease is the unifying element. Many of the diseases in group 5 are rare, or PH is an uncommon manifestation of the disease. This in part contributes to group 5 being a less studied, often overlooked, and underrecognized group. By its very nature, diseases in group 5 may need to be reclassified. The evolution of group 5 mirrors our progressive understanding of PH and its associated diseases.[1]

BRIEF REVIEW OF GROUP 5: PH WITH UNCLEAR AND/OR MULTIFACTORIAL MECHANISMS

In general, PH is due to increased pulmonary vascular resistance to flow, increased cardiac output, and/or increased postcapillary pressure. Group 5 encompasses disorders that cause PH through all of these pathways or those in which understanding for the pathway is incomplete.[1,8]

5.1 Hematologic Disorders

Chronic Hemolytic Anemia: The association of PH with chronic hemolytic anemia is both incompletely understood and multifactorial. Sickle cell disease is complicated by PH in approximately 10% of patients through multiple mechanisms and is associated with increased mortality. Interestingly, echocardiogram has been found to significantly overestimate the prevalence of PH in this cohort, and RHC is paramount in diagnosing these patients. The hemodynamic profile is also unique and characterized by increased cardiac output and relatively low pulmonary vascular resistance. Among patients found to have PH by RHC, both precapillary and postcapillary PH are present. Proposed mechanisms include an increase in cardiac output in the setting of anemia, increased resistance due to thromboembolic disease, altered blood viscosity, nitric oxide and arginine depletion due to free plasma hemoglobin scavenging and the effects on endothelial production of nitric oxide, chronic inflammation, injury from acute chest syndrome, and lastly, an increase in postcapillary pressure due to restrictive cardiomyopathy.[1,9]

There is limited data on the association of α-thalassemia and PH. Severe forms of α-thalassemia, specifically when there are 3 alleles affected, are associated with PH. β-thalassemia intermedia and major are also associated with PH. In patients with β-thalassemia intermedia, 1 gene is affected, and transfusions are often not required. PH in these patients is thought to be due to chronic low-grade hemolysis and the subsequent depletion of nitric oxide and arginine. In patients with β-thalassemia major, there are 2 defective genes, leading to more severe anemia, and these patients are often transfusion dependent. Iron overload, from chronic transfusions, plays a role in PH in β-thalassemia major by causing oxidative stress and endothelial dysfunction. Additionally, iron accumulation in cardiac tissues can lead to both right and left cardiac dysfunction. Iron overload in the lung can additionally lead to excess hemosiderin deposits resulting in fibrosis and arterial stiffening. Splenectomy increases the risk of PH in both forms of β-thalassemia.[10–12]

Other less common hemolytic processes linked to PH include hereditary spherocytosis, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria.[12]

Myeloproliferative Disorders: Chronic myeloproliferative disorder (CMPD) describes a group of diseases where a multipotent hematopoietic progenitor cell overproduces a type of blood cell without significant dysplasia.

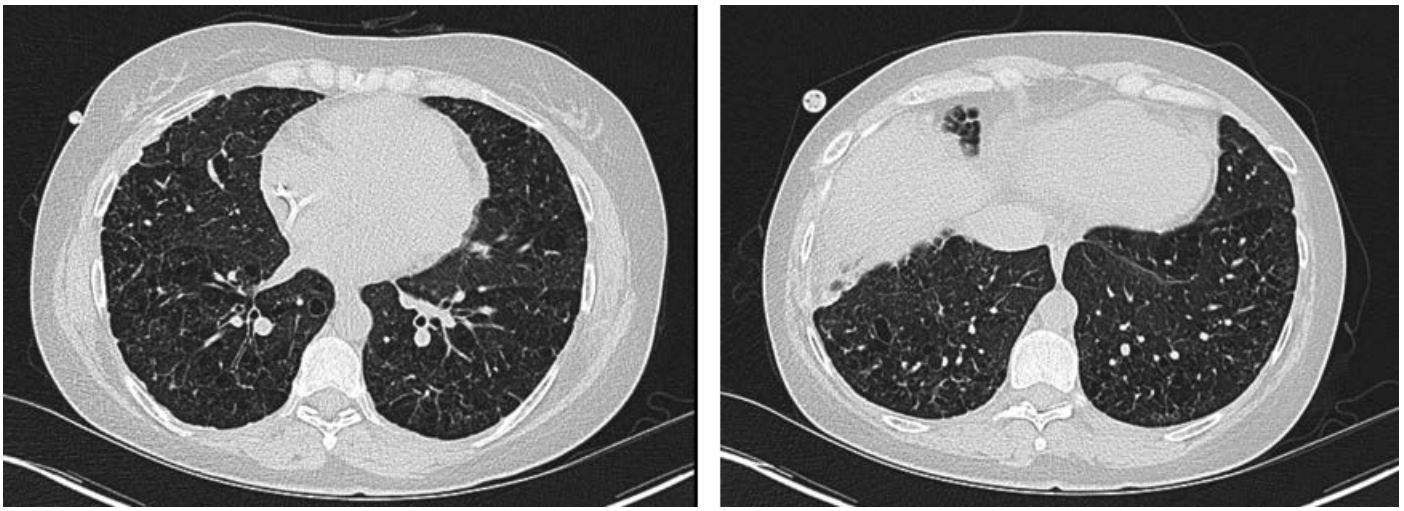

Figure 1: 33-year-old female with pulmonary Langerhans cell histiocytosis by biopsy complicated by severe pulmonary hypertension. Computed tomography images with thin-walled, irregular cysts, architectural distortion of the lungs, and small nodules. Initiated on sildenafil, macitentan, and intravenous trepositinil with improvement in pro B-type natriuretic peptide and 6-minute walk. Referred for lung transplant evaluation.

The prevalence of PH in patients with CMPD is unknown.[8,13]

CMPD is associated with both precapillary and postcapillary pathology. Precapillary causes of PH in CMPD include portal hypertension secondary to myeloid metaplasia as a complication of myelofibrosis and dasatinib, a tyrosine kinase inhibitor and frequently used treatment for chronic myeloid leukemia. Tumor microembolism can occur in CMPD related to translocation of megakaryocytes. Megakaryocytes and myeloid progenitor cells are larger than the alveolar capillary diameter and can occlude these vessels leading to obstruction and secondary microthrombosis.[13,14] It has been proposed that cytoreductive therapy may have a role in treatment of precapillary PH in patients with CMPD. Additionally, there appears to be a relationship between elevated pulmonary artery pressures and elevated platelet counts in myeloid metaplasia and essential thrombocytosis. Elevated platelet-derived growth factor released from activated platelets stimulates smooth muscle hyperplasia and is one suggested causal mechanism. Additionally, elevated hemoglobin in polycythemia vera has been associated with PH though not fully established. Last, pulmonary veno-occlusive disease can occur and can be secondary to CMPD or secondary to treatment of the CMPD with cytotoxic chemotherapy and hematopoietic stem cell transplant.[13]

In addition to pulmonary arterial pathology in patients with CPMD, patients also demonstrate findings consistent with chronic thromboembolic PH (CTEPH). CTEPH is most often linked to polycythemia vera and essential thrombocytosis. Both diseases can lead to a thrombophilic state. In polycythemia vera, the elevated hemoglobin levels lead to hyperviscosity and disturbances in blood flow increasing platelet activation. Blood cell aggregates in both polycythemia vera and essential thrombocytosis can induce platelet activation and thrombosis in small vessels. Additionally, spontaneous erythropoietin-independent erythroid colony formation as seen in polycythemia vera, particularly in the hepatic veins, increases thrombotic risk. Unlike the association with elevated platelet counts and PH in precapillary disease from essential thrombocytosis, the degree of thrombocytosis has not been found to be associated with risk for thrombosis in CTEPH.[13]

5.2. Systemic and Metabolic Disorders

PLCH: PLCH is a rare smoking-related interstitial lung disease predominantly affecting young adults (Figure 1). PH is a known complication of PLCH and tends to occur in more severe disease. The mechanism is incompletely understood and appears multifactorial. Based on histologic evidence both pulmonary arterial remodeling and postcapillary involvement are noted. A decline in the diffusing capacity of the lungs for carbon monoxide can be indicative of the development of PH in these patients. Vasodilator therapies may improve World Health Organization functional class in this population. However, due to the histologic evidence of venule involvement in those with PH associated with PLCH, there is a potential risk for pulmonary edema related to vasodilator therapy, and their use should be approached with caution. Ultimately, patients may benefit from lung transplantation.[15,16]

Gaucher Disease: Gaucher disease is an inherited lysosomal storage disease caused by a defect in the gene encoding β-glucocerebrosidase. Lack of functional β-glucocerebrosidase leads to an accumulation of lipid in reticuloendothelial cells. These lipid-laden cells are predominantly macrophages and accumulate in the liver, spleen, bone marrow, brain, and lungs. Additionally, these lipid-laden cells activate macrophages leading to the release of cytokines and lysosomal proteins. Three major forms of Gaucher disease have been described. Type 1 is associated with PH.[17] The exact mechanism is unclear, though splenectomy, female sex, family history of Gaucher disease complicated by PH, and lack of treatment with enzyme replacement therapy are risk factors. Fortunately, enzyme replacement therapy has effectively reduced the need for splenectomy in

these patients with an expectant decline in associated PH. One case series reported favorable outcomes in patients with Gaucher disease complicated by PH who were treated with enzyme replacement and occasionally pulmonary vasodilators.[18]

Glycogen Storage Disease: Glycogen storage disorders are characterized by abnormal glycogen deposit due to deficiencies in enzymes responsible for the storage or breakdown of glycogen. This leads to hypoglycemia, hyperlipidemia, hepatomegaly, myopathy, and growth retardation. The type of glycogen storage disorder is associated with the particular enzyme deficiency.[8] While PH has been reported in multiple types of glycogen storage disorders, it is most commonly associated with type 1a.8.[19,20] A clear causal mechanism has not been established. Pathology indicates plexiform lesions, intimal fibrosis, and medial hypertrophy consistent with precapillary PH. An increase in serotonin levels in these patients has also been described and thought to play some role in the causal pathway.[19,20]

Neurofibromatosis: Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder leading to the loss of neurofibromin. Neurofibromin has a known role in tumor suppression, and without it, there is constitutive activation and deregulation of pathways involved in cell proliferation and differentiation. The classic skin findings include café au lait spots, axillary and inguinal freckling, and dermal neurofibromas. These patients are predisposed to tumors, malignancy, learning disabilities, epilepsy, and less commonly, interstitial lung disease. Cardiac abnormalities include atrial septal defects, ventricular septal defect, mitral and aortic insufficiency, hypertrophic cardiomyopathy, and intracardiac tumors. Vascular lesions are severe though less common and cause renovascular hypertension, myocardial infarction, cerebral infarction, and ischemic bowel disease. PH is a rare but severe complication of NF1.[21]

Diagnosis of PH typically occurs late in the course of NF1 (50–65 years old) despite full penetrance by age 5 and in contrast to other heritable forms of pulmonary arterial hypertension (PAH). Like many forms of PAH, it has a female predominance. Unfortunately, based on case reports, it appears PAH-specific treatments have limited benefit in the population. In part, this may be related to the limited information on this disease process, as well as multiple causal pathways for PH in this population beyond pulmonary arterial remodeling including lung parenchymal disease, skeletal deformities leading to restrictive lung disease, left heart disease, as well as reports of pulmonary capillary hemangiomatosis and pulmonary veno-occlusive disease. Because of this and the high associated mortality after diagnosis, early referral for lung transplant assessment is recommended. The decision to pursue transplant must be coupled with the understanding that immunosuppressive therapy required posttransplant will increase the risk of cancer for these patients.[21]

Sarcoidosis: Sarcoidosis is a multisystem granulomatous disease which is thought to develop due to the interplay of extrinsic antigen exposure, human leukocyte antigen (HLA) class 2 molecules, and T-cell receptors. Genetic susceptibility may relate to carriage of particular HLA genes. Because there are no specific findings unique to sarcoidosis, it is a diagnosis of exclusion. Lung involvement is present in more than 90% of diagnosed patients, though presentations are variable and include restrictive disease, airflow obstruction, thoracic adenopathy, and parenchymal disease.[22] Consistent with the variable presentation of sarcoidosis, PH in patients with sarcoid can be a consequence of a variety of factors including parenchymal lung disease, extrinsic compression of pulmonary vessels from adenopathy, direct myocardial involvement, granulomatous arteriopathy, pulmonary veno-occlusive disease, and portopulmonary hypertension. Because of this, sarcoidosis is classified as group 5 despite characteristics consistent with group 3.[1] The diagnosis of sarcoid-associated PH increases morbidity and mortality. The utility of vasodilator therapy is unclear and, because of the multifactorial nature of disease, likely varies based on the patient's particular phenotype.[8,23]

5.3 Others

Chronic Renal Failure: Patients with chronic kidney disease (CKD) and with end-stage kidney disease maintained on long-term hemodialysis have an increased propensity to develop PH. Additionally, in this population, PH is an independent predictor of mortality. The underlying mechanisms to develop PH are multiple, though postcapillary PH is the predominant phenotype. Patients can have increased postcapillary pressure in the setting of left heart disease and volume overload.[24,25] Large arteriovenous fistulas, particularly with shunt flow greater than 2 L/min, can also lead to elevated pulmonary pressures in the setting of high cardiac output and excess pulmonary arterial flow.[25] Concomitant renal anemia can contribute to high output states. Lastly, precapillary PH may be present in dialysis patients, particularly with chronic uremia, due to impaired endothelial function, decreased bioavailability of nitric oxide, and increased levels of endothelin.[8,24] One prospective trial found that precapillary PH was only found in patients undergoing dialysis, as opposed to those with CKD not requiring renal replacement therapy. They also found an elevated transpulmonary gradient (>12–15 mmHg) signified a precapillary component regardless of volume status.[24]

Management of patients with PH in the setting of CKD with or without dialysis largely depends on the driving mechanism. Optimizing volume status with dialysis or diuretics, adequate iron and erythropoietin supplementation, maintaining acceptable calcium-phosphate levels, as well as shunt revisions in patients with high flows through their arteriovenous fistulas are all potentially useful interventions in this population to decrease pulmonary pressures.[8,24,25]

Fibrosing Mediastinitis: Fibrosing mediastinitis is a rare disease resulting from progressive fibrosis leading to compression of mediastinal structures. In North America, fibrosing mediastinitis is most associated with pulmonary histoplasmosis but can complicate several granulomatous diseases including sarcoidosis and tuberculosis. It has also been reported with several fungal infections including aspergillosis, blasto-

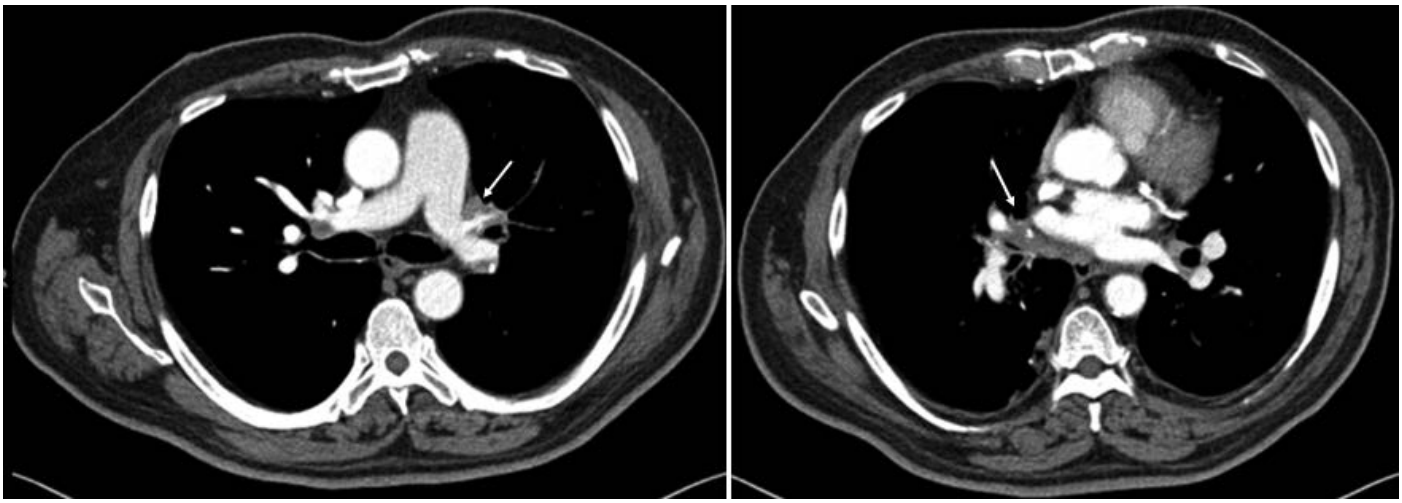

Figure 2: 78-year-old male with fibrosing mediastinitis complicated by pulmonary hypertension. Computed tomography images demonstrating infiltrative soft tissue with calcium deposits and consequent multifocal narrowing of the pulmonary arteries, veins, and bronchi.

mycosis, mucormycosis, cryptococcosis, coccidioidomycosis, and infection with *Wuchereria bancrofti*. Lastly, autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus, Behçet disease, mediastinal radiation, and silicosis, and specific drugs have been implicated in the development of fibrosing mediastinitis.[26–29] Fibrotic compression of the pulmonary artery and veins can lead to PH (Figure 2). Most patients demonstrate precapillary PH, though occasionally postcapillary PH is described likely due to significant occlusion of pulmonary veins. Depending on the area of involvement, pulmonary artery stenting is a potential treatment, though duration of benefit may be limited by stent stenosis.[28] Targeted PAH therapies have been attempted, but data are limited to case reports, and in some cases, vasodilators can lead to worsening oxygenation if lung parenchymal involvement or pulmonary venous involvement is extensive.[29] In patients with fibrosing mediastinitis due to histoplasmosis, biopsy demonstrated accumulation of CD20-positive B lymphocytes.[30] Subsequently, 1 case series used rituximab in 3 patients with fibrosing mediastinitis due to histoplasmosis with reduction in lesion size and metabolic activity.[31]

5.4 Complex Congenital Heart Disease

The last category in group 5 is complex congenital heart disease. This group is divided into patients with segmental PH, single ventricle physiology, and scimitar syndrome. Segmental PH includes those with differential blood flow through the pulmonary circulation due to an isolated pulmonary artery of ductal origin, an absent pulmonary artery, pulmonary atresia, or hemitruncus. Single ventricle patients are included regardless of operable status. These patients are unique given variable blood flow depending on their age, completion of Blalock-Taussig Shunt, Glenn procedure, or Fontan procedure. Additionally, the chronic nonpulsatile pulmonary circulation induces a form of PH that is dissimilar to other diseases associated with PH and may develop despite a relatively low mean pulmonary artery pressure.[7] Scimitar syndrome is a rare congenital cardiovascular defect with partial anomalous pulmonary venous connection. Typically, this occurs on the right, and these pulmonary veins drain into the inferior vena cava. The right lung is frequently hypoplastic and receives its blood supply from systemic arteries.[32] At this point, there is insufficient data showing that targeted therapies are safe and efficient in this population.[7]

CONCLUSIONS

Group 5 is an evolving, complex, and varied group of disorders causing PH. In general, this group is less well understood and varies from rare diseases to relatively common diseases such as CKD. Ongoing investigation into the mechanism of disease for group 5 will further unlock the intricacies of PH. Because of the multifactorial mechanisms that cause PH in this group, treatment modalities for these patients are varied and at times lacking. However, in all underlying diseases, PH often worsens morbidity and mortality and is important to evaluate and optimize. In general, pulmonary vasodilators are of limited utility in this group and should be used cautiously by providers with experience in both the mechanism of disease and pulmonary vasodilators.

References

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018
2. Newman JH. Pulmonary hypertension. *Am J Respir Crit Care Med*. 2005;172(9):1072–1077. doi:10.1164/rccm. 200505-684OE
3. Hatano S, Strasser T. *Primary Pulmonary Hypertension: Report on a WHO Meeting, Geneva, 15–17 October 1973*. Geneva: World Health Organization; 1975.
4. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med*. 1987;107(2):216–223. doi:10.7326/0003-4819-107-2-216
5. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2004;43(12 Suppl S):5S–12S. doi:10.1016/j.jacc. 2004.02.037
6. Nakanishi N. 2009 ESC/ERS pulmonary hypertension guidelines and connective tissue disease. *Allergol Int*. 2011;60(4):419–424. doi:10.2332/allergolint.11-RAI-0362

7. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J*. 2019;53(1):1801916. doi:10.1183/13993003.01916-2018
8. Lahm T, Chakinala MM. World Health Organization group 5 pulmonary hypertension. *Clin Chest Med*. 2013;34(4):753–778. doi:10.1016/j.ccm.2013.08.005
9. Fonseca G, Souza R. Pulmonary hypertension in sickle cell disease. *Curr Opin Pulm Med*. 2015;21(5):432–437. doi:10.1097/MCP.0000000000000200
10. Farmakis D, Aessopos A. Pulmonary hypertension associated with hemoglobinopathies: prevalent but overlooked. *Circulation*. 2011;123(11):1227–1232. doi:10.1161/CIRCULATIONAHA.110.988089
11. Haw A, Palevsky HI. Pulmonary hypertension in chronic hemolytic anemias: pathophysiology and treatment. *Respir Med*. 2018;137:191–200. doi:10.1016/j.rmed.2018.02.020
12. Fraidenburg DR, Machado RF. Pulmonary hypertension associated with thalassemia syndromes. *Ann N Y Acad Sci*. 2016;1368(1):127–139. doi:10.1111/nyas.13037
13. Adir Y, Elia D, Harari S. Pulmonary hypertension in patients with chronic myeloproliferative disorders. *Eur Respir Rev*. 2015;24(137):400–410. doi:10.1183/16000617.0041-2015.
14. Willems E, Canivet JL, Ghaye B, et al. Pulmonary veno-occlusive disease in myeloproliferative disorder. *Eur Respir J*. 2009;33(1):213–216. doi:10.1183/09031936.00157707
15. Le Pavec J, Lorillon G, Jaïs X, et al. Pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. *Chest*. 2012;142(5):1150–1157. doi:10.1378/chest.11-2490
16. Lorillon G, Tazi A. How I manage pulmonary Langerhans cell histiocytosis. *Eur Respir Rev*. 2017;26(145):170070. doi:10.1183/16000617.0070-2017
17. Linari S, Castaman G. Clinical manifestations and management of Gaucher disease. *Clin Cases Miner Bone Metab*. 2015;12(2):157–164. doi:10.11138/ccmbm/2015.12.2.157
18. Lo SM, Liu J, Chen F, et al. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. *J Inherit Metab Dis*. 2011;34(3):643–650. doi:10.1007/s10545-011-9313-9
19. Humbert M, Labrune P, Sitbon O, et al. Pulmonary arterial hypertension and type-I glycogen-storage disease: the serotonin hypothesis. *Eur Respir J*. 2002;20(1):59–65. doi:10.1183/09031936.02.00258702
20. Humbert M, Labrune P, Simonneau G. Severe pulmonary arterial hypertension in type 1 glycogen storage disease. *Eur J Pediatr*. 2002;161(Suppl 1):S93–S96. doi:10.1007/s00431-002-1012-y
21. Jutant EM, Girerd B, Jaïs X, et al. Pulmonary hypertension associated with neurofibromatosis type 1. *Eur Respir Rev*. 2018;27(149):180053. doi:10.1183/16000617.0053-2018
22. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Am J Respir Crit Care Med*. 2011;183(5):573–581. doi:10.1164/rccm.201006-0865CI
23. Parikh KS, Dahhan T, Nicholl L, et al. Clinical features and outcomes of patients with sarcoidosis-associated pulmonary hypertension. *Sci Rep*. 2019;9(1):4061. doi:10.1038/s41598-019-40030-w
24. O'Leary JM, Assad TR, Xu M, et al. Pulmonary hypertension in patients with chronic kidney disease: invasive hemodynamic etiology and outcomes. *Pulm Circ*. 2017;7(3):674–683. doi:10.1177/204589321771610
25. Basile C, Lomonte C. The complex relationship among arteriovenous access, heart, and circulation. *Semin Dial*. 2018;31(1):15–20. doi:10.1111/sdi.12652
26. Wu Z, Jarvis H, Howard LS, Wright C, Kon OM. Post-tuberculous fibrosing mediastinitis: a review of the literature. *BMJ Open Respir Res*. 2017;4(1):e000174. doi:10.1136/bmjresp-2016-000174
27. Debella YT, Mira-Avendano I, Rojas C, Khoor A, Kwon M. Silicosis-associated fibrosing mediastinitis a rare cause of pulmonary hypertension. *Am J Respir Crit Care Med*. 2018;197:A7017.
28. Argueta F, Villafuerte D, Castaneda-Nerio J, Peters J, Restrepo C. Successful management of fibrosing mediastinitis with severe vascular compromise: report of two cases and literature review. *Respir Med Case Rep*. 2019;29:100987. doi:10.1016/j.rmcr.2019.100987
29. Seferian A, Steriade A, Jaïs X, et al. Pulmonary hypertension complicating fibrosing mediastinitis [published correction appears in *Medicine (Baltimore)*. 2016;95(1):e64cd]. *Medicine (Baltimore)*. 2015;94(44):e1800. doi:10.1097/MD.0000000000001800
30. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore)*. 2011;90(6):412–423. doi:10.1097/MD.0b013e318237c8e6
31. Westerly BD, Johnson GB, Maldonado F, Utz JP, Specks U, Peikert T. Targeting B lymphocytes in progressive fibrosing mediastinitis. *Am J Respir Crit Care Med*. 2014;190(9):1069–1071. doi:10.1164/rccm.201407-1258LE
32. Vida VL, Padalino MA, Boccuzzo G, et al. Scimitar syndrome: a European Congenital Heart Surgeons Association (ECHSA) multicentric study. *Circulation*. 2010;122(12):1159–1166. doi:10.1161/CIRCULATIONAHA.109.926204

REGULAR ARTICLE

The Myriad Presentations of Sickle Cell Disease-Related Pulmonary Hypertension

Clare C. Prohaska, MD
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, IN

Roberto F. Machado, MD
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, IN

Background: Sickle cell disease (SCD) is characterized by repeated episodes of hemolysis and vaso-occlusion. Hemolysis is a risk factor for the development of pulmonary hypertension (PH), and currently SCD-related PH is classified as World Health Organization group 5 PH. Patients with SCD-related PH have unique hemodynamics, comorbidities, and phenotypes that may contribute to the development of PH.

Implications for Clinicians: SCD-related PH is defined as a mean pulmonary artery pressure >20 mm Hg, a pulmonary artery occlusion pressure ≤15 mm Hg and relatively low pulmonary vascular resistance (PVR) (>160 dynes·sec/cm^5 rather than the typical definition of ≥240 dynes·sec/cm^5), an important distinction because of a baseline high-cardiac output state in the setting of chronic anemia and low vascular resistance. Diastolic dysfunction is common, and right heart catheterization is warranted to determine if combined precapillary and postcapillary PH is present. Thromboembolism is common among patients with SCD, and screening for chronic thromboembolic pulmonary hypertension is essential. There are few studies evaluating advanced therapies in this population. The mainstay of treatment includes targeting correction of their primary hemoglobinopathy as well as aggressive management of underlying comorbid conditions.

Conclusions: SCD-related PH is common among patients with SCD and is associated with increased mortality. A high index of suspicion is warranted during evaluation to identify all potential factors that may be contributing to disease.

INTRODUCTION

Sickle cell disease (SCD), one of the most common genetic diseases in the world, is caused by a E6V missense mutation in the β globin gene leading to the formation of sickle hemoglobin (HbS), a variant of normal adult hemoglobin (HbA).[1,2] In hypoxic conditions, HbS abnormally polymerizes, leading to sickling of erythrocytes; the extent of sickling is the primary determinant of the severity of SCD.[3] SCD is characterized by 2 main pathologic events: hemolysis and recurrent vaso-occlusive crises. Over time, repeated episodes contribute to decreased quality of life, multiorgan system failure, and premature death. The acute chest syndrome and pulmonary hypertension (PH) are the most common causes of death in this population.[4-7]

PH is currently defined as a mean pulmonary artery pressure (mPAP) measured by right heart catheterization (RHC) as >20 mm Hg.[8] Individuals with SCD may develop PH with primary vascular involvement (World Health Organization [WHO] group 1, or pulmonary arterial hypertension [PAH]), secondary to left heart disease (group 2 PH), secondary to interstitial lung disease or pulmonary fibrosis (group 3 PH), or because of chronic thromboembolic PH (CTEPH, or group 4 PH). Because of these myriad presentations, PH related to SCD is currently listed in group 5 in the clinical classification of PH.

Key Words—sickle cell disease, pulmonary hypertension, hemolysis, high-output cardiac state
Correspondence: robmacha@iu.edu
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Epidemiology and Prevalence of SCD

Between 300 000 and 400 000 individuals are born annually with SCD worldwide,[9] and around 100 000 individuals in the United States live with the disease.[10] Individuals with one copy of HbS are protected against severe forms of *Plasmodium falciparum* malaria; therefore, the βs allele is found more frequently in sub-Saharan Africa, parts of the Mediterranean, the Middle East, and India.[9,11,12] Approximately 1 in 360 African American newborns has SCD.[13] Despite nearly 100 years of research, the natural history of SCD remains poorly described. Mortality rates have improved over the past 60 years, but the median age at death remains unacceptably low: between 42 to 53 years for men and 48 to 58.5 years for women.[5,14,15]

PATHOPHYSIOLOGY

Hemoglobin is a tetrameric protein comprised of various combinations of

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globin subunits. HbA, the most abundant hemoglobin, is comprised of two α and two β globin subunits; with a single point mutation in subunit β, HbS is produced. Individuals heterozygous for sickle hemoglobin are considered to have sickle cell trait rather than SCD. Individuals homozygous for sickle hemoglobin have sickle cell anemia.[16] Other forms of SCD include heterozygous combinations of HbS with hemoglobin C, HbS with β-thalassemia or HbS with other beta-globin variants; therefore, SCD is an umbrella term used to describe any form of disease in which there is enough HbS to cause significant intracellular sickling.[17]

Under hypoxic conditions, cells containing homozygous sickle hemoglobin polymerize, changing the shape and physical properties of the erythrocyte, leading to hemolysis and repeated episodes of vaso-occlusion. Compared to HbA, HbS has reduced oxygen affinity; this exacerbates polymerization of HbS. Through interactions with deoxygenated beta-globin subunits, hemoglobin oxygen affinity is further reduced.[18] Low HbS oxygen affinity kinetically favors an increase in the fraction of deoxygenated HbS, a form that readily polymerizes, which further promotes HbS polymerization and sickling of erythrocytes. HbS polymerization correlates exponentially with the concentration of HbS within the erythrocyte. Repeated episodes of HbS polymerization and sickling in low pO2 conditions and unsickling in high pO2 conditions may lead to severe alterations in erythrocyte membrane structure and function, which eventually result in an irreversibly sickled cell.[19-22]

Hemolysis releases plasma-free hemoglobin that inactivates nitric oxide (NO), an intrinsic vasodilator, as well as arginase-1, which depletes L-arginine, the substrate for NO synthesis.[23-25] As a result, there is decreased NO bioavailability and *resistance* to NO-dependent vasodilation.[25] There is also accumulation of redox-active heme and iron from lysed red blood cells, which contributes to the generation of reactive oxygen species that can exacerbate thrombosis and vascular proliferation.[26]

There is a correlation between the rate of hemolysis and levels of procoagulant factors in blood in patients with SCD.[27-29] Hemolysis and decreased NO bioavailability induce platelet and tissue factor activation and thrombin generation, which induce a procoagulant state.[30,31] Patients with SCD are at high risk for pulmonary embolism,[32] and microthrombotic and/or thromboembolic lesions are common findings as postmortem examination in patients with SCD.[33,34]

Splenectomy in SCD

Many individuals with SCD have functional asplenia. In fact, splenectomy has been identified as an independent risk factor for the development of PH, particularly in patients with underlying hemolytic disorders.[35-38] Loss of splenic function may also trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[39] Furthermore, after splenectomy, the rate of intravascular hemolysis increases.[29]

The Effect of Anemia on Cardiac Output

Hemolysis and anemia appear to have a synergistic effect on the heart and systemic and pulmonary vasculature. Anemia leads to decreased blood oxygen content, which causes a high cardiac output state; this is necessary to maintain oxygen delivery and is characterized by increased stroke volume, primarily from decreased blood viscosity. In this high-output state, patients with SCD are more sensitive to changes in hemoglobin concentration and less able to compensate to stressors from a cardiac output standpoint. Elevated cardiac output leads to the development of ventricular dilation, hypertrophy, and wall stress.[40-44] If anemia is corrected via transfusion, cardiac output returns to normal and systemic vascular resistance increases.[42]

In individuals with severe anemia, particularly those with underlying cardiopulmonary disease, anemic hypoxia can occur because of the decreased ability of blood to transport oxygen and participate in gas exchange. There is a strong correlation between the severity of hemolytic anemia and decreasing arterial hemoglobin saturation, likely because of increased cardiac output and altered perfusion of the pulmonary vasculature, which may lead to impaired ventilation-perfusion matching.[45,46]

Two Primary Phenotypes of SCD

There appears to be 2 distinct SCD clinical phenotypes: a vaso-occlusive phenotype and a hemolytic phenotype.[47] Although these distinctions occur on a spectrum and vary at the individual patient level, they are helpful to approach individuals with SCD from a clinical perspective. The vaso-occlusive phenotype is characterized by persistent leukocytosis, higher hemoglobin levels and bony pain, in which case recurrent episodes of acute chest syndrome tend to occur. The hemolytic phenotype is characterized by chronic kidney disease, cutaneous leg ulcers, priapism, and strokes, as well as vascular dysfunction, in which case PH tends to develop more frequently.[48]

Hemodynamic Profiles of PH in SCD

During the Sixth World Symposium in Pulmonary Hypertension the definition of precapillary PH was changed to a mPAP > 20 mm Hg and PVR ≥ 240 dynes·sec/cm^5.[8,49,50] Because of chronic anemia, patients with SCD have baseline increases in cardiac output and low vascular resistances. At baseline, PVR in patients with SCD ranges from 68 to 74 dynes·sec/cm^5, as compared to nonanemic healthy volunteers of 80 to 120 dynes·sec/cm^5. As a result, a PVR > 160 dynes·sec/cm^5 has been proposed as abnormal in patients with SCD.[51]

Studies using the former definition of PH (mPAP ≥ 25 mm Hg) suggest that the prevalence of PH in SCD is 6% to 11%.[52-55] (Table 1) Given the large body of literature published prior to this updated definition of disease, a significant number of individuals with SCD could be classified as having SCD-related PH. Approximately half of patients have precapillary PH (defined as mPAP ≥ 25 mm Hg and pulmonary artery occlusion pressure [PAOP] ≤ 15 mm Hg), and half have postcapillary PH (defined as mPAP ≥ 25 mm Hg and PAOP > 15 mm Hg).[52-56] Another clinical and hemodynamic phenotype that is common in SCD is one in which group 2 PH is present but the pulmonary vasculature

Table 1. Hemodynamic profiles in SCD patients with and without pulmonary hypertension[a]

Country of study	Parent et al		Fonseca et al		Mehari et al	
Number screened	385		80		531	
Underwent RHC	96		26		84	
PH status, n (%)	PH = 24 (6%)	No PH = 72	PH = 8 (10%)	No PH = 18	PH = 55 (10.4%)	No PH = 29
mPAP, mm Hg	30 ± 6	19 ± 3	33 ± 9	19 ± 3	36 ± 9	19 ± 4
PAOP, mm Hg	16 ± 7	11 ± 3	16 ± 6	13 ± 2	16 ± 5	11 ± 3
CO, L/min	9 ± 2	8 ± 2	5 ± 2[b]	5 ± 1[b]	8 ± 3	9 ± 2
PVR, dyn·s/cm^5	138 ± 58	72 ± 26	179 ± 120	64 ± 48	227 ± 149	72 ± 37
Precapillary PH, n (%)	11 (2.7%)	-	3 (3.75%)	-	31 (6%)	-
Postcapillary PH, n (%)	13 (3.3%)	-	5 (6.25%)	-	24 (4.5%)	-
Mortality (%)	12.5	1.4	38	5.5	36	13

Abbreviations: SCD, sickle cell disease; RHC, right heart catheterization; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance.

[a]Adapted from Parent et al[53], Fonseca et al[54], and Mehari et al.[55]
[b]Cardiac index (L/min/m^2).Table 2. Univariate and multivariate analysis of mortality risk factors in SCD.[a]

has been remodeled and the transpulmonary gradient (mPAP-PAOP) and PVR rise.[57,58] Therefore, although the mPAP is >20 mm Hg and PAOP is >15 mm Hg, the PVR is ≥240 dynes·sec/cm^5; this is now termed combined precapillary and postcapillary PH.[8]

PH in SCD may occur secondary to isolated pathologic remodeling of the pulmonary arterioles, beginning with vasoconstriction, hyperplasia of intima and smooth muscle and progressing to severe angioproliferation, occlusion, and recanalization, termed the plexiform lesion.[59] When disease is restricted to the pulmonary arterioles, mean pulmonary pressures increase but left ventricular end-diastolic pressures (measured on RHC by PAOP) are normal (≤15 mm Hg). According to autopsy studies, pulmonary vascular lesions characteristic of precapillary PH have been found in one-third to two-thirds of patients with SCD.[33,34]

Group 2 PH, defined by mPAP > 20 mm Hg and PAOP > 15 mm Hg, with a normal PVR, arises from left heart disease. In chronic anemia, the left ventricle compensates with an increase in stroke volume and chamber dilatation, leading to increased wall stress and an increase in left ventricular mass. This hypertrophy leads to impaired filling, which is characteristic of diastolic dysfunction, also known as heart failure with preserved ejection fraction.[41,43] Heart failure with reduced ejection fraction is much less common in patients with SCD, but is still an important cause of group 2 PH. Many patients with PH due to diastolic dysfunction also have an increased transpulmonary gradient consistent with combined precapillary and postcapillary PH. Importantly, diastolic dysfunction is associated with decreased exercise capacity and independently associated with increased mortality in individuals with SCD, despite adjusting for tricuspid regurgitant velocity (TRV).[40,41]

The majority of patients with SCD have hemodynamic profiles consistent with group 1 and group 2 disease. High-output heart failure may occur because of longstanding elevated cardiac output in the setting of anemia, although this is a rare etiology of PH. Advanced lung disease and pulmonary fibrosis leading to PH (group 3 PH) is exceedingly rare, even if patients develop recurrent episodes of acute chest syndrome (ACS) over time. However, patients should be screened and treated for obstructive sleep apnea or nocturnal hypoxemia if present.

Given that patients with SCD are at high risk of developing thromboembolism, they are at higher risk for developing CTEPH (group 4 PH), characterized by recurrent pulmonary thromboemboli followed by fibrotic remodeling of the occluded pulmonary vasculature.[59] Scintigraphic evidence suggestive of CTEPH occurs in approximately 5% of patients with SCD and severe PH,[60] and may be associated with more severe hemodynamic abnormalities, lower exercise capacity, and higher mortality.[61] Identification of CTEPH is important as these patients require lifelong anticoagulation. Specific medications may be approved for therapeutic use,[62] and surgical options may be available, including pulmonary artery balloon angioplasty or pulmonary endarterectomy.[63-67]

DIAGNOSTIC EVALUATION

The development of PH appears to increase with advancing age and is a major cause of early death. Diagnostic evaluation should assess for conditions that may also contribute to the development of PH, including iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and pulmonary thromboembolism. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) can identify patients with SCD at higher risk of PH, lower exercise capacity and increased mortality risk.[68-70]

Cardiac ultrasound is used to screen for PH and right heart failure, and the pulmonary artery systolic pressure can be estimated by measuring the TRV.[6] A value of ≥2.5 m/s is 2 standard deviations above the mean for patients aged 35 to 40 years, and a value ≥3.0 m/s is 3 standard deviations above the popula-

tion mean. Prospective and retrospective studies have shown that using a TRV of 2.5 m/s as a cutoff for elevated pulmonary artery systolic pressure estimates that 20% to 30% of individuals with SCD meet the criteria for PH, and approximately 8% to 10% have values 3 standard deviations above the normal mean (TRV ≥ 3 m/s).[6,52] These findings have been reproduced in multiple studies,[53,54,71,72] and it is accepted that even a mildly elevated TRV is associated with increased mortality.[6,71,73] However, a RHC remains the gold standard to confirm the diagnosis and hemodynamic etiology of PH.[74]

A 6-minute walk test inversely correlates with the severity of PH.[40,60] Although patients with PH may have less severe abnormalities in their hemodynamic profiles, their 6-minute walk test and WHO functional class may be severely abnormal, and these abnormalities are associated with increased mortality.[55] Pulmonary functional tests should also be pursued, as most adults with SCD develop abnormal pulmonary function, typically mild restriction and abnormal diffusing capacity due to mild pulmonary fibrosis. These defects may be slightly worse among individuals with SCD who also have PH,[75-78] but are rarely a major contributor to the development of PH. A ventilation-perfusion scan is also necessary to rule out evidence of CTEPH or chronic pulmonary thromboembolic disease and is superior to computed tomography pulmonary angiography.[61] Computed tomography chest may show mosaicism of lung parenchyma, demonstrating areas of hypoattenuation and decreased blood flow due to obstructed vasculature and decreased blood flow, juxtaposed to areas of normal lung parenchyma with normal blood flow.

Screening for Cardiovascular Disease

The American Thoracic Society published guidelines recommending that adult patients with SCD undergo screening echocardiography and/or NT-proBNP testing to assess the risk of death and of having PH for further diagnosis and intensification of sickle cell-specific therapies.[51] (Figure 1) Patients with a TRV value of 2.5 to 2.9 m/s are further risk stratified by 6-minute walk testing and plasma NT-proBNP testing, with abnormal values suggesting the need for RHC. Patients with values >2.9 m/s should undergo RHC, particularly if there is evidence of right heart dysfunction. Patients with PH should be screened for CTEPH. If patients develop symptoms suggestive of PH, initial screening with echocardiography and RHC may later be pursued.

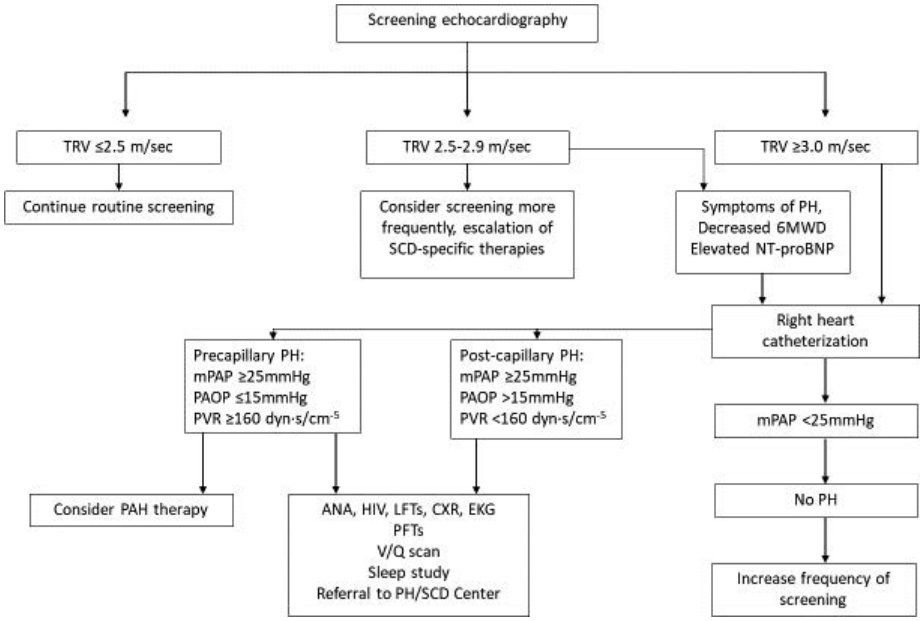

Figure 1: Diagnostic algorithm for evaluating PH in SCD. Adapted from Ghofrani et al.[63]

Mortality

The first study establishing a link between PH based on RHC and increased mortality was published in 2003. This study described a 55% mortality over 23 months and found that mPAP was inversely related to survival. Furthermore, for every increase in mPAP of 10 mm Hg, there is a 1.7-fold increase in the hazard ratio of death in patients with SCD.[73] Mortality is significantly higher in patients with PH defined by RHC, with significant correlation between hemodynamic markers and increased risk of death.[52-55] (Table 2) This has been validated by multiple subsequent studies, which have also found that an elevated transpulmonary gradient, diastolic pulmonary gradient (pulmonary artery diastolic pressure-PAOP), PVR, NT-proBNP, WHO functional class, and lower 6-minute walk test were all associated with increased mortality.[55,69,71]

Treatment Options

Data are limited on specific management of patients with SCD and PH; most treatment recommendations are extrapolated from data derived from other forms of PH or expert opinion.[51] Generally, maximization of SCD-specific therapy, treatment of hypoxia with supplemental oxygen therapy and treatment of associated cardiopulmonary conditions (for example, HIV, iron overload, nocturnal hypoxemia, thromboembolic disorders, left ventricular disease, and chronic liver disease) are warranted. Chronic red blood cell transfusions have been shown to reduce pulmonary pressures and increase 6-minute walk distance and functional classification in patients with SCD and PH.[79]

In SCD patients with PAH, namely, patients with a mPAP ≥ 25 mm Hg, PAOP ≤ 15 mm Hg and relatively high PVR (>160 dynes·sec/cm^5), PAH-specific therapy may be considered. There are no long-term data on specific treatment of PH in SCD, and choice of agent is empirical and based on the safety profile of the medication and physician preference. Sildenafil and other phosphodiesterase 5 inhibitors function by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. Sildenafil has been shown to im-

Table 2. Univariate and multivariate analysis of mortality risk factors in SCD[a]

Characteristic	Unadjusted HR (95% confidence interval)	*P* value	Adjusted HR (95% confidence interval)	*P* value
Age, per 10 yr	1.02 (0.76-1.38)	.89	-	-
sPAP, per 10 mm Hg	1.30 (1.06-43.6)	.048	1.30 (0.99-1.71)	.055
dPAP, per 10 mm Hg	1.91 (1.25-2.92)	.002	1.83 (1.09-3.08)	.022
mPAP, per 10 mm Hg	1.62 (1.17-2.24)	.003	1.61 (1.05-2.45)	.027
TPG, per 10 mm Hg	1.82 (1.28-2.61)	<.001	1.78 (1.14-2.79)	.011
PVR, per 1 Wood unit	1.35 (1.11-1.65)	.002	1.44 (1.09-1.89)	.009
PVRI, per 1 Wood unit/m^2	1.20 (1.08-1.33)	<.001	-	-
PP, per 10 mm Hg	1.29 (0.96-1.73)	.091	-	-
dPAP-PCWP, per 10 mm Hg	2.26 (1.43-3.58)	<.001	2.19 (1.23-3.89)	.008
CVP, per 10 mm Hg (n = 83)	1.36 (0.65-2.83)	.42	-	-
PCWP, per 10 mm Hg	0.97 (0.47-2.02)	.93	-	-
Cardiac output, L/min	0.98 (0.85-1.13)	.74	-	-
Cardiac index, L/min/m^2	0.87 (0.66-1.13)	.29	-	-
SVO2, % (n = 78)	0.98 (0.94-1.03)	.42	-	-
6MWD, m (n = 80)	0.56 (0.39-0.79)	<.001	-	-
WHO FC (III or IV vs I-II)	3.64 (1.64-8.05)	<.001	-	-

Abbreviations: 6MWD, 6 minute walk distance; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; HR, heart rate; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PP, pulmonary artery pulse pressure; PVC, pulmonary artery capacitance; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SCD, sickle cell disease; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index; SVO2, mixed venous oxygen saturation; SVR, systemic vascular resistance; TPG, transpulmonary gradient; WHO FC, World Health Organization functional class.

[a]Adapted from Mehari et al.[55]

prove pulmonary pressures and 6-minute walk distance in phase II studies,[80] but increased hospitalization due to painful crises was shown in one larger, randomized, double-blind, placebo-controlled trial.[56] Sildenafil is only recommended in patients with well-controlled and maximized SCD-specific therapy. Riociguat, a small molecule activator of soluble guanylate cyclase, is approved for the treatment of PAH and CTEPH, but its extrapolated use in individuals with SCD-related PH is limited to 1 case series of 6 patients.[62]

There is also limited published evidence with endothelin receptor agonists in the treatment of SCD-related PH. One retrospective study evaluating the use of ambrisentan and bosentan included 14 individuals with SCD-related PH found that therapy was well tolerated: there was a significant improvement in 6-minute walk distance, a trend toward lower BNP and TRV, and 3 individuals had decreases in their mPAP based on RHC. Therapy was stopped in 2 because of adverse reactions, but both tolerated the switch to the other endothelin-receptor agent.[81] However, the following year 2 randomized, double-blind, placebo-controlled studies were performed, the ASSET-1 and ASSET-2 trials.[82] Unfortunately, because of slow patient enrollment and site initiation, the studies were terminated prematurely. Preliminary analyses suggested that bosentan was well tolerated, with a trend toward increased CO and decreased PVR observed.

Prostacyclin-based therapies are the most effective agents for the treatment of traditional forms of PAH. Acutely, administration of epoprostenol decreases pulmonary artery pressure and PVR, and increases cardiac output.[73] Over time, prostacyclin-based therapy may reduce pulmonary pressure, increase 6-minute walk distance, and improve functional class.[83] However, its use remains off-label, with no prospective studies performed in patients with SCD.

Stem cell transplantation is the only curative option for individuals with SCD but is limited because of limited numbers of unaffected matched sibling donors and concerns regarding long-term toxicities.[84-88] Furthermore, bone marrow and lung transplantation have been shown to normalize pulmonary pressures and improve short-term outcome measures,[89,90] but may be associated with significant morbidity and mortality. Gene therapy remains an appealing option but remains limited in its application with further studies ongoing.[91,92]

CONCLUSIONS

Among individuals with SCD, PH is prevalent and remains a significant cause of morbidity and mortality. The underlying etiology of the development of PH in this population is complex and multifactorial, and a thorough workup is required to address all potential contributing disease states. Despite a growing body of evidence, advanced treatment options remain limited. However, with continued advances in therapy, quality of life and life expectancy will continue to improve.

References

1. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med*. Sep 11 1997;337(11):762-769. doi:10.1056/NEJM199709113371107.
2. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. *Am J Epidemiol*. May 1 2000;151(9):839-845. doi:10.1093/oxfordjournals.aje.a010288.
3. Brittenham GM, Schechter AN, Noguchi CT. Hemoglobin S polymerization: primary determinant of the hemolytic and clinical severity of the sickling syndromes. *Blood*. Jan 1985;65(1):183-189.
4. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med*. Jun 22 2000;342(25):1855-1865. doi:10.1056/NEJM200006223422502.
5. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. Jun 9 1994;330(23):1639-1644. doi:10.1056/NEJM199406093302303.
6. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. Feb 26 2004;350(9):886-895. doi:10.1056/NEJMoa035477.
7. Perronne V, Roberts-Harewood M, Bachir D, et al. Patterns of mortality in sickle cell disease in adults in France and England. *Hematol J*. 2002;3(1):56-60. doi:10.1038/sj.thj.6200147.
8. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. Jan 2019;53(1):1801913. doi:10.1183/13993003.01913-2018.
9. Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet*. Jan 12 2013;381(9861):142-151. doi:10.1016/S0140-6736(12)61229-X.
10. Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Hematol Oncol Clin North Am*. Feb 2010;24(1):199-214. doi:10.1016/j.hoc.2009.11.002.
11. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun*. Nov 2 2010;1:104. doi:10.1038/ncomms1104.
12. Allison AC. Protection afforded by sickle-cell trait against subtertian malareal infection. *Br Med J*. Feb 6 1954;1(4857):290-294. doi:10.1136/bmj.1.4857.290.
13. Ojodu J, Hulihan MM, Pope SN, Grant AM, Centers for Disease C, Prevention. Incidence of sickle cell trait–United States, 2010. *MMWR Morb Mortal Wkly Rep*. Dec 12 2014;63(49):1155-1158.
14. Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. *Lancet*. Mar 3 2001;357(9257):680-683. doi:10.1016/s0140-6736(00)04132-5.
15. Serjeant GR. The natural history of sickle cell disease. *Cold Spring Harb Perspect Med*. Oct 1 2013;3(10):a011783. doi:10.1101/cshperspect.a011783.
16. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers*. Mar 15 2018;4:18010. doi:10.1038/nrdp.2018.10.
17. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. Jul 15 2017;390(10091):311-323. doi:10.1016/S0140-6736(17)30193-9.
18. Rogers SC, Ross JG, d'Avignon A, et al. Sickle hemoglobin disturbs normal coupling among erythrocyte O2 content, glycolysis, and antioxidant capacity. *Blood*. Feb 28 2013;121(9):1651-1662. doi:10.1182/blood-2012-02-414037.
19. Smith CM II, Krivit W, White JG. The irreversibly sickled cell. *Am J Pediatr Hematol Oncol*. Fall 1982;4(3):307-315.
20. Evans EA, Mohandas N. Membrane-associated sickle hemoglobin: a major determinant of sickle erythrocyte rigidity. *Blood*. Nov 1987;70(5):1443-1449.
21. Nash GB, Johnson CS, Meiselman HJ. Rheologic impairment of sickle RBCs induced by repetitive cycles of deoxygenation-reoxygenation. *Blood*. Aug 1988;72(2):539-545.
22. Kuypers FA. Hemoglobin s polymerization and red cell membrane changes. *Hematol Oncol Clin North Am*. Apr 2014;28(2):155-179. doi:10.1016/j.hoc.2013.12.002.
23. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA*. Jul 6 2005;294(1):81-90. doi:10.1001/jama.294.1.81
24. Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med*. Dec 2002;8(12):1383-1389. doi:10.1038/nm1202-799.
25. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. Apr 6 2005;293(13):1653-1662. doi:10.1001/jama.293.13.1653.
26. Nath KA, Katusic ZS, Gladwin MT. The perfusion paradox and vascular instability in sickle cell disease. *Microcirculation*. Mar 2004;11(2):179-193. doi:10.1080/10739680490278592.
27. Ataga KI, Moore CG, Hillery CA, et al. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. *Haematologica*. Jan 2008;93(1):20-26. doi:10.3324/haematol.11763.
28. van Beers EJ, Spronk HM, Ten Cate H, et al. No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension. *Haematologica*. May 2008;93(5):e42-e44. doi:10.3324/haematol.12632.
29. Westerman M, Pizzey A, Hirschman J, et al. Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy. *Br J Haematol*. Jul 2008;142(1):126-135. doi:10.1111/j.1365-2141.2008.07155.x.
30. Hagger D, Wolff S, Owen J, Samson D. Changes in coagulation and fibrinolysis in patients with sickle cell disease compared with healthy black controls. *Blood Coagul Fibrinolysis*. Apr 1995;6(2):93-99. doi:10.1097/00001721-199504000-00001.
31. Villagra J, Shiva S, Hunter LA, Machado RF, Gladwin MT, Kato GJ. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. *Blood*. Sep 15 2007;110(6):2166-2172. doi:10.1182/blood-2006-12-061697.
32. Lim MY, Ataga KI, Key NS. Hemostatic abnormalities in sickle cell disease. *Curr Opin Hematol*. Sep 2013;20(5):472-477. doi:10.1097/MOH.0b013e328363442f.
33. Manci EA, Culberson DE, Yang YM, et al. Causes of death in sickle cell disease: an autopsy study. *Br J Haematol*. Oct 2003;123(2):359-365. doi:10.1046/j.1365-2141.2003.04594.x.
34. Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. *Am J Forensic Med Pathol*. Jun 2007;28(2):168-172. doi:10.1097/01.paf.0000257397.92466.50.
35. Hoeper MM, Niedermeyer J, Hoffmeyer F, Flemming P, Fabel H. Pulmonary hypertension after splenectomy? *Ann Intern Med*. Mar 16 1999;130(6):506-509. doi:10.7326/0003-4819-130-6-199903160-00014.
36. Atichartakarn V, Likittanasombat K, Chuncharunee S, et al. Pulmonary arterial hypertension in previously splenectomized patients with beta-thalassemic disorders. *Int J Hematol*. Aug 2003;78(2):139-145. doi:10.1007/BF02983382.
37. Chou R, DeLoughery TG. Recurrent thromboembolic disease following splenectomy for pyruvate kinase deficiency. *Am J Hematol*. Jul 2001;67(3):197-199. doi:10.1002/ajh.1107.
38. Hayag-Barin JE, Smith RE, Tucker FC Jr. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: a case report and review of the literature. *Am J Hematol*. Jan 1998;57(1):82-84. doi:10.1002/(sici)1096-8652(199801)57:1<82::aid-ajh15>3.0.co;2-b.
39. Atichartakarn V, Angchaisuksiri P, Aryurachai K, Chuncharunee S, Thakkinstian A. In vivo platelet activation and hyperaggregation in hemoglobin E/beta-thalassemia: a consequence of splenectomy. *Int J Hematol*. Apr 2003;77(3):299-303. doi:10.1007/BF02983790.
40. Sachdev V, Kato GJ, Gibbs JS, et al. Echocardiographic markers of elevated pulmo-

nary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. *Circulation*. Sep 27 2011;124(13):1452-1460. doi:10.1161/CIRCULATIONAHA.111.032920.
41. Sachdev V, Machado RF, Shizukuda Y, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. *J Am Coll Cardiol*. Jan 30 2007;49(4):472-479. doi:10.1016/j.jacc.2006.09.038.
42. Roy SB, Bhatia ML, Mathur VS, Virmani S. Hemodynamic effects of chronic severe anemia. *Circulation*. Sep 1963;28:346-356. doi:10.1161/01.cir.28.3.346.
43. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. *J Am Coll Cardiol*. Mar 27 2012;59(13):1123-1133. doi:10.1016/j.jacc.2011.10.900.
44. Vanderpool RR, Naeije R. Hematocrit-corrected pulmonary vascular resistance. *Am J Respir Crit Care Med*. Aug 1 2018;198(3):305-309. doi:10.1164/rccm.201801-0081PP.
45. Quinn CT, Ahmad N. Clinical correlates of steady-state oxyhaemoglobin desaturation in children who have sickle cell disease. *Br J Haematol*. Oct 2005;131(1):129-134. doi:10.1111/j.1365-2141.2005.05738.x.
46. Nouraie M, Lee JS, Zhang Y, et al. The relationship between the severity of hemolysis, clinical manifestations and risk of death in 415 patients with sickle cell anemia in the US and Europe. *Haematologica*. Mar 2013;98(3):464-472. doi:10.3324/haematol.2012.068965.
47. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest*. Mar 1 2017;127(3):750-760. doi:10.1172/JCI89741.
48. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med*. Nov 20 2008;359(21):2254-2265. doi:10.1056/NEJMra0804411.
49. Maron BA, Brittain EL, Choudhary G, Gladwin MT. Redefining pulmonary hypertension. *Lancet Respir Med*. Mar 2018;6(3):168-170. doi:10.1016/S2213-2600(17)30498-8.
50. Maron BA, Wertheim BM, Gladwin MT. Under pressure to clarify pulmonary hypertension clinical risk. *Am J Respir Crit Care Med*. Feb 15 2018;197(4):423-426. doi:10.1164/rccm.201711-2306ED.
51. Klings ES, Machado RF, Barst RJ, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med*. Mar 15 2014;189(6):727-740. doi:10.1164/rccm.201401-0065ST.
52. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. *JAMA*. Mar 28 2012;307(12):1254-1256. doi:10.1001/jama.2012.358.
53. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med*. Jul 7 2011;365(1):44-53. doi:10.1056/NEJMoa1005565.
54. Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. *Eur Respir J*. Jan 2012;39(1):112-118. doi:10.1183/09031936.00134410.
55. Mehari A, Alam S, Tian X, et al. Hemodynamic predictors of mortality in adults with sickle cell disease. *Am J Respir Crit Care Med*. Apr 15 2013;187(8):840-847. doi:10.1164/rccm.201207-1222OC.
56. Machado RF, Barst RJ, Yovetich NA, et al. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. *Blood*. Jul 28 2011;118(4):855-864. doi:10.1182/blood-2010-09-306167.
57. Levine AR, Simon MA, Gladwin MT. Pulmonary vascular disease in the setting of heart failure with preserved ejection fraction. *Trends Cardiovasc Med*. May 2019;29(4):207-217. doi:10.1016/j.tcm.2018.08.005.
58. Lai YC, Wang L, Gladwin MT. Insights into the pulmonary vascular complications of heart failure with preserved ejection fraction. *J Physiol*. Feb 2019;597(4):1143-1156. doi:10.1113/JP275858.
59. Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. *Circ Res*. Jun 20 2014;115(1):115-130. doi:10.1161/CIRCRESAHA.115.301146.
60. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med*. Jun 15 2007;175(12):1272-1279. doi:10.1164/rccm.200610-1498OC.
61. Mehari A, Igbineweka N, Allen D, Nichols J, Thein SL, Weir NA. Abnormal ventilation-perfusion scan is associated with pulmonary hypertension in sickle cell adults. *J Nucl Med*. Jan 2019;60(1):86-92. doi:10.2967/jnumed.118.211466.
62. Weir NA, Conrey A, Lewis D, Mehari A. Riociguat use in sickle cell related chronic thromboembolic pulmonary hypertension: a case series. *Pulm Circ*. Oct-Dec 2018;8(4):2045894018791802. doi:10.1177/2045894018791802.
63. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. Jul 25 2013;369(4):319-329. doi:10.1056/NEJMoa1209657.
64. Naik RP, Streiff MB, Haywood C Jr, Segal JB, Lanzkron S. Venous thromboembolism incidence in the Cooperative Study of Sickle Cell Disease. *J Thromb Haemost*. Dec 2014;12(12):2010-2016. doi:10.1111/jth.12744.
65. Yung GL, Channick RN, Fedullo PF, et al. Successful pulmonary thromboendarterectomy in two patients with sickle cell disease. *Am J Respir Crit Care Med*. May 1998;157(5 Pt 1):1690-1693. doi:10.1164/ajrccm.157.5.9710032.
66. Agrawal H, Petit CJ, Miro J, Miranda CD, Kenny D, Justino H. Contralateral pulmonary hypertension following resuscitation of unilateral ductal origin of a pulmonary artery: a multi-institutional review. *Pediatr Cardiol*. Jan 2018;39(1):71-78. doi:10.1007/s00246-017-1729-z.
67. Mahesh B, Besser M, Ravaglioli A, et al. Pulmonary endarterectomy is effective and safe in patients with haemoglobinopathies and abnormal red blood cells: the Papworth experience. *Eur J Cardiothorac Surg*. Sep 2016;50(3):537-541. doi:10.1093/ejcts/ezw062.
68. Gladwin MT, Barst RJ, Gibbs JS, et al. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. *PLoS One*. 2014;9(7):e99489. doi:10.1371/journal.pone.0099489.
69. Machado RF, Anthi A, Steinberg MH, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *JAMA*. Jul 19 2006;296(3):310-318. doi:10.1001/jama.296.3.310.
70. Machado RF, Hildesheim M, Mendelsohn L, Remaley AT, Kato GJ, Gladwin MT. NT-pro brain natriuretic peptide levels and the risk of death in the cooperative study of sickle cell disease. *Br J Haematol*. Aug 2011;154(4):512-520. doi:10.1111/j.1365-2141.2011.08777.x.
71. Ataga KI, Moore CG, Jones S, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *Br J Haematol*. Jul 2006;134(1):109-115. doi:10.1111/j.1365-2141.2006.06110.x.
72. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. *Am J Hematol*. Jan 2008;83(1):19-25. doi:10.1002/ajh.21058.
73. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood*. Feb 15 2003;101(4):1257-1261. doi:10.1182/blood-2002-03-0948.
74. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. Jun 16 2004;43(12 Suppl S):40S-47S. doi:10.1016/j.jacc.2004.02.032.
75. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)*. Jan 1988;67(1):66-76.
76. Koumbourlis AC, Hurlet-Jensen A, Bye MR. Lung function in infants with sickle cell disease. *Pediatr Pulmonol*. Oct 1997;24(4):277-281. doi:10.1002/(sici)1099-0496(199710)24:4<277::aid-ppul6>3.0.co;2-h.
77. Koumbourlis AC, Zar HJ, Hurlet-Jensen A, Goldberg MR. Prevalence and reversibility of lower airway obstruction in children with sick-

le cell disease. *J Pediatr*. Feb 2001;138(2):188-192. doi:10.1067/mpd.2001.111824.
78. Lonsdorfer J, Bogui P, Otayeck A, Bursaux E, Poyart C, Cabannes R. Cardiorespiratory adjustments in chronic sickle cell anemia. *Bull Eur Physiopathol Respir*. Jul-Aug 1983;19(4):339-344.
79. Turpin M, Chantalat-Auger C, Parent F, et al. Chronic blood exchange transfusions in the management of pre-capillary pulmonary hypertension complicating sickle cell disease. *Eur Respir J*. Oct 2018;52(4):1800272. doi:10.1183/13993003.00272-2018.
80. Machado RF, Martyr S, Kato GJ, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *Br J Haematol*. Aug 2005;130(3):445-453. doi:10.1111/j.1365-2141.2005.05625.x.
81. Minniti CP, Machado RF, Coles WA, Sachdev V, Gladwin MT, Kato GJ. Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. *Br J Haematol*. Dec 2009;147(5):737-743. doi:10.1111/j.1365-2141.2009.07906.x.
82. Barst RJ, Mubarak KK, Machado RF, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. *Br J Haematol*. May 2010;149(3):426-435. doi:10.1111/j.1365-2141.2010.08097.x.
83. Weir NA, Saiyed R, Alam S, et al. Prostacyclin-analog therapy in sickle cell pulmonary hypertension. *Haematologica*. May 2017;102(5):e163-e165. doi:10.3324/haematol.2015.131227.
84. Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood*. Oct 1 2007;110(7):2749-2756. doi:10.1182/blood-2007-03-079665.
85. Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. Mar 16 2017;129(11):1548-1556. doi:10.1182/blood-2016-10-745711.
86. Walters MC, De Castro LM, Sullivan KM, et al. Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. Feb 2016;22(2):207-211. doi:10.1016/j.bbmt.2015.10.017.
87. Le PQ, Gulbis B, Dedeken L, et al. Survival among children and adults with sickle cell disease in Belgium: benefit from hydroxyurea treatment. *Pediatr Blood Cancer*. Nov 2015;62(11):1956-1961. doi:10.1002/pbc.25608.
88. Dallas MH, Triplett B, Shook DR, et al. Long-term outcome and evaluation of organ function in pediatric patients undergoing haploidentical and matched related hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. May 2013;19(5):820-830. doi:10.1016/j.bbmt.2013.02.010.
89. George MP, Novelli EM, Shigemura N, et al. First successful lung transplantation for sickle cell disease with severe pulmonary arterial hypertension and pulmonary veno-occlusive disease. *Pulm Circ*. Dec 2013;3(4):952-958. doi:10.1086/674749.
90. Pittman C, Hsieh MM, Coles W, Tisdale JF, Weir NA, Fitzhugh CD. Reversal of pre-capillary pulmonary hypertension in a patient with sickle cell anemia who underwent haploidentical peripheral blood stem cell transplantation. *Bone Marrow Transplant*. Apr 2017;52(4):641-642. doi:10.1038/bmt.2016.335.
91. Hoban MD, Orkin SH, Bauer DE. Genetic treatment of a molecular disorder: gene therapy approaches to sickle cell disease. *Blood*. Feb 18 2016;127(7):839-848. doi:10.1182/blood-2015-09-618587.
92. Demirci S, Uchida N, Tisdale JF. Gene therapy for sickle cell disease: an update. *Cytotherapy*. Jul 2018;20(7):899-910. doi:10.1016/j.jcyt.2018.04.003.

Sarcoidosis and Pulmonary Hypertension

Dr Oksana Shlobin: Welcome to the roundtable on sarcoidosis-associated pulmonary hypertension (SAPH), moderated by myself and Dr Anjali Vaidya, Co-Director of the Pulmonary Hypertension, Right Heart Failure, and CTEPH Program at Temple University Lewis Katz School of Medicine. Our discussants are Dr Roxana Sulica, Associate Professor of Medicine and Director of the Pulmonary Hypertension Program at NYU Langone, Dr Bob Baughman, Professor of Medicine at University of Cincinnati, and Dr Stacy Mandras, Medical Director of Pulmonary Hypertension Program at AdventHealth.

Dr Anjali Vaidya: Sarcoidosis is probably one of the biggest topics within WHO group 5 PH. There are a lot of excellent publications and reviews on this topic, and many are written by all of you. We thought that rather than doing another review article on that topic, we would have a discussion with your expertise to talk about your experiences and observations in this broad area. One of the first things we thought we would touch upon is the multiple mechanisms by which patients with sarcoidosis can develop pulmonary hypertension.

I would like to start by focusing on a few main mechanisms: the parenchymal lung disease causing vascular destruction, the granulomatous involvement of the pulmonary arterial bed to resemble PAH, and the extrinsic and external compression of bulky lymphadenopathy. I want to get a sense from your experiences in terms of what you see most frequently and what you think the prevalence of PH is in your patients with pulmonary sarcoid.

Dr Roxana Sulica: I can start the conversation. The prevalence question depends on the kind of practice you have: a sarcoid practice in which you end up diagnosing patients with pulmonary hypertension versus a pulmonary hypertension practice with sarcoidosis referrals when patients are referred to you for suspicion of PH.

Currently, 100% of the patients I am seeing have pulmonary hypertension. When I was in Mount Sinai with a dedicated sarcoidosis clinic, we observed SAPH in 20% of patients. Again, if you look at patients from advanced lung programs evaluated for transplantation, pulmonary hypertension can be seen in up to 75% of that referral patient population. To summarize, SAPH is a well-recognized complication of sarcoidosis, but the prevalence depends on the clinical setting.

In terms of the mechanism, there is a myriad of reasons for patients with sarcoid to develop pulmonary hypertension. Hence, they are placed in group 5 pulmonary hypertension. As it has been shown in multiple series, most of the time patients with SAPH have parenchymal lung disease and chronic hypoxemia. However, probably in about 20% to 30% of the people in each series reported, there is another pathophysiologic mechanism besides pulmonary fibrosis involved. For example, many years ago, Robyn Barst reported a small series with patients with SAPH with pulmonary arteriopathy, fairly similar to iPAH. Subsequently, there were a lot of other series describing the SAPH histopathology in explanted lungs or postmortem examinations. We started to identify this process of granulomatous inflammation, in the arterioles but mainly in the venules of the pulmonary vasculature, a mechanism similar to pulmonary vaso-occlusive disease (PVOD). In addition, a small percent of people with SAPH has significant extrinsic compression of the pulmonary vasculature by the mediastinal and hilar adenopathy of fibrotic disease.

Some people, in theory at least, have granulomatous hepatitis from sarcoid and can develop portal hypertension, and consequently porto-pulmonary hypertension. About one-third of them will have pulmonary hypertension due to left heart disease, as Bob Baughman has shown in one series. It is very important to identify the dominant phenotype to help guide further medical management.

Dr Bob Baughman: I primarily work in a sarcoidosis clinic, although I have had a strong interest in pulmonary hypertension and have collaborated with Dr Peter Engel at University of Cincinnati for many years.

Dr Shlobin: Bob, maybe you can mention or comment on disease prevalence given that you mostly see patients with sarcoidosis versus Roxana and Stacy, who mostly see patients with pulmonary hypertension.

Dr Baughman: I think you have to think in terms of where you're coming from. In a tertiary clinic like ours, which includes a lot of patients with refractory parenchymal disease, it's around 7 to 10%. In some published series, it is as high as 20%. In Athol Wells' group in London, where mostly fibrotic sarcoidosis patients are seen, nearly a quarter have PH. In general, I think it's somewhere between 5% and 20%.

Dr Shlobin: Thank you Bob. A follow-up question is for Stacy and also Anjali. As advanced heart failure cardiologists, can you comment on the various mechanisms the sarcoidosis can affect the heart and cause PH, as well as the importance of right and left heart catheterization in teasing out a specific diagnosis, and why it is especially important in sarcoidosis population?

Dr Stacy Mandras: As a heart failure specialist, we do see a small percentage of patients who come to us with an underlying diagnosis of cardiac sarcoidosis. I'd say less than 10% of our referrals with advanced heart failure have cardiac sarcoidosis. In the general sarcoidosis

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population, cardiac disease is often subclinical, and we may not even make the diagnosis until the time of transplantation when we review the pathology after the heart has been explanted. At least a third of these patients will have pulmonary hypertension due to elevated left sided pulmonary pressures associated with diastolic dysfunction. Often these patients also present with ventricular arrhythmias, which will ultimately lead to their need for transplantation, as they tend to be very difficult to control despite antiarrhythmic drugs and ablations. Even sympathectomy can be completely ineffective in these situations, and in such cases, the management corners on treatment of the underlying LV dysfunction (rather than treatment of the pulmonary hypertension), and often ultimately leads to cardiac transplantation.

In my pulmonary hypertension practice, I see all of the mentioned mechanisms of SAPH—everything from WHO group 1 to group 5—the patients with concomitant left sided heart disease, fibrocystic lung disease, the patients who have extrinsic pulmonary artery compression, and the patients who truly do look like they have WHO group 1 pathophysiology.

Dr Shlobin: I wanted to ask the group if any of you use any kind of provocative maneuvers while doing the right heart catheterization in these patients.

Dr Sulica: Yes, I do as I always contemplate how to treat their PH. As you very well know, it is very difficult to get PAH-specific medications approved without a vasoreactivity maneuver. Obviously, patients with precapillary SAPH, even with positive vasoreactive maneuver, are not true *vasoreactors*, at least not by the definition that incorporates long-term response to calcium channel blockers.

Dr Vaidya: I agree with contemplating treatment. I think that's a whole other discussion and something that we all, in the PH space, have our minds open to. I always appreciate talking to colleagues from different places, because the insurance payer patterns are very different. I haven't done a vasoreactive study in years for the purpose of getting medications approved, and it probably depends what the payers require in your specific geographic area.

From a purely clinical purpose of understanding pathophysiology and its affecting management, I actually don't do vasoreactive studies in the sarcoid PH patients. But from a broader sense, in terms of provocative maneuvers, I do often include exercise physiology into the right heart catheterizations in these patients to identify their true cause of dyspnea. This ties into Stacy's point about the mixed left heart failure phenotype, which often actually can coexist with a PAH phenotype in the sarcoid PH patient. These are some of the most challenging patients that we are facing that have the mixed physiology, precapillary and postcapillary PH.

I'll use provocative maneuvers in the Cath Lab with rest and perform an exercise RHC with simultaneous CPET (aka invasive CPET) to get a sense as to what their true underlying physiology and limitation with exertion is. From a hemodynamic perspective, if they have mixed physiology and their wedge pressure goes up by two-fold or three-fold while the right atrial pressure goes up only minimally and their pulmonary vascular resistance falls, that indicates that this is more of a WHO group 2 left heart failure PH phenotype. Whereas, if their VE/VCO_2 climbs to 45 with exercise and their PVR does not fall, or it goes up and the right atrial pressure goes up to a magnitude greater than left atrial pressure, then I might say, "The phenotype of this patient is more clearly that of pulmonary vascular disease or more resembling the iPAH patient." These provocative maneuvers can be quite helpful.

Dr Shlobin: Stacy, do you also prefer exercise right heart catheterization with CPET versus fluid loading in this patient population?

Dr Mandras: Absolutely agree with Anjali. I like to exercise patients in the Cath Lab to attempt to unmask diastolic dysfunction. We use an *under the desk* exercise bike pedal exerciser that we literally put on the Cath table once the pulmonary artery catheter is in place and we have obtained baseline hemodynamic measurements. We have the patients pedal for exercise, and we record what happens to their systemic pressure, their filling pressures, PA pressure, and cardiac output. I prefer doing that to fluid loading. I have partners that do fluid challenge their patients, but I feel that we get more information from having them exercise and try to simulate what happens when they're active to try to understand why it is that they're getting short of breath with activity.

Dr Vaidya: Exercise cath is much more physiologic than a fluid challenge. If I can build off of what Stacy said, going back to the left heart failure component of the conversation, I want to bring it even to the next level in terms of the transplant consideration, because in the lung transplant world, sarcoid is a big player. In the heart transplant world, sarcoid is a big player. We have a large exposure to the combined heart-lung transplant world, relative to our other left heart failure partners or other lung transplant partners.

I find the sarcoid population is the most commonly represented diagnosis in this population of combined heart-lung transplant. I also find it to be very challenging sometimes, because the isolated indication for lung transplant might not be as obvious, and the isolated indication for heart transplant may not be as strong. In other words, their fibrotic lung disease might not be as severe or their PAH might not be as severe or their left heart failure might not be as severe, but when you combine them together, a heart-lung transplantation is the indicated treatment.

Sometimes the lung disease will preclude PH management, or the left heart involvement will preclude PH management, and the additive sum component of infiltrative granulomatous disease causing arrhythmia, diastolic dysfunction, systolic dysfunction, right heart failure from PH, gas exchange limitation is often a rapid accelerator driver to combined heart-lung transplant. I'd like to hear what the rest of the group has experienced in that regard?

Dr Baughman: I'm probably the only non-"transplanter" here. I think a lot of the time that sarcoidosis PH can be medically managed, but I think it's an evolution management. Often patients present with a combined precapillary and postcapillary PH, which is initially managed with diuretic therapy. Once their volume status is well controlled, if the patient is still short of breath, they may benefit from treatment of the precapillary component of their pulmonary hypertension as well. I agree that it's very good to do the exercise challenge in Cath Lab to try to uncover the predominant phenotype in these mixed PH cases.

In our original paper with Peter Engel, of 120 sarcoidosis patients that underwent catheterization, a significant number of patients had diastolic dysfunction. We weren't doing routine cardiac MRIs at that time and we've never had an opportunity to analyze another large group of dyspneic sarcoidosis patients to determine how many may have myocardial involvement by cardiac MRI.

Has any of you seen any data on how often a cardiac MRI uncovers potential causes for diastolic dysfunction in these sarcoid patients?

Dr Shlobin: I have not. In my experience, patients with significant cardiac sarcoid do not usually have precapillary pulmonary hypertension and vice versa. In our experience, it's either severe PH (with or without parenchymal disease) or bad cardiac sarcoid. To follow up on Anjali's question, you're absolutely right. Other than congenital heart diseases, sarcoidosis is the most common indication for combined heart-lung transplant. In my experience it's a combination of end stage burnt out parenchymal lung disease and active cardiac sarcoidosis causing arrhythmias that cannot be controlled medically, or significant left systolic ventricular dysfunction that is the most common indication. Per our lung transplant work up protocol, we always look for cardiac sarcoidosis with a combination of cardiac MRI and PET.

Dr Shlobin: I wanted to go back to the basics and ask Bob and Roxana, when do you suspect pulmonary hypertension in patients with sarcoidosis, and then how do you work them up?

Dr Baughman: Our clinic approach was initially driven by Roxana's publication, when she was at Mount Sinai and analyzed a large number of patients referred for echo. We then began looking at our persistently dyspneic patients, those failing anti-inflammatory therapy such as prednisone, methotrexate, and/or infliximab, and found that over half of these patients had pulmonary hypertension. So when I see someone in sarcoidosis clinic who I'm treating for lung disease with anti-inflammatory therapy and they're just not getting better, I start the work up for pulmonary hypertension.

The other clues there that helped me include a reduced six-minute walk test (6MWT) distance. Certainly somebody who walks under 300 meters or who desaturates during their 6MWT needs a screening echo and probably right heart catheterization to look for either precapillary or postcapillary PH. An elevated BNP is another clue. The Dutch have actually suggested that a sarcoidosis patient with fibrosis on chest imaging should get an annual ECHO. The term *parenchymal fibrosis* is a bit difficult in sarcoid, because there are a lot of people with a little bit of fibrosis on their imaging. Therefore I would modify that to say that patients with at least 20% fibrosis on CT scan should be considered for screening ECHOs.

I still think that the main trigger for work up is persistent or out-of-proportion shortness of breath. The other factor that I don't use as much as others is an enlarged pulmonary artery (PA) or PA/aorta diameter ratio on chest CT scan. There is interesting data in sarcoidosis showing the denominator should not be the aorta diameter but the body surface area. Two large series (1 from Holland, 1 from France) showed that the PA diameter when corrected for the body surface area was a better predictor of SAPH.

Dr Sulica: How about diffusing lung capacity (DLCO)?

Dr Baughman: A reduced DLCO is probably much more useful than a reduced forced vital capacity. The things that should bring PH for consideration are: a reduced DLCO (probably less than 60% or predicted), a 6MWT distance of less than 300 meters, new or worsening desaturation with exercise, more than 20% fibrosis on high-resolution CT scan, or dyspnea that seems out of proportion to their clinical presentation and the amount of lung disease. Those patients should be further worked up for pulmonary hypertension.

Dr Vaidya: That's great. Roxana, what about the next step in the work up algorithm?

Dr Sulica: My workup is very similar to what most of us do for patients with PH in general. In addition, you need to determine the specific and dominant mechanism of pulmonary hypertension it is, as we just said at the very beginning that the mechanisms of pulmonary hypertension in sarcoid are multifactorial. I tend to do a cardiac MRI, because I want to see how the myocardium looks. Sometimes we use PET scans as well if we want to tease out how much active inflammation there is. We do exercise right heart catheterizations fairly often, although we don't have the capability of doing simultaneous CPET during RHCs.

Otherwise, we do everything else that you do for PH patients: VQ scans, CAT scans, and full pulmonary function test, because the DLCO, as Bob was saying, is important in the diagnosis and prognosis for these patients. We also look for sarcoidosis liver involvement, test for HIV, and screen for concomitant connective tissue disorders. Throughout the years we had a small number of patients that had more than one risk factor for pulmonary hypertension besides sarcoid; we had patients with both sarcoidosis and HIV or lupus.

Dr Shlobin: What about chronic clots in patients with SAPH?

Dr Sulica: We do get VQ scans and CT with PE protocol, absolutely. Sometimes in sarcoidosis a VQ scan may

show perfusion defects that are sizeable and mismatched. Then the differential becomes more extensive with extrinsic compression versus intrinsic chronic thromboembolic disease. We do have a very good radiology department with excellent postprocessing for the CT with PE protocols. Less and less we are using the pulmonary angiograms, but obviously in situations when you're really not clear if it's intrinsic CTEPH-like disease or not, you will need to get a formal pulmonary angiogram.

Dr Shlobin: Anjali, given that you co-direct a major CTEPH center, what has your experience been?

Dr Vaidya: Yes, I'm glad to hear this discussion. I agree completely. I would say the concomitant presence of clinically significant CTEPH that warrants advanced CTEPH intervention along with intrinsic sarcoid is on the lower side. However, I always say anybody with chronic heart failure or chronic lung disease can also have recurrent venous thromboemboli. Although this does exist, it's a very common scenario for the abnormal VQ scan to lead us down the CTEPH evaluation in patients with sarcoid, and it's a fake-out, a CTEPH mimicker, and there actually is not a truly intravascular thromboembolic disease.

As Roxana nicely stated, often abnormal VQ scans are caused by extrinsic compression of pulmonary segmental or sub-segmental branches by bulky lymphadenopathy or fibrotic scarring granulomatous disease, and it gives the impression of perfusion defects on the VQ scan. There's a nuance I think in the evaluation from that perspective where we're always hearing that the gold standard diagnostic study for CTEPH is an invasive pulmonary angiogram. I think I'd like to continue to question that in the modern era, because it really is only a luminogram, and the CTA really is the most informative comprehensive study. It's particularly valuable in our sarcoid patients, because you can then visualize that compression and get that appreciation which the invasive angiogram would not provide and would only lead us down a false impression of CTEPH. I just had a patient like that in the last couple of weeks.

I think there's an important concept - in CTEPH at least - even in the presence of significant thromboembolic disease. Let's say the patient has CTEPH and it is deemed proximal and operable and accessible. There's an important concept of "not perfusing bad lung," so to speak. We don't want to generate ventilatory inefficiency and worsen dead space ventilation. This is the case for anyone—be it advanced sarcoid lung disease or other chronic lung disease.

I just wanted to mention that if there is a patient that has significant lung scarring via parenchymal involvement by sarcoidosis with concomitant true thromboembolic disease, it's extremely complicated. One always has to question if CTEPH treatment will result in reperfusion of an area affected by advanced scarring and actually harm the patient. A little restraint in treatment sometimes goes a long way.

One may also raise a question about balloon pulmonary angioplasty (BPA). Our program has done over 100 BPAs. In sarcoidosis patients with significantly hemodynamically severe PH related to distal thromboembolic disease, staged BPA may be a very reasonable consideration, rather than PTE.

Dr Shlobin: Sounds like a paper in making.

Dr Vaidya: Yes. I'll add it to the list.

Dr Shlobin: Thanks Anjali. Another question to the whole group: When you have someone with significant extrinsic compression, what factors do you consider for intervention for either pulmonary arterial or pulmonary venous constriction by bulky lymphadenopathy?

Dr Mandras: There are a couple of case series of small numbers of patients—5 to 8 patients—of angioplasty with or without stenting for patients who have extrinsic compressions not related to thromboembolic disease, which did demonstrate an improvement in hemodynamics and did not come with an increase in morbidity and mortality. Again, these are very small numbers. There's definitely more information that's needed for that patient population.

Dr Shlobin: Stacy, maybe while you're answering that question, what about pulmonary venous stenting?

Dr Mandras: Similar results. Again, from small case series.

Dr Shlobin: I agree, this area definitely needs more research. In someone who has bulky lymphadenopathy, one does need to think about both the arterial and venous strictures due to extrinsic compression. Sometimes it can really change one's treatment approach, because if you can stent the artery or vein with a resultant drop in pulmonary pressures, a patient may not need as much diuretics or pulmonary arterial vasodilators.

Dr Baughman: The French registry of 160 SAPH patients found 9 patients who had an improvement in PA pressure after giving corticosteroids to reducing the adenopathy. There is also a prospective study from China**,** which Stacy alluded to, demonstrating that almost 10% of their SAPH patients improved with stenting.

In our clinic, we've only had 1 patient that we've ever stented for pulmonary hypertension, and I have over 2500 sarcoidosis patients and nearly 100 patients with SAPH. I would like to make a general comment on treatment of SAPH. If you are a PH specialist, you need to make sure that the underlying parenchymal lung disease has been aggressively managed with anti-inflammatory therapy (such as steroids, methotrexate, infliximab), as patients' hemodynamics and symptoms may improve with appropriate treatment. If you are a sarcoidosis specialist and you have managed to control the inflammatory parenchymal component, or your patient has burnt out fibrotic parenchymal disease, if they have evidence of PH, they should be considered for further pulmonary vascular evaluation and treatment with pulmonary vasodilator medications, stenting, etc.

Dr Vaidya: That's an excellent segue into our last series of questions. In the current era of PAH medical therapy, we have over a dozen treatment options. Sarcoid-associated PH spans across, as Stacy nicely said, all 5 WHO groups in terms of phenotype and physiology. Roxana mentioned that she considers PAH medical therapy and follow them thoroughly for that.

With that in mind, how do you determine if a patient may be appropriate for medical therapy? I think that's one of the hardest decisions. Then we'll segue into what classes of drugs or approaches to treatments themselves. How do you initially consider a patient being appropriate for consideration of PH medical therapy?

Dr Mandras: I think you have to take each patient on a case-by-case basis. I think that what Roxana said, that the first step is to try to figure out what the underlying etiology for the patient's pulmonary hypertension is, ie, which WHO group they fall into. Often it's not straightforward. They may fall into one or two or three or more of these groups.

I inherited a pulmonary hypertension practice in 2009 that originally was started in the 1990s. I had SAPH patients that were initiated on a 3 drug therapy at that time, and remained stable and did very well for over a decade on therapy. Likewise, I had newly incident cases that seemed very straightforward without significant parenchymal lung disease and with normal left-sided filling pressure, so very much a WHO group 1 PAH-like phenotype. Yet the way these patients are managed in the current era may be very different because now, often pulmonary vasodilators are not paid for by insurance if the diagnosis of sarcoidosis is present, and this can make things very challenging. As soon as the diagnosis of sarcoidosis appears on the chart, no form of a prostacyclin will be approved. You may be caring for a high-risk patient who you feel strongly would benefit from parenteral therapy, and the payer denies coverage. It's very challenging to manage the sicker sarcoid patient. For the patients that are lower risk, treatment is fairly straightforward. We have data from a handful of mixed trials—some prospective, some retrospective—that show benefits of ERAs and PDE5s and combination therapy in this patient population, which demonstrated improvement in 6MWT, functional capacity, and improved hemodynamics without worsening in oxygenation, and for the most part we are able to obtain insurance authorization for these drugs.

Dr Shlobin: Well said. Roxana, what do you think?

Dr Sulica: Yes, one always has to take into account the payer situation. As Stacy mentioned, there are a couple of smaller and larger studies that looked at the effect of PAH specific therapies in SAPH. Unfortunately, they are small studies, some of them with a high drop-out rate, but they did show improvement. Until recently, the one placebo-controlled trial of bosentan showed no increase in 6-minute walk distance despite clear hemodynamic improvement. I am not very surprised of the dichotomy given the multiple comorbidities that may have led to decreased exercise capacity in SAPH. As Stacy mentioned, there are also case series as well as anecdotical reports in which PAH advanced therapies have been used in SAPH on a compassionate basis. Interestingly, some of those patients have responded beautifully to therapy, even with hemodynamic normalization. We do not know if that response translates into long-term survival benefit. When we plan SAPH trials, we have to be very careful to rule out pathology that can potentially lead to harmful effect from PAH drugs use (such as left heart disease). In addition, we do have to learn more about the type of endpoints that are meaningful in SAPH treatment trials.

Dr Shlobin: There is certainly a spectrum of diseases, just very much like interstitial lung diseases, where there is a more vascular phenotype and a more parenchymal phenotype of sarcoidosis. An ideal trial patient is the one with a vascular phenotype. Having said that, a recent trial of inhaled treprosinil in ILD-PH targeted all-comers with fibrotic lung disease and showed improvement in 6MWT distance, markers of right heart failure and delay in clinical worsening. With that, I wanted to ask Bob to comment on the recently submitted data on riociguat in SAPH.

Dr Vaidya: The only one comment I'll say before we open it to Bob on his perspective as well is that, in the growing interest—rapidly growing interest—in the pulmonary hypertension field and all of our young trainees going out into the community with so much more interest to treat these patients, I would emphasize the PH associated with sarcoid, as Stacy said, has many faces. It's one of the specific diagnoses that I think still very much should be referred to expert centers, to individuals such as all of you, to do that very high-level assessment that Roxana described beautifully.

Dr Shlobin: Bob, the Rioci-guat data will be presented at ATS, can you comment on the results of the RioSAPH trial?

Dr Baughman: While I've done several trials in SAPH, there have been limitations to all of these trials to date. One issue is that we do not have really good endpoints. Up until a few years ago, we really had struggled about whether we should be looking at the 6MWT or hemodynamics. Our group became intrigued by the idea of time to clinical worsening, because we thought that this would still be a good endpoint in SAPH given its multifactorial nature. Steve Nathan and Oksana Shlobin have worked with us on a recently completed trial, and we were able to demonstrate a difference in time to clinical worsening between the patients treated with riociguat therapy compared to placebo. This was the first long-term trial of SAPH patients, and I think that contributed to a clearer outcome of therapy. This is all preliminary data, which needs to be further validated. There's a larger SAPH study being currently conducted looking at time to clinical worsening as

a secondary endpoint after intervention with selexipag. I do think this approach should be a standard for outcomes in SAPH—these endpoints have become the standard in group 1 PAH.

My bias, of course, is that we should treat precapillary phenotype of SAPH. SAPH is an independent factor predicting mortality in sarcoidosis. Oksana led the recently published analysis of survival of 215 patients in our Registry for Sarcoid-Associated Pulmonary Hypertension (ReSAPH) and found only a 72% transplant-free survival at 3 years. Overall in ReSAPH, a third of the US patients were not treated for their SAPH at the time of entry into the registry, including patients with moderate to severe pulmonary hypertension.

Dr Vaidya: There's so much more we could discuss but we are at the top of the hour. On behalf of Oksana and myself, thank you so much, Stacy, Roxana, Bob, for taking the time and sharing your expertise for this discussion. We really enjoyed it.

An Interesting Case of Sarcoidosis-Associated Pulmonary Hypertension

Section Editor
Deborah Jo Levine, MD

Kirsten J. Alman, MD
Department of Medicine
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

Corey J. Sadd, MD
Department of Medicine
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

Michaella M. Reif, MD
Department of Medicine
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

Jeffrey P. Kanne, MD
Department of Radiology
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

James R. Runo, MD
Department of Pulmonary and Critical Care Medicine
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI

BACKGROUND

Sarcoidosis-associated pulmonary hypertension (SAPH) is classified in World Health Organization group 5 pulmonary hypertension (PH) due to the various potential mechanisms of disease pathogenesis including pulmonary arterial hypertension (PAH), left heart disease, fibrotic lung disease, pulmonary vascular stenosis, compressive adenopathy, and fibrosing mediastinitis.[1,2] Although patients with sarcoidosis-associated advanced fibrotic lung disease are at the highest risk and comprise a majority of SAPH patients,[3,4] pulmonary sarcoidosis involving the pulmonary veins presents a unique management challenge and mortality risk. We present a patient with SAPH due to pulmonary vein compression from adenopathy who required multiple pulmonary vein balloon dilations and stents in the setting of large-volume hemoptysis and right heart failure.

PRESENTATION

A 40-year-old female with a history of cutaneous and pulmonary sarcoidosis presented to the emergency department (ED) with large volume hemoptysis. Symptoms began approximately 3 days prior with cough productive of light green sputum accompanied by increasing dyspnea, posttussive emesis, and chills. She estimated having 2 L of hemoptysis over the course of the day with active hemoptysis (650 mL) in the ED.

Before this presentation, she had been on chronic steroids for sarcoidosis, although she was noted to be a poor steroid responder. She had additionally been on methotrexate but notably had been out of her medications including prednisone, losartan, nicardipine, and Symbicort, for 3 weeks before her ED presentation.

On physical examination, she was hypotensive and tachycardic. Jugular venous distention was present, but no murmurs or gallops on auscultation. Pulmonary exam revealed inspiratory and expiratory wheezes and bibasilar crackles.

WORKUP AND THERAPEUTIC INTERVENTIONS

She was admitted to the Intensive Care Unit, and an emergent bronchoscopy was performed which demonstrated bleeding localized to the lingula in addition to hyperemia of the mucosa with bright red streaking capillaries. Due to persistent bleeding, the patient underwent an attempt at embolization with interventional radiology. However, no site of bleeding was identified by arteriogram. The patient was in shock on admission, requiring norepinephrine and dobutamine, presumed from severe right heart failure and PH.

Computed tomography chest revealed interlobular septal thickening and edema pattern predominantly in the upper lobes with significant mediastinal and hilar lymphadenopathy in addition to pulmonary vein stenoses (Figures 1 and 2). Transthoracic echo was performed and demonstrated severe right ventricular dysfunction in addition to severe PH and can be seen in Table 1. Ultimately, pulmonary venous hypertension second-

Key Words—sarcoidosis-associated pulmonary hypertension, pulmonary veno-occlusive disease, pulmonary venous hypertension, echocardiogram
Correspondence: kalman@uwhealth.org
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ary to pulmonary vein obstruction was presumed to be the underlying etiology. As such, she went for heart catheterization for further evaluation.

Right and left heart catheterization was performed which showed almost systemic pulmonary artery pressures with pulmonary capillary wedge pressure of around 30 but with left ventricular end diastolic pressure of only 11, consistent with pulmonary vein stenosis. Attempted decompression of the left lower and lingular pulmonary veins with balloon dilation was performed. Heart catheterization data both preballoon and postballoon dilation are presented in Table 2. Cardiac catheterization demonstrated a significant reduction in stenosis with less than 20% residual stenosis postdilation in the left lingular pulmonary vein and left lower pulmonary vein.

After pulmonary vein dilation, a cardiac magnetic resonance venous scan was completed, which demonstrated moderate stenosis of the right upper and right middle lobe pulmonary veins, no stenosis involving the left upper or left lower veins, and delayed myocardial enhancement at the inferior basilar wall, suggestive of myocardial sarcoidosis. Cardiac positron emission tomography was not pursued during or after her hospitalization, and her prior immunosuppressive regimen was continued. Vasopressors were weaned during admission, and she was successfully extubated. Lung transplantation was considered, but she was deemed not to be a candidate due to persistent tobacco use.

FOLLOW UP

Recurrent hemoptysis in the months after her initial admission raised concern for recurrent pulmonary vein obstruction. Radiographic workup showed continued mediastinal lymphadenopathy and improved interstitial edema from prior study. Transthoracic echocardiogram was obtained 4 months after initial presentation and showed mild increase in pulmonary artery pressure, right ventricular dysfunction, and reduction in right ventricular size. Echocardiogram data are shown in Table 1. Magnetic resonance imaging and magnetic resonance angiography showed severe stenosis of the left upper pulmonary vein which was unchanged from prior, stable left upper lobe hypoperfusion with slight decrease in the left inferior pulmonary vein narrowing, minimal decrease in stenosis at the confluence of the right upper and middle pulmonary veins, as well as normal left and right ventricular systolic function.

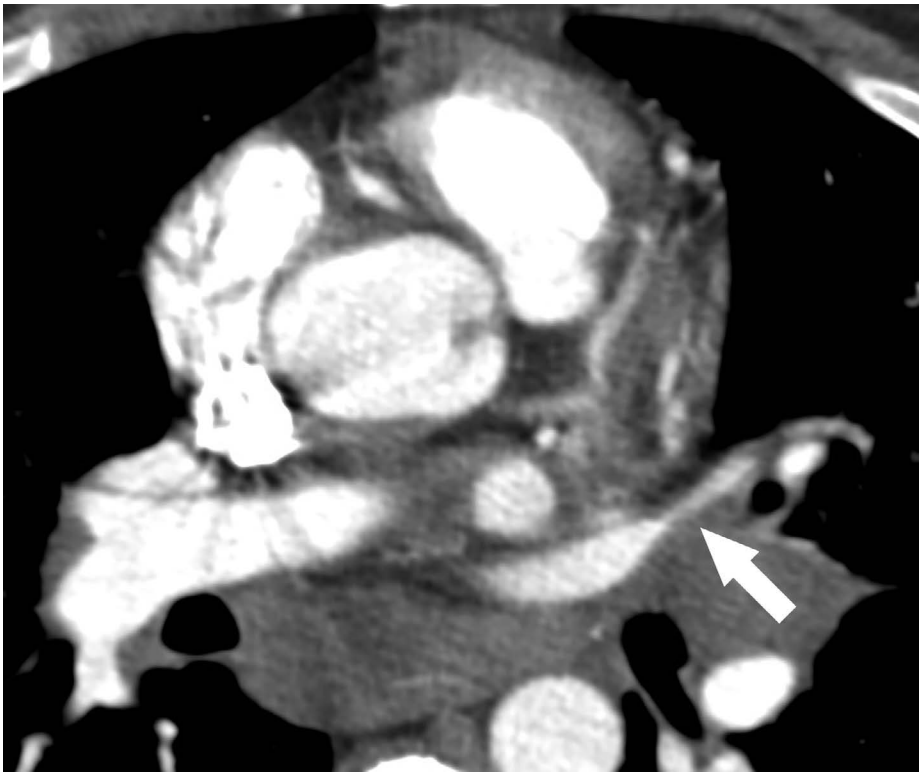

Figure 1: Contrast-enhanced chest computed tomography image shows stenosis of the left superior pulmonary vein (arrow) and left hilar and subcarinal lymphadenopathy.

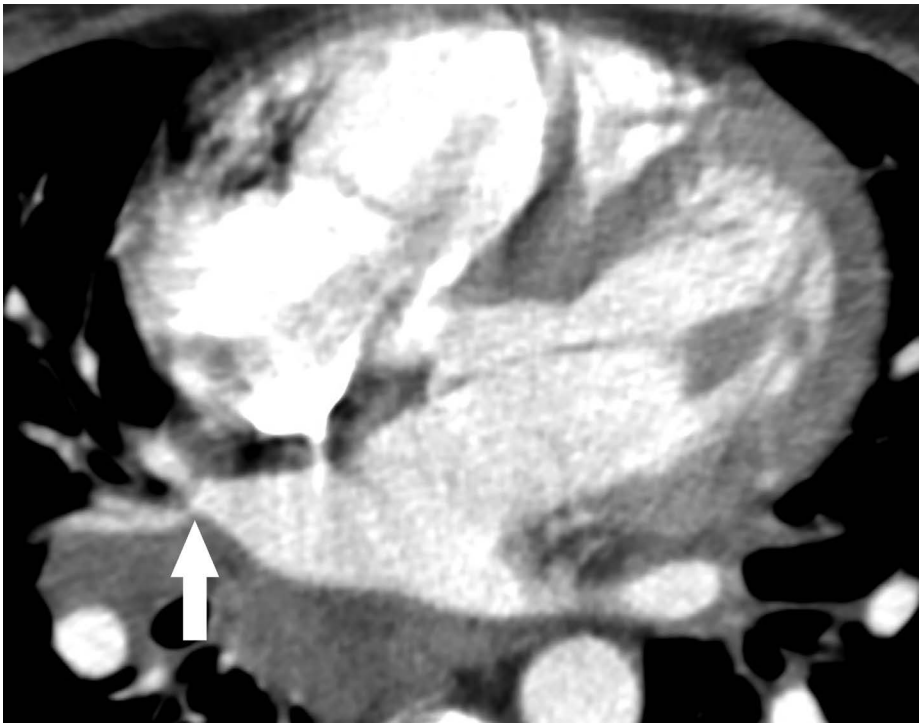

Figure 2: Contrast-enhanced chest computed tomography image shows stenosis at the confluence of the middle lobe pulmonary veins (arrow) and right hilar and subcarinal lymphadenopathy.

Table 1. Echocardiographic data from initial presentation, both preballon and postballoon angioplasty of left lingular and left lower pulmonary veins; 4-month follow up; 12-month urgent evaluation of right heart function before stenting; 21 months later, both preballoon and postballoon angioplasty; and admission for severely progressive pulmonary hypertension requiring veno-arterial extracorporeal membrane oxygenation

	Initial presentation		Time from initial presentation (mo)				
			4	12	21		29
Echocardiogram	Baseline	Postballoon	Baseline	(Limited exam)	Baseline	Postballoon	Baseline
LVEF (%)	85	70	65	70	70	65	70
LV size (mm)	28.5	37.4	24.3	NA	36.8	45.9	33.5
LVOT peak velocity (cm/s)	196	115.9	127	NA	124.1	125.8	129
PA peak pressure (mmHg)	106	50	62	91	70	77	109
RV size (mm)	43.7	NA	39	NA	36.1	41.3	42.7
TAPSE (cm)	1.3	1.8	2.4	NA	2.3	2	1.7
Estimated CVP (mmHg)	25	NA	8	15	5	5	15
RV function	Severely reduced	Normal	Mildly reduced	Moderately reduced	Moderately reduced	Mildly reduced	Moderately reduced
RA size	43.7	NA	39	NA	36.1	41.3	42.7
PV regurgitation	Moderate	Mild	None	Mild	Mild	Mild	Mild
TV regurgitation	Moderate	Mild	Mild	NA	Moderate	Mild	Moderate
AV regurgitation	Mild	Moderate	None	NA	Mild	Mild	Mild
MV regurgitation	Mild	Trivial	None	NA	None	None	None

Abbreviations: AV, aortic valve; CVP, central venous pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MV, mitral valve; NA, not applicable; PA, pulmonary artery; PV, pulmonic valve; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

Due to persistent significant thoracic adenopathy despite compliance with prednisone and methotrexate, she was initiated on infliximab, which unfortunately did not result in any shrinkage of her hilar and mediastinal lymphadenopathy and was ultimately discontinued.

She subsequently underwent multiple pulmonary vein stents and balloon dilations performed at 12, 21, and 29 months after her initial presentation, and catheterization data are presented in Table 2. Left lower pulmonary vein, left upper pulmonary vein, and right lower pulmonary vein stents were placed 1 year after her initial hospitalization for hemoptysis. Nifedipine was initiated for possible pulmonary venodilation effect but was ineffective.

Two and a half years from initial presentation, she was again hospitalized for severe PH and right heart failure with hemoptysis and possible pneumonia. Mechanical ventilation, inotropic support, and veno-arterial extracorporeal membrane support was provided, but she unfortunately suffered a subarachnoid hemorrhage, and life-supporting measures were withdrawn.

DISCUSSION

In our patient, pulmonary venous hypertension due to pulmonary vein obstruction secondary to compressive adenopathy from underlying sarcoidosis was temporized with pulmonary vein dilation and stenting with subsequent improvement in pulmonary vascular pressures and functional status. Agents including prednisone, methotrexate, and infliximab were unfortunately unsuccessful in significantly improving her compressive adenopathy. Despite this, pulmonary vein balloon dilations and stenting were able to provide 2.5 additional years and allow her to return home.

Pulmonary sarcoidosis is not limited to the lung parenchyma and lymph nodes but can affect the pulmonary vasculature as well. This can be from compressive adenopathy or granuloma formation within the pulmonary arterial and venous systems. On autopsy, granulomas have been observed in multiple pulmonary venous vascular layers, causing vessel fibrosis and luminal narrowing.[5] Our patient was diagnosed with postcapillary PH secondary to pulmonary venous obstruction from compressive mediastinal and hilar adenopathy in the setting of underlying sarcoidosis. As in our patient, pulmonary venous stenosis can present with massive hemoptysis, which can be life threatening and difficult to diagnose on routine imaging.[6] Corticosteroids are the foundation of sarcoidosis management, but their efficacy for SAPH has been mixed.[7] If the pulmonary venous stenosis is secondary to extrinsic compression from bulky mediastinal and hilar adenopathy, then corticosteroids can lead to an improvement in pulmonary vascular pressures. In a study by Nunes et al,[8] treatment with corticosteroids led to a reduction in systolic pulmonary arterial pressures in patients with nonfibrotic SAPH, but there was no benefit in patients with fibrotic SAPH. In our patient, corticosteroids

Table 2. Left and right heart catheterizations from initial presentation, both preballoon and postballoon dilatation of left lingular and left lower pulmonary veins; 12 months later, both pre-intravascular and postintravascular stenting of left lingular, left lower, and right lower pulmonary veins; 21 months later, both preballon and postballoon dilatation of in-stent and native stenosis of the left lower, left upper, and right lower pulmonary veins; and 29 months later, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) insertion and attempt balloon angioplasty of pulmonary veins

Cardiac catheterizations, mean pressure (mmHg)	Initial presentation		Mo after initial presentation				
			12		21		29
	Preballoon	Postballoon	Prestent	Poststent	Preballoon	Postballoon	VA-ECMO, balloon dilatation
RA	15	17	12	NA	10	12	NA
RVEDP	27	25	10	NA	15	NA	108
PA	NA	NA	NA	49	51	NA	66
LPA	66	66	51	NA	49	NA	NA
RPA	66	NA	48	NA	50	NA	42
LPCWP	30	23	NA	NA	NA	NA	NA
RPCWP	26	NA	18	14	15	NA	29
Ao	79	88	NA	NA	75	NA	80
LVEDP	11	NA	NA	14	10	NA	NA
LA	11	12	10	14	10	NA	11
LLPV	16	26	28	14	14	12	12
LLiPV	68	25	NA	NA	NA	NA	NA
LUPV	25	NA	38	14	35	12	NA
RUPV	NA	NA	14	14	11	11	NA
RLPV	NA	NA	35	14	22	12	NA
% Stenosis							
RLPV	60–70	NA	NA	NA	NA	NA	50
LLiPV	70–80	<20	NA	NA	NA	NA	NA
LLPV	70	<20	NA	NA	NA	NA	50–75
LUPV	NA	NA	NA	NA	NA	NA	100

Abbreviations: Ao, aorta; LA, left atrium; LLiPV, left lingular pulmonary vein; LLPV, left lower pulmonary vein; LPA, left pulmonary artery; LPCWP, left pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; LUPV, left upper pulmonary vein; NA, not applicable; PA, main pulmonary artery; RA, right atrium; RLPV, right lower pulmonary vein; RPA, right pulmonary artery; RPCWP, right pulmonary capillary wedge pressure; RUPV, right upper pulmonary vein; RVEDP, right ventricular end diastolic pressure.

were not effective in improving pulmonary venous obstruction and PH.

Patients with pulmonary venous obstruction due to external vascular compression can undergo pulmonary vein angioplasty and stenting to relieve the obstruction in an effort to improve pulmonary vascular pressures and right heart failure.[9,10] In a small case series, pulmonary vein angioplasty and stenting in the setting of pulmonary vascular compression from bulky lymphadenopathy led to clinical and hemodynamic improvement.[9] Pulmonary vein angioplasty and stenting is a viable option for patients interested in prolonging life or as a bridge to lung transplantation.

Based on small series and nonrandomized trials, pulmonary vasodilator therapy may have a role in treatment of patients with precapillary SAPH but carries an increased risk of developing pulmonary edema and respiratory failure in patients with postcapillary component. Despite the increased risk, there have been case reports and small case series of pulmonary veno-occlusive disease (PVOD) patients improving with pulmonary vasodilator therapy.[11,12] For example, a small case series demonstrated hemodynamic improvement with cautious epoprostenol therapy as a bridge to lung transplant in 12 patients with PVOD.[13] In SAPH patients, granuloma formation may not be limited to the pulmonary venous system but can involve the pulmonary arterial system, a scenario in which PH vasodilatory therapy could be beneficial.

Patients with SAPH have poor long-term prognosis, with a 5-year survival ranging from 40%–55%.[10] The multifactorial nature of these patients' PH can create diagnostic dilemmas when trying to elucidate the primary driver of right ventricular failure, which in turn leads to difficulty while choosing the most appropriate treatment options. Ultimately, lung transplantation is the curative treatment option but carries its own risks and benefits. These patients

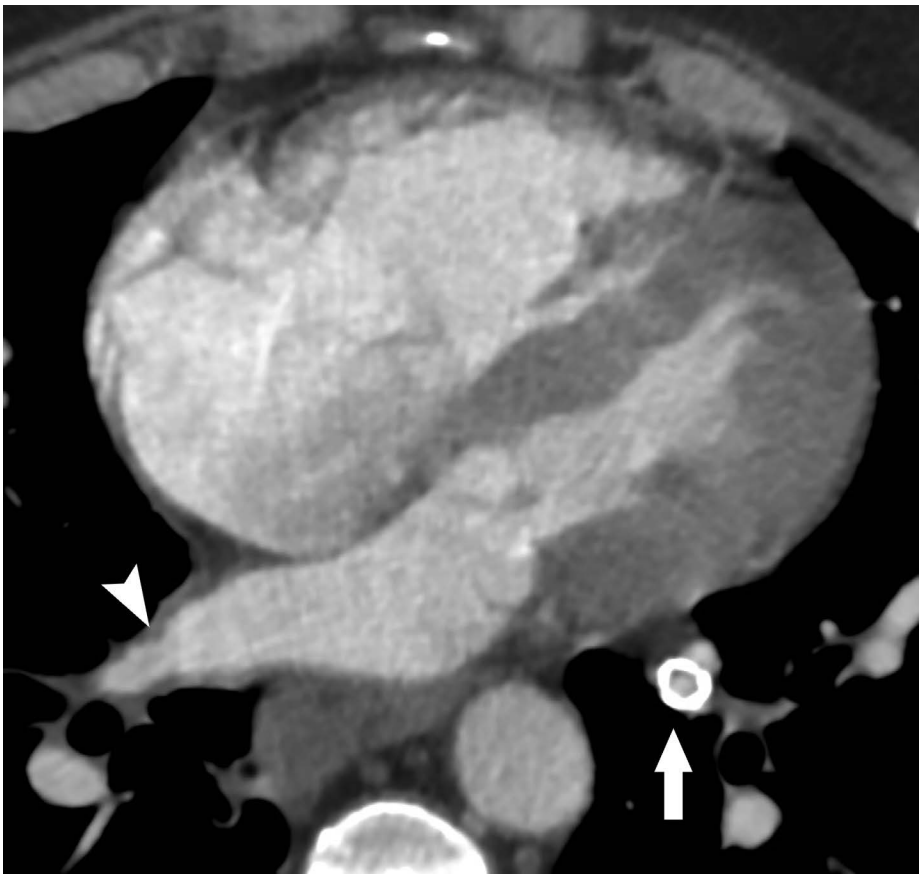

Figure 3: Contrast-enhanced chest computed tomography image shows mild stenosis of the right inferior pulmonary vein (arrowhead) and stent in a left inferior pulmonary vein branch (arrow).

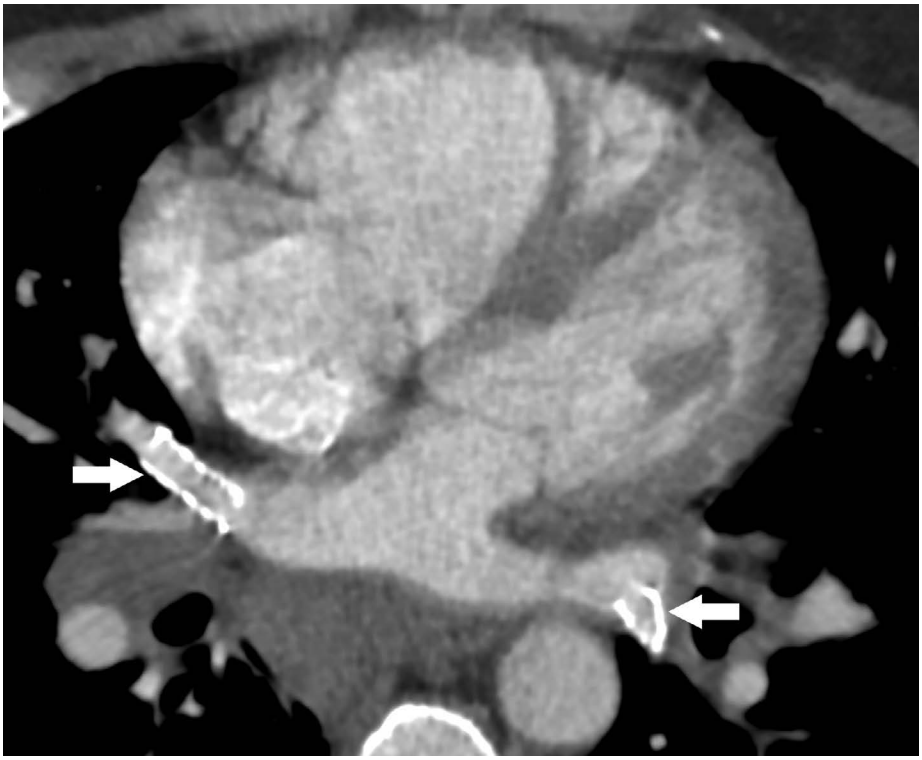

Figure 4: Contrast-enhanced chest computed tomography image shows patent pulmonary venous stents (arrows) in a middle lobe vein branch and in the left inferior pulmonary vein. Lymphadenopathy persists.

should be managed in an experienced PH center given the complex nature of their PH.

TEACHING POINTS

1. SAPH has several mechanisms of pathogenesis including PAH, left heart disease, fibrotic lung disease, pulmonary vascular stenosis, compressive adenopathy, and fibrosing mediastinitis.
2. Hemoptysis is a rare presentation of SAPH from pulmonary venous obstructive disease.
3. The multifactorial pathogenesis of SAPH portends high mortality and diagnostic challenges, with 5-year survival estimated at 40%–55%.
4. There is insufficient data with corticosteroids improving SAPH from all mechanisms.
5. Pulmonary venous stenosis from compressive adenopathy may initially be treated with corticosteroids, with consideration for balloon angioplasty if there is no improvement.
6. Vasodilator therapy can be cautiously considered in patients with SAPH if granulomatous involvement of the pulmonary arterial system is a suspected mechanism.

References

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34–D41. doi:10.1016/j.jacc.2013.10.029
2. Duong H, Bonham CA. Sarcoidosis-associated pulmonary hypertension: pathophysiology, diagnosis, and treatment. *Clin Pulm Med*. 2018;25(2):52–60. doi:10.1097/CPM.0000000000000252
3. Sulica R, Teirstein AS, Kakarla S, Nemani N, Behnegar A, Padilla ML. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. *Chest*. 2005;128(3):1483–1489. doi:10.1378/chest.128.3.1483
4. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J*. 2005;25(5):783–788. doi:10.1183/09031936.05.00083404
5. Takemura T, Matsui Y, Saiki S, Mikami R. Pulmonary vascular involvement in sarcoidosis: a report of 40 autopsy cases. *Hum Pathol*.

1992;23(11):1216–1223. doi:10.1016/0046-8177(92)90288-E
6. Braun S, Platzek I, Zöphel K, et al. Haemoptysis due to pulmonary venous stenosis. *Eur Respir Rev*. 2014;23:170–179. doi:10.1183/09059180.00003713
7. Jones RM, Dawson A, Jenkins GH, Nicholson AG, Hansell DM, Harrison NK. Sarcoidosis-related pulmonary veno-occlusive disease presenting with recurrent haemoptysis. *Eur Respir J*. 2009;34:517-520. doi:10.1183/09031936.00044609
8. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. *Thorax*. 2006;61(1):68–74. doi:10.1136/thx. 2005.042838
9. Condado JF, Babaliaros V, Henry TS, Kaebnick B, Kim D, Staton GW Jr. Pulmonary stenting for the treatment of sarcoid induced pulmonary vascular stenosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2016;33(3):281–287.
10. Weatherald J, Savale L, Humbert M. Medical management of pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5): is there a role for pulmonary arterial hypertension medications? *Curr Hypertens Rep*. 2017;19(11):86. doi:10.1007/s11906-017-0783-5
11. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2010;31(15):1898–1907. doi:10.1093/eurheartj/ehq170
12. Montani D, Girerd B, Jaïs X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med*. 2017;5(2):125–134. doi:10.1016/S2213-2600(16)30438-6
13. Montani D, Jaïs X, Price LC, et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. *Eur Respir J*. 2009;34(6):1348–1356. doi:10.1183/09031936.00017809

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